Multicomponent Reactions

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Nickel-Catalyzed Borylative Coupling of Alkynes, Enones, and Bis(pinacolato)diboron as a Route to Substituted Alkenyl Boronates**

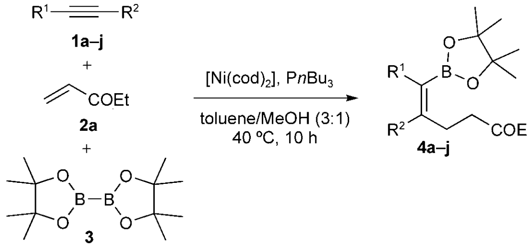
*Subramaniyan Mannathan, Masilamani Jeganmohan, and Chien-Hong Cheng**

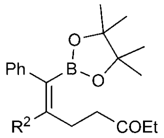
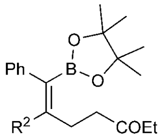
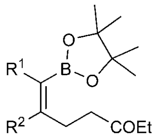
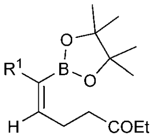
Nickel-catalyzed sequential coupling of two different π components with an organometallic reagent or a metal hydride is a practical method for the one-pot assembly of three different stable components with consecutive formation of two chemical bonds.[1] In 1995, the Ikeda research group demonstrated the intermolecular sequential coupling of alkynes, enones, and organometallic reagents, such as organostannane, organozinc, and organoaluminum reagents.[2] In the meantime, Montgomery and co-workers reported the intramolecular sequential coupling of enynes with various organometallic reagents.[3] Later, the sequential coupling of two different π components and organometallic reagents or metal hydrides was demonstrated.[4,5] Recently, we also described an intermolecular coupling of benzynes with activated alkenes and organoboronic acids.[6] In these sequential coupling reactions of two different π components, only organometallic reagents and metal hydrides have been used as the terminating agents.

Our continuing interest in metal-catalyzed sequential coupling reactions and the addition of dimetal reagents[7] to carbon–carbon π components[8] prompted us to explore the use of a diboron reagent as a terminating agent in coupling reactions of alkynes and enones. Herein, we report a highly regio- and stereoselective three-component coupling of alkynes, alkenes, and bis(pinacolato)diboron (**3**) to afford highly substituted alkenyl boronates in good to excellent yields.[9] The alkenyl boronates formed in this way are useful synthetic intermediates in various organic transformations.[10]

The treatment of 1-phenyl-1-propyne (**1a**) with ethyl vinyl ketone (**2a**) and bis(pinacolato)diboron (**3**) in the presence of [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene; 5 mol%) and PnBu$_3$ (10 mol%) in a 3:1 mixture of toluene and methanol at 40 °C for 10 h gave the highly substituted alkenyl boronate **4a** in 85% yield (Table 1, entry 1). Control experiments revealed that in the absence of either [Ni(cod)$_2$] or PnBu$_3$, no **4a** was obtained. The catalytic reaction is highly regioselective, with a boron group of **3** adding very selectively to the phenyl-substituted alkyne carbon atom and with C–C bond formation occurring between the methyl-substituted alkyne carbon atom of **1a** and the β carbon atom of vinyl ketone **2a**. The

Table 1: Three-component coupling of alkynes with ethyl vinyl ketone (**2a**) and bis(pinacolato)diboron (**3**).[a]



Entry	Alkyne **1**	Product **4**	Yield [%][b]
	$Ph-\!\equiv\!-R^2$		
1	**1a**: R^2 = Me	**4a**	85 (92)
2	**1b**: R^2 = Et	**4b**	80
	$Ph-\!\equiv\!-R^2$		
3[c]	**1c**: R^2 = (CH$_2$)$_2$OH	**4c**/**4c′** (82:18)	81
4[c]	**1d**: R^2 = CH$_2$OMe	**4d**/**4d′** (80:20)	79
5[c,d]	**1e**: R^2 = CO$_2$Me	**4e**/**4e′** (98:2)	72
	$R^1-\!\equiv\!-R^2$		
6[d]	**1f**: R^1 = R^2 = Ph	**4f**	72
7	**1g**: R^1 = R^2 = nPr	**4g**	55
	$R^1-\!\equiv\!-H$		
8[e]	**1h**: R^1 = Ph	**4h**	78
9[e]	**1i**: R^1 = 4-OMeC$_6$H$_4$	**4i**	79
10[e]	**1j**: R^1 = pyridyl	**4j**	75

