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blocks by cross-dimerisation toward cross-coupling**

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Ru(0)-Catalysed synthesis of borylated polyene building blocks by cross-dimerisation toward cross-coupling†

Masafumi Hirano*[a] and Sayori Kiyota[a]

Conjugated and non-conjugated polyenes are important substructures and often found in biologically active compounds and natural products. These preparations often need multiple steps or iterative reactions and as a result they have poor step economies. In this feature article, we show a new methodology to prepare these substructures by combinations of cross-dimerisation giving borylated polyenes and subsequent cross-coupling reactions. This divergent reaction allows for opportunity to access many bioactive compounds and natural products as well as some electronic materials.

1. Introduction

Organoboronic acids and their derivatives have been widely used in modern synthetic organic chemistry. One of the most significant developments in this field is cross-coupling reactions.[1] In subsequent studies, iterative cross-coupling methods allowed selective synthesis of target molecules.[2,3] Today, the reaction methods have been developed that allow even stable masks to be used for direct cross-coupling without deprotection,[4] but the iterative cross-coupling methods need multiple steps for the reaction. On the other hand, the conversion of mono- and multi-boronated compounds without loss of boronato groups is an important reaction in terms of constructing synthetic building blocks from simple raw materials.[5] We have developed a linear cross-dimerisation catalysed by zero-valent ruthenium complexes,[6,7] which tolerates boronato groups in the reactants, and have therefore set up a project to synthesise borylated non-conjugated and conjugated polyene building blocks starting from simple borylated alkenes, alkynes and dienes. In this feature article, we focus on the historical background of cross-dimerisation, synthesis of borylated non-conjugated dienes, borylated polyenes and applications to synthetic building blocks.

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†This paper was dedicated to the late professor Steve Westcott at Mount Allison University (Canada) for his outstanding contribution to boron chemistry.

2. Cross-dimerisation

Masafumi Hirano is a professor in Department of Applied Chemistry at Tokyo University of Agriculture and Technology (TUAT) since 2014. He received his PhD degree at Saitama University under supervision of late professor Akira Miyashita in 1993. He started his academic carrier since 1993 as a research associate at TUAT under Prof. Sanshiro Komiya, during which he visited the Australian National University, RSC, under supervision of Prof. Martin A. Bennett as a research fellow. His current interest is focusing on molecular catalyses, asymmetric C–C bond forming reactions and catalytic depolymerisations.

Masafumi Hirano

Sayori Kiyota received her doctor of engineering at Tokyo University of Agriculture and Technology (TUAT) under supervision of Masafumi Hirano in 2018 for catalytic transformations of nitriles and alkynes using mono- and dinuclear ruthenium complexes. She currently works as a technical profession at TUAT and studies about the molecular catalysis giving conjugated molecules. Her current interest is focusing on the synthesis of donor-acceptor (DA) polymers by the addition polymerisations and their photo- and electro-chemical properties.

Sayori Kiyota

2-1.   Historical background

Cross-couplings are reactions between electrophiles and nucleophiles; in the Suzuki-Miyaura coupling, organoboronate compounds are the nucleophiles. In terms of reaction mechanism, this is a redox reaction involving three steps; oxidative addition of organohalides to the catalyst, transmetallation and reductive elimination. They are also regarded as substitution reactions. Cross-dimerisations are known as cross-reactions that are completely different from these, both in terms of reaction pattern and mechanism. In fact, cross-dimerisations are addition reactions that do not use nucleophiles and electrophiles. They are also different from hydrovinylations, which must use ethylene as one of the coupling partners.[8] To our best knowledge, the cross-dimerisation reaction extends back to the first brief report by Wittenberg in 1963 for butadiene with methyl acrylate by a cobalt complex.[9] Unfortunately, however, the catalyst and reaction details were not described in this brief report. For other overall historical background on cross-dimerisation see our review,[10] and some selected examples are listed below.

In 1992, Mitsudo and co-workers pioneeringly documented [Ru(η^4-1,5-cod)(η^6-1,3,5-cot)]-catalysed (cod: cyclooctadiene, cot: cyclooctatriene) cross-dimerisation of butadiene with methyl acrylate giving a mixture of 1,3- and 1,4-dienes (eqn (1)).[11] Note that although they used a zero-valent ruthenium complex as the catalyst precursor, the in situ generated hydridoruthenium(II) species did catalyse this reaction via hydrido-insertion mechanism.


(1)
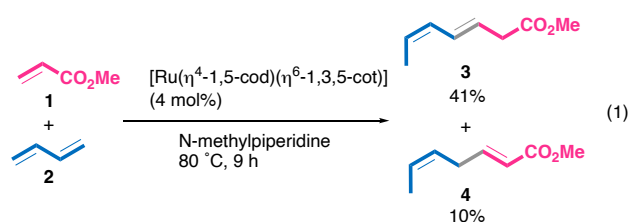
Fujiwhara and co-workers reported the cross-dimerisation of isoprene with vinyl acetate using [RuCp*Cl(η^4-1,5-cod)] (eqn (2)).[12]

(2)
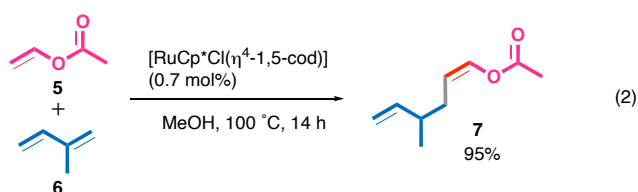
After this report, Trost and co-workers also showed high catalytic activity of cationic ruthenium(II) complexes having a cyclopentadienyl or pentamethylcyclopentadienyl ligand for cross-dimerisations.[13] These reactions proceed via oxidative coupling mechanism,[14] giving a ruthenium(IV) intermediate, and this catalyst appeared to be less active on electron-deficient substrates.[15]

In situ generated mono-valent cobalt complexes are also efficient catalysts for cross-dimerisation. Hilt and co-workers

reported cross-dimerisation of 2,3-dimethylbutadiene (**9**) with butyl acrylate (**8**) under very mild conditions (eqn (3)).[16]


(3)
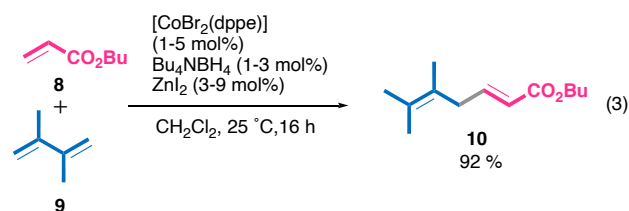
2-2.   Our cross-dimerisations

We reported cross-dimerisation of **1** with **9** using [Ru(η^4-2,3-dimethylbutadiene)(η^4-1,5-cod)(NCMe)] (**13**)[17] as the catalyst, which was easily derived from [Ru(η^6-naphthalene)(η^4-1,5-cod)] (**14**)[18] to give the cross-dimer products in high total yields (Table 1, Entry 1).[19] Naphthalene complexes with 1,5-cod (**14**), dibenzocyclooctatetraene (**15**) and 5-phenyldibenzocyclooctatetraene (**16**) also catalysed the cross-dimerisation under ambient conditions.[20] According to the stoichiometric reactions, deuterium-label experiments and the DFT calculations, this process proceeds from a zero-valent ruthenium complex via oxidative coupling mechanism.[19,21]

Table 1. Ruthenium(0)-catalysed cross-dimerisation.

Entry	Cat.	Temp/°C	**11/%**	**12/%**
1	**13** (2 mol%)	65	71 (*E*/*Z* = 100/0)	26
2	**14** (1 mol%)	30	34 (*E*/*Z* = 53/47)	2
3	**15** (1 mol%)	30	51 (*E*/*Z* = 51/49)	1
4	**16** (1 mol%)	30	75 (*E*/*Z* = 100/0)	0
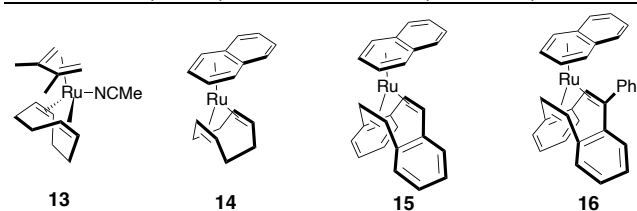
With internal alkynes, a unique cross-dimerisation of conjugated dienes produced conjugated trienes for the first time, and this reaction was formally regarded as a *cis* insertion of the internal alkynes into the terminal C−H bond in conjugated dienes (eqn (4)).[7] Because these ruthenium(0)-catalysed cross-

(4)
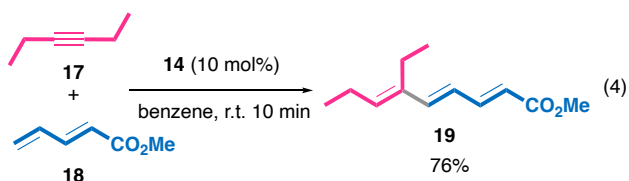
dimerisation carried out in non-polar solvents under neutral conditions, boronato groups are tolerated during the process. We therefore work on the synthesis and reaction development

