Catalytic Bismetallative Multicomponent Coupling Reactions: Scope, Applications, and Mechanisms

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TUTORIAL REVIEW

Catalytic bismetallative multicomponent coupling reactions: scope, applications, and mechanisms

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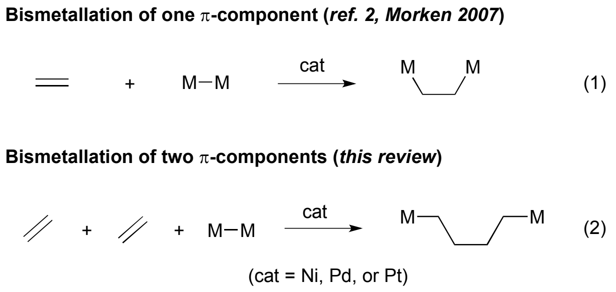
Catalytic reactions have played an indispensable role in organic chemistry for the last several decades. In particular, catalytic multicomponent reactions have attracted a lot of attention due to their efficiency and expediency towards complex molecule synthesis. The presence of bismetallic reagents (*e.g. B–B*, *Si–Si*, *B–Si*, *Si–Sn*, etc.) in this process renders the products enriched with various functional groups and multiple stereocenters. For this reason, catalytic bismetallative coupling is considered an effective method to generate the functional and stereochemical complexity of simple hydrocarbon substrates. This review highlights key developments of transition-metal catalyzed bismetallative reactions involving multiple π components. Specifically, it will highlight the scope, synthetic applications, and proposed mechanistic pathways of this process.

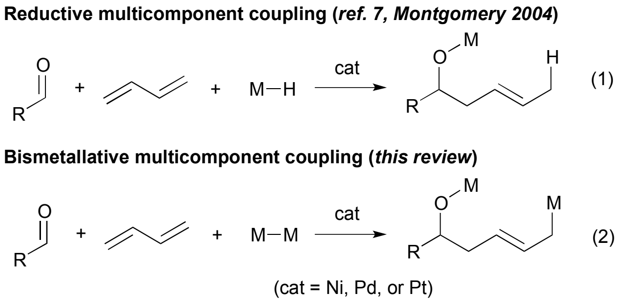
1. Introduction

Catalytic multicomponent reactions are regarded as one of the most attractive strategies for organic synthesis, since they can generate molecular diversity and complexity from simple substrates.[1] Recent investigations in this area have revealed that the incorporation of bismetallic reagents (*e.g.* $R_2B{-}BR_2$, $R_3Si{-}SiR_3$, $R_2B{-}SiR_3$, $R_3Si{-}SnR_3$, etc.) into this process allows access to functionalized products in a stereo- and regioselective fashion.[2, 3, 4] The resulting organometallic compounds are synthetically valuable intermediates due to their versatility and reactivity in organic synthesis. [2] Compared to bismetallation of one π-component (Scheme 1, eq. 1), bismetallation of two (or more) π-components (Scheme 1, eq. 2) are particularly noteworthy due to their applications towards complex molecule syntheses.



Scheme 1 Bismetallative coupling with one vs. two π-components.

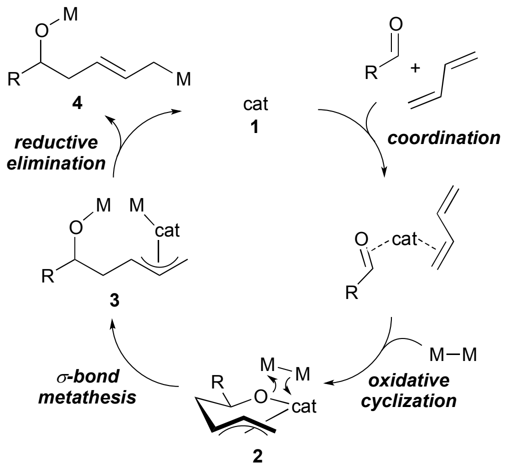
The coupling reactions of organometallic reagents with diene components were pioneered by Mori[5] and Tamaru[6] (Scheme 2, eq. 1). These powerful reductive coupling reactions, involving organometallic reagents (*M*–R) or metal hydrides (*M*–H), have attracted much attention and have expanded on earlier reports by Sato and Montgomery.[7] However, the coupling of bismetallic reagents (*M–M*) with two π components (Scheme 2, eq. 2) has gained relatively less attention in spite of its potential for providing an efficient method in multiple bond-forming reactions. This review focuses on the major developments in the bismetallative multicomponent coupling reactions that are catalyzed by group 10 transition metals.



Scheme 2 Reductive vs. bismetallative multicomponent coupling.

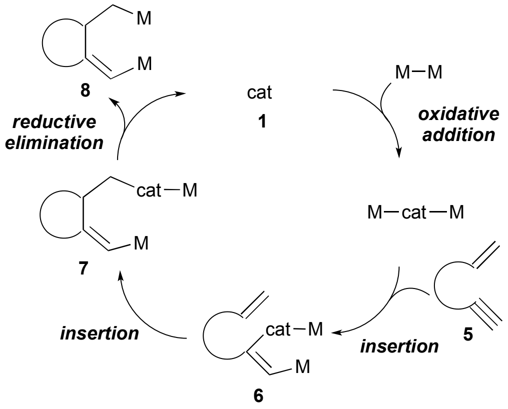
2. Mechanistic Considerations

Several different mechanistic pathways have been suggested for the bismetallative multicomponent coupling reactions that are catalyzed by Ni, Pd, or Pt. One possible mechanism (oxidative cyclization mechanism)[8, 9] commences with the coordination of the π-components with the catalyst **1** and the subsequent formation of a metallocyclic intermediate **2** (Scheme 3).[10] In the presence of bismetallic reagents, this cyclic intermediate (**2**) may undergo σ-bond metathesis forming a bismetallic complex **3**. Finally, reductive elimination would afford the product **4** and regenerate the catalyst (**1**).



Scheme 3 Oxidative cyclization mechanism.

In some cases, however, the initial oxidation of the catalyst (**1**) occurs by insertion with bismetallic reagents (oxidative addition mechanism, Scheme 4).[11] Next, subsequent insertion of one π-component of substrate **5** would give an intermediary complex **6**. The intermediate **6** then can undergo additional insertion reaction with the other π-component of the substrate to generate cyclic intermediate **7**. Lastly, reductive elimination of **7** would afford the product **8** and close the catalytic cycle.



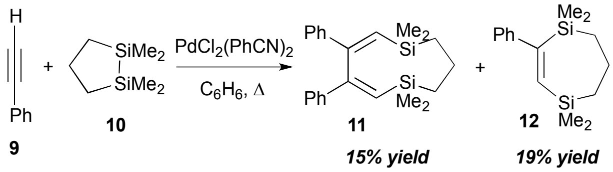
Scheme 4 Oxidative addition mechanism.

The above-described catalytic cycles represent some of the most typical reaction pathways suggested for this process, but they are not meant to be comprehensive. Mechanisms for these reactions can vary depending on catalysts, substrates, and other reaction conditions. More detailed mechanistic considerations for each category of the process will be discussed accordingly in the corresponding sections.

3. Pd-Catalyzed Bismetallative Multicomponent Coupling

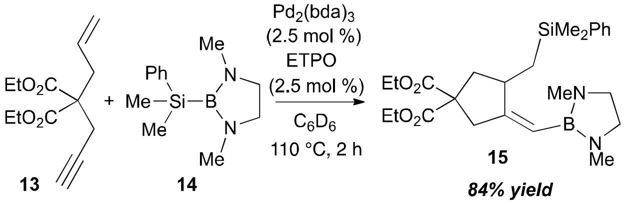
3.1. Coupling of Alkyne–Alkyne and Alkyne–Alkene

The Pd-catalyzed bismetallative alkyne–alkyne and alkyne–alkene coupling reactions have been investigated in a variety of contexts by several research groups. One of the earliest observations of this type of coupling was reported by Sakurai (Scheme 5).[12] The main goal of this study was to investigate the properties of silicon–silicon bond of 1,2-disilacycloalkanes, focusing on the donor ability of the Si–Si bond. During their study of cycloaddition reactions of organodisilane reagents to various acetylenes, it was observed that the disilane reagent (**10**) can participate in a coupling reaction between two acetylenes (**9**) to give **11** (15% yield), along with product (**12**). Although the yield of the two-π-component-coupling product was not great, its presence demonstrated the potential of bismetallic reagents towards multicomponent reactions.



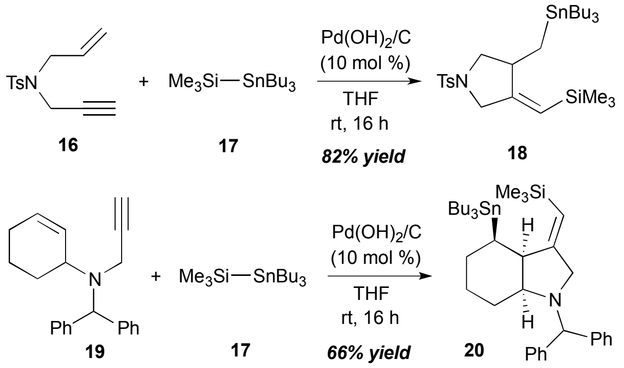
Scheme 5 Sakurai's intermolecular alkyne–alkyne coupling (1975).

