Synthetic Application of Intramolecular Cyanoboration on the Basis of Removal and Conversion of a Tethering Group by Palladium-Catalyzed Retro-Allylation

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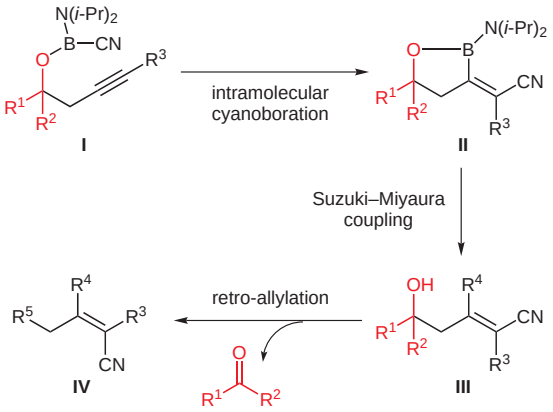
Abstract: A new synthetic strategy, involving utilization of a tethered intramolecular reaction with a removable tether, was demonstrated by the intramolecular cyanoboration–retro-allylation sequence.

Key words: alkenes, arylation, nitriles, palladium, retro-allylation

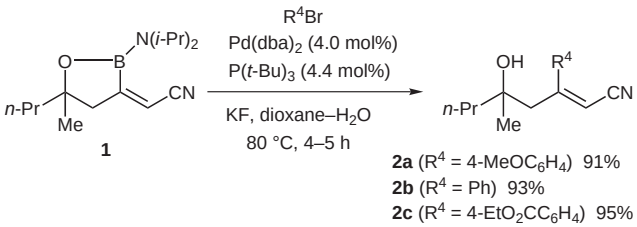
Silicon- and boron-tethered intramolecular reactions are attractive methods for the synthesis of organic molecules that are not easily accessible via the corresponding intermolecular reactions.[1–3] Attractive features of the intramolecular reaction involve high reaction efficiency, regioselectivity, and stereoselectivity. On the other hand, a major drawback of the intramolecular reactions is the need for the tethering groups, which significantly limit the variation of the substrate scope. It seems to be highly desirable to remove and convert the tethering group into other functional groups after the intramolecular cyclization step.

We expected that the removal and conversion of the tethering group would be possible by palladium-catalyzed retro-allylation, in which allylic C–C bonds in homoallylic alcohols are cleaved and converted into other C–C bonds.[4] Because many silicon- and boron-tethered reactions are designed for homopropargylic alcohol derived substrates,[3g,5] the retro-allylation would work well. Herein, we demonstrate the strategy involving palladium-catalyzed intramolecular cyanoboration, which allows for the addition of boryl and cyano groups to alkynes.[6,7] The Suzuki–Miyaura coupling of the cyanoboration products **II** followed by retro-allylative coupling allows the synthesis of highly substituted α,β-unsaturated nitriles **IV**, in which no tethering group is left (Scheme 1).

We first carried out Suzuki–Miyaura coupling of borylalkene **1**, which was prepared via palladium-catalyzed intramolecular cyanoboration of cyanoboryl homopropargyl ether. The coupling reactions with aryl bromides took place under the Fu's conditions,[8] giving cyano-substituted homoallylic alcohols **2a**–**c** in high yields (Equation 1).



Scheme 1 A synthetic application of intramolecular cyanoboration based on removal of tethering unit



Equation 1

We then examined palladium-catalyzed retro-allylative coupling of **2** with aryl bromides **3**. Reaction of cyano-substituted homoallylic alcohol **2a** with 4-bromotoluene (**3a**) was carried out in the presence of $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), and Cs_2CO_3 (1.2 equiv) (entry 1 in Table 1).[4] Retro-allylative coupling took place smoothly by heating the reaction mixture at 110 °C, giving alkene **4a** in 90% yield after three hours. It should be noted that the reaction proceeded efficiently even for the homoallylic alcohol bearing the trisubstituted C–C double bond, in spite of the fact that the retro-allylation has been found difficult with internal alkenes.[4] It is also noted that the geometry of the double bond isomerized from *Z* to *E* (*E*/*Z* = 85:15) in the course of the reaction, indicating that the reaction proceeded via a π-allyl palladium intermediate (see below). A small amount of protonated product **5a** (9%) was formed along with **4a**.