of these non-conjugated and conjugated polyene building blocks containing boronato group(s).
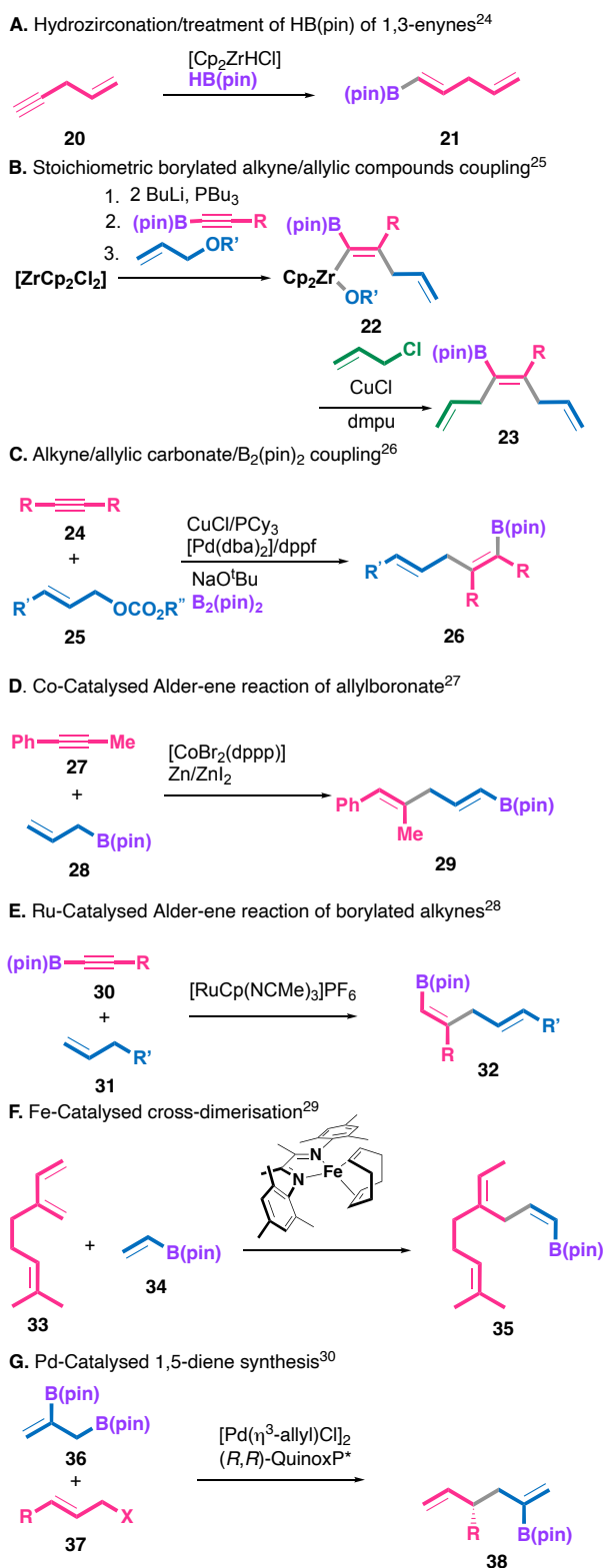
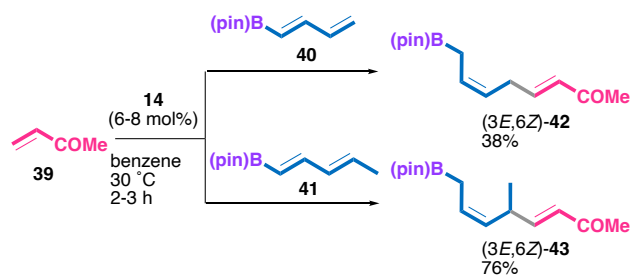## Borylated dienes[22,23]

3-1.   Synthesis of borylated dienes

As shown in Scheme 1, previously reported methods for the synthesis of mono-borylated 1,4-dienes involve the hydrozirconation/HB(pin) (B(pin): 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl) of 1,3-enyne (Scheme 1A),[24] the stoichiometric reaction of borylated alkynes with allylic compounds in the presence of Negishi reagent (Scheme 1B),[25] the copper/palladium-catalysed three-component coupling using allylic carbonate, alkyne and B₂(pin)₂ (Scheme 1C),[26] the Alder-ene type reaction using allylboronate (Scheme 1D)[27] or borylated alkynes (Scheme 1E),[28] and iron(0)-catalysed cross-dimerisation of β-myrcene with vinylB(pin) (Scheme 1F).[29] 1,5-Dienes are prepared by the palladium-catalysed allyl-allyl cross-coupling of allylic boronate with allylic halide (Scheme 1G).[30] The ruthenium(0)-based cross-dimerisation of alkenes with dienes presented below has the advantage that it has a wide scope and also allows the synthesis of substituted skipped dienes and diborylated products.

We commenced the cross-dimerisation of 3-buten-2-one (**39**) with borylated conjugated dienes catalysed by **14** (Scheme 2). Interestingly, the cross-dimerisation of **39** proceeded more efficiently with the more sterically bulky 1,3-pentadienylB(pin) (**41**) than with butadienylB(pin) (**40**). These products were obtained as 6*Z*-structure, which suggests the *cisoid*-η⁴-coordination of diene to the ruthenium(0) species like **13** in Table 1.

Cross-dimerisations of **41** with a series of alkenes are summarised in Table 2. Notably, **41** did react with borylated alkenes giving diboryated dienes. For examples, treatment of **41** with vinlB(pin), vinylB(OBu)₂ and vinylB(dan) (dan: 2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborininyl) produced corresponding (1*E*,5*E*)-1,6-diborylated-1,5-dienes (**50-52**). This reaction can be operated on a gram-scale reaction. 1,3-Pentadiene selectively reacted with vinyl boronates at the 4-position giving mono-borylated skipped dienes (**54-57**). Although reaction of isoprene with vinylB(pin) gave a borylated 1,4-diene **58**, but 1,3-dienes were also

A. Hydrozirconation/treatment of HB(pin) of 1,3-enynes[24]

B. Stoichiometric borylated alkyne/allylic compounds coupling[25]

C. Alkyne/allylic carbonate/B₂(pin)₂ coupling[26]

D. Co-Catalysed Alder-ene reaction of allylboronate[27]

E. Ru-Catalysed Alder-ene reaction of borylated alkynes[28]

F. Fe-Catalysed cross-dimerisation[29]

G. Pd-Catalysed 1,5-diene synthesis[30]

Scheme 1. Selected pioneering examples for synthesis of mono-borylated 1,4- and 1,5-dienes. Only the major regio- and stereoisomers

Scheme 2. Ruthenium(0)-catalysed cross-dimerisation of 3-buten-2-one (**39**) with borylated dienes.

Table 2. Cross-dimerisation of dienes with alkenes giving borylated dienes.[a]
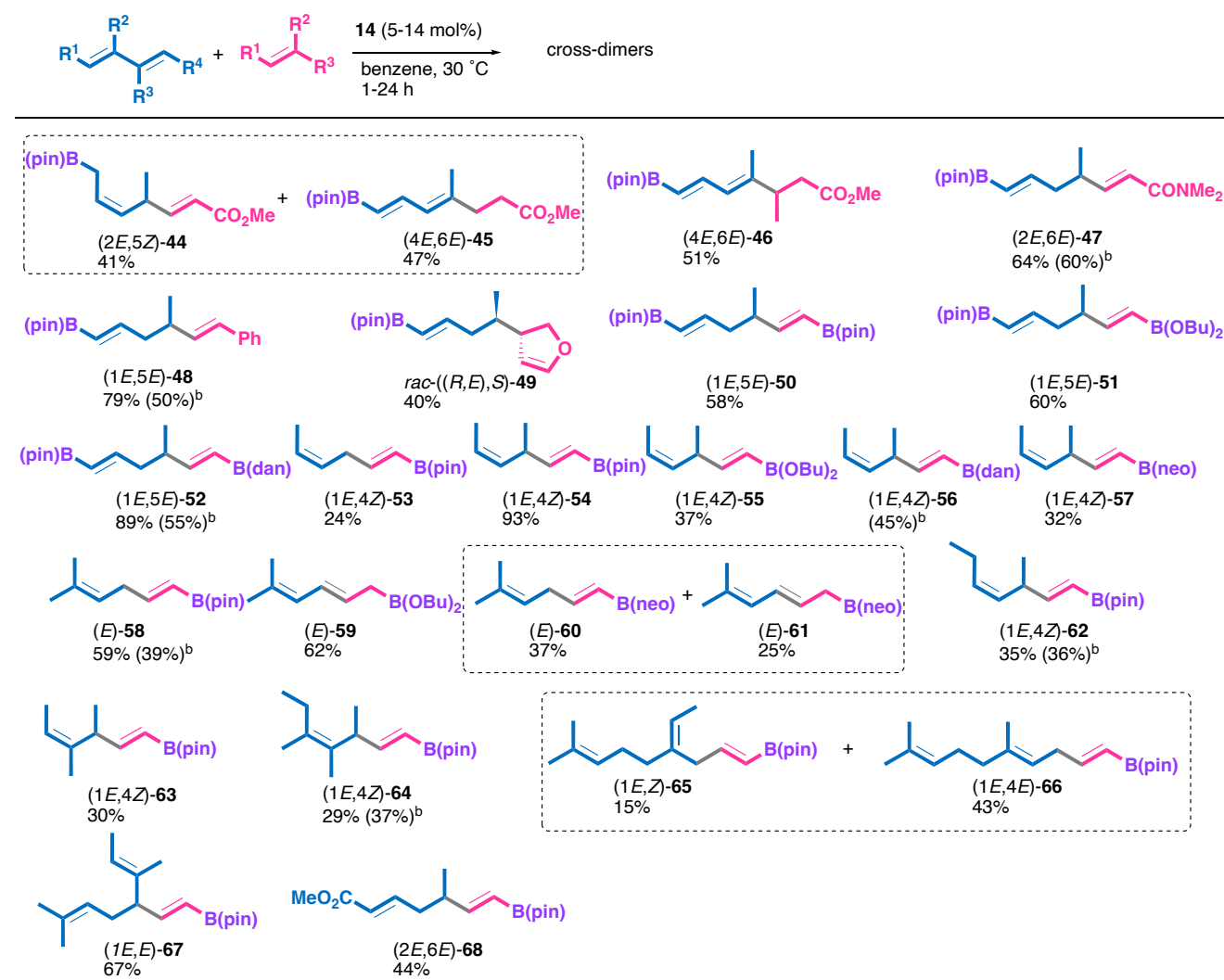
[a]The product yields were estimated based on ^{1}H NMR. [b]Isolated yields. B(pin): boronic acid pionacolate ester. dan: naphthalene-1,8-diaminoboranyl. B(neo): boronic acid neopentylglycol ester.

formed in the case of vinylB(OBu)$_2$ and vinylB(neo) (**59**-**61**) (B(neo): 5,5-dimethyl-1,3,2-dioxaborinanyl). These dienylboronate products could not be purified by column chromatography in the same way as other organoboron compounds, when chain alkyl esters such as B(OBu)$_2$ are masked. The present ruthenium(0)-catalysed cross-dimerisation using borylated dienes/alkenes showed a wide scope and the ability to produce diboryl-1,5-dienes in a single-step reaction is a major developmental feature. Chirik and co-workers documented the iron(0)-catalysed cross-dimerisation of β-myrcene with vinylB(pin), where the C1/C4 selectivity was >98/2 (Scheme 1F).[29] The regioselectivity by the present ruthenium(0)-catalysed reaction (**65** and **66**) was less selective than the iron(0)-system, although present system selectively produced the *E*-boryl alkenyl fragments.