More synthetically useful methods in this type of reaction were developed later by Tanaka,[13] Lautens,[14] Mori,[11] and RajanBabu.[15] The Tanaka group (Scheme 6) observed intramolecular alkyne–alkene coupling reactions that are promoted by a *B–Si* reagent in the presence of a palladium catalyst.[13a] An intramolecular alkyne-alkyne coupling reaction with 4,4-bis(ethoxycarbonyl)hep-6-en-1-yne (**13**) and **14** was catalyzed by $Pd_2(dba)_3$ and ETPO (4-ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane) to afford **15** in 84% yield (detected by ^1H NMR). Along with the desired cyclization product, the formation of a byproduct (9% yield, not shown), which was speculated to have come from silaboration of the triple bond, was also observed by ^1H NMR.



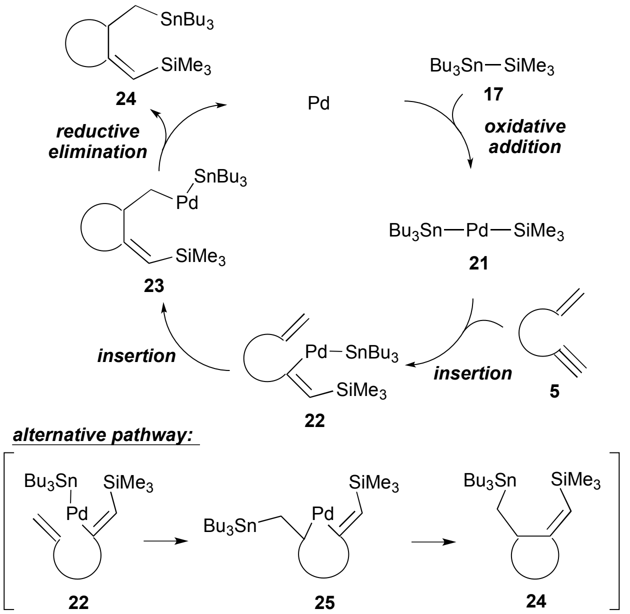
Scheme 6 Tanaka's intramolecular alkyne–alkene coupling (1997).

In Mori's work (Scheme 7),[11] enyne **16** was reacted with 1.5 equivalents of $Me_3Si–SnBu_3$ (**17**) in the presence of 10 mol % of $Pd(OH)_2$ on charcoal at room temperature to furnish the bismetallation product **18** in 82% yield. With the use of $Pd_2(dba)_3$ as a ligand (3 mol %) under the same reaction conditions, the product was obtained in a slightly lower yield (57%). Also, a saturated indole moiety **20** was constructed (66% yield, with $Pd(OH)_2/C$) from 3° amine-substituted enyne **19** in a stereospecific fashion. In this study, it was observed that using a palladium catalyst in the *absence* of phosphine ligands tends to suppress the formation of the bismetallation product of alkyne, which is an undesired product of the reaction.



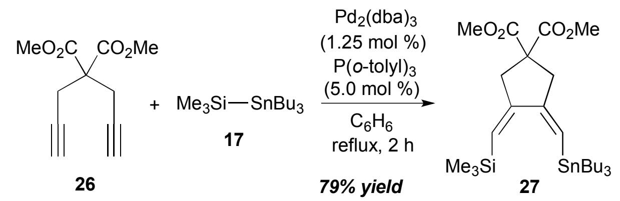
Scheme 7 Mori's intramolecular alkyne–alkene coupling (2001).

Two possible pathways for this process were considered as illustrated in Scheme 8. The reaction commences with oxidative addition of $Me_3Si–SnBu_3$ (**17**) to a Pd catalyst to give **21**, which is followed by insertion of the alkyne moiety of **5** into the Pd–Si bond to form intermediate **22**. Then, an insertion of the alkene portion of **22** into the Pd–C bond occurs intramolecularly to afford a Pd complex **23**. Finally, reductive elimination would furnish cyclized product **24**, and the palladium catalyst is regenerated. Mori and co-workers also consider an alternate pathway; it involves the formation of **25**, which is the product of insertion of the alkene into the Pd–Sn bond of **22**. From the intermediate complex **25** the identical cyclized product **24** would be afforded via reductive elimination.



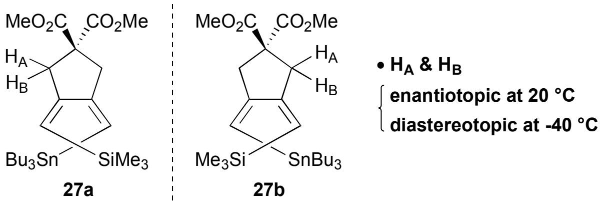
Scheme 8 Proposed mechanism for enyne cyclization (Mori, 2001).

One of RajanBabu's many contributions in this field is the preparation of functionalized bisalkylidenes from 1,6-diynes, as described in Scheme 9.[15] The construction of a (*Z,Z*)-1,3-diene **27** (79% yield) was accomplished by reaction of di-*O*-methyl dipropargylmalonate (**26**) with $Me_3Si–SnBu_3$ (**17**) with a catalytic amount of $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$.



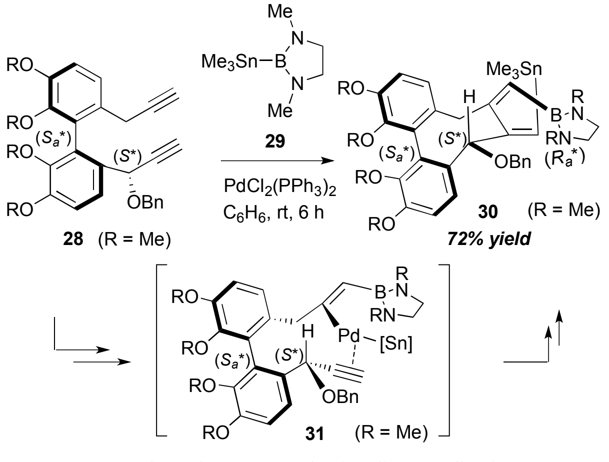
Scheme 9 RajanBabu's intramolecular alkyne–alkyne coupling (2000).

One of the interesting features of molecule **27** is that sterically-encumbered silicon and tin groups enforce a nonplanar/helically chiral structure for a usually planar diene (Scheme 10). The fluxional nature and stereochemistry of the (*Z,Z*)-1,3-diene **27** were analysed by NMR spectroscopy. The ^1H NMR shows two distinctive sets of signals (two quartets) for H_A and H_B at –40 °C, while broad signals for the ring methylene protons appeared at 20 °C. Except for a highly unlikely conformational equilibrium involving the cyclopentane, such chirality must have originated from the helical arrangement of substituents in the (*Z,Z*)-diene **27**.



Scheme 10 Enantiomers of **27** at –40 °C (RajanBabu, 2000).

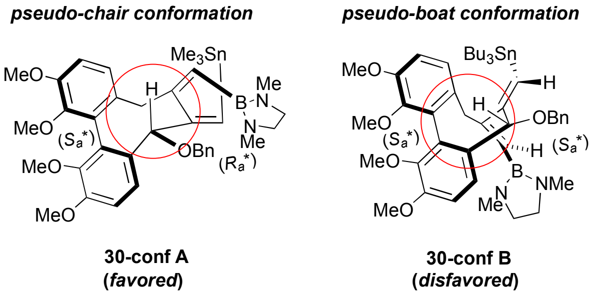
In a recent study, the RajanBabu group explored more details of the stereochemistry in these cyclization reactions.[16] For this study, cyclization reactions of diynes with a *B–Sn* reagent **29** were investigated. The regio- and stereoselectivities of this process were rationalized by the assumption that the addition of **29** to the diyne substrate **28** occurs at the less substituted, electron-rich alkyne forming a C–B bond in the product **30** (Scheme 11). The cyclization via carbometalation of the palladium intermediate **31**, followed by reductive elimination, will result in the formation of C–Sn bond in the product **30**.



Scheme 11 RajanBabu's stereoselective diyne cyclization (2012).

In this report, the group speculated that the cyclization step with the carbometalation process is the stereoselectivity-determining step and proposed a possible origin of stereoselectivity (Scheme 12). When the 7,8-

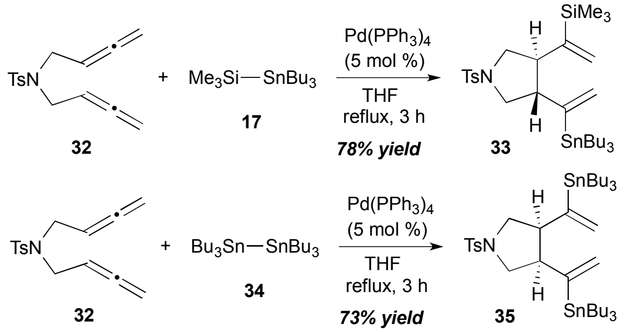
bisalkylidenecyclooctadiene moiety of the product **30** is formed via carbometalation, the configuration of the newly-formed axial chiral element (R_a) is determined. The (S_a, R_a) configuration of the product (**30-conf A**) and, thereby, its transition state have relatively strain-free pseudo-chair conformation, compared to more strained pseudo-boat conformation (**30-conf B**).



