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Document type: Article

Key Factors for High Diastereo- and Enantioselectivity of Umpolung Cyclizations of Aldehyde-Containing Allylpalladium Intermediates

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Received: June 5, 2019; Accepted: July 16, 2019; Web Released: July 24, 2019

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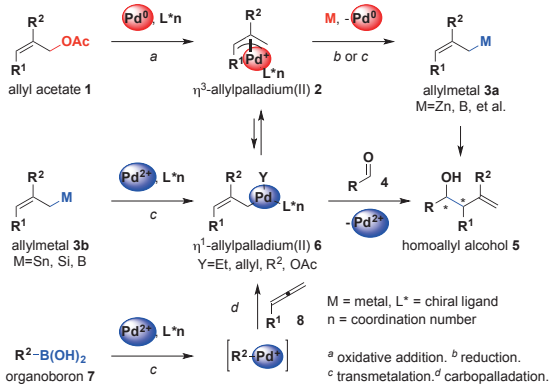
Abstract

Two palladium/chiral diphosphine-catalyzed umpolung cyclizations of aldehyde-containing allylic acetates and allenes with arylboronic acid are fully investigated to establish key factors in their high stereoselectivities. Both cyclization reactions afford *cis*-disubstituted pyrrolidine and tetrahydrofuran. These occur in high diastereo- and enantioselectivities through a common cationic (*Z*)-η^1-allylpalladium, toward which a ring strain generated in the cyclization step leading to *trans*-isomers biases the equilibrium through η^3-η^1-η^3-complex in the former cyclization. Varied diastereoselectivities were observed in the formation of five-membered carbocycles and six-membered heterocycles. These reflect release of a ring strain generated in the cyclization step leading to *trans*-isomers and a different distribution of the (*Z*)- and the (*E*)-η^1-allylpalladium intermediates generated by the oxidative addition of allylic acetates to Pd(0) or carbopalladation of allenes, respectively. A sterically demanding substituent at the center of the allyl moiety is necessary for high diastereo- and enantioselectivity. The enantioselectivity of the former cyclization was lowered by the presence of organometallic reductants or reagents, possibly causing the formation of neutral η^1-allylpalladium species. We used a chiral allylic acetate containing (*E*)-deuterium-labeled alkene to demonstrate that the electrophilic attack of the aldehyde to the allyl ligand occurred on the side where the palladium existed, consistent with the Zimmerman-Traxler transition state.

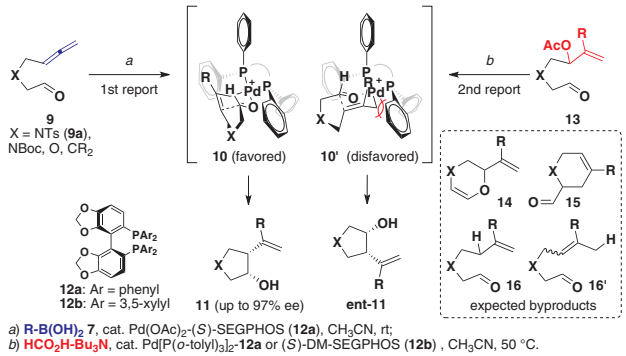
Keywords: Oxidative addition of allylic acetates | Carbopalladation of allenes | Umpolung cyclization

1. Introduction

The allylpalladium species is one of the most versatile intermediates in organic synthesis and it exists in equilibrium between η^3- and η^1-complexes **2** and **6** with electrophilic and nucleophilic properties, respectively (Scheme 1).[1,2] In combination with chiral ligands, both asymmetric allylation of nucleophiles[3] (Tsuji-Trost reaction) and electrophiles[4] are possible. η^3-Allylpalladium **2** is readily formed by oxidative



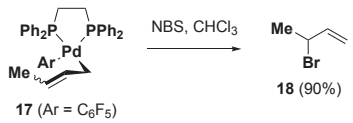
Scheme 1. Pd-catalyzed umpolung allylation of aldehydes leading to homoallyl alcohol **5** through allylmetal **3a** and η^1-allylpalladium **6**.



Scheme 2. SEGPHOS-ligated Pd-catalyzed cyclizations of allene **9** and allylic acetate **13** leading to **11**.

addition of allylic acetate **1** to Pd(0), and undergoes nucleophilic substitution to afford Tsuji-Trost reaction product and Pd(0), which enables the catalytic process.[1] The isomerization of η^3- to η^1-complex **6** and the subsequent electrophilic substitution can lead to the umpolung allylation. Its catalytic reaction, however, needs stoichiometric metallic reductants to convert the resulting Pd(II) into Pd(0).[2] The Et_2Zn- or Et_3B-mediated catalytic and asymmetric nucleophilic allylation of aldehyde **4** was pioneered by Zanoni,[4a] while Minnaard[4b] and Zhou[4c,4d] built upon the method and proposed that the organometallics function as reducing alkylating agents, forming η^1-allylpalladium **6** bearing an Et group and a chiral monophosphorus ligand. Previously, the asymmetric nucleophilic allylation was considered unfeasible because Tamaru assumed allyl-zinc and–borane **3a**, generated by transmetalation of η^3-allylpalladium **2** with Et_2Zn or Et_3B, were intermediates for the non-asymmetric variant.[2a] The transmetalation of Pd(II) with either allylmetal **3b**[5–10] or a combination of organoboron reagent **7** and allene **8**[11,12] is more suitable for the formation of η^1-allyl complex **6**, because a reducing agent is unnecessary for its catalytic nucleophilic allylation. However, a special ligand like bis(π-allyl),[5,6] PCP pincer,[7,8] or *N*-heterocyclic carbene[9,10] is necessary to generate η^1-allyl complex **6**, which is in equilibrium with **2**, but rarely detected. Nakamura and Yamamoto proposed η^1-allylpalladium **6** with a chiral π-allyl ligand as the intermediate in enantioselective imine allylations.[5] Consequently, any Pd-catalyzed umpolung allylations involve stoichiometric metallic reagents. Umpolung allylations not requiring metallic reagents are advantageous: neither the stoichiometric metallic byproducts nor multiple allylmetal species (leading to difficult chiral control) are generated.[13,14]

In contrast to the intermolecular asymmetric umpolung allylation of aldehyde and imine functionalities under palladium catalysis, the intramolecular variant remained undeveloped[15] until we reported.[12a,16] We expected that the umpolung cyclization would occur more readily because thermodynamically unstable η^1-allylpalladium is effectively captured by the adjacent electrophile and that the above special ligands are unnecessary. Firstly, we developed the arylative cyclization of allene-aldehyde **9** with arylboronic acid **7** under Pd(II) catalysis to afford the homoallylic alcohol **11** in high diastereo- and enantioselectivity (Scheme 2).[12a] We proposed the highly stereoselective reaction originates from the Zimmerman-Traxler transition state **10**[17–19] consisting of the aldehyde and



Scheme 3. Kurosawa's report on electrophilic addition of neutral (η^1-allyl)arylpalladium **17**.

cationic η^1-allylpalladium ligated with 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole (SEGPHOS, **12a**), a commercially available chiral diphosphine.[20] However, the η^1-allylpalladium derived from **9** can further react with **7**, to produce neutral (η^1-allyl)arylpalladium, reported by Kurosawa,[21] Szabo,[7] Minnaard,[4b] and Zhou[4d] as nucleophilic (Scheme 3). Secondly, to explore the participation of the aryl ligand in the cyclization, we developed the Pd(0)/SEGPHOS or the DM-SEGPHOS-catalyzed enantioselective cyclization of allylic acetate-aldehyde **13** with the aid of a formate reductant.[16] The successful cyclization proved that the two cyclization reactions proceed through the common cationic η^1-allylpalladium and that enantiodifferentiation happens in the aldehyde allylation instead of in the allylpalladium formation. Interestingly, neither Tsuji-Trost-type products **14**[22] and **15**[23] nor reduced products **16** and **16′** formed, although formate can reduce η^3-allylpalladium.[24] The latter cyclization is advantageous in: 1) there is no need for metallic reagents to generate the stoichiometric metallic byproducts and multiple allylmetal species; 2) it has the ability to introduce a wide variety of substituent R (other than aryl group) into the vinyl group of the products.

The two cyclization reactions proceed through a common intermediate but yield different stereoselectivities, in some cases. Although some related *cis*-selective cyclizations under transition metal catalysis exist, the reason for the diastereoselectivity remains unclear.[18,19,25] Herein, the two asymmetric umpolung cyclization reactions are investigated to establish the key factors responsible for the excellent stereoselectivity. In addition to preliminarily reported data,[12a,16] further experimental results are shown here to compare the effects of factors on the stereoselectivity.