3-2.   Reaction mechanisms giving borylated 1,4- and 1,5-dienes[22]

In order to understand the mechanism, we tried the stoichiometric reaction [Ru(η^4-*cisoid*-1,3-pentadienylB(pin))(1,5-cod)(NCMe)] with

vinylB(dan), that is expected to give **52** in Table 2 by the ^{1}H NMR experiment. However, a complex mixture was formed and no useful information was observed. So then, we conducted the cross-dimerisation of **41** with 2,2-dideuteriostyrene (**69**-*d$_2$*) catalysed by a natphthalene complex **14** and this isotopic labelling experiment showed the present reaction could be regarded as a formal 1,2-insertion of **41** into the terminal alkenyl C–D bond in **69**-*d$_2$* giving **70**-*d$_2$* (eqn (5)).
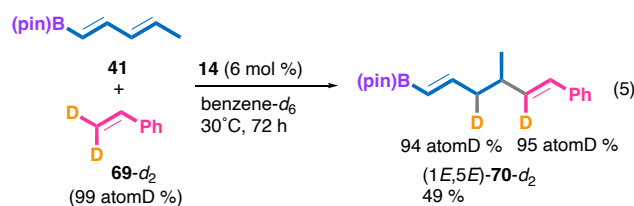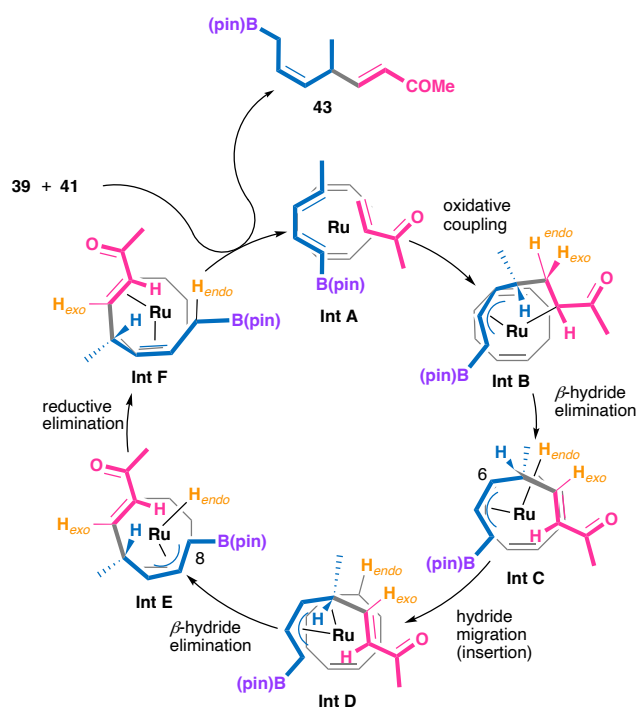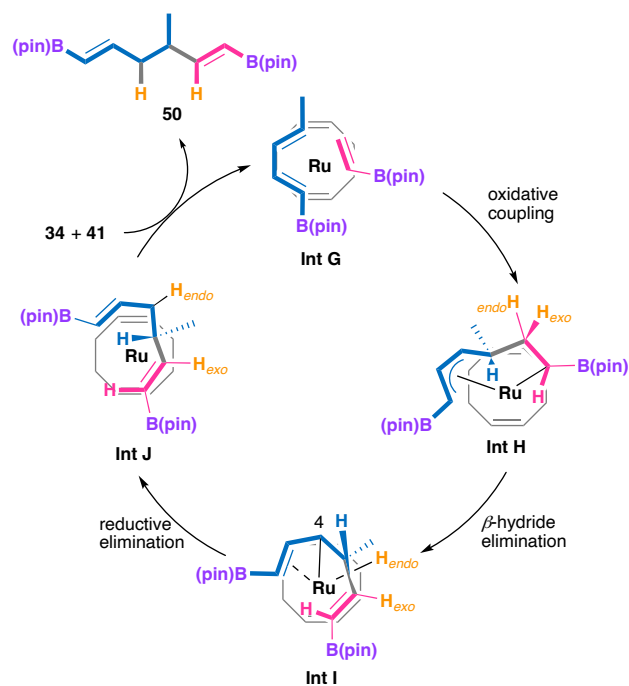
Scheme 3. Ruthenium(0)-catalysed cross-dimerisation of 3-buten-2-one (**39**) with borylated diene **41**

Scheme 4. Ruthenium(0)-catalysed cross-dimerisation of vinylB(pin) (**34**) with borylated diene **41**.

According to this reaction and the DFT calculations, we proposed the mechanism for cross-dimerisations of 1,4-dienes and 1,5-dienes. Scheme 3 illustrates the proposed mechanism for the formation of borylated-1,4-diene from **39** with **41**. Naphthalene is a 10π aromatic compound and the "Ru(η^4-1,5-cod)" fragment, a 12e complex, requires additional 6e ligand to satisfy the 18-electron rule in **14**. Once naphthalene coordinates as a 6π donor to the "Ru(η^4-1,5-cod)" fragment, the uncoordinated 6 membered ring in naphthalene remains as a 4π ring. This means that the aromaticity of the uncoordinated 6 membered ring is lost. This is why naphthalene is exceptionally labile among aromatic ligands. After removal of the naphthalene ligand, **41** (4π) and **39** (2π) selectively coordinate to the ruthenium fragment to satisfy the 18-electron rule (**Int A**). This is the origin of the substrate selectivity in this cross-dimerisation. After the oxidative coupling, a ruthenacycle intermediate (**Int B**) is formed, from which β-hydride elimination occurs to remove the H$_{endo}$ proton giving **Int C**. In order for the hydride to come close to the π-allyl fragment, a site change of the allyl fragment is needed. However, it cannot change the position of the allyl as it is, so once the hydride is inserted into the cod (**Int D**), it becomes cyclooctenyl and the allyl changes position before becoming a hydride complex again (**Int E**). After the C(8)−H reductive elimination and substrate exchange give the borylated 1,4-diene to close the catalytic cycle.

The proposed mechanism for the formation of a borylated 1,5-diene using **34** with **41** is shown in Scheme 4. Similar to Scheme 3, this cycle starts from **Int G**. After the oxidative coupling reaction, the β-hydrogen elimination occurs from **Int H** and the H$_{endo}$ proton was selectively removed to give **Int I**. In this case, a question arises here. Why do only 1,5-dienes form in these diborylated products? The DFT calculations suggest the direct C(4)−H elimination form **Int I** is the dominant process because the C(4) and the hydride in **Int I** are in

close proximity and will undergo reductive elimination. Finally, the substrate exchange occurs from **Int J** to release **50** and **Int G**.

3-3. Cross-coupling of 1,6-diboryl-1,5-dienes

Because we succeeded to prepare unsymmetrical 1,5-dienes with two different boryl groups, introduction of two different aryl groups to the 1,5-dienes were conducted. Treatment of vinylB(OBu)$_2$ (**71**) with 1,3-pentadienylB(pin) (**41**) produced a diborylated 1,5-diene **51** as shown in Table 2. A one pot synthesis of the cross-dimerisation giving **51** and subsequent palladium(0)-catalysed cross-coupling with 1 equiv of PhI gave (1E,5E)-**72** in only 24% yield (Scheme 5). A similar treatment with PhI and then 4-MeC$_6$H$_4$I produced (1E,5E)-**73** in only 29% yield. These experiments suggested that the regioselective cross-coupling based on these mask differences could proceed, but the efficiency was not satisfactory. Then, we studied the cross-coupling using (1E,5E)-**52** having B(pin) and B(dan) groups.
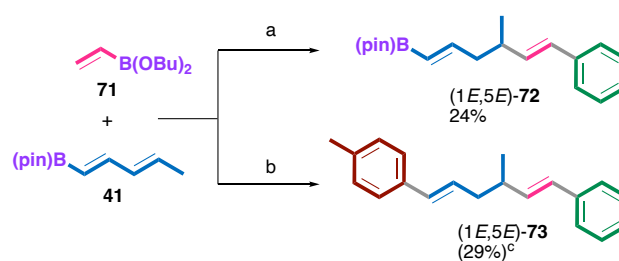
Scheme 5. Successive cross-dimerisation/cross-coupling. a) 1. **14** (10 mol%), thf, 40 ˚C, 3 h, 2. [Pd(PPh$_3$)$_4$] (8 mol%), Cs$_2$CO$_3$ (2.7 equiv), PhI (1 equiv), thf, 40 ˚C, 8 h. b) 1. **14** (10 mol%), thf, 40 ˚C, 2 h, 2. [Pd(PPh$_3$)$_4$] (5 mol%), Cs$_2$CO$_3$ (2.1 equiv), PhI (1 equiv), thf, 40 ˚C, 48 h, 3. [Pd(PPh$_3$)$_4$] (5 mol%), Cs$_2$CO$_3$ (2.1 equiv), 4-MeC$_6$H$_4$I (1 equiv), thf, 65 ˚C, 18 h, c) isolated yield.
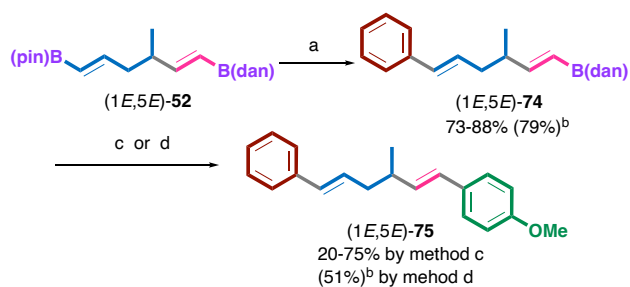
Scheme 6. Regioselective cross-coupling using **52**. a) [Pd(PPh$_3$)$_4$] (5 mol%), Cs$_2$CO$_3$ (2 equiv), PhI (1 equiv), thf, 50 ˚C, 11 h. b) isolated yield.   c) [Pd$_2$(dba)$_3$]·C$_6$H$_6$ (5 mol%), XPhos (10 mol%), 4-MeOC$_6$H$_4$I (1 equiv), KO^{t}Bu (3 equiv), thf, 70 ˚C, 24 h. d) 1. HCl aq. (5 M), thf, r.t., 20 h. 2. [Pd(OAc)$_2$] (1.5 mol%), SPhos (3 mol%), K$_3$PO$_4$ (2.5 equiv), thf, 50 ˚C, 24 h.