Scheme 12 Proposed origin of stereoselectivity (RajanBabu, 2012).

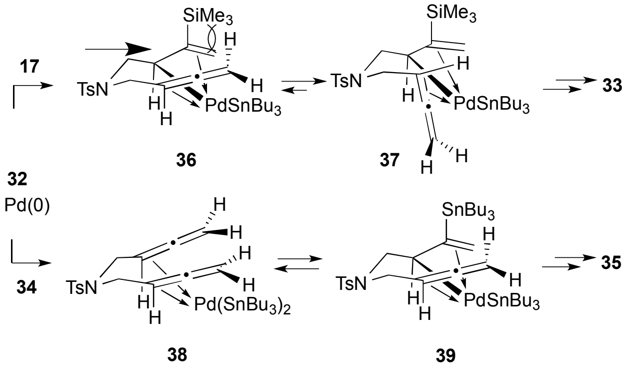
3.2. Coupling of Allene–Allene and Allene–Alkyne

Pd-catalyzed bismetallative allene-allene coupling reactions with bismetallic reagents were first demonstrated by the Kang group.[17] In this study, it was demonstrated that silylstannanes (*Si–Sn*) or distannanes (*Sn–Sn*) can promote the palladium-catalyzed addition–cyclization reaction of tethered bis(allenes). As described in Scheme 13, the cyclization reaction proceeds with bis(allene) **32** and (trimethylsilyl)tributylstannane (**17**) in the presence of Pd(Ph_3P)$_4$ (5 mol %) to afford a *trans*-fused cyclized product **33** in 78% yield. On the other hand, when distannane $Bu_3Sn–SnBu_3$ (**34**) was used for this process with the same bis(allene) **32** and Pd(PPh_3)$_4$ (5 mol %), a *cis*-fused distannane **35** was obtained in 73% yield.



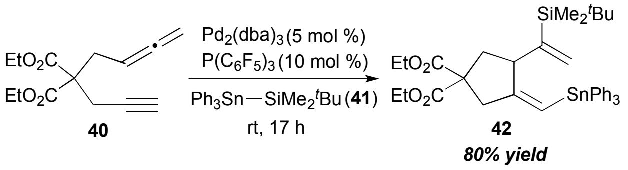
Scheme 13 Kang's intramolecular allene–allene coupling (2000).

The different stereochemical outcomes between two bismetallic reagents (i.e. *cis* vs. *trans* fusion at ring junction) were rationalized in this report (Scheme 14). For the *Si–Sn* reagent, allylpalladium complex **37** is formed by the addition of the $Bu_3Sn–Pd–SiMe_3$ species to the allene moiety. Intermediate **37** should be favoured over **36** due to the steric hindrance of the nearby TMS (trimethylsilyl) group. The cyclization reaction of this intermediate (**37**) and subsequent reductive elimination would result in the *trans* bicyclic product **33**. In the case of the *Si–Sn* reagent, however, the chelated σ-allylpalladium intermediate **39** is preferably formed from the coordinated compound **38**. Then, the rapid carbocyclization of **39** and reductive elimination would give the *cis*-fused bicycle **35**. It is conjectured that the differentiation between the two types of the reagents comes from the different bond lengths (C–Sn bond vs. C–Si bond). In other words, the steric encumbrance of the TMS group in those allylpalladium complexes is more severe than that of the Bu_3Sn group due to the shorter bond length of the C–Si bond.



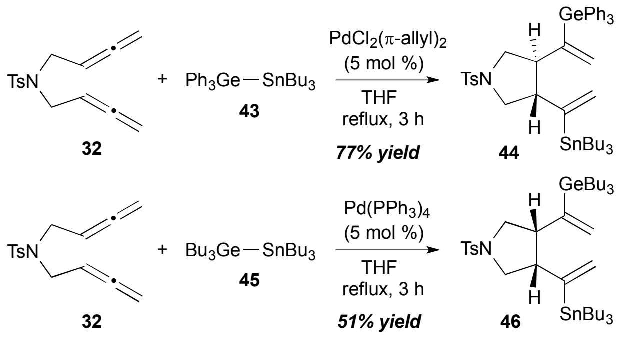
Scheme 14 Rationale for stereochemical outcome (Kang, 2000).

With the same types of organometallic reagents (i.e. *Si–Sn* and *Sn–Sn*), RajanBabu and co-workers showed that an allene and alkyne can be coupled intramolecularly with a palladium catalyst (Scheme 15).[18] In the presence of $Ph_3Sn–SiMe_2{}^tBu$ (**41**), $Pd_2(dba)_3{\cdot}CHCl_3$ and P(C_6F_5)$_3$, alleneyne **40** was cleanly transformed into the cyclic product **42** in 80% yield at room temperature. It was found that the source of Pd affects the efficiency of the reaction in the order of the following: (C_6F_5)$_3$P:($PhCN$)$_2$$PdCl_2$ ≈ [Pd(allyl)Cl]$_2$/AgOTf > $Pd_2(dba)_3{\cdot}CHCl_3$ >> $PdCl_2$. It was also observed that the silyltin reagents are generally superior to other bismetallating reagents (*Sn–Sn* or *Sn–B*) for the cyclization of allenynes.



Scheme 15 RajanBabu's intramolecular allene–alkyne coupling (2001).

For allene–allene coupling, *Ge–Sn* reagents can also participate as a coupling component; this process was investigated by Yu *et al* (Scheme 16).[19] They pointed out that the stereochemistry of the outcomes is dependent on the *Ge–Sn* reagents and the catalysts that are used in the reactions. Bis(allene) **32** can react with $Ph_3Ge–SnBu_3$ (**43**) with a catalytic amount of (π-allyl)$_2$$Pd_2Cl_2$ (5 mol %) to afford the *trans*-cyclized product **44** (77% yield). On the other hand, the same bis(allene) **32** furnished the *cis*-cyclized product **46** (51% yield) when it was reacted with $Bu_3Ge–SnBu_3$ (**45**) in the presence of Pd(PPh_3)$_4$.

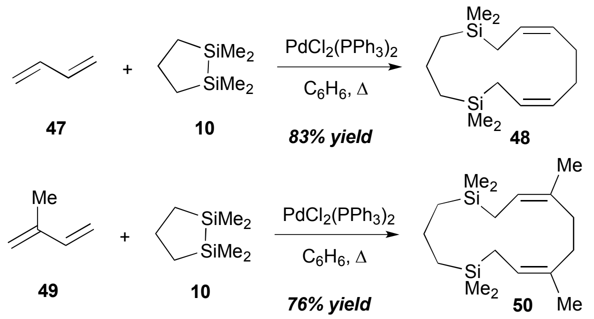


Scheme 16 Yu's intramolecular allene–allene coupling (2004).

3.3. Coupling of Diene–Diene

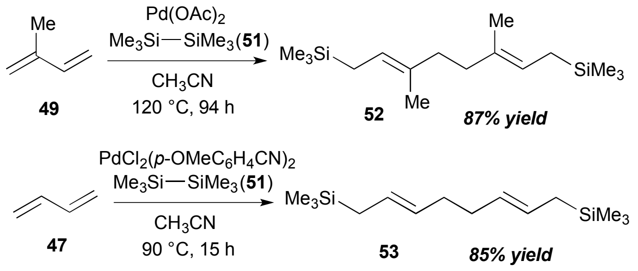
Among bismetallative multicomponent coupling reactions, the Pd-catalyzed diene–diene bismetallative coupling is one of the most frequently-observed reaction categories. Earliest studies were reported by Sakurai *et al.*, in which dienes are intermolecularly coupled in the presence of cyclic disilane reagents to generate allyl silanes (Scheme 17).[20] Since the initial Sakurai report, preliminary observations of this type of coupling were reported by a number of research groups including Kumada,[21] West,[22] Seyferth,[23] Manners,[24] and Ando[25] groups. Then, more synthetically applicable versions of this method were examined by the Tsuji group.[26]

According to the Sakurai's account,[20] when 1,3-butadiene (**47**) was treated with 1,1,2,2-tetramethyl-1,2-disilacyclopentane (**10**) in the presence of a Pd(II) catalyst, 1,1,5,5-tetramethyl-1,5-disilacyclotrideca-7,11-diene (**48**) was obtained in 83% yield (Scheme 17). Isoprene (**49**) also gave the corresponding allyl silane **50** in 76% yield under the same reaction conditions.