[a] Unless otherwise mentioned, reactions were carried out with the alkyne **1** (1.5 mmol), **2a** (1.0 mmol), **3** (1.5 mmol), [Ni(cod)$_2$] (5 mol%), and PnBu$_3$ (10 mol%) in a 3:1 mixture of toluene and methanol (2 mL) at 40 °C for 10 h. [b] Yield of the isolated product; the yield in parenthesis was determined by ^{1}H NMR spectroscopic analysis with mesitylene as an internal standard. [c] Two regioisomers of the product were formed: **4** (major) and **4′** (minor). [d] The reaction was carried out at 50 °C for 10 h (entry 5) or at room temperature for 12 h (entry 6). [e] The reaction was carried out in an 8:1 mixture of toluene and methanol (4.5 mL) at room temperature for 2 h.

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[*] S. Mannathan, Dr. M. Jeganmohan, Prof. Dr. C.-H. Cheng
Department of Chemistry, National Tsing Hua University
Hsinchu 30013 (Taiwan)
Fax: (+886) 3572-4698
E-mail: chcheng@mx.nthu.edu.tw
Homepage: http://mx.nthu.edu.tw/%7Echcheng

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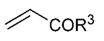
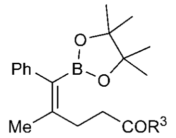
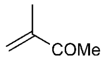
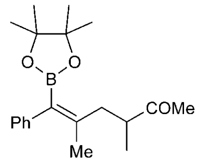
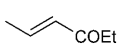
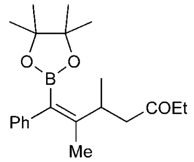
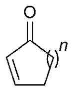
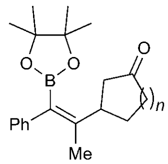
catalytic reaction is also highly stereoselective; the phenyl and methyl groups in the product are *cis* to each other.

To optimize the present coupling reaction, we examined the reaction of **1a** with **2a** and **3** in the presence of various phosphine ligands and [Ni(cod)$_2$] (5 mol %). The monodentate phosphine ligands PPh$_3$, P(2-furyl)$_3$, PCy$_3$ (Cy = cyclohexyl), and P*n*Bu$_3$ (10 mol %), and the bidentate phosphine ligands 1,2-bis(diphenylphosphanyl)ethane (dppe) and 1,3-bis(diphenylphosphanyl)propane (dppp; 5 mol %) were examined. With P*n*Bu$_3$, the most effective ligand, the reaction afforded **4a** in 92 % yield. Other ligands were less effective and gave **4a** in 5–57 % yield. A binary solvent system comprising toluene and methanol (3:1) was also crucial for the success of the reaction. In methanol alone, the product of borylative coupling **4a** was formed in only 50 % yield, along with the product of reductive coupling, (*E*)-PhCH=CH(Me)-(CH$_2$)$_2$COEt (**5a**), in 45 % yield.[11] The formation of the reductive-coupling product **5a** was totally suppressed in the 3:1 toluene/methanol system. When the catalytic reaction was performed in toluene only, neither **4a** nor **5a** was observed. On the basis of these studies, we chose [Ni(cod)$_2$] (5 mol %) and P*n*Bu$_3$ (10 mol %) in a 3:1 mixture of toluene and methanol as the standard conditions for the reactions in Tables 1 and 2.

To explore the scope of the three-component reaction, various alkynes were examined under the optimized reaction conditions (Table 1). Thus, the treatment of 1-phenyl-1-butyne (**1b**) with **2a** and **3** also afforded a single isomeric product **4b** in 80 % yield (Table 1, entry 2). Both 2-hydroxyethyl-substituted phenylacetylene (**1c**) and the related substrate **1d** with a CH$_2$OMe substituent gave regioisomeric products: **4c**/**4c′** (82:18) and **4d**/**4d′** (80:20), respectively (Table 1, entries 3 and 4). In terms of regio- and stereoselectivity, the reactions to give the major isomers **4c** and **4d** were equivalent to the formation of **4a**. The transformation of methyl phenylpropiolate (**1e**) also gave two regioisomers, **4e** and **4e′**, in a 98:2 ratio and 72 % combined yield with C–C bond formation occurring at the CO$_2$Me-substituted alkyne carbon atom of **1e** (Table 1, entry 5). By contrast, in the reported cobalt-catalyzed reductive coupling of **1e** with alkenes, C–C bond formation occurs at the phenyl-substituted alkyne carbon atom.[11] Under similar reaction conditions, the symmetrical alkynes diphenyl acetylene (**1f**) and 3-octyne (**1g**) afforded **4f** and **4g** in 72 and 55 % yield, respectively, in a completely stereoselective manner (Table 1, entries 6 and 7).