Treatment of (1*E*,5*E*)-**52** with 1 equiv of PhI in the presence of palladium catalyst allowed for the introduction of phenyl group as the first substituent to the B(pin) fragment under conventional cross-

Table 3. Regioselective cross-coupling starting from **74**. Yields in parentheses are isolated yields.
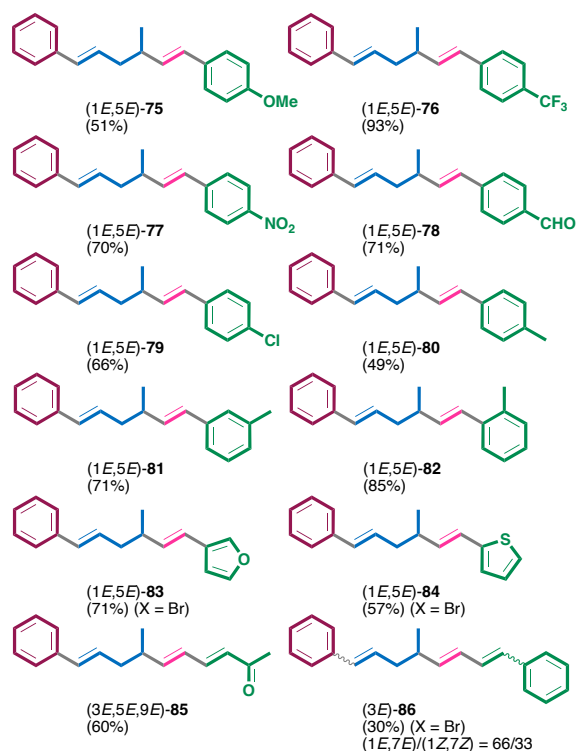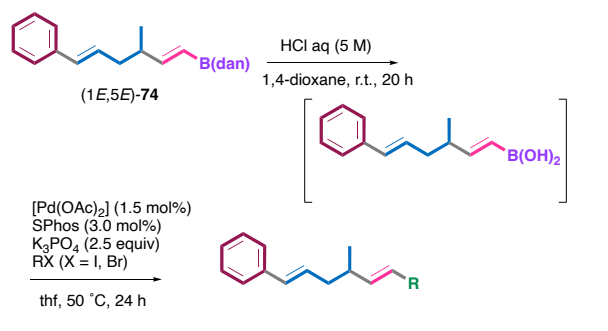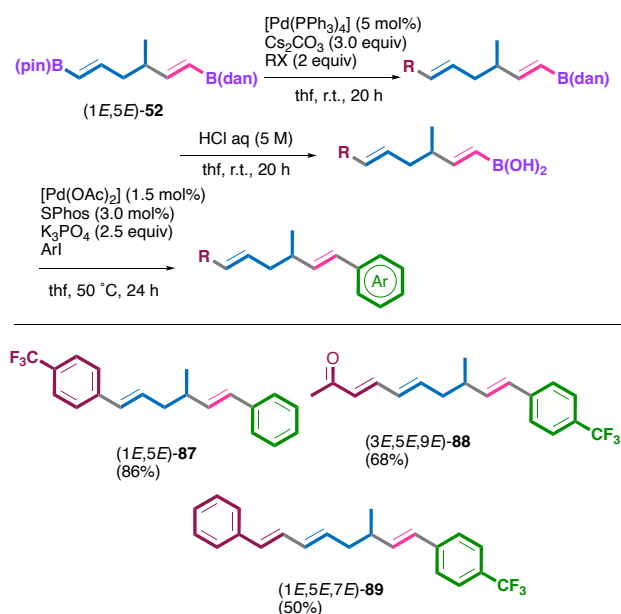

Table 4. Regioselective cross-coupling starting from **52**. Yields in parentheses are isolated yields.

coupling conditions, giving (1*E*,5*E*)-**74** in 79% isolated yield (Scheme 6). The direct transformation of the B(dan) fragment in the cross-coupling is recently developed,[4,31] and the subsequent reaction with anisyl iodide did produce **75**. However, the yield by these direct methods was not reproducible in the range of 20-75% for the 1,5-dienylB(dan). Therefore, the second cross-coupling was performed after the demasking of the B(dan) group in order to achieve a reliable reaction. This procedure gave (1*E*,5*E*)-**75** in 51% isolated yield
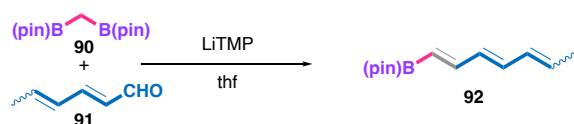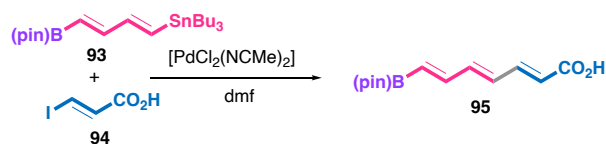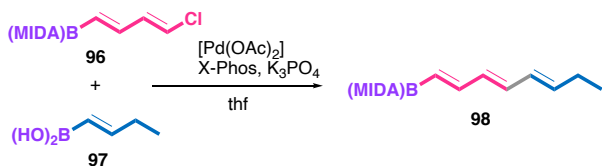
Table 3 summarises the regioselective cross-coupling by this indirect procedure starting from (1*E*,5*E*)-**74**. In this reaction, electron-rich and -deficient aryl groups, heteroaryls and alkenyl groups were introduced by the cross-coupling reaction. In addition to phenyl group, substituents could also be introduced on the B(pin) side in **52**, and some examples are shown in Table 4. By this method using **52**, an electron-deficient aryl, alkenyl group could be introduced for the B(pin) side giving **87**, **88** and **89** in high to moderate isolated yields. As shown in this section, diborylated 1,5-dienes can be easily prepared by the cross-dimerisation and subsequent regioselective cross-coupling provides a series of non-conjugated dienes and trienes in high or moderate yields. The B(dan) fragment acts as an inert mask in the diborylated 1,5-dienes. However, the removal of mask from B(dan) is necessary for the regioselective second cross-coupling to give the product as a reliable method.

4. Borylated polyenes[23,32]

4-1. Cross-dimerisation of borylated alkynes with dienes

Conjugated polyenes with a boronato group are undoubtedly useful synthetic building blocks in the synthesis of natural products, pharmaceutical molecules and electronic materials. However, only limited methods of synthesis of these have been known so far. De Lera and co-workers reported a beautiful review in this field. [1d] The

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A. Boron-Wittig reaction[33]

(pin)B—B(pin)
90
+
$\sim\sim$CHO
91

LiTMP
———→
thf

(pin)B$\sim\sim\sim\sim\sim$
92

B. Migita-Kosugi-Stille coupling reaction[34]

(pin)B$\diagup\diagup$SnBu$_3$
93
+
I$\diagup$CO$_2$H
94

[PdCl$_2$(NCMe)$_2$]
————→
dmf

(pin)B$\sim\sim\sim$CO$_2$H
95

C. Suzuki-Miyaura coupling reaction[35]

(MIDA)B$\diagup\diagup$Cl
96
+
(HO)$_2$B$\diagup\diagup$
97

[Pd(OAc)$_2$]
X-Phos, K$_3$PO$_4$
————→
thf

(MIDA)B$\sim\sim\sim\sim$
98

D. Mizoroki-Heck reaction[36]

(MIDA)B$\diagup\diagup$I
99
+
$\diagup\diagup$CO$_2$Me
18

[Pd(OAc)$_2$]
AgOAc
————→
MeCN

(MIDA)B$\sim\sim\sim\sim$CO$_2$Me
100
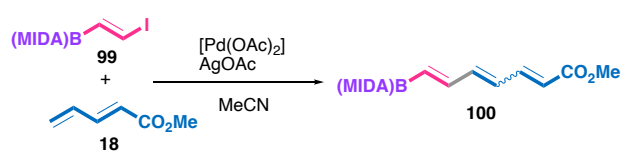
Scheme 7. Selected pioneering examples for synthesis of borylated polyenes. B(MIDA): *N*-methyliminodiacetatic acid boronatate.

pioneering examples involve the boron-Wittig reaction using methylenebis(pinacolato)diboron (**90**) with hexa-2,4-dienal (**91**) (Scheme 7A),[33] the Migita-Kosugi-Stille coupling of a borylstanylbutadiene (**93**) with 3-iodopropenoic acid (**94**) (Scheme 7B),[34] the Suzuki-Miyaura coupling of a masked borylchlorobutadiene (**96**) with an alkenylboronic acid (**97**) (Scheme 7C)[35] and the Mizoroki-Heck reaction of a protected boryliodoalkene (**99**) with **18**.[36] All these methods are substitution reactions and the synthesis of boron compounds with leaving groups take time and efforts in general. More straightforward methods are therefore awaited.