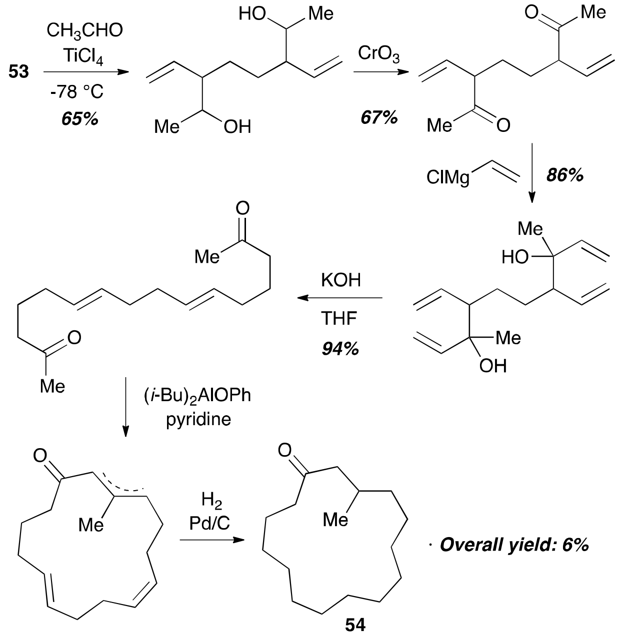


Scheme 17 Sakurai's intermolecular diene–diene coupling (1975).

Besides the cyclic organodisilane **10**, acyclic organodisilanes have been utilized for diene–diene coupling reactions by the Sakurai group (Scheme 18).[27] The reaction of hexamethyldisilane (**51**) with isoprene (**49**) in the presence of a catalytic amount of Pd(OAc)$_2$ afforded 1,8-disilyloctadiene **52** (87% yield) in a regio- and stereoselective fashion. Also, 1,3-butadiene (**47**) can participate in this coupling reaction with hexamethyldisilane (**51**) and a palladium catalyst, PdCl$_2$(p-MeOC$_6$H$_4$CN)$_2$, to afford **53** in 85% yield. The coupling product **53** was used as a starting material for the synthesis of *dl*-muscone (**54**),[28] as described in Scheme 19.

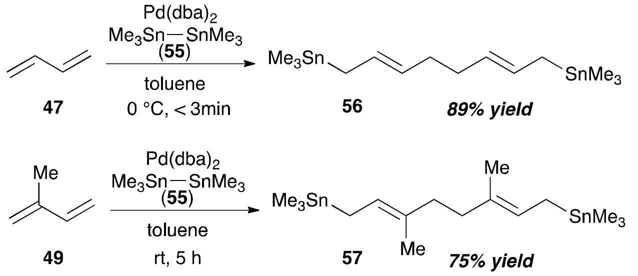


Scheme 18 Sakurai's disilylative dimerization of dienes (1984).



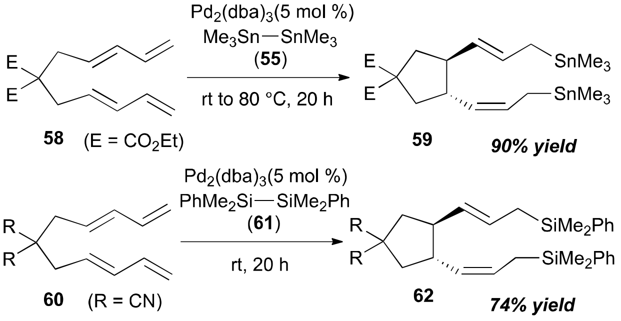
Scheme 19 Synthesis of *dl*-muscone **54** (Sakurai, 1984).

The Tsuji group investigated coupling reactions of 1,3-dienes with use of distannane and disilane reagents in the presence of a palladium catalyst (Scheme 20).[26] Employing hexamethyldistannane (**55**), 1,3-butadiene (**47**), and a catalytic amount of Pd(dba)$_2$, Tsuji and co-workers were able to prepare a single isomer of double-stannated dimer **56** in 89% yield. Under the same conditions, a reaction with isoprene (**49**) furnished the coupling product **57** (75% yield) in a highly regio- and stereoselective manner.

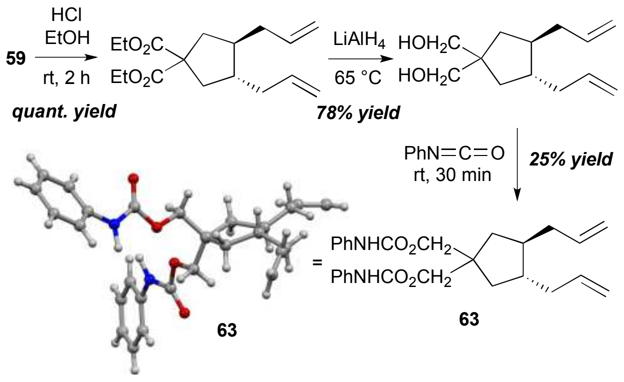


Scheme 20 Tsuji's intermolecular diene–diene coupling (1992).

Intramolecular coupling reactions of dienes were also surveyed by the Tsuji group (Scheme 21).[29] The Pd-catalyzed reaction of Me$_3$Sn–SnMe$_3$ (**55**) with ethoxycarbonyl-substituted bisdiene **58** afforded the cyclized/distannylated product **59** in 90% yield in a highly regio- and stereoselective manner. A disilane reagent, $Bu_3Si–SiBu_3$ (**61**), also promoted intramolecular coupling of cyanosubstituted bisdiene **60** to provide **62** in 74% yield with a catalytic amount of $Pd(dba)_2$. The stereochemistry of the alkenes of the product was confirmed by 2D heteronuclear multiple bond coherence (HMBC) spectra; the stereochemistry at the ring was determined by X-ray crystallography of urethane **63**, which was transformed from the product **59**. The X-ray structure (ORTEP drawing with 30% probability ellipsoids) and the derivatization details of diester **59** to diurethane **63** are described in Scheme 22.



Scheme 21 Tsuji's intramolecular diene–diene coupling (1995).

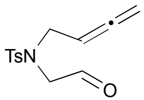
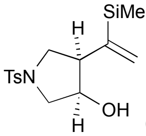
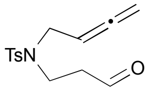
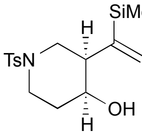
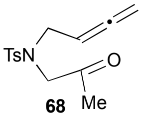
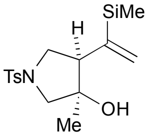
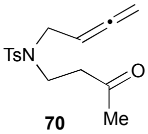
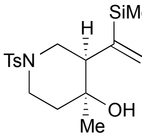


Scheme 22 Synthesis and crystal structure of **63** (Tsuji, 1995).

3.4. Coupling of Aldehyde–Allene and Ketone–Allene

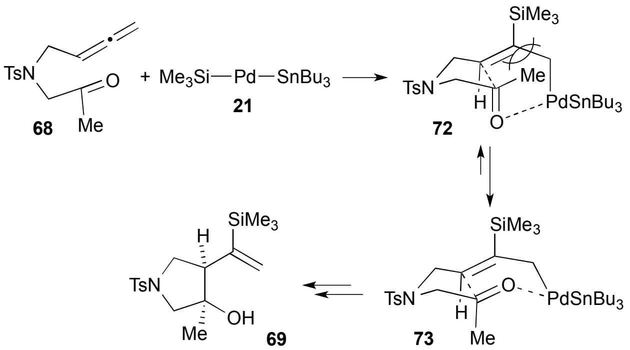
The Pd-catalyzed carbonyl–allene coupling reactions with a *Si–Sn* reagent were demonstrated by Kang *et al.* (Table 1).[30] Allene-aldehyde **64** efficiently underwent silastannylative coupling of multiple π components to produce *cis*-cyclopentanol **65** (71% yield), when it was treated with $Me_3Si–SnBu_3$ in the presence of $(\pi\text{-allyl})_2Pd_2Cl_2$ at ambient temperature (entry 1). This method was also effective for the preparation of cyclohexanol derivatives; allene aldehyde **66** was transformed into *cis*-cyclohexanol **67** under the same reaction conditions in 62% yield (entry 2). In addition to these aldehyde–allene couplings, they tackled more challenging tasks, ketones–allene couplings (entries 3 & 4). More sterically-hindered and less reactive allene ketones, **68** and **70**, smoothly cyclized to give the corresponding coupling products **69** and **71**, respectively, when they were reacted with 1.1 equivalents of $Me_3Si–SnBu_3$ (**17**) and 5 mol % of $(\pi\text{-allyl})_2Pd_2Cl_2$.

Table 1 Kang's intramolecular carbonyl–allene coupling (2002).[a]

Entry	Allene carbonyl	Product	Yield (%)
1	 **64**	 **65**	71
2	 **66**	 **67**	62
3	 **68**	 **69**	67
4	 **70**	 **71**	67

(a) Reaction conditions: 1.0 equiv. of allene carbonyls, 1.1 equiv. of $Me_3Si–SnBu_3$ (**17**), 5 mol % of $(\pi\text{-allyl})_2Pd_2Cl_2$, THF, room temperature, 10 min.

