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Nickel-Catalyzed Chemo- and Stereoselective Alkenylative Cyclization of 1,6-Enynes with Alkenyl Boronic Acids

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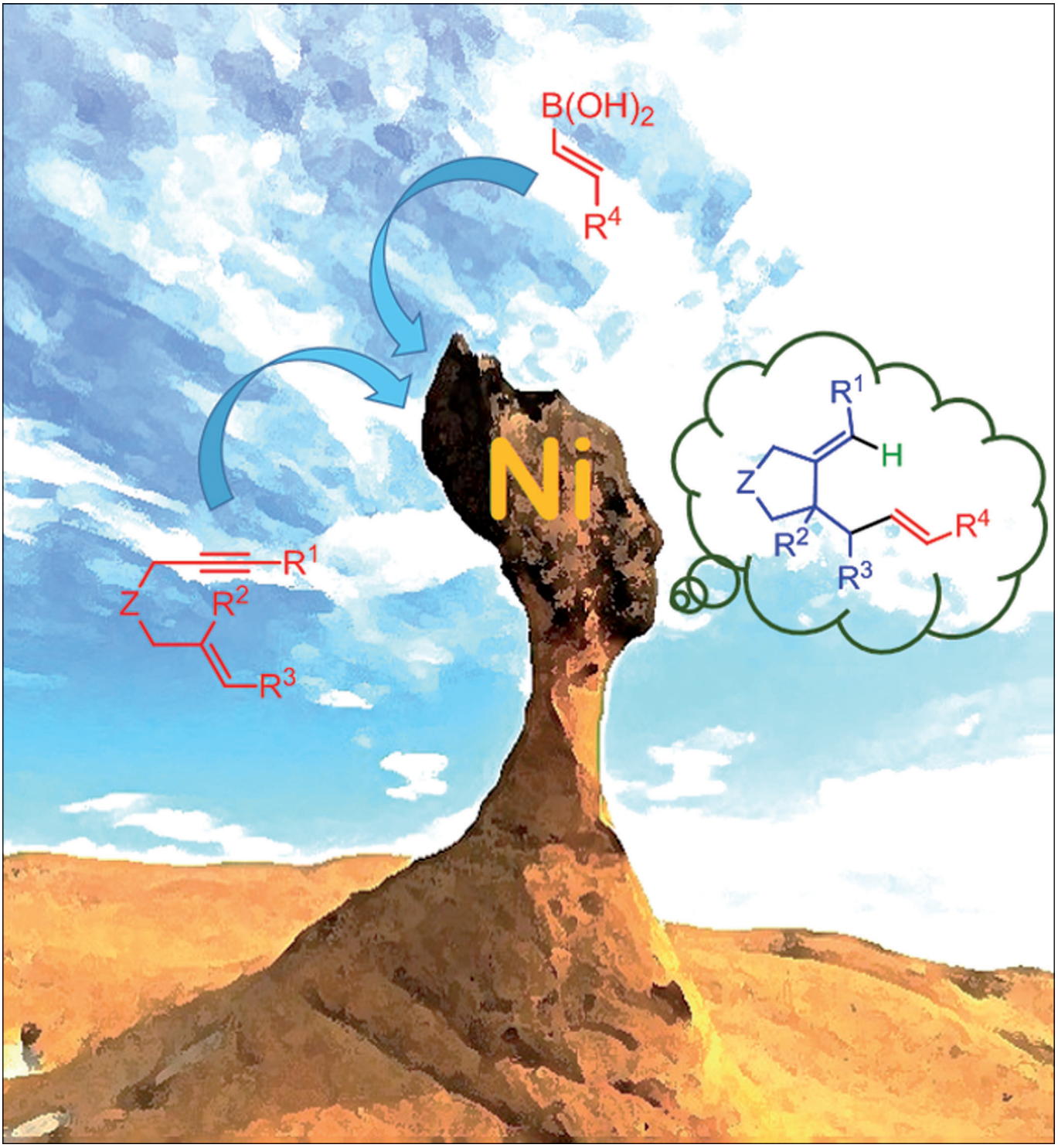
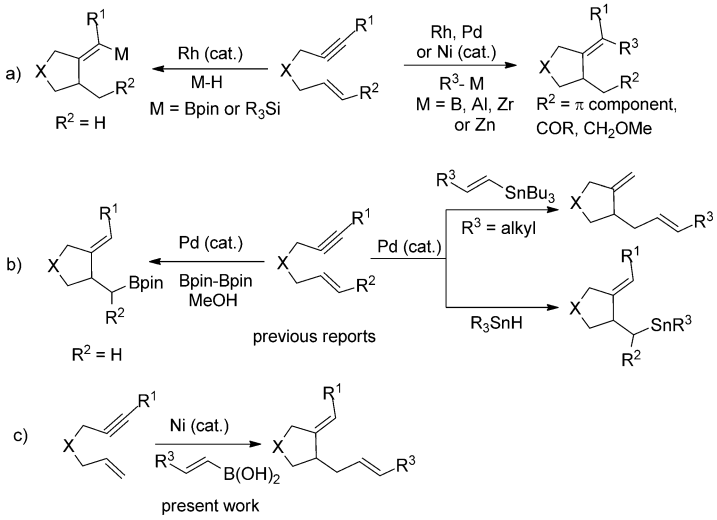