Although cross-dimerisation of dienes with alkenes was reported to proceed by some transition-metal complexes, the transition-metal catalysed linear cross-dimerisation of dienes with alkynes had been unprecedented. We found the unique linear cross-dimerisation of dienes with alkynes giving conjugated trienes shown in eqn (4) by use of a zero-valent ruthenium complex. With a borylated diene **40**, we screened potent catalysts for this reaction (Table 5). A ruthenium(0) complex **14** showed quite high activity toward this cross-dimerisation to give **101** in 89% yield within 0.5 h in benzene (Table 5, entry 1). An in situ generated "Ru(1,5-cod)" species by the treatment of ruthenium(II) with BuLi,[37] also catalysed this reaction in high yield (Table 5, entry 2). The other potent catalytic systems, which are effective for cross-dimerisation of dienes with alkenes, such as [Rh(cod)$_2$]BF$_4$/BINAP,[38] [RuCp*(NCMe)$_3$]PF$_6$,[12,13,39] [FeCl$_2${(1-phenl-*N*-pyridine-2-ylmethylene)ethanamine}]/Mg*,[40] [CoBr$_2$(PPh$_3$)$_2$]/PPh$_3$/Zn[41] and [CoBr$_2$(dppp)]/Zn/ZnI$_2$[27,42] practically did not work at all (Table 5, entries 3-7). The **14**-catalysed cross-

Table 5. Scope of catalysts for linear cross-dimerisation of hex-3-yne (**17**) with butadienylB(pin) (**40**) giving a conjugated hexatriene **101**.[a]
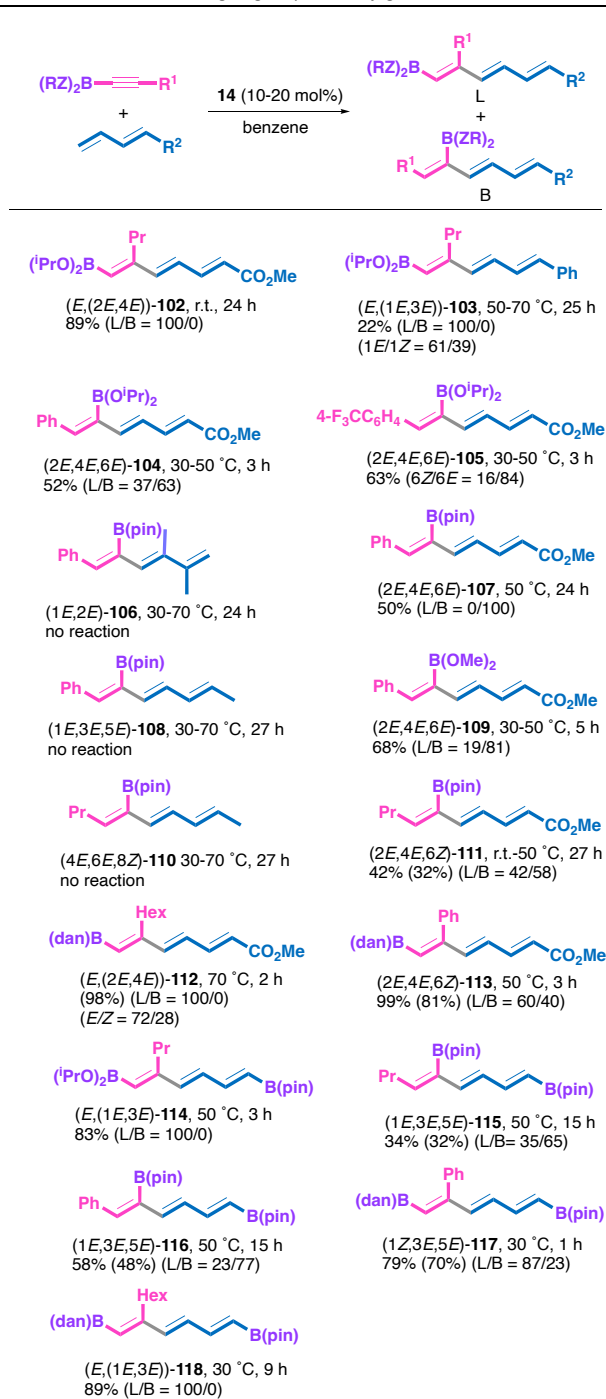
$\diagdown\diagup\diagup$
17
+
$\diagdown\diagup\diagup$B(pin)
40

cat (10 mol%)
————→
solvent, r.t.

$\diagdown\diagup\diagup\diagdown\sim\sim$B(pin)
101

Entry	Cat.	solvent	Time/h	**101**/%
1	**14**	benzene	0.5	89
2	[Ru(acac)$_2$(cod)]/BuLi	hexane	7	83
3	[Rh(cod)$_2$]BF$_4$/BINAP	C$_2$H$_4$Cl$_2$	24	0
4	[RuCp*(NCMe)$_3$]PF$_6$	acetone	20	trace
5	[FeCl$_2$L$_1$]/active Mg[b]	Et$_2$O	23	trace
6	[CoBr$_2$(PPh$_3$)$_2$]/PPh$_3$/Zn	MeCN	24	4
7	[CoBr$_2$(dppp)]/Zn/ZnI$_2$	CH$_2$Cl$_2$	24	0
8	**14**	toluene	0.5	87
9	**14**	acetone	0.5	90
10	**14**	hexane	0.5	60
11	**14**	Et$_2$O	0.5	70
12	**14**	dioxane	0.5	70

[a]These yields were estimated by ^{1}H NMR. [b]L$_1$ = (1-phenyl-*N*-pyridine-2-ylmethylene)ethanamine.

dimerisation can be conducted in benzene, toluene, acetone, Et$_2$O and 1,4-dioxane (Table 5, entries 1, 8-12). However, benzene was used as a solvent in the following screening for ease of analysis.

The present direct cross-dimerisation of internal alkynes with diene is a very unique catalysis because any related catalytic systems, that catalyse the cross-dimerisation of alkenes with dienes, failed to produce the conjugated trienes product.

With the active catalyst **14** in hand, cross-dimerisation of a series of borylated alkynes with dienes was conducted (Table 6). In the case of cross-dimerisation of unsymmetrical alkynes with dienes, two regioisomers are potentially produced. Table 6 suggested the regioselectivity could be controlled by the mask on the boronato group and the organic substituent on the alkynyl group. B(O^{i}Pr)$_2$ and B(dan) groups favour the linear (L) products (for examples: **102**, **103**, **112**, **113**, **114**, **117** and **118**) and B(pin) group favours the branch (B) products (for examples: **110**, **111** and **115**). We have studied the origin of the regioselectivity using a series of unsymmetrical alkynes. It depends on the substituent-inducive effect and finds that the regioselectivity is proportional to the difference between the Hammett's σ values ($\Delta\sigma_p$) of the two substituents in the unsymmetrical 1,2-diarylalkynes.[43] On the other hand, no significant correlation was found with Taft's steric substituent constants.[43] The phenyl and aryl group prefer the external position (for examples: **104**, **105**, **106**, **107**, **108**, **109** and **116**), which is thought to be due to the fact that the phenyl group cannot be in the same plane as the conjugated chain if it comes internally, but the aromatic ring can be in the same plane as the conjugated chain at the external position. One of the limitations of this reaction is that the widely-used B(pin) fragment dominantly comes to the internal positions and the control of the regioselectivity strongly depends on the mask on the boronato

Table 6. Cross-dimerisations giving borylated conjugated trienes.[a]

(E,(2E,4E))-**102**, r.t., 24 h
89% (L/B = 100/0)

(E,(1E,3E))-**103**, 50-70 °C, 25 h
22% (L/B = 100/0)
(1E/1Z = 61/39)

(2E,4E,6E)-**104**, 30-50 °C, 3 h
52% (L/B = 37/63)

(2E,4E,6E)-**105**, 30-50 °C, 3 h
63% (6Z/6E = 16/84)

(1E,2E)-**106**, 30-70 °C, 24 h
no reaction

(2E,4E,6E)-**107**, 50 °C, 24 h
50% (L/B = 0/100)

(1E,3E,5E)-**108**, 30-70 °C, 27 h
no reaction

(2E,4E,6E)-**109**, 30-50 °C, 5 h
68% (L/B = 19/81)

(4E,6E,8Z)-**110** 30-70 °C, 27 h
no reaction

(2E,4E,6Z)-**111**, r.t.-50 °C, 27 h
42% (32%) (L/B = 42/58)

(E,(2E,4E))-**112**, 70 °C, 2 h
(98%) (L/B = 100/0)
(E/Z = 72/28)

(2E,4E,6Z)-**113**, 50 °C, 3 h
99% (81%) (L/B = 60/40)

(E,(1E,3E))-**114**, 50 °C, 3 h
83% (L/B = 100/0)

(1E,3E,5E)-**115**, 50 °C, 15 h
34% (32%) (L/B= 35/65)

(1E,3E,5E)-**116**, 50 °C, 15 h
58% (48%) (L/B = 23/77)

(1Z,3E,5E)-**117**, 30 °C, 1 h
79% (70%) (L/B = 87/23)

(E,(1E,3E))-**118**, 30 °C, 9 h
89% (L/B = 100/0)

[a]These yields were estimated by ^{1}H NMR and the isolated yields were noted in parentheses. L and B stand for linear and branch products, respectively.

groups. On the other hand, this is a direct method to give a series of hexatriene linear conjugated products, and production of diborylated hexatriene compounds with the same and different masks are also obtained. These compounds are effective as synthetic building blocks for polyenes by the Suzuki-Miyaura cross-coupling (*vide infra*).

4-2. Stoichiometric reactions and the mechanism
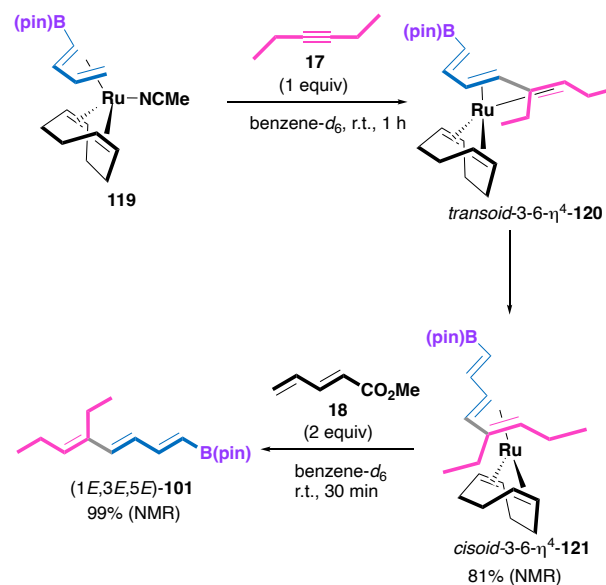
Scheme 8 Stoichiometric reactions of hex-3-yne (**17**) with butadienylB(pin) (**40**) on a ruthenium(0) complex by NMR experiments.