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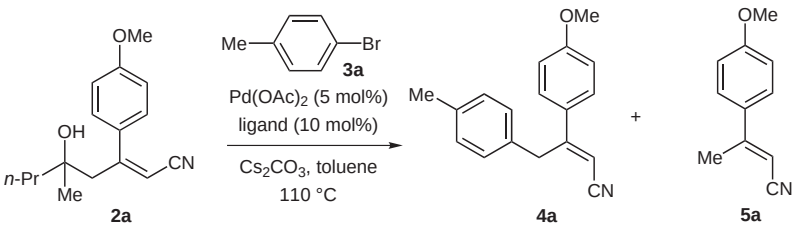
Table 1 Screening of Ligand in Palladium-Catalyzed Retro-Allylative Coupling of **2a** with **3a**[a]



Entry	Ligand	Time (h)	Yield (%),[b] (*E*/*Z*)[c]	
			4a	**5a**
1	PCy_3	3	90 (77)[d] (85:15)	9 (n.a.)[e]
2	PCy_2Ph	18	31 (84:16)	37 (88:12)
3	$PCyPh_2$	18	74 (84:16)	23 (87:13)
4	PPh_3	18	57 (n.a.)	7 (n.a.)
5	$P(4\text{-}MeOC_6H_4)_3$	6	87 (75:25)	8 (n.a.)
6	$P(4\text{-}CF_3C_6H_4)_3$	18	78 (85:15)	15 (90:10)
7	$P(Oi\text{-}Pr)_3$	6	31 (76:24)	52 (91:9)
8	$P(OPh)_3$	2	0	85 (88:12)
9[f]	$P(OPh)_3$	2	–	(89)[d] (88:12)

[a] Reaction conditions: $Pd(OAc)_2$ (0.010 mmol), ligand (0.020 mmol), Cs_2CO_3 (0.24 mmol), **2a** (0.20 mmol), and **3a** (0.24 mmol) were stirred at 110 °C unless otherwise noted.
[b] GC yield.
[c] Determined by ^1H NMR of crude mixture.
[d] Isolated yield.
[e] n.a.: not analyzed.
[f] Carried out in the absence of **3a**.

As reported recently,[4b] PCy_3 was found to be the most effective ligand for the reaction of **2a** with **3a** (entry 1). Slower reaction rate or formation of a significant amount of **5a** was observed with PCy_2Ph, $PCyPh_2$, and PPh_3 (entries 2–4). The reaction was also catalyzed well by electron-donating $P(4\text{-}MeOC_6H_4)_3$, whereas the reaction rate was reduced by the use of electron-deficient $P(4\text{-}CF_3C_6H_4)_3$ (entries 5 and 6). It is interesting to note that phosphite ligands tended to promote protonative retro-allylation (entries 7 and 8). Alkene **5a** was selectively obtained by a palladium catalyst bearing $P(OPh)_3$ (entry 8). The protonative retro-allylation took place with a Pd–$P(OPh)_3$ catalyst even in the absence of aryl halides, giving **5a** in 89% yield (entry 9).

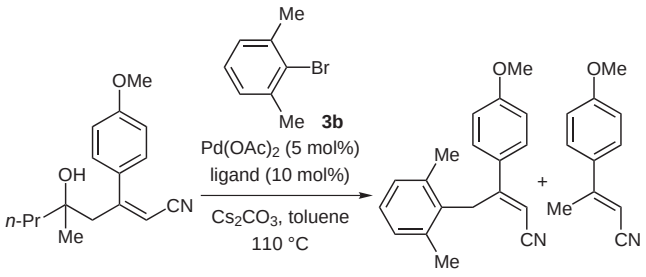
When a bulky aryl bromide was used in the coupling reaction, we observed different tendency of the ligands–selectivity relationship. Thus, retro-allylative coupling of **2a** with sterically hindered 2-bromo-1,3-dimethylbenzene (**3b**) afforded **4b** in only 19% yield along with major formation of **5a** under the conditions using PCy_3 (entry 1 in Table 2). Improvement of the reaction yield was achieved by the use of Pd–$PCyPh_2$ or PPh_3 catalysts, with which **4b** was obtained in good yields (entries 3 and 4).

Retro-allylative coupling of **2a**–**c** with various aryl bromides **3** was then examined (Table 3). The coupling with bromobenzene (**3c**) and *para*-substituted bromobenzenes **3a** and **3d**–**f** was carried out in the presence of Pd–PCy_3 catalyst (entries 1–4, 7, and 9).[9] These reactions were completed within 4–10 hours, and the corresponding **4** was isolated in 61–77% yields. The results indicate that the electronic property of the aryl groups (R^4 and R^5) did not affect the reaction. On the other hand, coupling reactions with bulky aryl bromide **3b**, **3g**, and **3h** also gave the coupling product in high yields after 7–15 hours in the presence of the Pd–PPh_3 catalyst (entries 5, 6, 8, and 10).

