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Nickel-catalyzed regio- and diastereoselective intermolecular three-component coupling of oxabicyclic alkenes with alkynes and organoboronic acids†

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Reaction of oxabicyclic alkenes with alkynes and organoboronic acids in the presence of $Ni(cod)_2$, $P(\textit{t}\text{-}Bu)_3$, and CsF in a binary solvent toluene–methanol (1 : 3) at 75 to 85 °C provided *exo*-5,6-disubstituted 7-oxanorbornene derivatives in good to excellent yields.

Transition-metal-catalyzed domino reactions are versatile and powerful tools for modern organic synthesis.[1] Particularly, nickel-catalyzed multicomponent reactions have attracted immense interest due to the facile construction of complex and diverse structures from readily accessible starting materials in a one-pot process.[2] A variety of nickel-catalyzed sequential coupling reactions involving two π-systems, including aldehydes, alkenes, alkynes, allylic halides, imines, dienes, and allenes, with the main group organometallics was successfully demonstrated.[3–6] Among such reactions, sequential coupling involving bicyclic alkene as a π-component is hardly studied. In 1998, Ikeda and his co-workers found a diastereo-differentiative tandem coupling of norbornenes with enones and alkynyltin.[3e] Fukuzawa and Ogata described a three-component reaction of norbornenes with two alkynes leading to 1,5-enyne *via* C–H activation of terminal alkynes.[7a] Very recently, the same group disclosed a diastereoselective three-component coupling reaction between aryl aldehydes, norbornenes, and silanes to synthesize silylated indanol derivatives.[7b] Typically, these reactions were demonstrated with norbornenes and therefore the application of heterobicyclic alkenes in the multi-component reactions remains in demand.

Previously, we had demonstrated reductive cyclization[8a,b] and [2+2] cycloaddition[8c] of oxa- and azabicyclic alkenes with alkynes catalysed by Ni(II) systems. Subsequently, we reported $Ni(cod)_2$-catalyzed intermolecular three-component coupling reaction of benzynes (or alkynes) with enones and organoboronic acids,[8d,e] and a borylative coupling of alkynes with enones to synthesize alkenyl boronates.[8f] As part of our ongoing interest in metal-catalyzed π-component coupling reactions[9] and bicyclic chemistry,[10] we started to explore the possibility of using hetero-bicyclic alkenes in the sequential coupling reaction. Herein, we describe a new nickel-catalyzed intermolecular sequential coupling of oxanorbornenes with alkynes and organoboronic acids to obtain *exo*-5,6-disubstituted 7-oxanorbornene derivatives[11] in high regio- and diastereoselectivity. It is noteworthy that 1,2,3,4-tetrahydro-1,4-epoxynaphthalenes are valuable substrates for various transformation reactions.[12]

Treatment of oxabenzonorbornadiene (**1a**) with 1-phenyl-1-propyne (**2a**) and (*E*)-styrylboronic acid (**3a**) in the presence of $Ni(cod)_2$ (10 mol%), $P(\textit{t}\text{-}Bu)_3$ (10 mol%) and CsF (1 equiv.), using a toluene and methanol (1 : 3) binary solvent system, at 75 °C for 15 min afforded **4a** in 92% yield with high diastereo-selectivity. The reaction is highly regio- and stereoselective in which the styryl group of **3a** and the alkenyl group of **2a** are all added very selectively to the *exo* face of **1a** and the C–C bond formation occurred at the alkene carbon of **1a** and the methyl substituted alkyne carbon of **2a**. Moreover, the phenyl and methyl groups of **2a** in the product are *cis* to each other.