In order to understand the mechanism, we conducted a stoichiometric reaction of (E)-butadienylB(pin) (**40**) with hex-3-yne (**17**) with a ruthenium(0) complex (Scheme 8). A η^4-butadienylB(pin) complex of ruthenium(0) (**119**) was easily prepared by treatment of **14** with **40** in the presence of acetonitrile. Treatment of **119** with **17** at room temperature in benzene-d_6 immediately produced a *transoid*-η^4-coordinated conjugated triene complex **120** which isomerised to the more stable *cisoid*-η^4-triene intermediate **121** in 81% yield. In these intermediates, acetonitrile was displaced. When methyl pentadienoate (**18**) was added to replace the conjugated
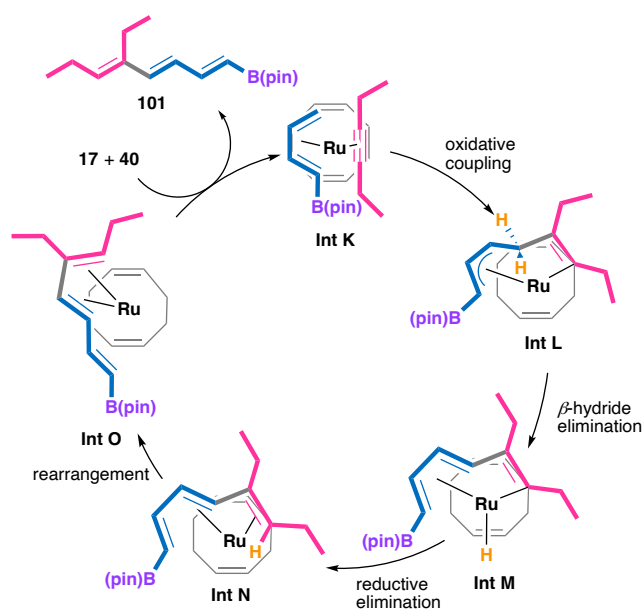

Scheme 9. Proposed catalytic cycle for the cross-dimerisation of **17** with **40**.

triene ligand, **101** was released in 99% yield. We also performed the DFT calculations (not shown).[32] A proposed mechanism for the formation of **101** is shown in Scheme 9. The substrate-selective coordination of **17** and **40** on a ruthenium(0) species gives an intermediate **Int K**. After the oxidative coupling giving a ruthenacycle intermediate **Int L**, the diastereoselective β-hydride elimination gives the *trans* C=C bond (**Int M**) and reductive elimination occur to give **Int N**. This intermediate was observed by the ^{1}H NMR spectrum as a transient species **120**. The *transoid*-triene fragment rearranges to *cisoid*-triene to give **Int O**, which is clearly characterised by the stoichiometric reactions as **121** (Scheme 8). The exchange from the *transoid*-η⁴- to *cisoid*-η⁴-triene complexes needs rotation of a single bond. The details are not yet clear but this transformation would occur by the thermodynamic reason. Finally, the coordinated *cisoid*-η⁴-triene is released by the upcoming diene **40** and alkyne **17** comes to close the catalytic cycle. The DFT calculations also support observations of this stoichiometric reaction.

## 4-3. Cross-coupling reactions of externally and internally borylated compounds

The optimisations for cross-coupling using the externally borylated compounds were screened. The best conditions were found to use [Pd(PPh₃)₄] as the catalyst with sodium ethoxide in EtOH at 70˚C. Table 7 shows the one-pot cross-dimerisation/cross-coupling using these conditions. After cross-dimerisation of **17** with **40** catalysed by **14**, that produced **101**, organic bromide, [Pd(PPh₃)₄] and sodium ethoxide in EtOH were then added to the system giving the cross-coupling products **122**-**125** in generally high yields. In this case, an external borylated conjugated triene **101** is a possible intermediate and the cross-coupling reactions with electron-rich and -deficient aryl groups are favourable coupling partners. With β-bromostyrene, a conjugated tetraene was obtained. This methodology is regarded as a divergent reaction to introduce a variety of organic halides.

Table 7. One-pot cross-dimerisation/cross-coupling.[a]
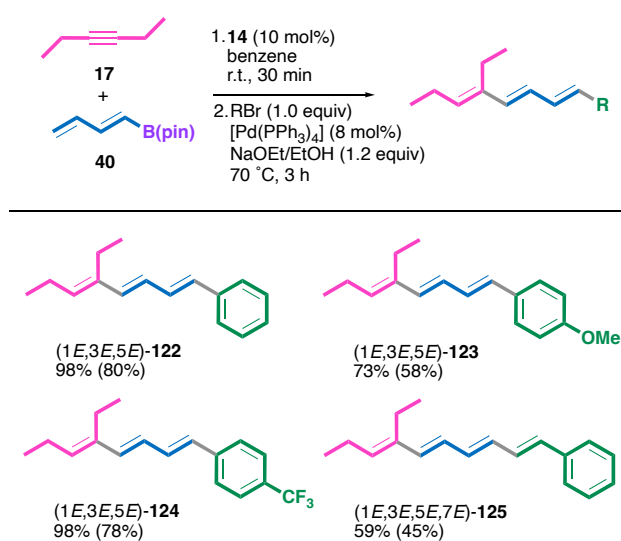
^{a}These yields were estimated by ^{1}H NMR and the isolated yields were noted in parentheses.

Table 8. Cross-coupling of internally borylated trienes.[a]
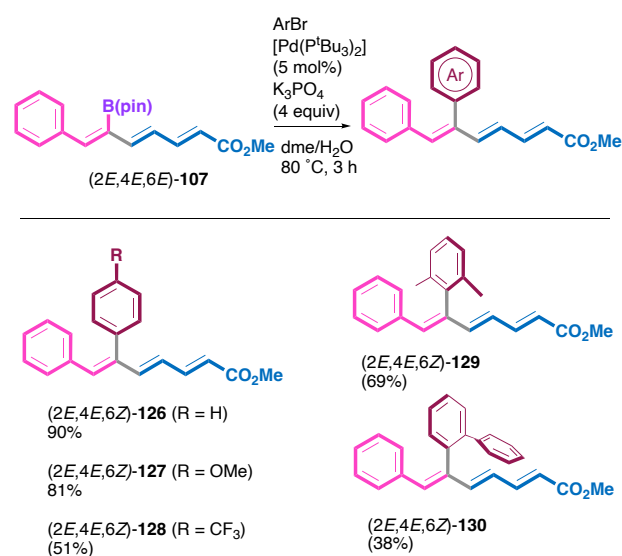
^{a}These yields were estimated by ^{1}H NMR and the isolated yields were noted in parentheses.

On the other hand, the cross-coupling of the internal boronato groups was difficult and that using the optimised conditions for the external boronato groups produced the cross-coupling product only in a low yield.[44] We thought this low reactivity of the internally borylated compounds is due to the steric repulsion like the steric effect of the peri-position. Fu and co-workers reported cross-coupling of sterically bulky arylboronates with a bulky aryl halide catalysed by [Pd(P^{t}Bu₃)₂] complex,[45] and we used the Fu catalyst for this internal cross-coupling reaction (Table 8). The Fu catalyst worked well and the cross-coupling of **107** with phenyl bromide produced **126** in 90% yield. This reaction could be applied for the electron-rich and -deficient aryl groups to give **127** and **128**. Moreover, very bulky aryl bromides such as 2,6-xylyl and 2-biphenyl bromides also reacted with **107** to give **129** and **130** in moderate yields.

## 4-4. Cross-coupling reactions of diborylated compounds

The cross-coupling reactions using diborylated compounds are also important issue from the synthetic point of view. A one-pot cross-dimerisation of **131** with **40** catalysed by **14**, which was expected to give **114**, followed by the cross-coupling with 2 equiv of vinyl iodide catalysed by [Pd(PPh₃)₄] dominantly produced (3*E*,5*E*,7*E*)-**132** in 48% yield along with **133** in 20% yield. This is the first example to produce a decapentaene on a one-pot reaction (eqn (6)).
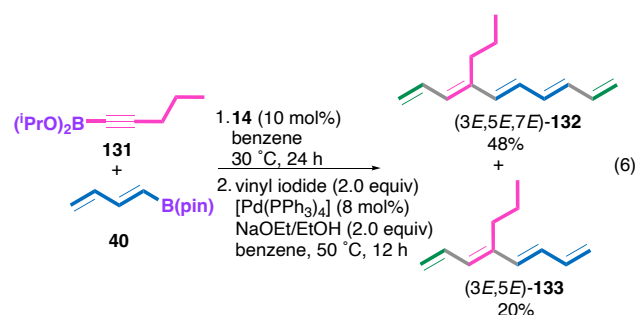
In this reaction, octatetraene (3E,5E)-**133** was also produced as a side product, suggesting the cross-coupling of the B(O^{i}Pr)$_2$ group proceeded effectively but the proto-deborylation of the B(pin) fragment occurred before the second cross-coupling reaction under basic conditions. A similar one-pot reaction involving cross-dimerisation of **131** with **40** followed by the palladium-catalysed cross-coupling with 2 equiv of phenyl iodide produced (1E,3E,5E)-**134** in 97% isolated yield (eqn (7)). In this case, the cross-dimerisation and cross-coupling proceed efficiently.
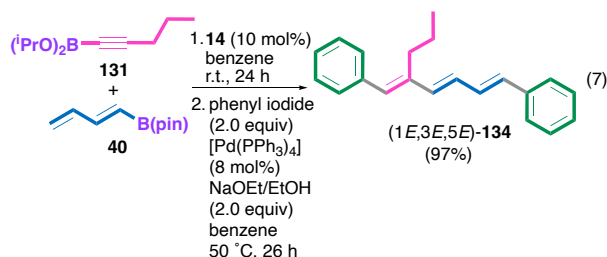
As an extension of this reaction, two different organic groups could be introduced because of the putative diborylated triene contains two boronato groups with different mask. In reality, trials for the cross-dimerisation of **131** with **40** followed by the regioselective cross-coupling using difference in the reactivity between the B(O^{i}Pr)$_2$ and B(pin) group failed. This was attributed to the instability of the B(O^{i}Pr)$_2$ group. Therefore, the regioselective stepwise cross-dimerisation and cross-coupling were next examined. Cross-dimerisation of 1-phenylethynylB(dan) (**135**) with **40** followed by the cross-coupling with 1 equiv of phenyl iodide produced (1Z,3E,5E)-**136** in 71% isolated yield, where the B(pin) group selectively reacted with phenyl iodide in the event of cross-coupling (eqn (8)). The B(dan) fragment remained attached in this reaction. However, all attempts to directly convert the B(dan) fragment[31] were unsuccessful and led to the decomposition, probably owing to the instability of the conjugated triene under the acidic conditions.
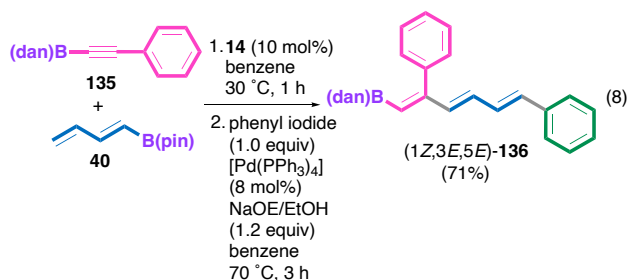
5. Applications to synthetic building blocks