2. Experimental

General Procedure for Umpolung Cyclization of Aldehyde-Containing Allylic Acetates (±)-13a·d–g·j and Carbonates (±)-13b·h·i (Table 1, Entry 1, Table 2, Entry 2 and Scheme 5). To a test tube containing a solution of **(±)-13a·b·d–j** (1.0 equiv) in anhydrous MeCN (0.05 M) were added Pd[P(*o*-tolyl)$_3$]$_2$ (10 mol%), (*S*)-SEGPHOS or (*S*)-DM-SEGPHOS (15 mol%), and reductant (HCO_2H-Bu_3N (3.0 equiv) for **13a·d–g·j** and HCO_2H (1.0 equiv) for **13b·h·i**) under argon. The resulting mixture was sealed with a screw cap and stirred at 50 °C. After starting material **13** was consumed, the mixture was concentrated *in vacuo*. The residue was purified by preparative TLC to afford **11a·d–j** and **11(f–j)′**. Enantiomeric excess of the products was determined by chiral HPLC. The relative configuration was determined by NOESY correlation. The absolute configurations were determined by modified Mosher's method[26] using its (*R*)- and (*S*)-MTPA esters, which were obtained by condensation of the products (DCC, DMAP and DCM) with (*R*)- and (*S*)-Mosher's acids, respectively.

General Procedure for Phenylative Cyclization of Allene-Aldehydes 9a·e–j with Phenylboronic Acid (Table 4, Entry 1 and Scheme 6). To a test tube containing a solution of **9a·e–j** (1.0 equiv) in anhydrous MeCN (0.1 M) were added $Pd(OAc)_2$ (10 mol%), (*S*)-SEGPHOS (10 mol%), and $PhB(OH)_2$ (1.5 equiv) under argon. The resulting mixture was sealed with a screw cap and stirred at 50 °C. After starting material **9** was consumed, the mixture was cooled down to room temperature and then treated with PS-DEAM MP resin™ (polymer-bound diethanolamine, 1.8 mmol/g, 3.0 equiv) and $CHCl_3$ to remove an excess of $PhB(OH)_2$. The mixture was agitated at room temperature for 2 h, then filtered, and washed with $CHCl_3$ thoroughly. The filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC to afford **11a·e–j** and **11(f–j)′**. Enantiomeric excess of the products was determined by chiral HPLC.

Phenylative Cyclization of Allene-Aldehyde 9a in THF by Gradual Addition of $PhB(OH)_2$ (Scheme 4). To a solution of **9a** (12.0 mg, 0.045 mmol) in anhydrous THF (0.1 M) were added $Pd(OAc)_2$ (1.0 mg, 4.5 µmol) and (*S*)-SEGPHOS (2.8 mg, 4.6 µmol) under argon. To the stirring solution was added 0.1 M $PhB(OH)_2$ (8.3 mg, 0.068 mmol) solution in anhydrous THF with a syringe pump over 2 h at 50 °C. The resulting mixture was stirred at the same temperature for another 5 h. The mixture was cooled down to room temperature and then treated with PS-DEAM MP resin™ (1.8 mmol/g, 3.0 equiv) and $CHCl_3$ to remove an excess of $PhB(OH)_2$. The mixture was agitated at room temperature for 2 h, then filtered, and washed with $CHCl_3$ thoroughly. The filtrate was concentrated *in vacuo* and the residue was purified by preparative TLC (50% EtOAc/hexane) to afford (3*S*, 4*S*)-**11a** (8.0 mg, 0.023 mmol, 52%, 95% ee).

Two-Step Conversion of 13l′ into 11k via 11l (Scheme 8). Reductive Cyclization of 13l′: To a test tube containing a solution of **13l′** (*E*:*Z* = 1:2.5, 8.4 mg, 0.023 mmol) in anhydrous MeCN (0.05 M) were added $Pd[P(o\text{-tolyl})_3]_2$ (1.7 mg, 2.4 µmol), (*S*)-DM-SEGPHOS (2.5 mg, 3.5 µmol), and HCO_2H-Bu_3N (2.6 µL–16.0 µL, 0.069 mmol) under argon. The resulting mixture was sealed with a screw cap and stirred at 50 °C for 1.5 h. Then the mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (20% EtOAc/toluene) to afford **11l** (4.4 mg, 0.015 mmol, 64%). Enantiomeric excess of **11l** (87% ee) was determined by chiral HPLC (Daicel Chiralpak AD-H, *i*-propanol/hexane = 10:90, 0.5 mL/min, λ = 254 nm): t_R(3*R*, 4*R*) = 33.0 min (minor enantiomer), t_R(3*S*, 4*S*) = 35.8 min (major enantiomer).

Reduction of Cl Group in 11l: To a test tube containing a solution of **11l** (15.9 mg, 0.053 mmol, 87% ee) in anhydrous DMA (0.2 mL) were added $PdCl_2(PhCN)_2$ (2.0 mg, 5.2 µmol), dppf (3.2 mg, 5.8 µmol), and HCO_2Na (5.4 mg, 0.079 mmol)[27] under argon. The resulting mixture was sealed with a screw cap and stirred at 80 °C for 10 h. The mixture was treated with water and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC (20% EtOAc/toluene) to afford the reduced product identical to (3*S*, 4*S*)-**11k** (13.1 mg, 0.049 mmol, 93%). Chiral HPLC of the product (87% ee) showed that optical purity of **11l** was retained during the reduction.

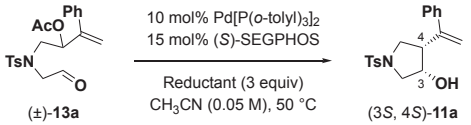
One-Pot, Two-Step Conversion of 13n′ into 11m via 11n (Scheme 9). To a test tube containing a solution of **13n′** (14.2 mg, 0.038 mmol) in anhydrous MeCN (0.05 M) were added $Pd[P(o\text{-tolyl})_3]_2$ (2.7 mg, 3.8 µmol), (*S*)-SEGPHOS (3.5 mg, 5.7 µmol), and HCO_2H-Bu_3N (4.3 µL–25.9 µL, 0.114 mmol) under argon. The resulting mixture was sealed with a screw cap and stirred at 50 °C for 24 h. The mixture was treated with PBu_3 (2.0 µL, 8.1 µmol) and HCO_2H-Bu_3N (2.9 µL–17.3 µL, 0.077 mmol). After being stirred at 50 °C for another 6 h, the mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (20% EtOAc/toluene) to afford **11m** (5.7 mg, 0.025 mmol, 66%). After conversion of **11m** (5.7 mg, 0.025 mmol) to 4-(prop-1-en-2-yl)-1-tosylpyrrolidin-3-ol (5.8 mg, 0.021 mmol, 82%) [1) TFA, CH_2Cl_2, 2) TsCl, Et_3N, CH_2Cl_2], enantiomeric excess of **11m** (94% ee) was determined by chiral HPLC.

Umpolung Cyclization of (+)-13u under Pd(0)-Dppe Catalysis (Scheme 14). To a solution of (*S*, *E*)-**13u** (20.8 mg, 0.084 mmol) in anhydrous MeCN (0.05 M) were added $Pd[P(o\text{-tolyl})_3]_2$ (6.0 mg, 8.4 µmol), dppe (5.0 mg, 13 µmol), and HCO_2H-Bu_3N (9.5 µL–59 µL, 0.25 mmol) under argon. The resulting mixture was sealed with a screw cap and stirred at 50 °C for 1 d. Then the mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (10% EtOAc/toluene) to afford (1*R**, 2*R**)-**11u** and (1*S**, 2*R**)-**11u′** (*dr* = 2:1, 24.9 mg, 0.072 mmol, 86%) as a faster- and slower-moving component, respectively. (1*R**, 2*R**)-**11u** was further purified by chiral HPLC (Daicel Chiralpak OD-H, *i*-propanol/hexane = 1:10, 0.5 mL/min, λ = 254 nm, recycled 3 times) to afford (1*S*, 2*S*)-**11u** (pseudo enantiomer) (t_R = 26.2 min) and (1*R*, 2*R*)-**11u** (t_R = 29.5 min). ^{1}H NMR analysis showed the respective inversion and retention of the alkene geometries in (1*S*, 2*S*)- and (1*R*, 2*R*)-**11u**. (1*S**, 2*R**)-**11u′** was further purified by chiral HPLC (Daicel Chiralpak AS-H, *i*-propanol/hexane = 1:10, 0.5 mL/min, λ = 254 nm, recycled 2 times) to afford (1*R*, 2*S*)-**11u′** (t_R = 10.1 min) and (1*S*, 2*R*)-**11u′** (pseudo enantiomer) (t_R = 11.5 min). ^{1}H NMR analysis showed the respective retention and inversion of the alkene geometries in (1*R*, 2*S*)- and (1*S*, 2*R*)-**11u′**.