Homoallylic alcohols **6** bearing a tetrasubstituted double bond were subjected to retro-allylative coupling with **3a** in the presence of Pd–PCy_3 catalyst (Equation 2). The reaction of **6a** (R^3 = Ph) completed in six hours and gave the desired product **7a** in 30% yield along with a significant amount of the protonated product **8a**. On the other hand, **6b** (R^3 = Me) gave **7b** selectively (72%), despite the much slower reaction rate.

Homoallylic alcohols **2** and **6** were also subjected to the Pd–$P(OPh)_3$ catalyst system that promotes the protonative

Table 2 Screening of Ligand in Palladium-Catalyzed Retro-Allylative Coupling of **2a** with Sterically Hindered **3b**[a]



2a **4b** **5a**

Entry	Ligand	Time (h)	Yield (%),[b] (*E*/*Z*)[c]	
			4b	**5a**
1	PCy_3	3	19 (90:10)	44 (92:8)
2	PCy_2Ph	3	40 (89:11)	29 (94:6)
3	$PCyPh_2$	1	70 (89:11)	4 (n.a.)[d]
4	PPh_3	2.5	88 (84)[e] (87:13)	3 (n.a.)

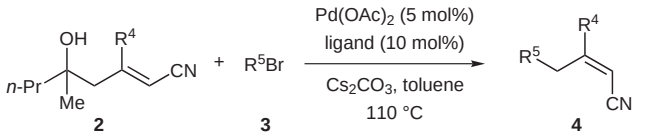
[a] Reaction conditions: $Pd(OAc)_2$ (0.010 mmol), ligand (0.020 mmol), Cs_2CO_3 (0.24 mmol), **2a** (0.20 mmol), and **3b** (0.24 mmol) were stirred at 110 °C.
[b] GC yield.
[c] Determined by ^1H NMR of crude mixture.
[d] n.a.: not analyzed.
[e] Isolated yield.

retro-allylation (Table 4).[10] The reactions of **2b**, **2c**, and **6a** took place at 110 °C within two hours to give crotononitrile derivatives **5b**, **5c**, and **8a** in good to high yields (entries 1–3). Although a slow reaction rate was observed for the reaction of **6b**, **8b** was finally isolated in 97% yield after 42 hours (entry 4). It should be noted that the palladium-catalyzed retro-allylative coupling described above and the protonative retro-allylation worked effectively for the homoallylic alcohols bearing a tetrasubstituted double bond (Equation 2 and entries 3 and 4 in Table 4), while the previous study demonstrated the failure of the retro-allylation of homoallylic alcohols bearing *E*-alkene moiety.[4]

The present retro-allylative coupling reaction is remarkable in that a substituted C=C bond including tetrasubstituted alkene is involved. To understand the high reactivity of the present retro-allylation, we examined the reaction of **9** (Equation 3). Homoallylic alcohol **9**, which does not have the aryl groups on the double bond, was subjected to the retro-allylative coupling with **3b** in the presence of the Pd–PPh_3 catalyst (Equation 3). The reaction proceeded smoothly to afford alkene **10** in 69% yield, in contrast to the poor reactivity of internal disubstituted alkenes such as the (*E*)-pent-3-en-1-ol derivatives observed previously.[4] This result clearly indicates that the cyano group enhances the reactivity of homoallylic alcohol in palladium-catalyzed retro-allylation.

The possible reaction mechanism for the retro-allylative coupling is shown in Scheme 2. Oxidative addition of Ar^1Br to Pd(0) followed by the substitution of the halogen atom on Pd with the alkoxide gives intermediate **T**. Retro-allylation of **T** provides σ-allylpalladium complex **U**, which isomerizes to π-allylpalladium complex **V**. The following reductive elimination affords product **W** with regeneration of Pd(0). The cyano group may decrease the

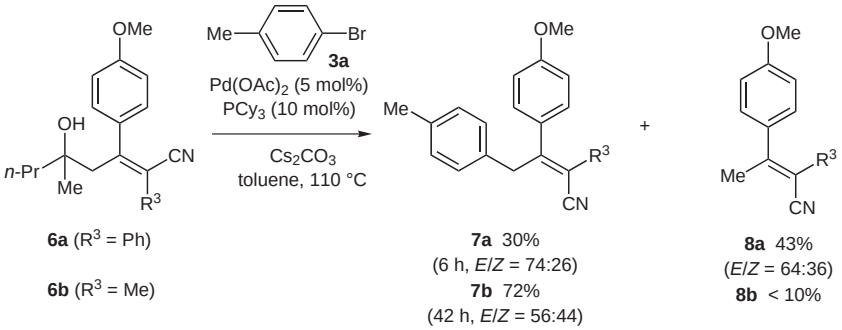
Table 3 Palladium-Catalyzed Retro-Allylative Coupling of **2**[a]