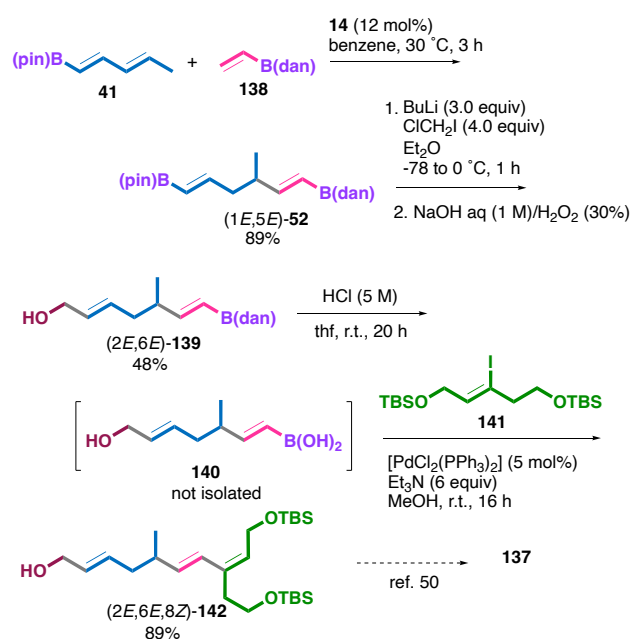### 5-1. Formal synthesis of *rac*-bongkrekic acid[22]

Chart 1. Bongkrekic acid (**137**).

Figure 1. Tempeh made from fermented soybeans.

As shown in this feature article, we succeeded to produce diborylated 1,5-diene building blocks. 1,5-Diene moiety was found in natural products and biologically active compounds, and we decided to work on the formal synthesis of bongkrekic acid (**137**) (Chart 1). Bongkrekic acid is produced by a bacterium *Burkholderia gladioli* in nature and this compound specifically inhibits the mitochondrial inner membrane protein adenine nucleotide translocator and is also associated with apoptosis.[46] This compound is also known to be produced by bacterial contamination in the production of tempeh, a typical Indonesian fermented food (Figure 1), causing serious food poisoning. Strict controls are therefore now applied. The first total synthesis of **137** was achieved by Corey and Tramontano,[47] and the improved total syntheses were also reported.[48-50]

We applied the diborylated 1,5-diene **52** in the formal synthesis of bongkrekic acid. Cross-dimerisation of **41** with vinylB(dan) (**138**)

Scheme 10. Formal synthesis of *rac*-bongkrekic acid (**137**) using cross-dimerisation of pentadienylB(pin) with vinylB(dan). (TBS = *t*-butyldimethylsilyl)

catalysed by a ruthenium(0) complex **14** produced a diborylated 1,5-diene (1*E*,5*E*)-**52** in 89% yield (Scheme 10). Then, treatment of **52** with BuLi with chloroiodomethane followed by the treatment of basic hydrogen peroxide produced an alcohol **139** in 48% yield. After removal of the mask on the B(dan) fragment by the acidic conditions gave a boronic acid **140**, and then the cross-coupling with the TBS-protected alkenyl iodide **141** produced (2*E*,6*E*,8*Z*)-**142** in 89% isolated yield. Shindo and co-workers reported this compound as an intermediate in the total synthesis of **137**,[50] and the total yield of **137** was 43% yield from **52** in 3 step reactions. This reaction demonstrated a new approach of an unsymmetrical 1,5-diene substructure in the synthesis of a natural product.

### 5-2.   Conjugated ferrocenes as electronic materials[51]

Conjugated polyenes are also attractive for electronic materials. Recently, we also reported the first donor-acceptor type conjugated polymers by the addition polymerisation[52] and conjugated heteroacene compounds.[53] As an application of this methodology to electronic materials, we prepared a series of redox active conjugated ferrocenes. Ferrocenes with conjugated polyenyl groups are attracted as molecular wires and interesting as a research subject for charge transfer. They were normally prepared by Hornor-Wadsworth-Emmons reaction,[54] Wittig reaction[55] or Hunsdiecker-Mizoroki-Heck reaction.[56] However, these methods are problematic in terms of step economies and it is difficult to create multiple variations.

1-Propynylferrocene (**143**) is easily prepared from acetylferrocene in 90% yield.[57] Cross-dimerisation using alkynylferrocene with conjugated dienes is very challenging because the volume required by the ferrocenyl group was evidently high. Reaction of 1-propynylferrocene (**143**) with butadienylB(pin) (**40**) gave a conjugated hexatrienylferrocene **144** in 88% isolated yield. This reaction proceeded regioselectively and the ferrocenyl fragment exclusively comes to the external position (eqn (9)). This is a unique reaction because a conjugated polyenylferrocene could be obtained directly from alkynylferrocene.

(9)

144
92% (88%)
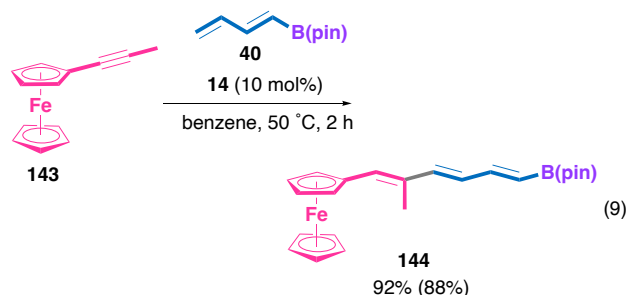
With the borylated conjugated hexatrienylferrocene in hand, a series of conjugated ferrocenes having a variety of aryl and alkenyl groups has been prepared divergently by the cross-coupling reaction with aryl or alkenyl halides (Scheme 11). Conjugated trienylferrocenes with electron-rich and -deficient aryl groups, a conjugated tetraenylferrocene and a diferrocenyl compound bridged with a conjugated trienyl chain are prepared.

These compounds were characterised by CV, UV and TD-DFT calculations. According to the TD-DFT calculations of **149**, the dominant contributor of the λ_{max} (390.8 nm) is the HOMO-LUMO
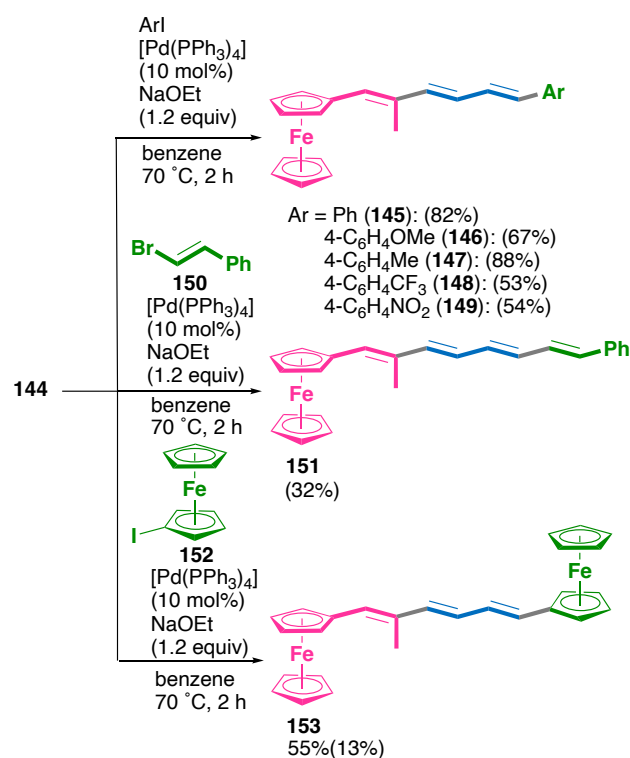
Scheme 11 Cross-coupling of **144** with a series of aryl and alkenyl halides. Yields in parentheses are isolated yields.

transition and Chart 2 shows the LOMO and HOMO of **149**. This band features transitions from the filled π orbitals of polyenylferrocene to the π* orbitals of the aromatic ring. The *aci*-nitro extreme would promote the HOMO-LUMO transition. Note that although there are many reports on the electron transfer properties of polyynes,[58] such studies using polyenes are limited.
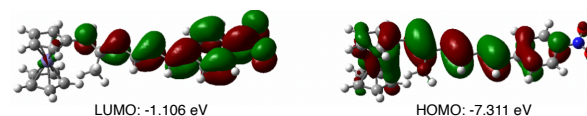
LUMO: -1.106 eV   HOMO: -7.311 eV

Chart 2. HOMO and LUMO of **149** by TD-DFT calculations.