3. Results and Discussion

Effect of Reductant on the Allylic Acetate-Aldehyde Cyclization. The effects of the reaction conditions on the stereoselectivity of the reductive cyclization of allylic acetate-aldehyde **13a** were investigated and data are presented in Table 1. As expected, the choice of the reductant crucially influenced the enantioselective cyclization. Hydride sources like formic acid in combination with tributylamine[28] (Entry 1) and triethylsilane (Entry 2) gave (3*S*, 4*S*)-**11a** in high yield with excellent diastereo- and enantioselectivity.[29] Interestingly, the reduction of acetate[24] to **16** or **16′** (Scheme 2) was absent under the reaction conditions. Meanwhile, organometallic reagents including Et_3B and Et_2Zn employed in the intermolecular variant[4] lowered the yield and the optical purity of **11a** (Entries 3 and 4). The use of THF as a solvent instead of acetonitrile allowed partial enantioselectivity recovery by the borane reagent, whereas that with zinc generated only a trace amount of the product (Entries 5 and 6). Additionally, the Et_2Zn failed to promote the cyclization reaction even under Minnaard's reaction conditions.[4b]

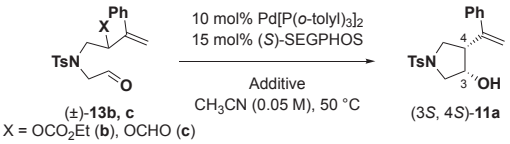
Table 1. Effects of the reductant on the enantioselectivity of allylic acetate-aldehyde cyclization.



Entry	Reductant	Solvent	Time (h)	Yield (%)	*Ee* (%)[a]
1[b]	HCO_2H-Bu_3N	CH_3CN	4	87	95
2	Et_3SiH	CH_3CN	6	78	94
3	Et_3B[c]	CH_3CN	72	41	49
4	Et_2Zn[d]	CH_3CN	36	11	79
5	Et_3B[c]	THF	72	43	83
6	Et_2Zn[d]	THF	36	trace	—

[a] Enantiomeric excess of *cis*-isomer **11a** was determined by chiral HPLC. [b] reported in ref. 16. [c] 5 equiv of Et_3B was used. [d] 3.5 equiv of Et_2Zn was used.

Table 2. Effects of the leaving group on the reductive cyclization.

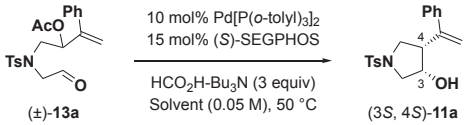


Entry	X	Additive	Time (h)	Yield (%)	*Ee* (%)[a]
1	OCO_2Et	HCO_2H-Bu_3N (3 equiv)	4	84	95
2[b]	OCO_2Et	HCO_2H (1 equiv)	7	70	90
3[b]	OCHO	None	72	54	91
4	OCHO	HCO_2H-Bu_3N (1 equiv)	17	66	93
5	OCHO	HCO_2H (1 equiv)	24	60[c]	91
6	OCHO	AcOH (1 equiv)	108	29[d]	nd[e]

[a] Enantiomeric excess of *cis*-isomer **11a** was determined by chiral HPLC. [b] reported in ref. 16. [c] (−)-*Trans*-isomer was also obtained in 15% yield. [d] (−)-*Trans*-isomer was also obtained in 3% yield. [e] nd = not determined.

Similar to acetate **13a**, carbonate **13b** underwent cyclization even without an amine, because of *in situ* basic alkoxide generation from the leaving group through decarboxylation[30] (Table 2, Entries 1 and 2). The slightly lower reaction rate and the product yield are attributed to the lower concentration of the reductant. Similarly, an *in situ* generated hydride from the leaving group of formate **13c** enabled omission of the external reductant, but seemed insufficient for the reaction rate (Entry 3).[24] The sluggish reaction was therefore accelerated using an external formate salt (Entry 4). These results highlight the necessity of a high concentration of the reductant for a rapid catalytic cycle. Although formic acid also promoted the reductive cyclization of carbonate **13b** and formate **13c**, the *trans*-diastereomer[18a,18b,19c] was also obtained as a minor product of the **13c** (Entries 2 vs. 5). Since acetic acid also lowered the diastereoselectivity (Entry 6), protic media hinders the cyclic transition state for high stereoselectivity.[18d] Variants of the reaction conditions enabled reductive cyclization of other substrates (*vide infra*).

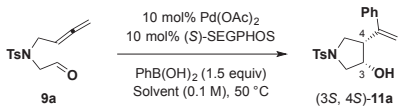
Table 3. Effects of the solvent on the enantioselectivity of allylic acetate-aldehyde cyclization.



Entry	Solvent	Time (h)	Yield (%)	*Dr* (*cis*:*trans*)[a]	*Ee* (%)[b]
1[c]	CH_3CN	4	87	>20:1	95
2	THF	3	71	>20:1	95
3	DMF	6	69	>20:1	95
4	DCM	1.5	83	19:1	95
5	MeOH	48	70	3.7:1	90

[a] Diastereomeric ratio was determined by ^{1}H NMR analysis of a mixture of diastereomers. [b] Enantiomeric excess of *cis*-isomer was determined by chiral HPLC. [c] reported in ref. 16.

Table 4. Effects of the solvent on the enantioselectivity of allene-aldehyde cyclization.

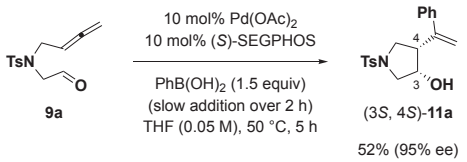


Entry	Solvent	Time (h)	Yield (%)	*Dr* (*cis*:*trans*)[a]	*Ee* (%)[b]
1[c]	CH_3CN	2	93	*cis* only	97
2	THF	2.5	81	18:1	77
3	DMF	5	84	>20:1	82
4	DCM	3	81	>20:1	86
5	MeOH	48	39	15:1	67

[a] Diastereomeric ratio was determined by ^{1}H NMR analysis of a mixture of diastereomers. [b] Enantiomeric excess of *cis*-isomer **11a** was determined by chiral HPLC. [c] reported in ref. 12a.

Comparison of Solvent Effect. Since the reaction conditions for the reductive cyclization were adapted to those for the arylative cyclization of allene-aldehydes,[12a] acetonitrile, the best solvent for the latter was chosen as the solvent. Although the enantioselectivity of the allylic acetate-aldehyde cyclization was unaffected by the aprotic solvent, that of allene-aldehyde cyclization was partially affected (Table 3 vs. Table 4). It is noteworthy that the protic media (i.e., methanol), again caused low diastereoselectivity particularly in the former cyclization (Table 3, Entry 5).

Excess organometallic reagent likely decreases enantioselectivity through the formation of neutral η^1-allylpalladium species like **17** in Scheme 3. The loss of enantioselectivity observed in the THF (Table 4, Entry 2) was dramatically suppressed by gradual addition of phenylboronic acid to maintain

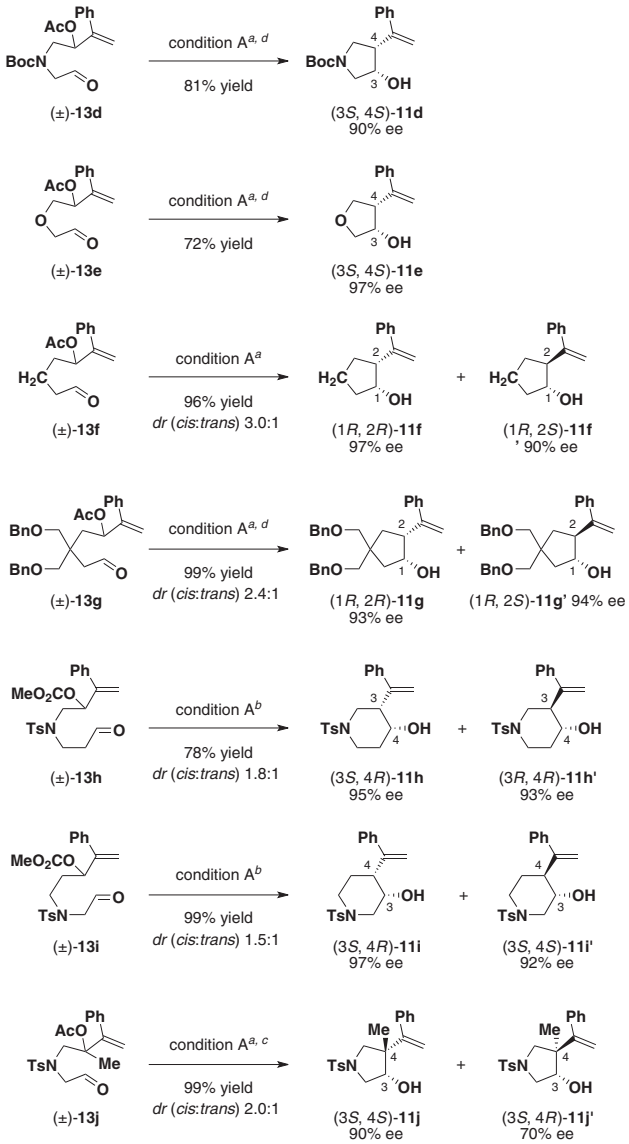


Scheme 4. Effects of gradual addition of $PhB(OH)_2$ on the enantioselectivity of the arylative cyclization of **9a**.

its low concentration (Scheme 4). The use of acetonitrile as a solvent prevents cationic η^1-allylpalladium intermediates from further transmetalation because of its high coordination ability to the palladium center.