2 **3** **4**

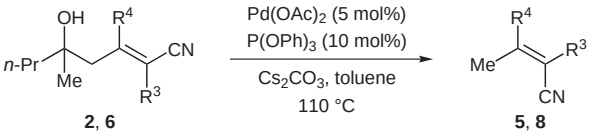
Entry	**2**	R^5Br	Ligand	Time (h)	Product	Yield (%),[b] (*E*/*Z*)[c]
1	**2a**	PhBr (**3c**)	PCy_3	9	**4c**	68 (86:14)
2	**2a**	4-$MeOC_6H_4Br$ (**3d**)	PCy_3	4	**4d**	63 (85:15)
3	**2a**	4-$EtO_2CC_6H_4Br$ (**3e**)	PCy_3	4	**4e**	67 (82:18)
4	**2a**	4-$CF_3C_6H_4Br$ (**3f**)	PCy_3	6	**4f**	77 (83:17)
5	**2a**	2-MeC_6H_4Br (**3g**)	PPh_3	15	**4g**	61 (90:10)
6	**2a**	1-bromonaphtalene (**3h**)	PPh_3	11	**4h**	60 (92:8)
7	**2b**	**3a**	PCy_3	10	**4i**	68 (84:16)
8	**2b**	**3b**	PPh_3	7	**4j**	89 (90:10)
9	**2c**	**3a**	PCy_3	8	**4k**	61 (82:18)
10	**2c**	**3b**	PPh_3	7	**4l**	73 (90:10)

[a] Reaction conditions: $Pd(OAc)_2$ (0.010 mmol), ligand (0.020 mmol), Cs_2CO_3 (0.24 mmol), **2** (0.20 mmol), and **3** (0.24 mmol) were stirred at 110 °C.
[b] Isolated yield.
[c] Determined by ^1H NMR of crude mixture.



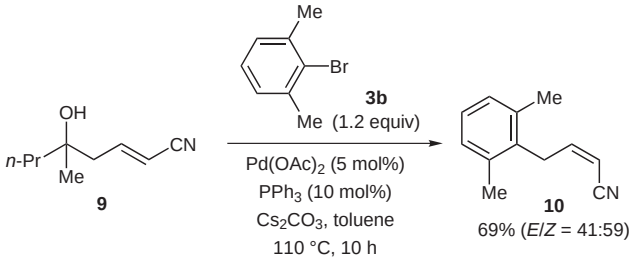
Equation 2

Table 4 Palladium-Catalyzed Protonative Retro-Allylation of **2** and **6**[a]



Entry	Substrate	R^3	R^4	Time (h)	Product	Yield (%),[b] (*E*/*Z*)[c]
1	**2b**	H	Ph	2	**5b**	67 (89:11)
2	**2c**	H	4-$EtO_2CC_6H_4$	2	**5c**	63 (89:11)
3	**6a**	Ph	4-$MeOC_6H_4$	6	**8a**	92 (62:38)
4	**6b**	Me	4-$MeOC_6H_4$	42	**8b**	97 (33:67)

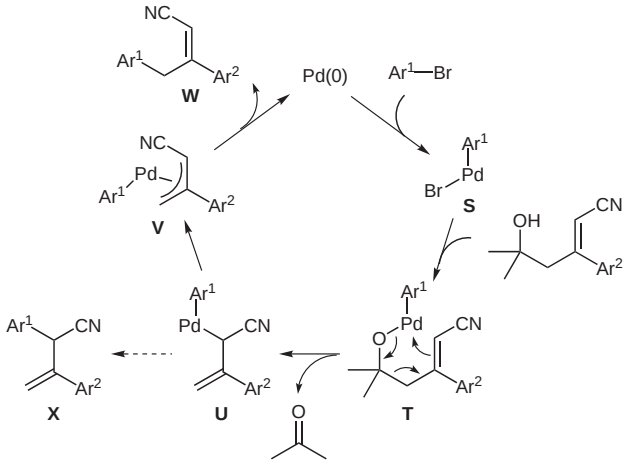
[a] Reaction conditions: $Pd(OAc)_2$ (0.010 mmol), $P(OPh)_3$ (0.020 mmol), Cs_2CO_3 (0.24 mmol), and **2** or **6** (0.20 mmol) were stirred at 110 °C.
[b] Isolated yield.
[c] Determined by ^1H NMR of crude mixture.