Transition-metal-catalyzed cyclization of 1,6-enynes is a powerful method for constructing carbo- and heterocyclic molecules.[1,2] Among such reactions, the cyclization of 1,6-enynes with the main-group organometallics or metal hydrides is particularly attractive because they offer new approaches for the highly stereoselective formation of ring systems with exocyclic tri- or tetrasubstituted C=C bonds.[3–8] Important examples include rhodium- and palladium-catalyzed cyclization reactions of 1,6-enynes with organoboronic acids,[3,5,6] and nickel-catalyzed cyclization reactions of activated 1,6-enynes with organozinc, -aluminum, -boron, -silane, and -zirconium (Scheme 1a).[4,10b] In these cyclization has not yet been studied.[3e,g] Moreover, the use of less expensive metal catalysts in such enyne cyclization reactions has not been extensively investigated and remains in demand.



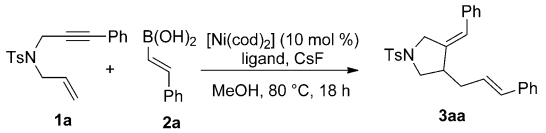
Scheme 1. Metal-catalyzed tandem cyclization of 1,6-enynes with organometallics and bimetals. Bpin = B-pinacol.

tion–coupling reactions, a highly chemoselective addition of an organometallic reagent to an alkyne moiety was observed. In contrast, Kibayashi and co-workers reported a Pd^{II}-catalyzed alkenylative cyclization of 1,6-enyne with vinyltributyltin in which the vinyl group from the tin reagent added selectively to the alkene moiety instead of the alkynyl group in a rare chemoselective manner (Scheme 1b).[7a] Recently, similar chemoselective cyclization reactions involving 1,6-enynes with metal hydrides[7b] or bimetallic reagents[8] in the presence of palladium catalyst were also demonstrated (Scheme 1b). Despite these developments, the cyclization–coupling of 1,6-enyne by using organoboronic acid as the coupling reagent in the rare chemoselective addition reac-

Organoborons are one of the versatile organometallics that have been widely used in transition-metal-catalyzed C–C (multiple) bond-formation reactions due to their multifarious advantages, comprising safe handling, availability, and stability to air and moisture.[9] Recently, we investigated nickel-catalyzed intermolecular three-component coupling reactions involving organoboronic acids, alkynes (or benzynes), and alkenes,[10a–c] and a borylative coupling of alkynes with enones to synthesize alkenylboronates.[10d] As part of our continuing efforts to extend the metal-catalyzed enyne coupling[11] and multicomponent reactions,[10] we observed a new nickel-catalyzed chemoselective tandem cyclization of electronically unactivated 1,6-enynes with alkenyl boronic acids in which the organic group of the boronic acid added selectively to the ene carbon atom of 1,6-enyne instead of the well-known alkyne carbon atom as shown in Scheme 1c. This reaction offers a new approach to substituted pyrrolidines and dihydrofurans, which are found in a variety of natural products and biologically active molecules.[12]