Comparison of Diastereoselectivities. The best reaction conditions for the reductive cyclization of sulfonamide-tethered allylic acetate **13a** (Tables 1 and 3, Entry 1), converted Boc-protected nitrogen-tethered **13d** into **11d** in 53% yield and 90% ee (data not shown). We presumed reduced electrophilicity of the adjacent carbonyl group due to the weak electron-withdrawing carbamate, causing lower chemical yield. Gratifyingly, slightly modified conditions involving more σ-donating DM-SEGPHOS (**12b**) than SEGPHOS (**12a**) produced **11d** in much better yield, with retention of high enantioselectivity (Scheme 5). The σ-donating phosphines aid the allyl ligand to become nucleophilic rather than electrophilic. The DM-SEGPHOS ligand also served effectively for reductive cyclization of other substrates **13e–i** (Scheme 5). The oxygen-tethered substrate **13e** converted to *cis*-disubstituted tetrahydrofuran **11e** in high diastereo- and enantioselectivities. Unfortunately, the diastereomeric ratio of five-membered carbocycles **11f** and **11g**, and six-membered heterocycles **11h** and **11i** were *cis*/*trans* = 1.5:1–3.0:1, although diastereomers **11f–i** and **11(f–i)′** possess high optical purities. The modified Mosher's method[26] revealed the same absolute configuration for each pair of diastereomers at the α-position of the hydroxyl group, and the opposite stereochemistry substituted by the α-styryl group. It should be noted that the treatment of the acetate counterparts of **13h** and **13i** with formic acid and tributylamine accompanied the formation of side-products **19**[31] and **20**, respectively, which were derived from base-promoted β-elimination of sulfonamide followed by reduction of η^3-allylpalladium and Tsuji-Trost type reaction, respectively (Figure 1). The base-free conditions employed for the cyclization of the carbonate **13b** (Table 2, Entry 2) completely suppressed the side reactions and converted carbonates **13h** and **13i** into *cis*- and *trans*-products **11h–i** and **11h–i′**. Moreover, the cyclization of tertiary allylic acetate **13j** produced a 2:1 diastereomeric mixture of a quaternary carbon-containing pyrrolidine **11j** and **11j′** in 90% and 70% ee, respectively. The diastereoselectivity was significantly below that of secondary allylic acetate **13a** (Table 1, Entry 1).

These products are also obtained by the phenylative cyclization of allene-aldehydes **9e–i** (Scheme 6). Regardless of the tethered atom and the length in the substrates, the latter cyclization showed superior diastereoselectivity than the former, generating *cis*-disubstituted tetrahydrofuran **11e**, five-membered carbocycles **11f** and **11g**, and six-membered heterocycles **11h** and **11i**, exclusively or preferentially (Scheme 5 vs. 6). The two cyclizations showed comparably high enantioselectivities. In contrast, the phenylative cyclization of methyl-



condition A: 10 mol% Pd[P(*o*-tolyl)$_3$]$_2$, 15 mol% (*S*)-DM-SEGPHOS, reductant, CH_3CN (0.05 M), 50 °C. [a] reductant = 3 equiv HCO_2H–Bu_3N. [b] reductant = 1 equiv HCO_2H. [c] (*S*)-SEGPHOS was used as a ligand. [d] reported in ref. 16.

Scheme 5. The reductive cyclizations of aldehyde-containing allylic acetates **13d–g·j** and carbonates **13h·i**.

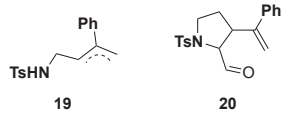
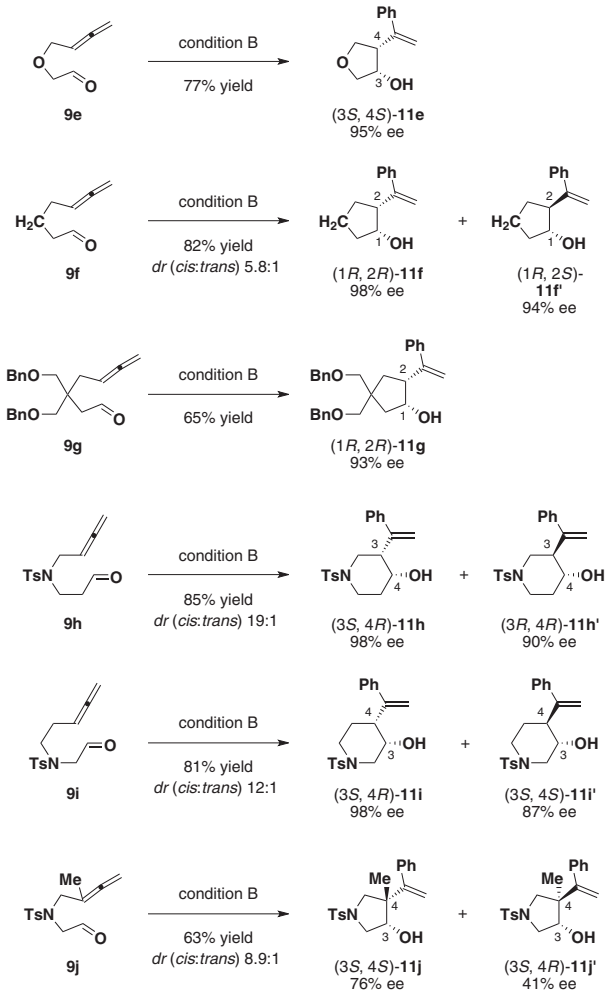


Figure 1. Side-products **19** and **20** obtained from the acetate counterparts of **13h** and **13i** under basic conditions.

substituted allene **9j** was more diastereoselective, but less enantioselective than the reductive equivalent of **13j** to yield common products **11j** and **11j′** containing a quaternary carbon.

Diastereoselectivities of the Reductive Cyclizations of Isomeric Primary Allylic Acetate-Aldehydes. Further experiments to understand the differences in the diastereoselectivities of two types of the cyclizations were still required, because the

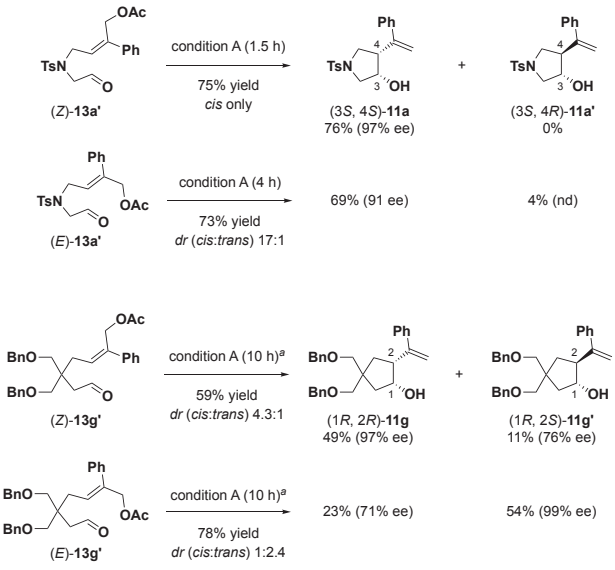


condition B: 10 mol% $Pd(OAc)_2$, 15 mol% (*S*)-SEGPHOS, 1.5 equiv $PhB(OH)_2$, CH_3CN (0.1 M), 50 °C.

Scheme 6. Highly diastereoselective phenylative cyclizations of allene-aldehydes **9e–j**.

use of secondary allylic acetates **13a** and **13g** renders the ratio of the *anti*- and *syn*-η^3-allylpalladium intermediates kinetically generated *in situ* obscure. The stereo-defined η^3-allylpalladiums were prepared predominantly from the (*Z*)- and the (*E*)-primary allylic acetates **13a′** and **13g′** (Scheme 7).[32] Interestingly, both of the nitrogen-tethered isomers (*Z*)- and (*E*)-**13a′** converted into *cis*-diastereomer **11a** exclusively or preferentially, although the latter substrate caused a slight decrease in the optical purity of **11a**. In contrast, the (*Z*)- and the (*E*)-allylic acetates **13g′** containing a carbon-tether also underwent cyclization to produce diastereomeric mixtures of **11g** and **11g′**, but with reverse selectivity, i.e., 4.3:1 and 1:2.4, respectively. It is noteworthy that minor diastereomers derived from primary allylic acetates **13g′** showed enantiomers of lower purity than those from secondary allylic acetate **13g** (Scheme 5).