5-3.   Synthesis of navenone B[32]

Conjugated polyenes are also found in many natural products and bioactive molecules.[59] As an extension of this study, we tried to synthesise a trail-breaking pheromone from the marine opisthobranches, navanax inermmis, navenone B (**158**).[60] The key point in this synthesis is undoubtedly the construction of the conjugated C=C double bonds. The total synthesis of **158** was achieved by Wittig reaction,[61] iterative 1,3-hydroxy rearrangement,[62] reductive elimination from 1,6-diol-diyne,[63] retro-Buchner reaction,[64] reduction of homopropargylic alcohol,[65] Migita-Kosugi-Stille coupling[66] and cross-metathesis reaction.[67] The present contribution in this synthesis is the construction of the C=C double bond by the cross-dimerisation.

Cross-dimerisation of a silylalkyne **154** with butdienylB(pin) (**40**) catalysed by **14** (10 mol%) produced the cross-dimer **155**, where the
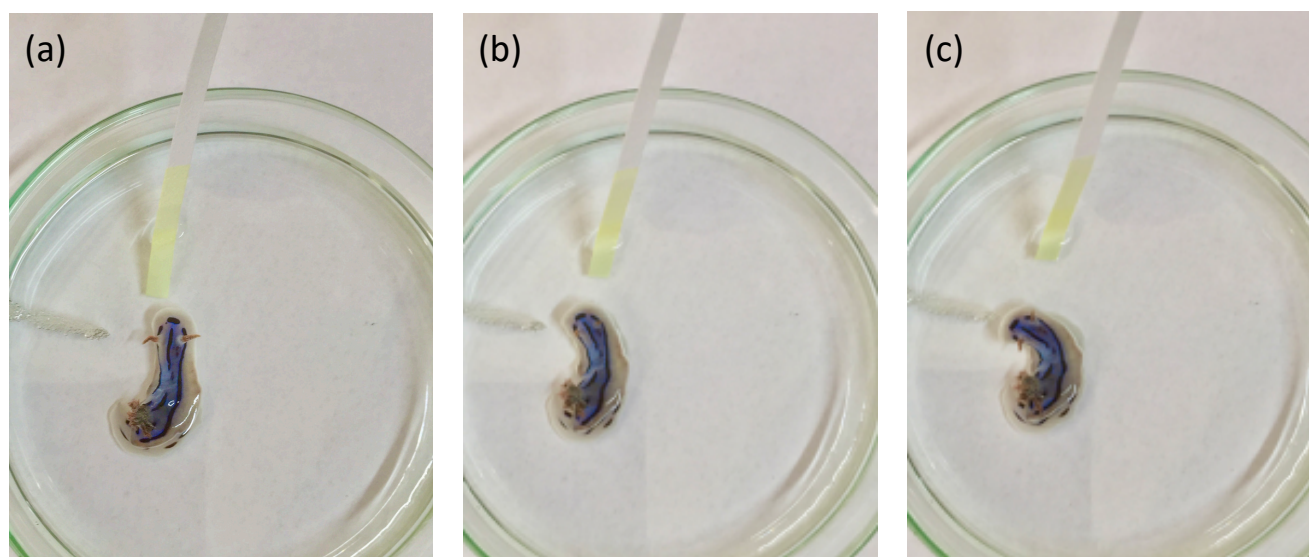
Figure 2. Sea slug behavior with respect to a trail-breaking pheromone navenone B (**158**) (1.0 M soaked in a filter paper). The time lapse is in the order a, b and c. The yellow area of the filter paper is the colour of navenone B.

trimethylsilyl group exclusively came to the internal position, presumably because of the inductive effect of the silyl group and high external-philic property of the phenyl group (Scheme 12). This is because we have known that any silyl groups in the alkynylsilane come to the internal position in the cross-dimerisation with conjugate dienes and the resulting silyl group is easily detachable by the proto-desilylation.[68] Although we intended to prepare the 1*Z* product of **155**, we dominantly obtained the 1*E*-**155** in reality. This cis-trans selectivity did not depend on the reaction temperature and since the isolated 1*E* compound did not isomerise spontaneously under these conditions, some hydride species in the catalysis would concern to this isomerisation. Nonetheless, we continued the cross-coupling of the 1*E*/1*Z*-mixture of **155** with 4-iodobut-3-en-2-one
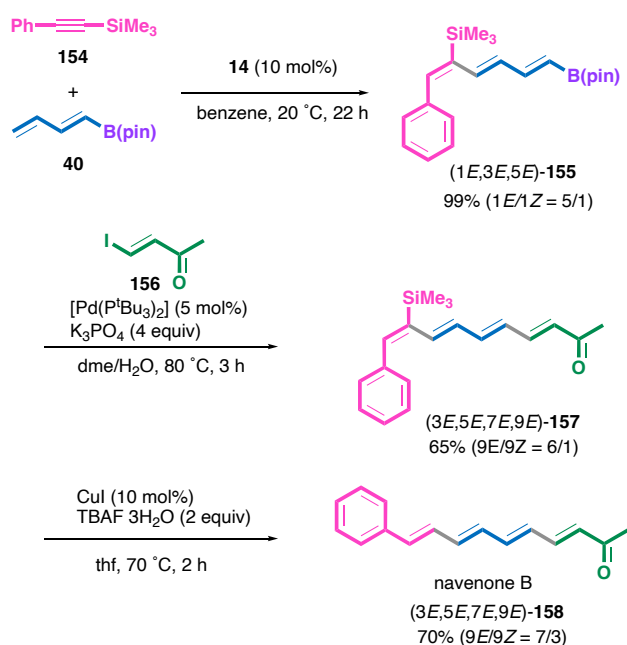
(**156**) to give a conjugated tetraene **157** in 65% yield. After some trials, the Fu's catalyst gave the best result for this cross-coupling reaction using alkenyl iodide **156**. Trost and co-workers reported the trans hydrosilylation of an internal alkyne but subsequent proto-desilylation to give a trans alkene.[69] We applied the Trost's conditions for the proto-desilylation of **157** using TBAF·3H$_2$O in the presence of catalytic amount of CuI.[70] The C=C bond at the 9-position inverted to the *E* configuration to dominantly give (3*E*,5*E*,7*E*,9*E*)-**158** in 70% yield. The mechanism for the C=C bond rotation is not clear, but one possibility is that bond alternation and the conjugated carbonyl fragment are perturbed during the proto-desilylation under these conditions. Takeda and co-workers suggested formation of organocopper(I) species in the Brook rearrangement in the presence of CuO^{t}Bu,[71] trienylcopper(I) species would be formed in this reaction. We also showed the acid-promoted *E*/*Z* isomerization of conjugated polyenes with a carbonyl group.[72] This protocol showed that navenone B can be achieved from a simple silylalkyne **154** with butadienylB(pin) (**40**) by the successive cross-dimerisation/cross-coupling in 3 steps in 45% total yield.

Although **158** was obtained as a mixture of 9*E*/9*Z* isomers in a 7/3 ratio and they were difficult to separate, the formation of **158** was undoubtedly characterised by spectroscopic methods including high-resolution MS. Because **158** is a trail-breaking pheromone of sea slugs, we conducted a short exposure test of **158** using a sea slug, chromodoris willani. **158** was originally produced in a specialized gland referred to in earlier studies as the "yellow gland" and is reported to be effective at a concentration limit of 1 × 10^{-5} M, and this trail-breaking pheromone is known to have low species specificity.[73] Figure 2 shows the sea slug took evasive action against the filter paper soaked in 1.0 M navenone B (**158**).

Scheme 12 Total synthesis of navenone B using cross-dimerisation of **154** with **40**.

Conclusions

This feature article shows new synthetic approaches to borylated non-conjugated and conjugated polyenes by

ruthenium(0)-catalysed cross-dimerisations and subsequent cross-coupling reactions. The catalytic cross-dimerisation proceeds under the neutral and ambient conditions, and the boronato groups, even with highly reactive butyl and isopropyl esters, are tolerated during the catalysis. Thus, a new methodology for the synthesis of borylated 1,4- and 1,5-dienes and conjugated trienes as synthetic building blocks has been established. With this cross-dimerisation, we succeeded to prepare unsymmetrical diborylated non-conjugated and conjugated polyenes. In diborylated compounds, regioselective substituent introduction using cross-coupling was also established with different masks on boronato groups. We also demonstrated formal and total syntheses of bioactive natural products and electronic materials by these methods. These reactions result in shortened processes for conventional reactions and are useful in complex bioactive molecules and electronic materials.

However, this approach also has its limitations. Firstly, although this reaction uses conjugated dienes as a coupling partner, internally substituted dienes are not applicable to this reaction. As the stoichiometric reaction proceeds with these internally substituted dienes, this disadvantage is due to the difficulty of releasing the products coordinated to the ruthenium(0) complex by the coming internally substituted diene. Secondly, terminal alkynes cannot be used in the reaction to synthesise borylated conjugated polyenes. The borylated conjugated polyenes synthesised by this method therefore have internal substituents. In order to synthesise conjugated polyenes without side chains, *e.g.* molecules such as navenone B (**158**), proto-desilylation of the silyl groups is necessary, as shown in Scheme 12. With terminal alkynes, a complex mixture including the [2+2+2] cycloaddition products was obtained. Thirdly, the fact that when alkenylB(pin) is used, the B(pin) fragment comes internal position in the reaction with dienes is also an issue from the perspective of high versatility of B(pin) and the general preference for linear polyene substructures. It should be also noted that proto-deborylation reactions can proceed during the reaction, as has been described in some reactions. In this context we are already developing similar reactions with stannyl and silyl analogues as reactive functional groups, and we will publish somewhere soon. One of the possible future directions of this methodology is the enantioselective synthesis of borylated non-conjugated dienes, and we are working with ruthenium(0) complexes with a chiral cyclic diene ligand. Finally, we would like to thank the readers for their interest in the synthesis of borylated non-conjugated and conjugated polyene building blocks by this method.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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