The presumed mechanism of this process is illustrated in Scheme 23. The *Si–Sn* reagent **17** will oxidatively add to the palladium catalyst to form $Me_3Si–Pd–SnBu_3$ (**21**); then, it will add to the allene moiety of **68** to give a palladium complex **73**, which is in a more stable conformation than **72**. Subsequently, the σ- or π-allyl Pd complex **73** would undergo intramolecular allylation to the carbonyl and reductive elimination to afford *cis*-cyclopentanol **69**. It is speculated that the stereochemistry of the reaction originated from the energy difference between intermediates **72** and **73**. In other words, the steric interference between the TMS and the methyl group may render intermediate **73** energetically more stable than **72**.



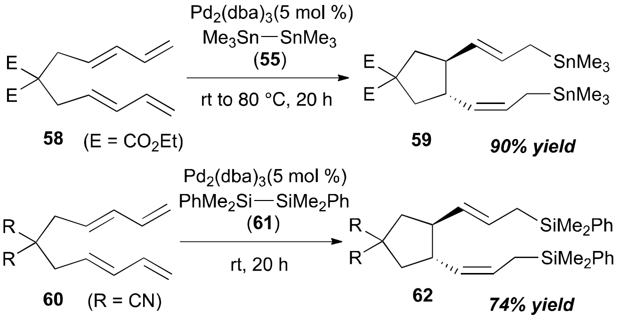
Scheme 23 Rationale for stereochemical outcome (Kang, 2002).

4. Pt-Catalyzed Bismetallative Multicomponent Coupling

Platinum (Pt) catalyzed bismetallative multicomponent reactions are relatively sparse, compared to those catalyzed by other group 10 transition metal complexes (Pd or Ni). The main contributors in this area are the Miyaura group who studied diene–diene coupling (section 4.1), and the Ito group for aldehyde–diene coupling reactions (section 4.2).

4.1. Coupling of Diene–Diene

Pt-catalyzed diborylative diene–diene coupling reactions were examined by Miyaura *et al.* (Scheme 24).[31] The reaction of isoprene (**49**) with bis(pinacolato)diboron (**74**) that is catalyzed by Pt(dba)$_2$ afforded a borylated dimer product **75** in 94% yield. The process shows high stereoselectivity as well as great regioselectivity; only the (*E*,*E*) isomer was observed in this reaction (eq. 1). This three-component coupling product was obtained as a major product only when Pt(dba)$_2$ was used as a catalyst. When Pt(PPh$_3$)$_4$ is employed as a catalyst in the same reaction, on the other hand, the 1:1 adduct of B$_2$(pin)$_2$ and diene (**76**) is formed exclusively (eq. 2).

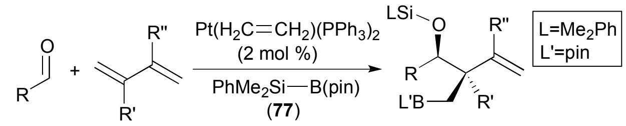


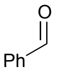
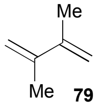
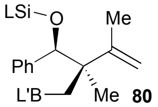
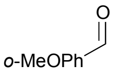
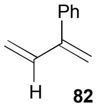
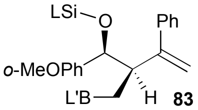
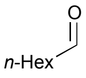
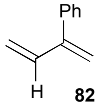
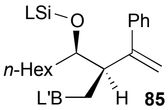
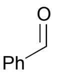
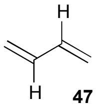
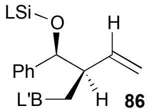
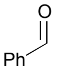
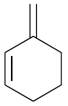
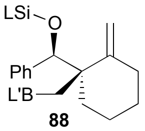
Scheme 24 Miyaura's intermolecular diene–diene coupling (1996).

4.2. Coupling of Aldehyde–Diene

Pt-catalyzed silaborative intermolecular aldehyde–diene coupling reactions were accomplished by the Ito group (Table 2).[32] It was observed that benzaldehyde (**78**), 2,3-dimethyl-1,3-butadiene (**79**), and silylborane **77** can be coupled in the presence of Pt(CH$_2$=CH$_2$)(PPh$_3$)$_2$ at 120 °C to give **80** in 85% yield (entry 1). An unsymmetrical diene, 2-phenyl-1,3-butadiene (**82**), can also be employed in this process to be coupled with both aromatic and aliphatic aldehydes (**81** and **84**) under similar reaction conditions to afford the coupling products **83** and **85** (entries 2 & 3). Also, this coupling reaction occurs under butadiene (**47**) atmosphere (1 atm) to give the correspondent product **86** in 63% yield with excellent stereoselectivity (entry 4). Notably, a cyclic diene **87** that is fixed in an *s-cis* conformation turned out to be an efficient coupling partner in this process to furnish **88** as a single diastereomer (entry 5).

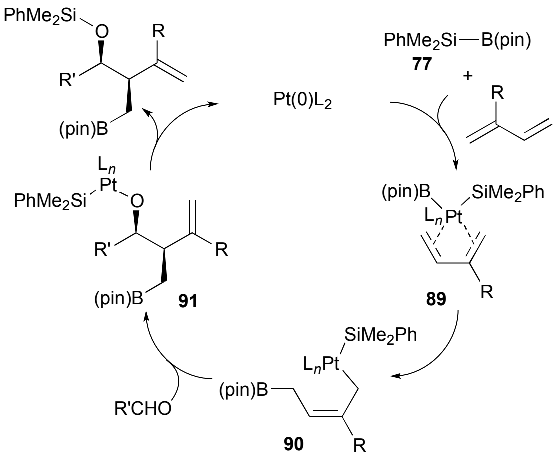
Table 2 Ito's intermolecular aldehyde–diene coupling (1998).[a]



Entry	Aldehyde	Diene	Product	Yield	d.r.
1	 **78**	 **79**	 **80**	85	96:4
2	 **81**	 **82**	 **83**	83	99:1
3	 **84**	 **82**	 **85**	71	93:7
4	 **78**	 **47**	 **86**	63	95:5
5	 **78**	 **87**	 **88**	60	99:1

(a) Reaction conditions: 2 mol % Pt(0), 1.5–3.0 equiv. aldehyde, hexane or octane, 80–120 °C.

The proposed mechanism for the Pt-catalyzed silaborative aldehyde–diene coupling reaction is illustrated in Scheme 25. The Si–B bond of **77** will be oxidatively added to the platinum(0) catalyst, and subsequent coordination of a diene will form a platinum(II) complex **89**. Then, insertion of the diene to the Pt–B bond can occur to give *cis*-crotylplatinum complex **90** forming a C–B bond at the terminal carbon of the less substituted alkene. Reaction of the platinum complex **90** with an aldehyde will form a C–C bond at the γ position to the Pt atom, which will generate an (alkoxy)(silyl)platinum(II) complex **91**. Finally, reductive elimination will afford the coupling product, in which a Si–O bond is present.

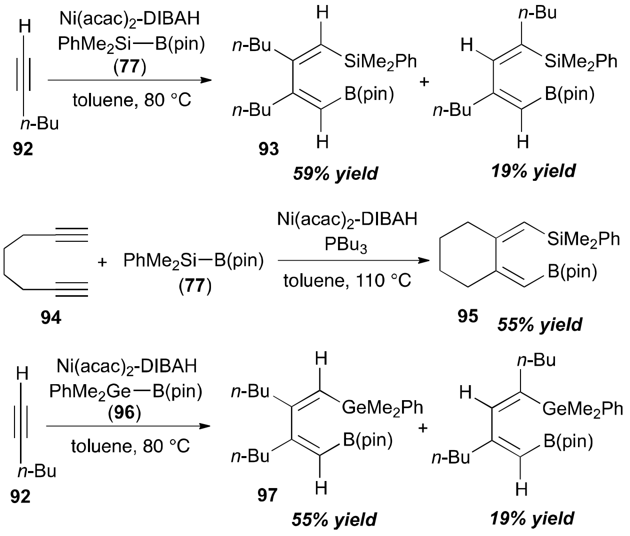


Scheme 25 Proposed mechanism for Pt-catalyzed coupling (Ito, 1998).

5. Ni-Catalyzed Bismetallative Multicomponent Coupling

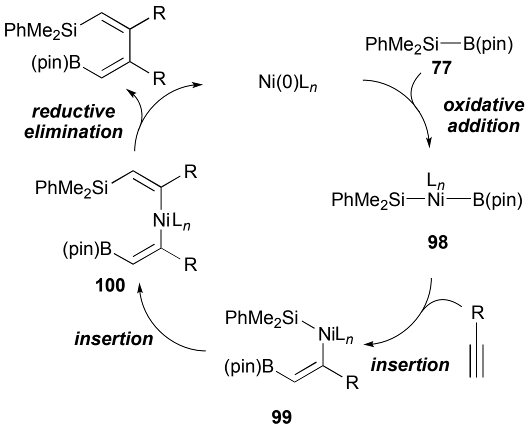
5.1. Coupling of Alkyne–Alkyne

The Ni-catalyzed bismetallative alkyne–alkyne coupling reactions was introduced by the Ito group.[33] It was demonstrated that a nickel(0) catalyst can couple two 1-hexyne (**92**) molecules with a *B–Si* reagent (**77**) in a regio- and stereoselective manner to provide **93** as a major product. This silaborative dimerization was applied to intramolecular cyclization of diyne (**94**) to afford **95** in 55% yield. The diyne dimerization with a germylborane (*Ge–B*) reagent **96** was also reported; a head-to-head dimer **97** was obtained as a major product.