To understand the nature of the catalytic reaction and to optimize the reaction conditions, we began our investigation by treating **1a** (1.00 mmol) and **2a** (1.00 mmol) with **3a** (1.00 mmol) in the presence of $Ni(cod)_2$ (10 mol%) as the catalyst, using methanol as the solvent. The reaction proceeded well at 75 °C affording three component coupling product **4a** in 54% yield along with [2+2] cycloaddition product[8c] **5a** and ring-opening reductive coupling product[8b] **6a** in 22% and 10% yields, respectively (Scheme 1). In order to suppress the formation of **5a** and **6a**, various types of phosphine ligands and additives were examined under similar reaction conditions (see ESI†). After the systematic studies, we found that the combination of $P(\textit{t}\text{-}Bu)_3$ (10 mol%) as the ligand and CsF (1.00 mmol) as the additive gave **4a** in 82% yield along with **6a** in 10% yield. In the present catalytic reaction, it appears that the use of $P(\textit{t}\text{-}Bu)_3$ as the ligand limits the formation of **5a** to a trace and the presence of CsF (without CsF, yield of **4a** is 62%) remarkably increases the yield of **4a**. A binary solvent system, a 1 : 3 mixture of toluene and methanol, is also essential to suppress the formation of **6a**

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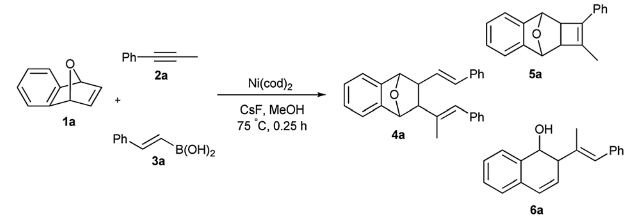


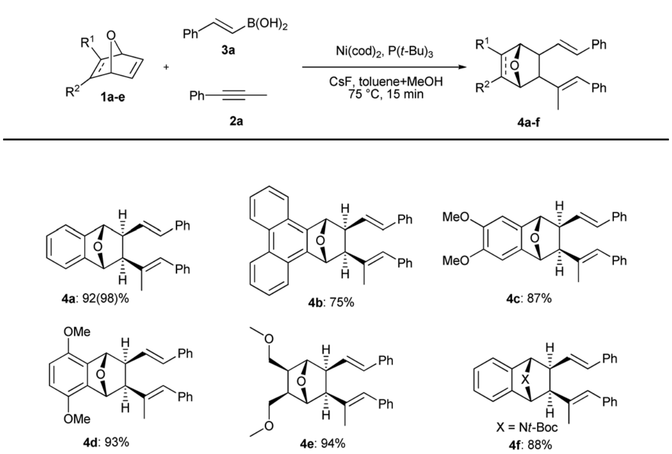
Scheme 1

and afforded **4a** in 86% yield. Finally, increasing the molar ratio of **1a** (1.50 mmol) and **2a** (1.50 mmol) with respect to **3a** (1.00 mmol) provided product **4a** in 92% isolated yield.

Under the optimized reaction conditions, the reactions of various 7-oxanorbornenes **1b–e** with **2a** and **3a** were examined (see Table 1, footnote a). Thus, 1,4-epoxytriphenylene **1b** afforded the three component coupling product **4b** in 75% yield. Similarly, dimethoxy substituted oxanorbornadienes **1c** and **1d** effectively coupled with **2a** and **3a** to give **4c** and **4d** in high yields. Aliphatic functionalized oxanorbornene, **1e**, also successfully participated to give the diastereoselective coupling product **4e** in 94% yield. Gratifyingly, 7-azabenzonorbornadiene **1f** underwent three-component coupling to afford **4f** in 88% yield. It is noteworthy that the present reaction conditions are not suitable for norbornenes.

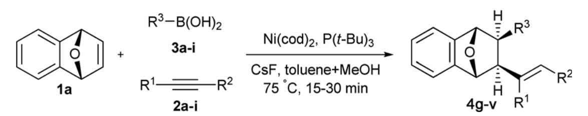
To broaden the scope of the present sequential coupling reaction, reactions of various types of alkynes **2** and organoboronic acids **3** with **1a** were investigated (see Table 2, footnote a). Thus, 1-phenyl-1-butyne (**2b**) afforded the corresponding product **4g** in high yield (entry 1). In a similar manner, diphenylacetylene (**2c**) furnished **4h** in 65% yield (entry 2). Electron-rich aromatic alkyne, 1-methoxy-4-(pent-1-ynyl)benzene (**2d**), afforded the three-component coupling product **4i** in 92% yield (entry 3). Terminal alkyne, phenylacetylene (**2e**), also reacted with **1a** and **3a** to give **4j** in 92% yield (entry 4). Functionalized alkynes, **2f** and **2g**, effectively participated to provide **4k** and **4l** in high yields (entries 5 and 6). Aliphatic alkyne, 3-hexyne (**2h**), did not furnish **4m** (entry 7) while 1,4-dimethoxy butyne (**2i**) gave **4n** in 86% yield (entry 8).