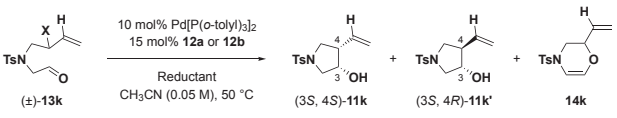
Substituent Effect on the Allylic Acetate-Aldehyde Cyclization. Since the arylative cyclization of allene-aldehydes accompanies the introduction of a sterically demanding aryl group into the allene central carbon,[12a] the steric effect of the substituent at the C-2 in the allylpalladium moiety on the



condition A: 10 mol% $Pd[P(o\text{-tolyl})_3]_2$, 15 mol% (*S*)-DM-SEGPHOS, 3 equiv HCO_2H–Bu_3N, CH_3CN (0.05 M), 50 °C. [a] reported in ref. 16.

Scheme 7. Reductive cyclizations of (*Z*)- and (*E*)-primary allylic acetates **13a′** and **13g′**.

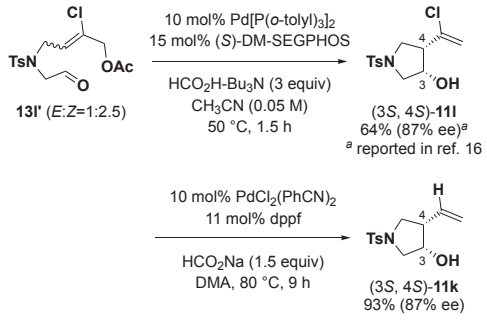
Table 5. Effect of the reaction conditions on the cyclization of allylic acetate- or carbonate-aldehydes.



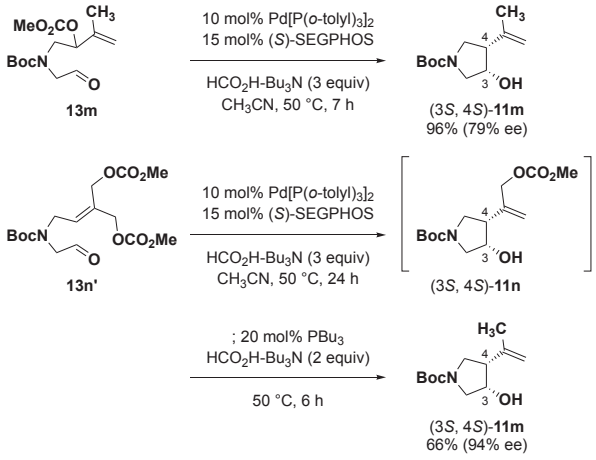
Entry	X	**12**	Reductant	Yield[a] of **11k**	Yield[a] of **11k′**
1[b]	OAc	**12a**	HCO_2H -Bu_3N (3 equiv)	26%, 66% ee	6%, 55% ee
2[b]	OAc	**12b**	HCO_2H -Bu_3N (3 equiv)	39%, 66% ee	7%, 55% ee
3	OCO_2Me	**12b**	HCO_2H (1 equiv)	68%, 65% ee	15%, 57% ee

[a] Enantiomeric excess of **11k** and **11k′** was determined by chiral HPLC. [b] **14k** was obtained in 40% and 37% yields in Entries 1 and 2, respectively.

diastereo- and enantioselectivities was unclear. In contrast to the phenyl-substituted substrate **13a**, the reaction of 2-unsubstituted allylic acetate **13k** (X = OAc) in the presence of tributylammonium formate produced Tsuji-Trost type *O*-allylation product **14k**[33] along with a diastereomeric mixture of cyclized products **11k** and **11k′** (Table 5, Entry 1). While the substitution of SEGPHOS (**12a**) with the σ-donating DM-SEGPHOS (**12b**) did not prevent the formation of side-product **14k** (Entry 2), the combination of the carbonate **13j** (X = OCO_2Me) and the formic acid caused suppression, generating **11k** and **11k′** in the highest combined yield (Entry 3). These results indicated that the presence of an amine promoted the formation of enolate, that is susceptible to electrophilic allylation with the less hindered η^3-allylpalladium. It is note-



Scheme 8. Alternative approach leading to **11k**.



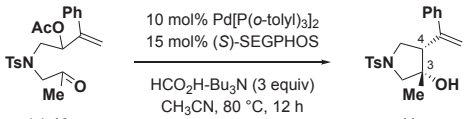
Scheme 9. Reductive cyclizations of **13m** and **13n′** producing **11m**.

worthy that the enantiomeric ratio of the *cis*-product **11k** was below that of the phenyl-substituted **11a** but was still good (*er* = ca. 4.7:1). The lower enantioselectivity reflects a lower difference in the activation energies of the Zimmerman-Traxler transition states **10** and **10′** (R = H) (Scheme 2).[34] Gratifyingly, the enantiomerically enriched product **11k** was obtained by the reduction of chloro-substituted **11l**,[27] which was prepared by the diastereo- and enantioselective cyclization of isomeric allylic acetate **13l′** (Scheme 8).[16]

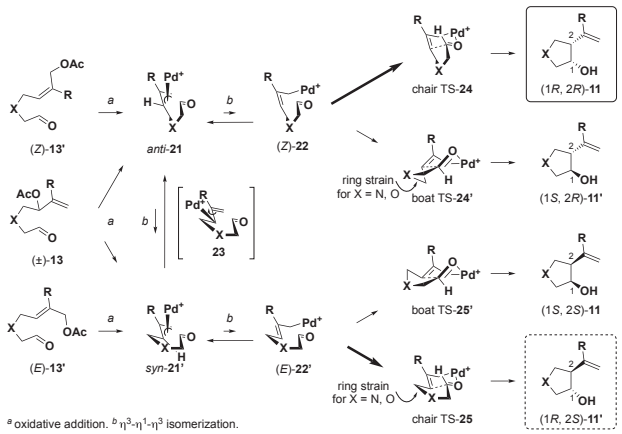
The methyl-substituted allylic carbonate **13m** also underwent reductive cyclization to yield 4-(1-methylethenyl)-pyrrolidin-3-ol derivative **11m**, but with low enantioselectivity (79% ee; Scheme 9, top). Instead, the use of di-carbonate **13n′** solved the problem and produced the **11m** in 94% ee after one-pot reduction of *in situ* generated mono-carbonate **11n** (Scheme 9, bottom). A (methoxycarbonyloxy)methyl group in **13n′** acted as a surrogate for the methyl group and improved the enantioselectivity in the cyclization step.

The substitution of an aldehyde with a methyl ketone also caused great loss in enantioselectivity (Scheme 10). This loss is ascribed to steric repulsion between the methyl group and pseudoequatorial phenyl group in the SEGPHOS ligand in transition state **10** shown in Scheme 2. This phenomenon is consistent with previous observations on the arylative cyclization of allene-ketone.[12a]