Scheme 26 Ito's Ni-catalyzed alkyne dimerization (1998).

Based on the observed experimental results, they suggest the following catalytic cycle for a plausible mechanism for this process (Scheme 27). According to their speculation, an oxidative addition of the Si–B bond onto the Ni(0) complex generates the (silyl)(boryl)Ni(II) intermediate (**98**). Then, an alkyne undergoes *cis*-insertion into the B–Ni bond of the Ni(II) complex. The resulting vinyl-substituted nickel(II) intermediate (**99**) gets involved in another *cis*-insertion event to furnish **100**. Finally, reductive elimination would give the product.

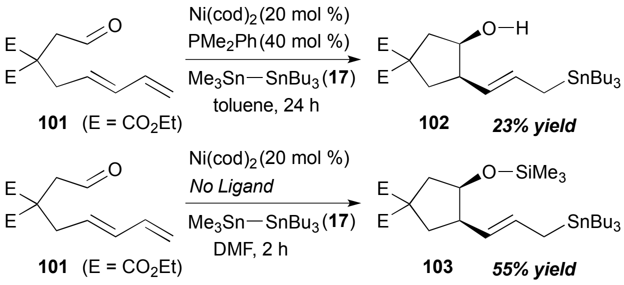


Scheme 27 Proposed mechanism for alkyne dimerization (Ito, 1998).

5.2. Coupling of Aldehyde–Diene

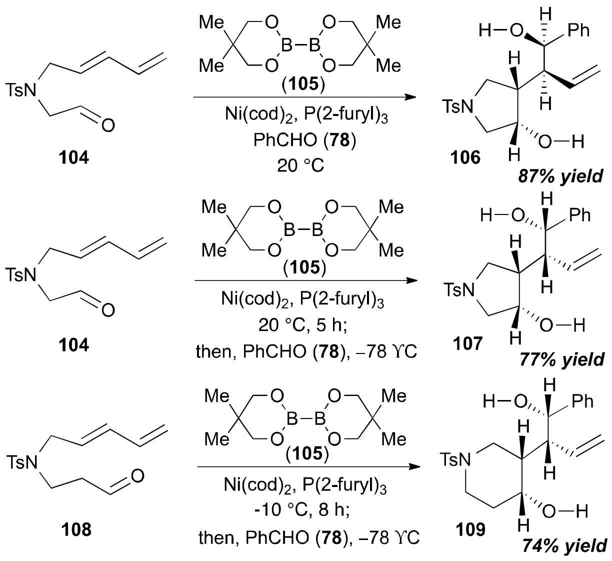
5.2.1. Intramolecular Aldehyde–Diene Coupling

The intramolecular coupling of a 1,3-diene and a tethered aldehyde was studied by the Mori group (Scheme 28).[34] With the use of Ni(cod)$_2$ and PMe$_2$Ph, a cyclic alcohol **102** (23% yield) was formed from a reaction of **101** and Bu$_3$Sn–SiMe$_3$ (**17**) in toluene. The product form of this process turned out to be sensitive to the ligands and solvents that are used in the reactions. The coupling reaction from the same starting material (**101**) with DMF as a solvent in the absence of any phosphine ligands afforded **103** as a sole product in 55% yield.



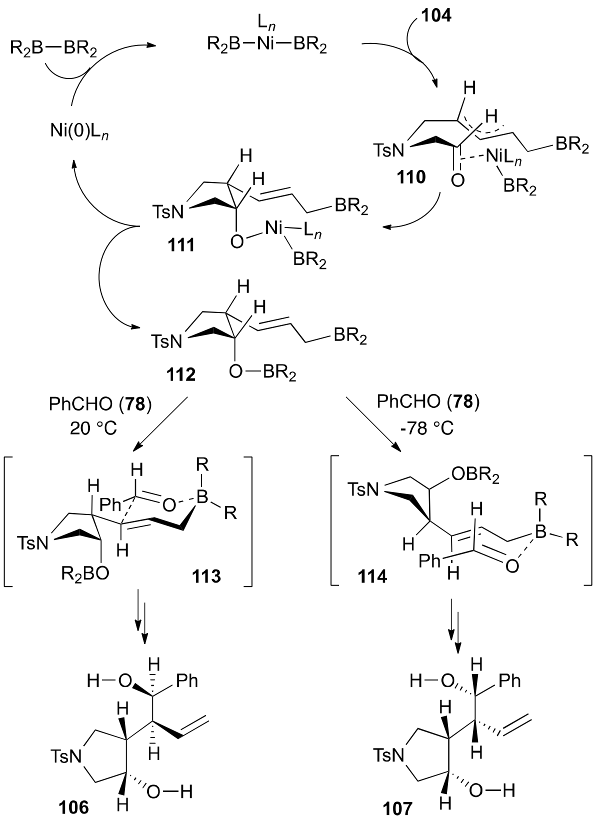
Scheme 28 Mori's intramolecular aldehyde–diene coupling (2002).

The Yu group examined sequential four-component coupling reactions (i.e. coupling of an aldehyde, a diene, and a diboron reagent followed by allylboration with another aldehyde) as shown in Scheme 29.[35, 36] The reaction of a diene-aldehyde **104**, benzaldehyde (**78**), and a diboron reagent **105** at 20 °C in the presence of Ni(cod)$_2$ and P(2-furyl)$_3$ afforded **106** in 87% yield. The unexpected stereochemical inversion of the product was observed at different reaction temperatures; when the subsequent allylation with benzaldehyde (**78**) was carried out at −78 °C (instead of at 20 °C), compound **107** was obtained as a single isomer. Additionally, a six-membered ring moiety (**109**) can be also prepared by this process from a diene-aldehyde **108**, benzaldehyde (**78**), and **105** in the presence of a nickel catalyst (74% yield). This method is particularly noteworthy given its efficiency for installing four contiguous stereogenic centers in a single operation.



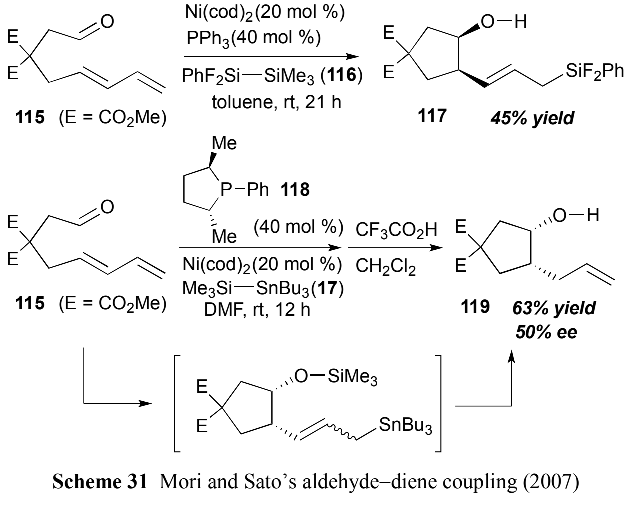
Scheme 29 Yu's sequential four-component coupling (2005).

The origin of the contrasting stereochemical outcomes, which vary depending on the temperatures, is speculated by the proposed pathways that are depicted in Scheme 30. The reaction begins with oxidative addition of the nickel catalyst to the diboron reagent. Then, diene insertion giving a π-allyl complex **110** and carbonyl insertion forming **111** would occur sequentially. After reductive elimination to give **112**, a subsequent intermolecular allylation with benzaldehyde (**78**) will furnish either **106** or **107** depending on the temperature for this step. The source of the stereochemical control is not revealed in this report, but subtle geometrical preferences of two intermediates **113** and **114** at two different temperatures are described in Scheme 30.



Scheme 30 Rationale for stereochemical outcome (Yu, 2005).

The Mori and Sato's laboratories investigated intramolecular disilylative and silastannylative coupling reactions of 1,3-diene and a tethered aldehyde (Scheme 31).[37] As for disilane reagents, it is known that halogenated disilane reagents tend to enhance the reactivity toward nickel catalysts.[38] Disilylative coupling of **115** and $PhF_2Si–SiMe_3$ (**116**) in the presence of 20 mol % of $Ni(cod)_2$ and 40 mol % of PPh_3 furnished **117** (45% yield) in a completely regio- and stereoselective manner. It is worth mentioning that catalytic enantioselective cyclizations were attempted in this study. With the use of $Ni(cod)_2$ and a chiral ligand **118**,[39] the reaction of **115** and $Me_3Si–SnBu_3$ (**17**) in DMF afforded **119** as a mixture of diastereomers.