An example of optimized reaction conditions for the nickel-catalyzed cyclization–addition reaction (Table 1, entry 7) includes 1,6-enyne **1a** (0.40 mmol) and *trans*-2-phenylvinylboronic acid (**2a**, 0.60 mmol) in the presence of [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene; 0.040 mmol, 10 mol%), P(*t*Bu)$_3$ (15 mol%), and CsF (0.80 mmol) in MeOH at 80°C for 18 h. The reaction gave the cyclized product **3aa** in 88% isolated yield (Table 2, entry 1). The reaction is highly chemo- and stereoselective; the alkenyl group from the organoboronic acid adds exclusively to the alkene moiety of **1a** and the exocyclic double bond of product **3aa** is in a *Z*

Table 1. Optimization studies.[a]



Entry	Ligand (mol%)	CsF [equiv]	Yield [%][b]
1	PPh_3 (10)	2.0	trace
2	P(*n*Bu)$_3$ (10)	2.0	–
3	P(*t*Bu)$_3$ (10)	2.0	88
4	P(2-furyl)$_3$ (10)	2.0	30
5	PMe_3 (10)	2.0	44
6	PPh_2Me (10)	2.0	55
7	P(*t*Bu)$_3$ (15)	2.0	93
8	P(*t*Bu)$_3$ (15)	–	52

[a] Unless otherwise mentioned, all reactions were carried out using enyne **1a** (0.40 mmol) and *trans*-2-phenylvinylboronic acid (**2a**) (0.80 mmol) in the presence of [Ni(cod)$_2$] (10 mol%), ligand (10–15 mol%), and CsF (0.80 mmol) in MeOH (2.00 mL) at 80°C for 18 h. [b] Yields were measured from the crude mixture by the ^{1}H NMR spectroscopic integration method by using mesitylene as an internal standard.

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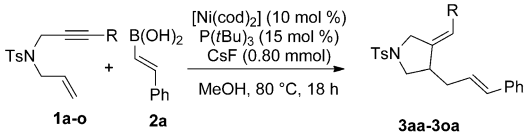
Table 2. Nickel-catalyzed alkenylative cyclization of enynes **1a–o** with *E*-styrylboronic acid **2a**.[a]



Entry	1	3	Yield [%][b]
1	**1a**	**3aa**: R = H	88 (93)
2	**1b**	**3ba**: R = 2-Me	80
3	**1c**	**3ca**: R = 3-Me	75
4	**1d**	**3da**: R = 4-Me	81
5	**1e**	**3ea**: R = 2-MeO	60
6	**1f**	**3fa**: R = 3-MeO	65
7	**1g**	**3ga**: R = 4-MeO	63
8	**1h**	**3ha**: R = 4-CH_3CO	68
9	**1i**	**3ia**: R = 4-CN	94
10	**1j**	**3ja**: R = 4-CF_3	85
11	**1k**	**3ka**	90
12	**1l**	**3la**	50
13	**1m**	**3ma**: R = H	44[c]
14	**1n**	**3na**: R = Me	83
15	**1o**	**3oa**: R = *n*Bu	77

[a] Unless otherwise mentioned, all reactions were carried out by using enynes **1** (0.40 mmol) and *trans*-2-phenylvinylboronic acid (**2a**) (0.80 mmol) in the presence of $[Ni(cod)_2]$ (10 mol%), $P(tBu)_3$ (15 mol%), and CsF (0.80 mmol) in MeOH (2.00 mL) at 80°C for 18 h. [b] Isolated yields; the yield in parentheses were determined by ^1H NMR spectroscopic methods by using mesitylene as an internal standard. [c] The reaction was carried out at 40°C.