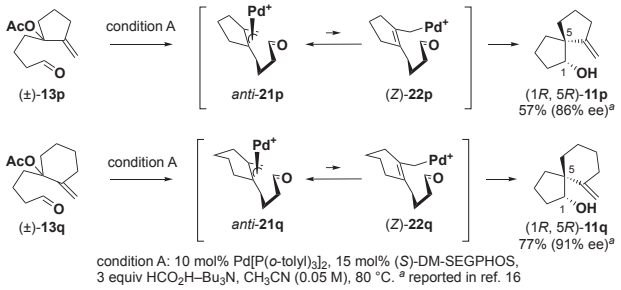
Plausible Mechanism of the Allylic Acetate-Aldehyde Cyclization. The diastereoselectivities observed in the reductive cyclization of allylic acetate-aldehydes (Schemes 5 and 7) provide clues to the generation and participation of allylpalladium intermediates in the cyclization (Scheme 11). Oxidative addition of allylic acetate (±)-**13** to Pd(0) produces *anti*- and *syn*-η^3-allylpalladiums **21** and **21′**, that are in equilibrium with the (*Z*)- and the (*E*)-η^1-allylpalladiums **22** and **22′**, respectively. A sterically demanding substituent R in the allylic moiety favors the *anti*-η^3-allylpalladium **21** over the *syn*-complex **21′** kinetically and thermodynamically through η^1-allylpalladium **23**.[35] Contrarily, S_N2- or S_N2'-type oxidative addition of the (*Z*)- and the (*E*)-allylic acetates **13′** to Pd(0) predominantly generates *anti*- and *syn*-η^3-allylpalladium **21** and **21′**, respectively.[32] Among the four six-membered transition states with R groups oriented toward the upper left to avoid a steric repulsion with the pseudoequatorial phenyl group in the (*S*)-SEGPHOS ligand (see Scheme 2), chair-like transition states **24** and **25** are much more favorable than boat-like **24′** and **25′**. The Zimmerman-Traxler transition states **24** and **25** generate (1*R*, 2*R*)- and (1*R*, 2*S*)-cyclopentanols **11** and **11′** (X = carbon), respectively, whereas minor transition states **25′** and **24′** provide counter enantiomers to reduce the optical purity of each diastereomer overall. Based on the experimental results on the formation of five-membered carbocycles **11g** and **11g′** (Schemes 5 and 7), the ratios of (1*R*, 2*R*)-**11g** to (1*S*, 2*R*)-**11g′** and those of (1*R*, 2*S*)-**11g′** to (1*S*, 2*S*)-**11g** are estimated at 99/1–97/3 and 94/6–92/8, respectively and reflect the degree of contribution of the transition states **24**/**24′** and **25**/**25′**. The relatively lower optical purities of the minor diastereomers *trans*-**11g′** and *cis*-**11g** prepared from the (*Z*)- and the (*E*)-allylic acetates **13g′** (Scheme 7) are attributed to partial participation of the boat transition states **24′** and **25′**. The reverse diastereoselectivity observed in the cyclizations of the (*Z*)- and



Scheme 10. Reductive cyclization of allylic acetate-methyl ketone **13o**.



Scheme 11. Plausible mechanism for the reductive cyclizations of **13** and (*Z*)- and (*E*)-**13′**.



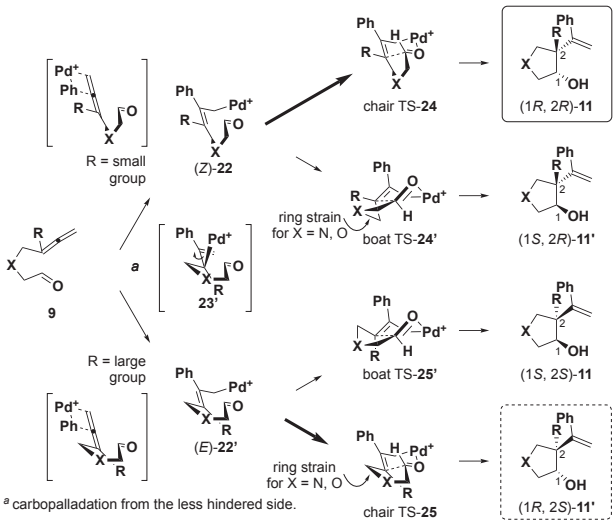
Scheme 12. Diastereoselective cyclizations of **13p** and **13q** leading to spiro compounds **11p** and **11q**.

the (*E*)-**13g′** indicates that the isomerization of each η^3-allylpalladium to a primary η^1-allylpalladium and the subsequent cyclization, are faster than the *syn*-*anti* isomerization through the secondary η^1-allylpalladium **23**. In addition to higher activation energies for transition states **25** and **25′**, S_N2'-type oxidative addition of (*Z*)- and (*E*)-allylic acetates **13g′**, which results in the direct formation of secondary η^1-allylpalladium **23** (an intermediate between **21** and **21′** formed via σ-bond rotation), may account for the incomplete diastereoselectivity observed with a different relative ratio (4.3:1 vs. 1:2.4, Scheme 7).

To support the interpretation above, cyclic allylic acetates **13p** and **13q** were employed as the substrates because of the provision of the geometrically fixed allyl complexes **21p·q** and **22p·q** (Scheme 12). Expectedly, the diastereoselective transformation of **13p** and **13q** into spiro compounds **11p** and **11q** was observed. The result demonstrates that the geometry of the η^3-allylpalladium intermediate considerably affects the diastereoselectivity of the reductive cyclization reaction.

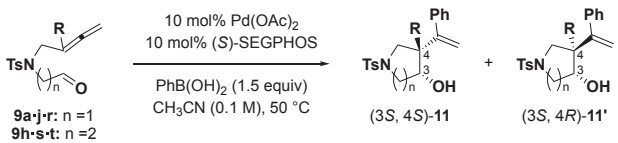
Meanwhile, the formation of five-membered heterocycles accompanies a ring strain in the *trans*-fused **25** and **24′.** This is explained by the shorter carbon-nitrogen and carbon-oxygen relative to carbon-carbon bonds, that raises the acitavation energy of **25** and **24′** and dramatically increases the ratio of the *cis*-**11** to *trans*-**11′** (Scheme 11). Again, the slight reduced optical purity of the *cis*-**11a** is attributed to participation of the boat transition state **25′** through the *syn*-η^3-allylpalladium **21′**, generated in higher quantities from (*E*)-allylic acetate **13a′** than the (*Z*)-isomer **13a′** (Scheme 7). As illustrated in Scheme 5, an elongation of the tether by a carbon releases the strain and increases the amount of the *trans*-adduct **11h′** and **11i′**. Low diastereoselectivity observed in the cyclization of tertiary allylic acetate **13j** (Scheme 5) indicates that the methyl substituent would block the isomerization between *anti*- and *syn*-η^3-allylpalladiums with a little difference in thermodynamic stabilities, which must be intermediated by tertiary η^1-allylpalladium **23′** (Scheme 13) formed unlikely.[32] In addition, a small R group (R = H, Me; Scheme 11) reduces thermodynamic stability of the *anti*-η^3-allylpalladium **21** and the difference in activation energies of the Zimmerman-Traxler transition states **10** and **10′** (Scheme 2) yielding lower diastereo- and enantioselectivity (Table 5, Entry 3).

Plausible Mechanism of the Allene-Aldehyde Cyclization. The arylative cyclization of allene-aldehyde **9** proceeds through (*Z*)-η^1-allylpalladium **22** (R = H, Me), that is kinetically



Scheme 13. Plausible mechanism for the phenylative cyclizations of **9**.

Table 6. Substituent effect on the stereoselectivity of allene-aldehyde cyclization.

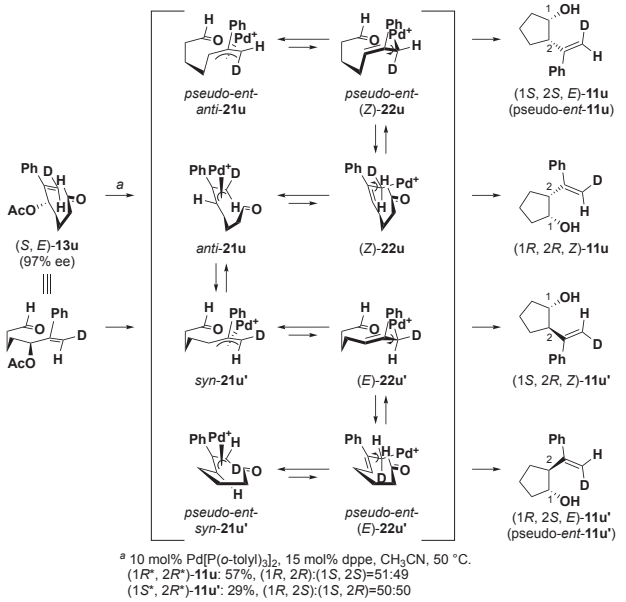


Entry	**9**	R	Yield (%)	*Dr* (*cis*:*trans*)[a]	*Ee* (*cis*)[b]	*Ee* (*trans*)[b]
1[c]	**9a**	H	93	*cis* only	97%	—
2	**9j**	Me	63	8.9:1	76%	41%
3	**9r**	*iso*-Bu	80	2.4:1	37%	22%
4	**9h**	H	85	19:1	98%	90%
5	**9s**	Me	78	9.0:1	80%	70%
6	**9t**	*iso*-Bu	59	2.9:1	71%	62%

[a] Diastereomeric ratio was determined by ^{1}H NMR analysis of a mixture of diastereomers. [b] Enantiomeric excess of **11** and **11′** was determined by chiral HPLC. [c] reported in ref. 12a.

formed by carbopalladation of the terminal double bond in **9** from the less hindered face (Scheme 13).[36,37] This retains the high *cis*-selectivity even during the formation of cyclopentanols **11f** and **11g**, six-membered heterocycles **11h** and **11i**, and pyrrolidine **11j** containing a tertiary carbon (Scheme 6).