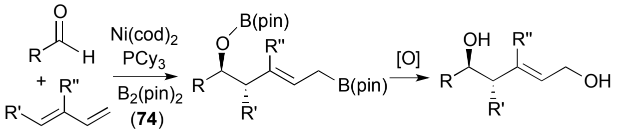


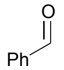
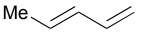
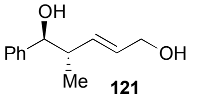
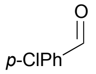
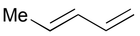
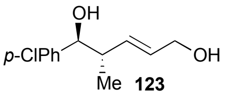
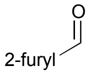
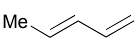
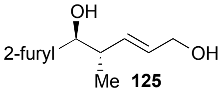
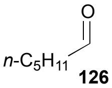
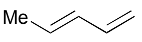
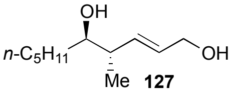
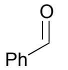
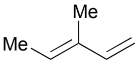
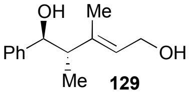
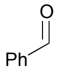
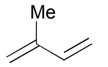
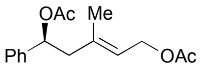
Scheme 31 Mori and Sato's aldehyde–diene coupling (2007)

5.2.2. Intermolecular Aldehyde–Diene Coupling

The intermolecular Ni-catalyzed diastereoselective bismetallative aldehyde–diene coupling reactions were demonstrated by the authors' laboratory.[8, 40] The coupling reactions of aldehydes, dienes, and $B_2(pin)_2$ (**74**) led to stereoselective formation of homoallylic boronic esters, which are synthetically valuable motifs (Table 3).[8] Various aromatic aldehydes (**78**, **122**, and **124**) are coupled a 1,3-diene **120** and $B_2(pin)_2$ (**74**) to give **121**, **123**, and **125**, respectively (entries 1–3); a reaction with an aliphatic aldehyde **126** affords **127** in a moderate yield (entry 4). Different diene substrates (**128** and **49**) also undergo the diboron-promoted three-component coupling reactions giving **129** and **130** under the same reaction conditions (entries 5–6). These reactions feature efficient preparatory methods for functionally and stereochemically enriched allylboronates.

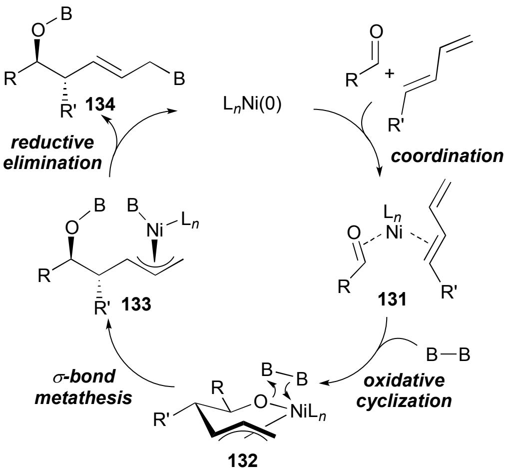
Table 3 Intermolecular aldehyde–diene coupling.[a]



Entry	Aldehyde	Diene	Product	Yield	d.r.
1	 **78**	 **120**	 **121**	66	>20:1
2	 **122**	 **123**	 **123**	63	>20:1
3	 **124**	 **120**	 **125**	63	>20:1
4	 **126**	 **120**	 **127**	47	>20:1
5	 **78**	 **128**	 **129**	70	>20:1
6[b]	 **78**	 **49**	 **130**	68	N/A

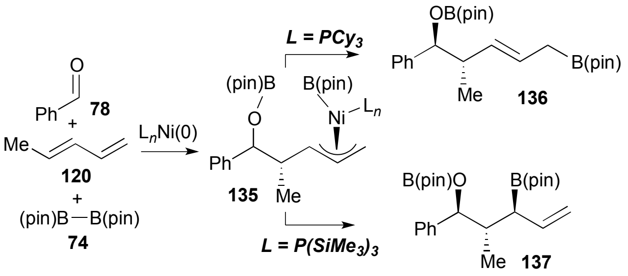
(a) Reaction conditions: 5 mol % $Ni(cod)_2$, 10 mol % PCy_3, 1.1 equiv. diene, 1.2 equiv. $B_2(pin)_2$, 0.2 M THF, rt, 6 h. Then, oxidation with H_2O_2 and NaOH. (b) Modified reaction conditions: 10 mol % $Ni(cod)_2$, 10 mol % $P(OEt)_3$. Acetylation improved the isolated yield.

Based on the mechanistic studies on these coupling reactions as well as relevant reductive coupling reactions, it was proposed the following catalytic cycle operates (Scheme 32). Initial oxidative cyclization will lead to the formation of nickelacyclic intermediate **132** from a nickel complex **131**. In the presence of diboron reagent, subsequent σ-bond metathesis will yield intermediate **133**. Then, reductive elimination will generate an allylic boronic ester **134** and restart the catalytic cycle.



Scheme 32 Proposed mechanism for borylative aldehyde-diene coupling.

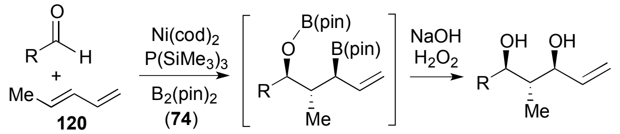
Surprisingly, the regioselectivity of the products in this process is reversed with the replacement of the ligand. In the presence of $P(SiMe_3)_3$ as a ligand, the nickel-catalyzed coupling of benzaldehyde (**78**), 1,3-pentadiene (**120**), and $B_2(pin)_2$ (**74**) afforded terminal boronate **137**, which is regioisomeric to the product **136** that comes from the reaction with PCy_3 (Scheme 33).[40] The ligand effect that is shown in this study is rationalized by unique characteristics of $P(SiMe_3)_3$. The electron accepting ability of $P(SiMe_3)_3$ was observed by both Bartik[41] and Helm.[42] It is plausible that the large cone angle of the ligand, together with its electron accepting property, would accelerate reductive elimination of **135** to form **137**, ahead of allyl isomerization that will lead to the formation of **136**.

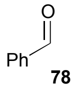
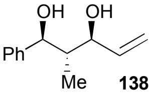
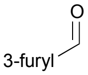
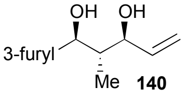
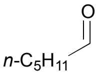
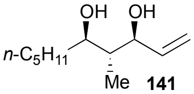
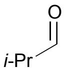
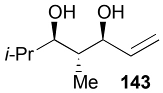
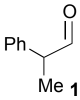
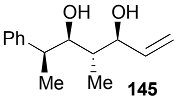


Scheme 33 Ligand effect on regioselectivity.

Using $P(SiMe_3)_3$ as a ligand, various aldehydes can be coupled with 1,3-pentadiene and $B_2(pin)_2$ (**74**) with excellent stereoselectivity by this process (Table 4). Generally, aromatic and heteroaromatic aldehydes (**78** and **139**) efficiently undergo the Ni-catalyzed coupling reactions with *trans*-piperylene (**120**) and $B_2(pin)_2$ (**74**) to provide **138** and **140** with great diastereoselectivities (entries 1–2). The coupling with aliphatic aldehydes (**126** and **142**) was also observed to be effective and afforded **141** and **143** under the same reaction conditions (entries 3–4). In addition, an α-chiral aldehyde (**144**) reacted with the Felkin selectivity to give **145** thereby revealing the potential for asymmetric synthesis (entry 5).

Table 4 Aldehyde–diene coupling for 1,3-diols.[a]

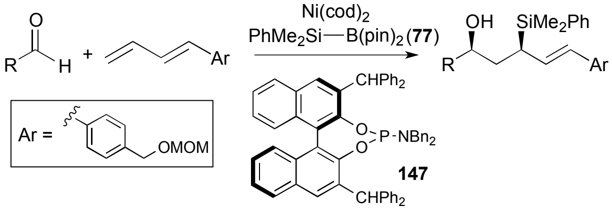


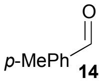
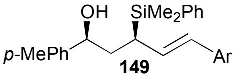
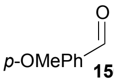
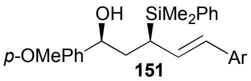
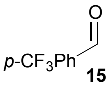
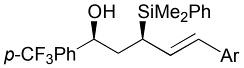
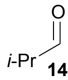
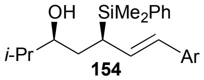
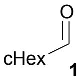
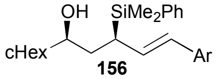
Entry	Aldehyde	Product	Yield	d.r.
1	 **78**	 **138**	67	>20:1
2	 **139**	 **140**	55	>20:1
3	 **126**	 **141**	58	>20:1
4	 **142**	 **143**	50	>20:1
5	 **144**	 **145**	49	6:1

(a) Reaction conditions: 10 mol % Ni(cod)$_2$, 15 mol % P(t-Bu)$_3$, 3.0 equiv. diene, 3.0 equiv. B$_2$(pin)$_2$ (**74**), 0.2 M THF, rt, 12 h. Then, oxidative workup with H$_2$O$_2$ and NaOH.