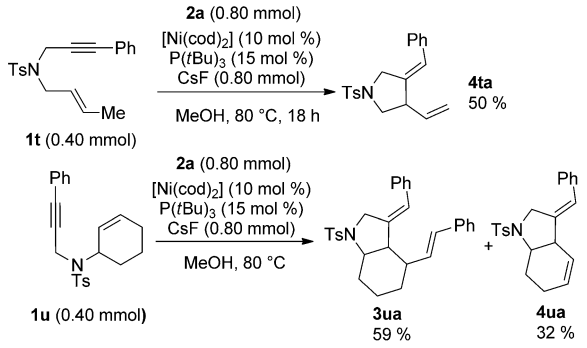
configuration, as supported by the results of single-crystal X-ray analysis of compound **3ad** (see the Supporting Information).[14]

The present nickel-catalyzed tandem reaction was initiated by treating N-tether 1,6-enyne **1a** with *trans*-2-phenylvinylboronic acid (**2a**) in the presence of a $[Ni(cod)_2/PPh_3]$ system.[10b] Unfortunately, the tandem cyclized product **3aa** was obtained only in a trace amount (Table 1, entry 1). To improve the product yield of **3aa**, we examined the reaction of **1a** and **2a** in the presence of various phosphine ligands (10 mol%; see Table 1). After extensive screening, we found that $P(tBu)_3$ is the most effective providing **3aa** in 88% yield (entry 3), whereas P(2-furyl)$_3$, PMe_3, and PPh_2Me gave the cyclization–coupling product **3aa** only in 30–55% yields (entries 4–6). The presence of CsF and MeOH are also essential for promoting the transmetalation of boronic acid, and offering a protic and soluble system. Finally, upon tuning the amount of $P(tBu)_3$ to 15 mol%, the catalyst system gave **3aa** in 93% yield, which was measured from the crude product by the ^1H NMR spectroscopic integration method (entry 7). The reaction also proceeded in the absence of CsF but afforded **3aa** only in 52% yield (entry 8).

Under similar catalytic reaction conditions for **3aa**, we examined the cyclization–coupling reaction of various N-tethered enynes **1a–y** with **2a** (Tables 2 and 3). Generally, 1,6-enynes bearing an aryl substituent at the alkyne terminus were compatible for the present cyclization reaction. However, the nature of the substituent on the aromatic ring affects the yield of product **3**. For example, substrates **1b–d** with a methyl substituent on the phenyl ring at *ortho*, *meta*, and *para* positions, respectively, gave the corresponding cyclized products **3ba–da** in good yields (entries 2–4), whereas **1e–g** containing a methoxy group at a different position furnished **3ea–ga** in 60–65% yield (entries 5–7). Similarly, **1h** with an acetyl group at the *para* position also gave **3ha** in 68% yield (entry 8). Substrates **1i–j** with electron-withdrawing substituents 4-CN and 4-CF_3 afforded products **3ia** and **3ja** in high yields (entries 9 and 10). 1-Naphthyl (**1k**) and 2-thienyl (**1l**)-substituted enynes also participated to furnish the corresponding products in 90 and 50% yields, respectively (entries 11 and 12). Notably, enyne **1m** containing a terminal alkyne also underwent tandem cyclization at 40°C to give **3ma** in moderate yield (entry 13). Substrates containing an alkyl substituent at the alkyne terminus also proceeded smoothly. Thus, **1n** and **1o** reacted with boronic acid **2a** to afford pyrrolidine derivatives **3na** and **3oa** in good yields (entries 14 and 15).