Equation 3

rate of reductive elimination from **U**, leading to **V** via σ–π isomerization that is not involved in the retro-allylation of cyano-free homoallylic alcohols.[4]

In summary, we have established a synthetic transformation of intramolecular cyanoboration products via C–C bond formation by Suzuki–Miyaura coupling followed by palladium-catalyzed retro-allylation. Efficient removal of a tethering group used in intramolecular cyanoboration was achieved through retro-allylation. Our new strategy, which utilizes 'intramolecular reaction with removable tether', allows collecting advantages of both the intra- and intermolecular reactions such as high reaction efficiency, selectivity, and wide reaction scope.



Scheme 2 Possible mechanism for retro-allylative coupling

Acknowledgment

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(9) **General Procedure for the Palladium-Catalyzed Retro-Allylative Coupling of 2 with 3 (Tables 1–3)**: Cesium carbonate was dried in vacuo by heating with a heat gun prior to use. Under a nitrogen atmosphere, a mixture of $Pd(OAc)_2$ (0.010 mmol), PCy_3 or PPh_3 (0.020 mmol), Cs_2CO_3 (0.24 mmol), **2** (0.20 mmol), and **3** (0.24 mmol) was heated at 110 °C. The reaction was monitored by GC. Heating was stopped as soon as **2** was consumed, since prolonged heating led to a drop in the product yield. Volatiles were removed and the crude product was purified by PTLC.
(*E*)-3-(4-Methoxyphenyl)-4-(4-methylphenyl)but-2-enenitrile (**4a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.8 Hz, 2 H), 7.02–7.12 (m, 4 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 5.65 (s, 1 H), 4.16 (s, 2 H), 3.80 (s, 3 H), 2.28 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.6, 161.2, 136.3, 134.0, 129.5, 129.4 (2 × C), 128.20 (2 × C), 128.18 (2 × C), 118.0, 114.1 (2 × C), 94.8, 55.3, 39.0, 21.0. IR (neat): 2211 (CN), 1605 (C=C) cm^{-1}. LRMS (EI): *m*/*z* = 263 (100) [M$^+$], 248 (18), 158 (38), 133 (40), 105 (41). HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{18}H_{17}NO$: 263.1310; found: 263.1311. The geometry of the double bond was assigned as *E* by NOE experiments.
(*E*)-4-(2,6-Dimethylphenyl)-3-(4-methoxyphenyl)but-2-enenitrile (**4b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–7.11 (m, 3 H), 6.98–7.03 (m, 2 H), 6.78 (d, *J* = 8.8 Hz, 2 H), 5.49 (t, *J* = 1.2 Hz, 1 H), 4.17 (d, *J* = 1.2 Hz, 2 H), 3.78 (s, 3 H), 2.29 (s, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.7, 160.6, 137.5 (2 × C), 133.5, 131.1, 128.3 (2 × C), 127.8 (2 × C), 127.1, 116.6, 113.7 (2 × C), 96.3, 55.2, 35.7, 20.5 (2 × C). IR (KBr): 2207 (CN), 1605 (C=C) cm^{-1}. LRMS (EI): *m*/*z* = 277 (80) [M$^+$], 237 (100), 119 (40). HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{19}H_{19}NO$: 277.1467; found: 277.1474. The geometry of the double bond was assigned as *E* by NOE experiments.

(10) **General Procedure for the Palladium-Catalyzed Protonative Retro-Allylation of 2 (Entry 9 in Table 1 and Table 4)**: Cesium carbonate was dried in vacuo by heating with a heat gun prior to use. Under a nitrogen atmosphere, a mixture of $Pd(OAc)_2$ (0.010 mmol), $P(OPh)_3$ (0.020 mmol), Cs_2CO_3 (0.24 mmol), and **2** (0.20 mmol) was heated at 110 °C. The reaction was monitored by GC. After consumption of **2**, volatiles were removed and the crude product was purified by PTLC.
(*E*)-3-(4-Methoxyphenyl)but-2-enenitrile (**5a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.45 (m, 2 H), 6.89–6.93 (m, 2 H), 5.55 (d, *J* = 0.8 Hz, 1 H), 3.85 (s, 3 H), 2.45 (d, *J* = 0.8 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.3, 158.8, 130.4, 127.3 (2 × C), 118.1, 114.1 (2 × C), 93.2, 55.4, 20.0. IR (KBr): 2205 (CN), 1603 (C=C) cm^{-1}. LRMS (EI): *m*/*z* = 173 (100) [M$^+$], 158 (41), 103 (35). HRMS (EI): *m*/*z* [M$^+$] calcd for $C_{11}H_{11}NO$: 173.0841; found: 173.0841. The geometry of the double bond was assigned as *E* by NOE experiments.