Table 1 Results of the three-component coupling of oxa- and azabenzonorbornadiene (**1a–f**) with alkynes **2a** and organoboronic acids **3a**[a,b]



[a] Unless otherwise mentioned, all reactions were carried out using oxanorbornene **1** (1.50 mmol), 1-phenyl-1-propyne **2a** (1.50 mmol), styryl boronic acid **3a** (1.00 mmol), Ni(cod)$_2$ (10 mol%), P(t-Bu)$_3$ (10 mol%), CsF (1.0 mmol) and toluene + methanol (1 : 3) (2.0 mL) at 75 °C for 15 min. [b] Isolated yields; yield in the parentheses was determined by the ^{1}H NMR method using mesitylene as an internal standard.

Table 2 Results of the three-component coupling of **1a** with various alkynes **2** and organoboronic acids **3**[a]



Entry	R^1	R^2	R^3	Yield[b] (%)
1	Et	Ph (**2b**)	*E*-Styryl (**3a**)	90 (**4g**)
2	Ph	Ph (**2c**)	*E*-Styryl (**3a**)	65[c] (**4h**)
3	*n*-Propyl	4-MeOC$_6$H$_4$ (**2d**)	*E*-Styryl (**3a**)	92 (**4i**)
4	H	Ph (**2e**)	*E*-Styryl (**3a**)	92 (**4j**)
5	CH$_2$OCH$_3$	Ph (**2f**)	*E*-Styryl (**3a**)	95 (**4k**)
6	(CH$_2$)$_2$OH	Ph (**2g**)	*E*-Styryl (**3a**)	90 (**4l**)
7	CH$_2$CH$_3$	CH$_2$CH$_3$ (**2h**)	*E*-styryl (**3a**)	0 (**4m**)
8	CH$_2$OCH$_3$	CH$_2$OCH$_3$ (**2i**)	*E*-Styryl (**3a**)	86 (**4n**)
9	CH$_3$	Ph (**2a**)	*E*-4-MeC$_6$H$_4$CH=CH (**3b**)	95 (**4o**)
10	CH$_3$	Ph (**2a**)	*Z*-CH$_3$CH=CH (**3c**)	78[e] (**4p**)
11[d]	CH$_3$	Ph (**2a**)	Ph (**3d**)	82 (**4q**)
12[d]	CH$_3$	Ph (**2a**)	2-MeOC$_6$H$_4$ (**3e**)	89 (**4r**)
13[d]	CH$_3$	Ph (**2a**)	4-MeC$_6$H$_4$ (**3f**)	82 (**4s**)
14[d]	CH$_3$	Ph (**2a**)	3-ClC$_6$H$_4$ (**3g**)	75 (**4t**)
15[d]	CH$_3$	Ph (**2a**)	3-FC$_6$H$_4$ (**3h**)	70 (**4u**)
16[d]	CH$_3$	Ph (**2a**)	2-MeC$_6$H$_4$ (**3i**)	85 (**4v**)

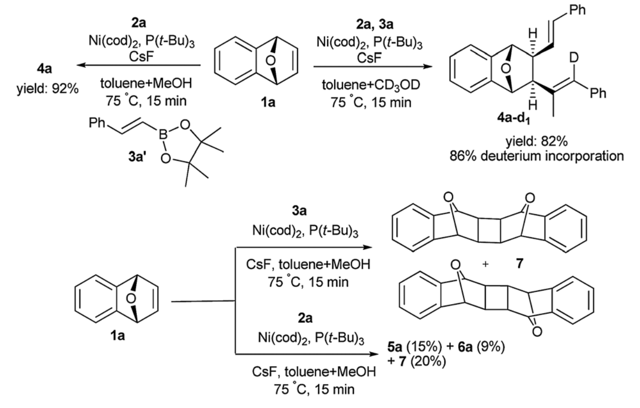
[a] Similar to the reactions shown in footnote *a*, Table 1. [b] Isolated yields. [c] Reaction was carried out at 85 °C. [d] For entries 11–16 the reaction time was 0.5 h. [e] *Z*/*E* ratio is 88 : 12.