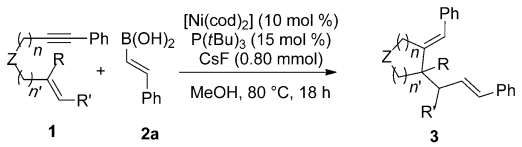
In addition to 1,6-enynes, N-tethered 1,7-enynes **1p** and **1q** also participated effectively to deliver the products **3pa** and **3qa** in 69 and 59% yields, respectively (Table 3, entries 1 and 2). Similarly, enynes containing 1,1- (**1r**) and 1,2-disubstituted alkenes (**1s**) furnished the relative products in good yields (entries 3 and 4). It is important to mention that enynes bearing an alkyl group at the alkene terminus led to the formation of Alder-ene[1] product **4** instead of **3**. For instance, **1t** afforded diene **4ta** in 50% yield, whereas **1u** gave **3ua** and **4ua** in 59 and 32% yields, respectively (Scheme 2).

To explore the scope of the reaction, a variety of tethered enynes **1v–y** were evaluated (Table 3, entries 5–8). Thus, N-tethered enynes containing a *N*-benzyl substituent **1v** gave **3va** in 83% yield (entry 5), whereas O-tethered enynes **1w** furnished the respective product in only 67% yield (entry 6). Malonate-tethered enynes, **1x** and **1y** also under-



Scheme 2. Cyclization of **1t** and **1u** with **2a**.

Table 3. Nickel-catalyzed alkenylative cyclization of enynes **1p–y** with **2a**.[a]



1 2a 3

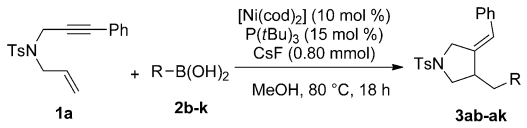
Entry	1	3	Yield [%][b]
1	**1p**	**3pa**	69
2	**1q**	**3qa**	59
3	**1r**	**3ra**	83
4	**1s**	**3sa**	77
5[c]	**1v**	**3va**	83
6	**1w**	**3wa**	67
7	**1x**	**3xa**	81
8	**1y**	**3ya**	90

[a] Similar reaction conditions as in Table 2. [b] Isolated yields. [c] Bn = benzyl.

went tandem cyclization to provide the substituted pyrrolidines **3xa** and **3ya** in good to excellent yields (entries 7 and 8).

The reactivity of various alkenyl boronic acids **2b–k** in the present catalytic reaction was also examined (Table 4). In all cases, the retention of stereochemistry of the alkenyl group from **2** in the products was observed. Thus, alkyl- (**2b–e**) and benzyl (**2f**)-substituted alkenyl boronic acids efficiently coupled with **1a** to give the respective products **3ab–af** in 70–77% yields (entries 1–5). Substituted (*E*)-styrylboronic acids also participated well in the tandem cyclization reaction (entries 6–10). Thus, biphenyl (**2g**) and electron-donating-substituted alkenyl boronic acids **2h** and **2i** gave **3ag–ai** in good to excellent yields (entries 6–8). Similarly, *p*-chlorostyrylboronic acid (**2j**) is compatible with the reaction conditions to furnish **3aj** in 72% yield (entry 9). Electron-withdrawing 4-CF_3-substituted alkenyl boronic acid **2k** also reacted smoothly with **1a** to provide **3ak** albeit in slightly lower yield (entry 10). Notably, the reaction of α-

Table 4. Scope of functionalized alkenyl boronic acids.[a]



1a 2b-k 3ab-ak

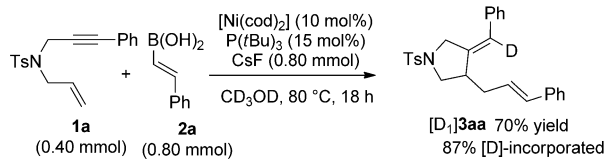
Entry	1	3	Yield [%][b]
1	**2b**	**3ab**	75
2	**2c**	**3ac**	70
3	**2d**	**3ad**: R = *n*Pr	71
4	**2e**	**3ae**: R = Cy[c]	70
5	**2f**	**3af**: R = Bn[c]	77
6	**2g**	**3ag**: R = 4-Ph	88
7	**2h**	**3ah**: R = 4-Me	82
8	**2i**	**3ai**: R = 4-OMe	85
9	**2j**	**3aj**: R = 4-Cl	72
10	**2k**	**3ak**: R = 4-CF_3	68
11	**2l**	**3al**	0
12	**2m**	**3am**	0