Terminal alkynes were also compatible with the present reaction. Thus, phenyl acetylene (**1h**), 4-methoxyphenylacetylene (**1i**), and 3-ethynylpyridine (**1j**) were transformed into the single regioisomeric products **4h**, **4i**, and **4j** in 78, 79, and 75 % yield, respectively (Table 1, entries 8–10). The use of an 8:1 solvent mixture of toluene and methanol is necessary for high product yields. The catalytic reaction is highly regio- and stereoselective, with a boron group of **3** adding at the substituted carbon atom, with C–C bond formation occurring at the unsubstituted carbon atom of the terminal alkyne moiety, and with the boryl and -(CH$_2$)$_2$COEt groups *cis* to each other in the product. In these reactions, homotrimerization products of the terminal alkynes were also observed in minor amounts.[12]

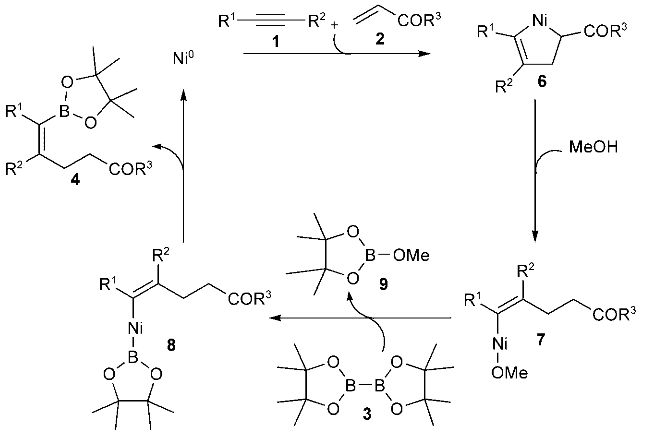
Table 2: Three-component coupling of alkyne **1a** with various substituted enones and bis(pinacolato)diboron (**3**).[a]

Entry	Enone **2**	Product **4**	Yield [%][b]
			
1	**2b**: R^3 = Me	**4k**	80
2	**2c**: R^3 = *n*Pr	**4l**	81
3	**2d**: R^3 = Ph	**4m**	83
			
4	**2e**	**4n**	78
			
5	**2f**	**4o**	69
			
6	**2g**: *n* = 1	**4p**	59
7	**2h**: *n* = 2	**4q**	55

[a] Unless otherwise mentioned, reactions were carried out with **1a** (1.5 mmol), the enone **2** (1.0 mmol), **3** (1.5 mmol), [Ni(cod)$_2$] (5 mol %), and P*n*Bu$_3$ (10 mol %) in a 3:1 mixture of toluene and methanol (2 mL) at 40 °C for 10 h. [b] Yield of the isolated product.

The present three-component coupling reaction was extended successfully to various substituted enones (Table 2). Methyl vinyl ketone (**2b**), *n*-propyl vinyl ketone (**2c**), and phenyl vinyl ketone (**2d**) reacted efficiently with **1a** and **3** under the optimized reaction conditions to give the corresponding coupling products **4k**, **4l**, and **4m** in 80–83 % yield (Table 2, entries 1–3). Similarly, the α- and β-methyl-substituted enones **2e** and **2f** were converted into **4n** and **4o** in 78 and 69 % yield, respectively (Table 2, entries 4 and 5). Cyclic enones were also good substrates for this reaction. Thus, 2-cyclopentenone (**2g**) and 2-cyclohexenone (**2h**) underwent coupling with **1a** and **3** to give **4p** and **4q** in 59 and 55 % yield, respectively (Table 2, entries 6 and 7). In these two reactions, simple reductive-coupling products from the corresponding enones **2** and **1a** were also observed in 15 and 19 % yield.[11]

A possible catalytic reaction mechanism for this three-component coupling reaction is shown in Scheme 1. Highly chemoselective coordination of the alkyne **1** and enone **2** to the Ni^0 center, followed by a regioselective oxidative cyclo-