A variety of organoboronic acids was tested in this reaction (Table 2, entries 9–16). In addition to **3a**, **3b** and (*Z*)-prop-1-enylboronic acid (**3c**) underwent three-component coupling reaction effectively with **1a** and **2a** to give **4o** and **4p** in 95 and 78% yield, respectively (entries 9 and 10). Phenylboronic acid (**3d**) also successfully participated to give the respective diastereoselective product **4q** in 82% yield (entry 11). In a similar manner, other arylboronic acids, **3e–i**, underwent coupling reaction with **1a** and **2a** smoothly to give the corresponding products **4r–v** in 70–89% yield, respectively (entries 12–16).

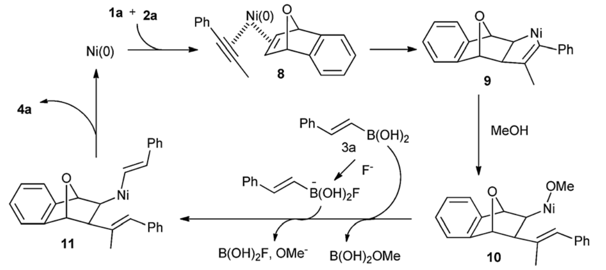
To understand the role of methanol, an isotope-labeling experiment involving **1a**, **2a** and **3a** under standard reaction conditions using CD$_3$OD as the solvent was carried out (Scheme 2). The reaction proceeded well and afforded the deuterated product **4a-d$_1$** in 82% yield with 86% deuterium incorporation.

Furthermore, the sequential coupling of **1a** and **2a** with *E*-styrylboronate (**3a′**) (Scheme 2) also gave **4a** in 92% yield. These results clearly revealed that the selective protonation of nickelacyclopentene **9** (Scheme 3) was done by methanol. Moreover, the reaction of **1a** and **3a** in the absence of **2a** results only in the formation of product **7** from [2+2] dimerization of **1a**[10e] supporting that the catalytic reaction proceeds *via* intermediate **9**.

Based on the observation in Scheme 2, a possible catalytic reaction mechanism for the present reaction is shown in Scheme 3. Highly chemoselective coordination of **1a** and **2a** to the Ni(0) center, followed by a regioselective oxidative cyclometalation, yields nickelacyclopentene intermediate **9**. Selective protonation of **9** by MeOH affords an alkyl(methoxy)-nickel intermediate **10**.[8b,c] Transmetallation of **10** with styrylboronic



Scheme 2 Mechanistic studies.



Scheme 3 Proposed mechanistic pathway.

acid **3a** gives nickel–styryl intermediate **11**. Reductive elimination affords product **4a** and regenerates the Ni(0) catalyst for further catalytic cycles. The highly regioselective oxidative cyclometalation in the present catalytic reaction might be controlled by both electronic and steric effects of alkyne and alkene.[9c] Moreover, the phenyl group from alkyne **2** favoring to stay at the position close to the Ni(II) center of nickelacyclopentene **9** is probably to stabilize the intermediate *via* an η^3-benzyl–Ni coordination.[13]

In conclusion, we have developed a highly regio- and diastereoselective nickel-catalyzed three-component reductive coupling of oxanorbornenes with alkynes and organoboronic acids to obtain *exo*-5,6-disubstituted 7-oxanorbornene derivatives in good to excellent yields. The wide scope of the three substrates was successfully demonstrated. Further extension to the coupling of two different π-components with an organometallic reagent is in progress.

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