[a] Unless otherwise mentioned, all the reactions were carried out by using **1a** (0.40 mmol) and alkenyl boronic acid **2** (0.80 mmol) in the presence of $[Ni(cod)_2]$ (10 mol%), P(*t*Bu)$_3$ (15 mol%), and CsF (0.80 mmol) in MeOH (2.0 mL) at 80°C for 18 h. [b] Isolated yields. [c] Cy = cyclohexyl, Bn = benzyl.

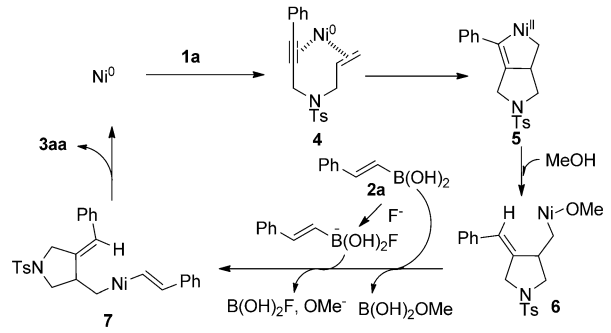
substituted alkenyl- **2l** and alkylboronic acid **2m** with **1a** did not give any cyclization–coupling product **3** (entries 11 and 12). It is important to mention that the reaction of arylboronic acids with 1,6-enynes under the standard reaction conditions afforded only a trace amount of tandem cyclized product.

To understand the role of methanol and to elucidate the mechanism of the present catalytic reaction, an isotope-labeling experiment by using CD_3OD for the tandem cyclization of enyne **1a** and **2a** was studied (Scheme 3). The reaction afforded the deuterated product [D_1]**3aa** in 70% yield with 87% deuterium incorporation at the exocyclic alkene position in a *Z* configuration. This result supported the hypothesis that the reaction proceeds via a nickelacyclopentene intermediate **5** (Scheme 4) and methanol acts as the proton source.

Based on the observation in Scheme 3, and from the reported enyne coupling reactions,[1,4] a possible catalytic reaction mechanism for the present reaction using **1a** and **2a** as the substrates is shown in Scheme 4. First, enyne **1a** is bonded to Ni^0 via the alkene and alkyne groups to form intermediate **4**. Then oxidative cyclometallation of **4** yields nickelacyclopentene intermediate **5**.[4,13,10a–c] Selective proto-



Scheme 3. A deuterium labeling study.



Scheme 4. Proposed mechanism for the nickel-catalyzed alkenylative cyclization reaction.

nation of **5** by MeOH affords an alkyl(methoxy)nickel intermediate **6**.[8,10c] Transmetallation of **6** with alkenyl boronic acid **2a** gives nickel–alkenyl intermediate **7**. Reductive elimination affords the final product **3aa** and regenerates the Ni^0 species for the following catalytic cycles.

In summary, we have demonstrated a new nickel-catalyzed tandem cyclization–coupling of electronically unactivated 1,6-enynes with alkenyl boronic acids to provide various substituted pyrrolidines and dihydrofurans. The reaction is highly chemo- and stereoselective. A variety of alkenyl boronic acids have been successfully employed in the reaction. The chemoselective protonation of the nickelacyclopentene intermediate leads unusually to the addition of the alkenyl group of boronic acid at the alkene terminus of 1,6-enyne in the final product. Further studies to expand the scope of the tandem cyclization are currently underway.

Acknowledgements

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Keywords: cyclization · enynes · nickel · nickelacyclopentene · organoboronic acids

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[14] CCDC-949413 (**3ad**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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