An outstanding accomplishment in this area was made by Saito and Sato in 2012; Ni-catalyzed enantio- and diastereoselective bismetallative aldehyde–diene couplings were demonstrated (Table 5).[43] A silylborane reagent, PhMe$_2$Si–B(pin) (**77**), was employed in this process along with 1,3-dienes and aldehydes in the presence of a nickel catalyst and a chiral phosphine ligand (**147**). Reactions with aldehydes that possess electron-donating groups (**148** and **150**) furnished the corresponding products (**149** and **151**) in good yields and with high enantioselectivities (entries 1–2). However, a reaction of an aldehyde with an electron-withdrawing group (**152**) exhibited a decreased yield (29% yield) giving **153**, even though the enantiopurity was still good (85% *ee*, entry 3). Aliphatic aldehydes (**142** and **155**) also participate in this process to give the corresponding products (**154** and **156**) with great enantioselectivities (entries 4–5). These reactions provide a new tool to prepare optically active α-chiral allylsilanes.

Table 5 Saito and Sato's enantioselective coupling reactions (2012).[a]

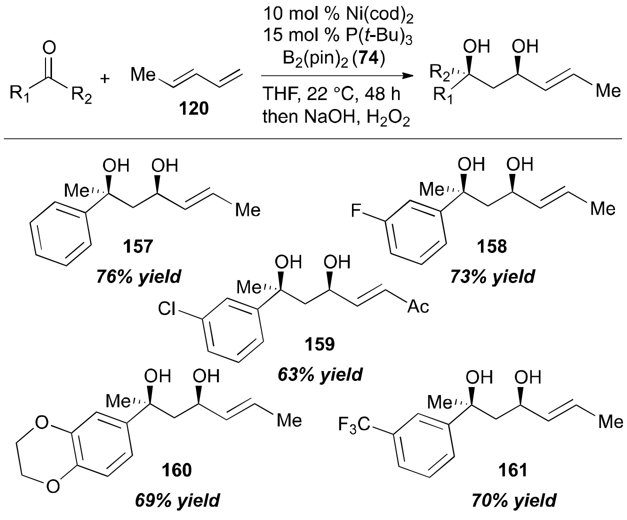


Entry	Aldehyde	Product	Yield	*ee*
1	 **148**	 **149**	89	96
2	 **150**	 **151**	92	92
3	 **152**	 **153**	29	85
4	 **142**	 **154**	68	96
5	 **155**	 **156**	74	94

(a) Reaction conditions: 10 mol % Ni(cod)$_2$, 10 mol % **147**, 1 equiv. diene, 2.5 equiv. aldehyde, 2.5 equiv. PhMe$_2$Si–B(pin) (**77**), DMF, room temperature.

5.3. Coupling of Ketone–Diene

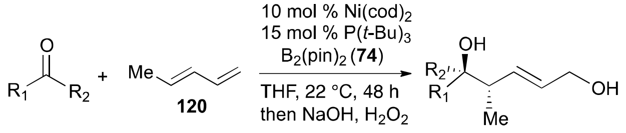
Ni-catalyzed ketone–diene diborylative coupling reactions have been reported by the authors' laboratory (Scheme 34).[44] The study has shown that ketones can participate in this process with high regio- and stereoselectivities to afford tertiary alcohols. Initial inquiry involved acetophenone, (E)-1,3-pentadiene (**120**), B$_2$(pin)$_2$ (**74**) with a nickel catalyst, which provided a tertiary alcohol **157** (76% yield) in a highly stereoselective fashion. As described in Scheme 34, halogenated aromatic methyl ketones are accommodated in this reaction (compounds **158**, **159**) as are the ketones with both electron-donating and electron-withdrawing substituents (compounds **160**, **161**). In all cases, excellent diastereoselectivity (> 20:1) was observed in the reaction products.

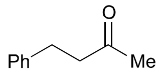
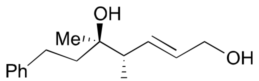
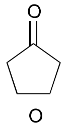
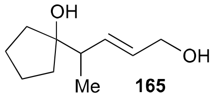
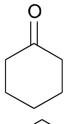
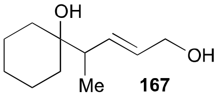
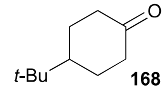
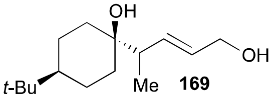


Scheme 34 Intermolecular ketone–diene coupling.

While reactions with aromatic methyl ketones furnish the 1,3-diols regioselectively, reactions of aliphatic ketones afford regioisomeric 1,5-diols (Table 6). For instance, the reaction with 4-phenyl-2-butanone (**162**) and 1,3-pentadiene gave the derived 1,5-diol **163** in 69% yield (entry 1). Also, constrained cyclic ketones (**164** and **166**) are found to undergo smooth coupling with the diene to afford 1,5-diols (**165** and **167**, entries 2–3). Notably, the coupling product **169** from **168** is acquired by preferred equatorial attack of the diene to the ketone electrophile (entry 4).

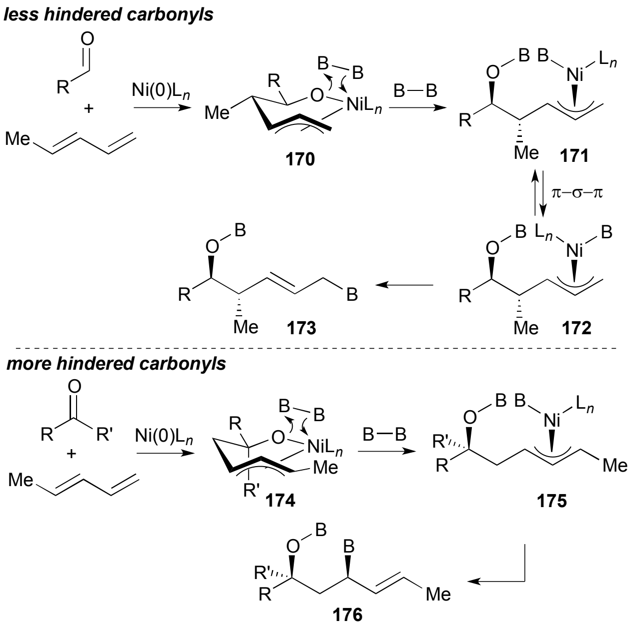
Table 6 Ketone–diene coupling for 1,5-diol synthesis.[a]



Entry	Ketone	Product	Yield	d.r.
1	 **162**	 **163**	69	7:1
2	 **164**	 **165**	56	N/A
3	 **166**	 **167**	52	N/A
4	 **168**	 **169**	53	>20:1

(a) Reaction conditions: 10 mol % Ni(cod)$_2$, 15 mol % P(t-Bu)$_3$, 2.0 equiv. diene, 2.0 equiv. B$_2$(pin)$_2$ (**74**), 0.2 M THF, rt, 48 h. Then, oxidative workup with H$_2$O$_2$ and NaOH.

Based on the observations from these ketone–diene reactions, along with the aldehyde–diene couplings (section 5.2.2.), it was suggested that following mechanistic operates (Scheme 35). With non-hindered carbonyls (i.e. substrates in Tables 3, 4, and 6), reaction will proceed to give nickelacycle **170**. Then, subsequent σ-bond metathesis would form π-allyl complex **171**. Prior to reductive elimination, this intermediate may undergo π-σ-π isomerization to give **172**, which would afford product **173**. However, in the case of more hindered carbonyls (i.e. substrates in Scheme 34), the less substituted end of the diene would add to the carbonyl giving **174** due to the steric effects. The 1,3-diol **176** is furnished by subsequent σ-bond metathesis with **174** and reductive elimination of **175**. In this case, the π-σ-π isomerization is likely impeded with the substituted π-allyl complex.



Scheme 35 Mechanistic rationale for borylative ketone-diene coupling.

6. Conclusions

Catalytic bismetallative coupling reactions involving multiple π-components are considered an effective method to build complex molecules. This one-step process features C–C bond formation, functionalization with bismetallic reagents, and the control of regio- and stereoselectivities.

The scope of this process in terms of both bismetallic reagents and the π-components are broad enough to be generally applied to more elaborate synthetic sequences. In particular, contemporary applications of the bismetallative multicomponent coupling reactions, in which high enantio- and/or diastereoselectivities are displayed, have enabled the study of this area to make a significant step forward.

Despite of these considerable improvements, there is still much room for further progress in this field. More detailed investigation of the reaction mechanisms and applications to the construction of biologically-active molecules will be of great interest. Additionally, development of catalytic enantioselective versions of many of these process is warranted as is extension of bis-metallative coupling to simple 2π-2π (i.e. alkene-carbonyl) systems.

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Notes and references

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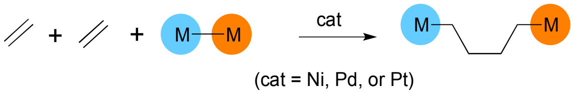

This review covers the bis-metallative coupling of unsaturated functional groups under the agency of transition metal catalysts.

Key Learning Points

(1) Mechanistic pathways for bismetallative coupling of multiple π-components.

(2) Stereochemical models for catalytic intra- and intermolecular bismetallative coupling reactions.

(3) Ligand effects in transition-metal-catalysed bismetallative coupling reactions.

(4) Bismetallative couplings can be a valuable tool for complexity-generating organic transformations.