The above reaction mechanism suggests that substitution by R larger than a methyl group in Scheme 13 renders the arylative cyclization of 1,1-disubstituted allenes less stereoselective. The isobutyl group in **9r** in fact caused a significant reduction in diastereo- and enantioselectivity (Table 6, Entries 1, 2 vs. 3). The low diastereoselectivity stems from the competitive carbopalladation producing (*E*)-η^1-allylpalladium **22′** (Scheme 13). In the case of the 1,1-disubstituted allene, the (*E*)-η^1-allylpalladium **22′** failed to undergo the isomerization into (*Z*)-η^1-allylpalladium **22**, because it proceeds through an unlikely tertiary η^1-allylpalladium **23′**.[32] Instead, the ring strain



Scheme 14. Reductive cyclization of deuterium-labeled chiral allylic acetate (*S*, *E*)-**13u** under Pd^0-dppe catalysis.

in the chair-TS **25** (X = NTs) relatively lowers the activation eneregies of boat TS-**25′** to generate (1*S*, 2*S*)-**11**, which accounts for the low enantioselectivity of *cis*-**11**. Although the reason for the *trans*-isomers **11j′** and **11r′** being much less enantiomerically enriched than *cis*-isomers **11j** and **11r** (Table 6, Entries 2 and 3) remains unclear, a disturbance in the chair TS-**25** caused by an alkyl group at the axial position rather than the boat TS-**24′** contributed. In contrast, the phenylative cyclization of the **9s** and **9t** homologues dramatically restored enantioselectivity and retained diastereoselectivity due to release of the ring strain in TS-**25** (Table 6, Entries 2 vs. 5, 3 vs. 6 and Scheme 13).

Facial Selectivity of the Reductive Allylation of Aldehyde. The Zimmerman-Traxler transition states involved in these cyclization reactions necessitate nucleophilic attacks of the allylpalladium intermediates to the intramolecular aldehyde from the side occupied by the palladium. To trace the facial selectivity, the chiral allylic acetate (*S*, *E*)-**13u** hosting (*E*)-deuterium-labeled alkene was utilized for cyclization under achiral diphosphine (dppe)-ligated palladium catalysis (Scheme 14). The oxidative addition of allylic acetate (*S*, *E*)-**13u** to Pd(0) provided a mixture of the *anti*-**21u** and the *syn*-**21u′** via a well-known inversion of the configuration.[38] The η^3-η^1 isomerization of the *anti*-**21u** and the *syn*-**21u′** produced (*Z*)- and (*E*)-η^1-allylpalladium **22u** and **22u′**, respectively, generating (1*R*, 2*R*)-**11u** and (1*S*, 2*R*)-**11u′** retaining the alkene geometry. In addition, the σ-bond rotations shown in Scheme 14 are faster than the cyclizations and cause the formation of pseudo-enantiomers of (1*S*, 2*S*)-**11u** and (1*R*, 2*S*)-**11u′** with inversion of the alkene geometry (fast epimerization is requisite for the asymmetric variant). In fact, each pseudo-diastereomer from the crude pseudo-racemic mixture was isolated by preparative TLC and separated by chiral HPLC to eventually produce four stereoisomers. The absolute configurations were determined by a modified Mosher's method[26] using MTPA esters of (1*R*, 2*R*)-**11f** and (1*R*, 2*S*)-**11f′** (Scheme 5), which were parent non-labeled counterparts of **11u** and **11u′**. ^{1}H NMR analysis of the isomers revealed that each pair of pseudo-enantiomers (1*R**, 2*R**)-**11u** and (1*R**, 2*S**)-**11u′** has the reverse alkene geometry. The distribution of these products was consistent with our prediction.

4. Conclusion

This study has uncovered the differences between two asymmetric umpolung cyclizations of aldehyde-containing allylpalladium intermediates generated *in situ* by the oxidative addition of allylic acetate and carbopalladation of allene. In the former cyclization, the use of organometallic reductants like Et_2Zn and Et_3B instead of formate and silane lowered the yield and the optical purity of products. The effects of solvent on the enantioselectivity were not observed in the former cyclization, but in the latter. The enantioselectivity lowered by THF for the latter cyclization was completely restored by gradual addition of phenylboronic acid. This again indicates that the presence of an excess organometallic reagent in the formation of a neutral (η^1-allyl)palladium complex causes loss of enantioselectivity. Although the cyclization reactions produced common *cis*-disubstituted five-membered heterocycles including pyrrolidine and tetrahydrofuran, in excellent yields with high diastereo- and enantioselectivity, different stereoselectivities were observed in the formation of five-membered carbocycles, six-membered heterocycles, and pyrrolidine containing a tertiary carbon. Comparison between nitrogen- or carbon-tethered primary (*Z*)- or (*E*)-allylic acetates **13a′** and **13g′**, which leads to geometrically defined η^3-allylpalladium, disclosed that the highly stereoselective formation of five-membered heterocycles in the former cyclization can be ascribed to a ring strain in the transition state to give *trans*-disubstituted one, and isomerization of (*E*)- to (*Z*)-η^1-allylpalladium through η^3-η^1-η^3-complex. The other different behaviors are attributed to the geometry of allylpalladium species; these behaviors depend on how the allylpalladium species is generated. The former cyclization commences with the oxidative addition of secondary allylic acetate to create geometrically obscure η^3-allylpalladium. The latter cyclization begins with carbopalladation of allene from the less hindered side, directly forming primary (*Z*)-η^1-allylpalladium. The stereochemistry of products provided useful information about allylpalladium intermediates which are difficult to isolate and characterize. The Zimmerman-Traxler transition state was supported by the chirality transfer reaction of the optically active allylic acetate with deuterium-labeled alkene. Further studies on another method that generates allylpalladium intermediates via allylic C-H activation are underway.

This work was partly supported by The Research Foundation for Pharmaceutical Sciences, SUNTORY FOUNDATION for LIFE SCIENCES, Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number JP18am0101095 and JP18am0101100, and JSPS KAKENHI Grant Numbers JP24590004 and JP15H05837 in Middle Molecular Strategy. The authors would like to thank Enago (www.enago.jp) for the English language review.

Supporting Information

Detailed experimental procedures, spectroscopic data, and copies of NMR spectra (PDF). This material is available on https://doi.org/10.1246/bcsj.20190167.

References

1 a) P. W. Jolly, *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 283. b) J. Tsuji, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. by E. Negishi, Wiley, New York, **2002**, Vol. 2, p. 1669. doi:10.1002/0471212466.ch70. c) L. Acemoglu, J. M. J. Williams, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. by E. Negishi, Wiley, New York, **2002**, Vol. 2, p. 1689. doi:10.1002/0471212466.ch71. d) G. Poli, G. Prestat, F. Liron, C. Kammerer-Pentier, *Top. Organomet. Chem.* **2012**, *38*, 1.

2 a) Y. Tamaru, *J. Organomet. Chem.* **1999**, *576*, 215. b) J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163. c) K. J. Szabó, *Chem.—Eur. J.* **2004**, *10*, 5268. d) Y. Yamamoto, I. Nakamura, *Top. Organomet. Chem.* **2005**, *14*, 211. e) H. C. Malinakova, *Lett. Org. Chem.* **2006**, *3*, 82. f) G. Zanoni, A. Pontiroli, A. Marchetti, G. Vidari, *Eur. J. Org. Chem.* **2007**, 3599. g) M. Jeganmohan, C.-H. Cheng, *Chem. Commun.* **2008**, 3101. h) K. Spielmann, G. Niel, R. M. de Figueiredo, J.-M. Campagne, *Chem. Soc. Rev.* **2018**, *47*, 1159.

3 a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395. b) B. M. Trost, D. R. Fandrick, *Aldrichimica Acta* **2007**, *40*, 59. c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921. d) B. M. Trost, M. L. Crawley, *Top. Organomet. Chem.* **2011**, *38*, 321. e) T. Hayashi, *J. Organomet. Chem.* **1999**, *576*, 195. f) T. Hayashi, *Acc. Chem. Res.* **2000**, *33*, 354.

4 a) G. Zanoni, S. Gladiali, A. Marchetti, P. Piccinini, I. Tredici, G. Vidari, *Angew. Chem., Int. Ed.* **2004**, *43*, 846. b) G. P. Howell, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2006**, *4*, 1278. c) S.-F. Zhu, Y. Yang, L.-X. Wang, B. Liu, Q.-L. Zhou, *Org. Lett.* **2005**, *7*, 2333. d) S.-F. Zhu, X.-C. Qiao, Y.-Z. Zhang, L.-X. Wang, Q.-L. Zhou, *Chem. Sci.* **2011**, *2*, 1135. e) X.-C. Qiao, S.-F. Zhu, W.-Q. Chen, Q.-L. Zhou, *Tetrahedron: Asymmetry* **2010**, *21*, 1216. f) T.-Z. Zhang, L.-X. Dai, X.-L. Hou, *Tetrahedron: Asymmetry* **2007**, *18*, 251. g) J.-J. Jiang, D. Wang, W.-F. Wang, Z.-L. Yuan, M.-X. Zhao, F.-J. Wang, M. Shi, *Tetrahedron: Asymmetry* **2010**, *21*, 2050.