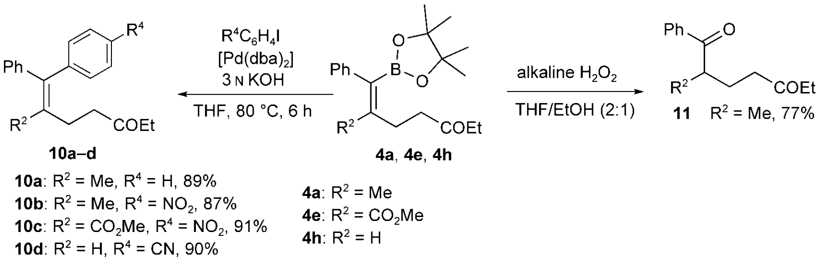
Scheme 1. Proposed mechanism for the three-component coupling reaction.

metalation, yields a nickelacyclopentene intermediate **6**.[11] Selective protonation of **6** by MeOH then affords an alkenyl(methoxy)nickel intermediate **7**,[11] which undergoes transmetalation with bis(pinacolato)diboron (**3**) to give the alkenyl–nickel–boryl intermediate **8** and borate **9**. Reductive elimination of **8** affords the product **4** and regenerates the Ni^0 catalyst for further catalytic cycles.

The proposed mechanism in Scheme 1 is supported by the stoichiometric reaction of 1-phenyl-1-propyne (**1a**, 1.5 mmol), ethyl vinyl ketone (**2a**, 1.5 mmol), and $[Ni(cod)_2]$ (1.0 mmol) in the presence of $PnBu_3$ (2.0 mmol) in a 3:1 mixture of toluene and methanol (2 mL) at 40 °C for 10 h. We obtained the double-protonation (reductive-coupling) product (*E*)-PhCH=CH(Me)$(CH_2)_2$COEt (**5a**) in 91 % yield. Although we were unable to isolate intermediate **7**, the formation of **5a** strongly indicates that the reaction proceeds via intermediates **6** and **7**.

An alternative mechanism involving oxidative addition of the diboron compound **3** to Ni^0,[13a–b] coordinative insertion of alkyne **1** into a nickel–boryl bond,[9] further insertion of the alkene **2**,[13c] and finally protonation by MeOH to give the product **4** and borate **9** cannot be ruled out.

Two applications of alkenyl boronates **4** in coupling and functional-group transformations are shown in Scheme 2. The coupling of iodoarenes with alkenyl boronates **4** (**4a**, **4e**,and **4h**) in the presence of $[Pd(dba)_2]$ (dba = dibenzylideneacetone) and aqueous KOH in THF at 80 °C for 6 h gave the corresponding products **10a–d** in 87–91 % yield.[14a] Furthermore, the boryl group in **4a** can be oxidized readily to the ketone: The treatment of **4a** with alkaline H_2O_2 in a 2:1 mixture of THF and ethanol at room temperature afforded diketone **11** in 77 % yield.[14b]



Scheme 2. Transformations of alkenyl boronates **4**.

In conclusion, we have demonstrated a nickel-catalyzed borylative coupling of alkynes with enones and a diboron reagent to provide synthetically useful, highly substituted alkenyl boronates in good to excellent yields. Dimetal compounds have not been used previously as terminating agents in sequential coupling reactions of π components in the presence of a nickel catalyst. The utility of alkenyl boronates in coupling reactions and functional-group transformations was demonstrated. The extension of the methodology to the coupling of two different π components with other dimetal reagents is in progress, as well as a detailed mechanistic investigation.

Experimental Section

General procedure: A round-bottomed side-arm flask containing $[Ni(cod)_2]$ (0.050 mmol, 5 mol %) and bis(pinacolato)diboron (**3**, 1.5 mmol) was evacuated and purged with nitrogen gas three times. Freshly distilled toluene (1.5 mL) and *n*-tributylphosphane (0.100 mmol, 10 mol %) were added, and the mixture was stirred until the solution became yellow.[11e] Enone **2** (1.0 mmol), the internal alkyne **1** (1.5 mmol), and methanol (0.5 mL) were then added to the reaction mixture, and the system was stirred at room temperature for 5 min and then at 40 °C for 10 h. The mixture was filtered through a short pad of celite and washed with ethyl acetate/hexane (70:30 v/v). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel with hexanes–ethyl acetate as the eluent to afford the alkenyl boronate **4**. For product **4e**, the reaction was carried out at 50 °C for 10 h, and for **4 f**, the reaction was carried out at room temperature for 12 h. For terminal alkynes **1h–j**, the reactions were carried out in an 8:1 mixture of toluene and methanol (4.5 mL) at room temperature for 2 h.

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