5 a) K. Nakamura, H. Nakamura, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 2614. b) R. A. Fernandes, A. Stimac, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 14133. c) R. A. Fernandes, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 735. d) R. A. Fernandes, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 3562.

6 a) H. Nakamura, H. Iwama, Y. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 6641. b) H. Nakamura, M. Bao, Y. Yamamoto, *Angew. Chem., Int. Ed.* **2001**, *40*, 3208.

7 a) N. Solin, J. Kjellgren, K. J. Szabó, *J. Am. Chem. Soc.* **2004**, *126*, 7026. b) N. Solin, O. A. Wallner, K. J. Szabó, *Org. Lett.* **2005**, *7*, 689. c) O. A. Wallner, K. J. Szabó, *Chem.—Eur. J.* **2006**, *12*, 6976. d) J. Li, A. J. Minnaard, R. J. M. K. Gebbink, G. van Koten, *Tetrahedron Lett.* **2009**, *50*, 2232.

8 a) O. A. Wallner, V. J. Olsson, L. Eriksson, K. J. Szabó, *Inorg. Chim. Acta* **2006**, *359*, 1767. b) J. Aydin, K. S. Kumar, M. J. Sayah, O. A. Wallner, K. J. Szabó, *J. Org. Chem.* **2007**, *72*, 4689.

9 N. T. Barczak, R. E. Grote, E. R. Jarvo, *Organometallics* **2007**, *26*, 4863.

10 W. Wang, T. Zhang, M. Shi, *Organometallics* **2009**, *28*, 2640.

11 a) C. D. Hopkins, H. C. Malinakova, *Org. Lett.* **2004**, *6*, 2221. b) C. D. Hopkins, L. Guan, H. C. Malinakova, *J. Org. Chem.* **2005**, *70*, 6848. c) C. D. Hopkins, H. C. Malinakova, *Org. Lett.* **2006**, *8*, 5971. d) X. Yu, X. Lu, *Org. Lett.* **2009**, *11*, 4366. e) X. Yu, X. Lu, *J. Org. Chem.* **2011**, *76*, 6350.

12 a) H. Tsukamoto, T. Matsumoto, Y. Kondo, *Org. Lett.* **2008**, *10*, 1047. b) X. Zhang, X. Han, X. Liu, *Org. Lett.* **2015**, *17*, 3910.

13 Ru-catalyzed carbonyl allylation with carbon monoxide as reductant: a) Y. Tsuji, T. Mukai, T. Kondo, Y. Watanabe, *J. Organomet. Chem.* **1989**, *369*, C51. b) T. Kondo, H. Ono, N. Satake, T. Mitsudo, Y. Watanabe, *Organometallics* **1995**, *14*, 1945. c) S. E. Denmark, S. T. Nguyen, *Org. Lett.* **2009**, *11*, 781. d) C.-M. Yu, S. Lee, Y.-T. Hong, S.-K. Yoon, *Tetrahedron Lett.* **2004**, *45*, 6557.

14 Ir-catalyzed enantioselective intermolecular carbonyl allylation with isopropanol as a reductant: a) I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 6340. b) I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14891.

15 Bimetal-catalyzed non-asymmetric cyclization: a) B. M. Trost, K. D. Moeller, *Heterocycles* **1989**, *28*, 321. b) N. Maezaki, H. Fukuyama, S. Yagi, T. Tanaka, C. Iwata, *J. Chem. Soc., Chem. Commun.* **1994**, 1835. c) W. Oppolzer, F. Flachsmann, *Helv. Chim. Acta* **2001**, *84*, 416. d) V. C. Nguyen, Y.-T. Kim, Y.-K. Yu, H.-Y. Kang, *Bull. Korean Chem. Soc.* **2005**, *26*, 711. e) A. G. Campaña, B. Bazdi, N. Fuentes, R. Robles, J. M. Cuerva, J. E. Oltra, S. Porcel, A. M. Echavarren, *Angew. Chem., Int. Ed.* **2008**, *47*, 7515. f) A. Millán, A. G. Campaña, B. Bazdi, D. Miguel, L. Álvarez de Cienfuegos, A. M. Echavarren, J. M. Cuerva, *Chem.—Eur. J.* **2011**, *17*, 3985.

16 H. Tsukamoto, A. Kawase, T. Doi, *Chem. Commun.* **2015**, *51*, 8027.

17 a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207. b) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763.

18 Pd^0-catalyzed arylative cyclization with aryl iodides and distannane or In: a) S.-K. Kang, S.-W. Lee, J. Jung, Y. Lim, *J. Org. Chem.* **2002**, *67*, 4376. b) Y.-H. Ha, S.-K. Kang, *Org. Lett.* **2002**, *4*, 1143. See also silylative and stannylative cyclization: c) S.-K. Kang, Y.-H. Ha, B.-S. Ko, Y. Lim, J. Jung, *Angew. Chem., Int. Ed.* **2002**, *41*, 343. d) C.-M. Yu, J. Youn, M.-K. Lee, *Org. Lett.* **2005**, *7*, 3733. e) S.-K. Kang, Y.-T. Hong, J.-H. Lee, W.-Y. Kim, I. Lee, C.-M. Yu, *Org. Lett.* **2003**, *5*, 2813.

19 Ni^0-catalyzed alkylative cyclization with organozinc reagents: a) J. Montgomery, M. Song, *Org. Lett.* **2002**, *4*, 4009. b) M. Song, J. Montgomery, *Tetrahedron* **2005**, *61*, 11440. c) S.-K. Kang, S.-K. Yoon, *Chem. Commun.* **2002**, 2634.

20 H. Shimizu, I. Nagasaki, K. Matsumura, N. Sayo, T. Saito, *Acc. Chem. Res.* **2007**, *40*, 1385.

21 a) H. Kurosawa, A. Urabe, *Chem. Lett.* **1985**, 1839. b) H. Kurosawa, A. Urabe, K. Miki, N. Kasai, *Organometallics* **1986**, *5*, 2002.

22 J.-E. Bäckvall, J.-O. Vågberg, K. L. Granberg, *Tetrahedron Lett.* **1989**, *30*, 617.

23 a) Y. T. Han, N.-J. Kim, J.-W. Jung, H. Yun, S. Lee, Y.-G. Suh, *Arch. Pharmacal Res.* **2011**, *34*, 1437. b) J. Agarwal, C. Commandeur, M. Malacria, S. Thorimbert, *Tetrahedron* **2013**, *69*, 9398.

24 J. Tsuji, T. Mandai, *Synthesis* **1996**, 1.

25 Rh-catalyzed ones: a) X.-X. Guo, T. Sawano, T. Nishimura, T. Hayashi, *Tetrahedron: Asymmetry* **2010**, *21*, 1730. Ru-catalyzed one: b) ref 13d.

26 The absolute configurations of major enantiomers were

determined by Mosher's method. a) I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092. b) J. A. Dale, D. L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543. c) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512.

27 C. Zhang, X. Li, H. Sun, *Inorg. Chim. Acta* **2011**, *365*, 133.

28 a) N. A. Cortese, R. F. Heck, *J. Org. Chem.* **1978**, *43*, 3985. b) S. Cacchi, E. Morera, G. Ortar, *Tetrahedron Lett.* **1984**, *25*, 4821.

29 The lower catalyst loading (5 mol%) resulted in longer reaction time (12 h) and lower yield (76% of **11a**).

30 a) J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, *Tetrahedron Lett.* **1982**, *23*, 4809. b) J. Tsuji, I. Shimizu, I. Minami, Y. Ohashi, T. Sugiura, K. Takahashi, *J. Org. Chem.* **1985**, *50*, 1523. c) J. Tsuji, I. Minami, *Acc. Chem. Res.* **1987**, *20*, 140.

31 a) G. Kresze, U. Wagner, *Liebigs Ann. Chem.* **1972**, *762*, 93. b) C. Zhang, S.-Q. Zhang, H.-J. Cai, D.-M. Cui, *Beilstein J. Org. Chem.* **2013**, *9*, 1045.

32 M. Kawatsura, Y. Uozumi, M. Ogasawara, T. Hayashi, *Tetrahedron* **2000**, *56*, 2247.

33 a) F. Cambeiro, S. López, J. A. Varela, C. Saá, *Angew. Chem., Int. Ed.* **2014**, *53*, 5959. b) Y. Wang, W.-Y. Zhang, S.-L. You, *J. Am. Chem. Soc.* **2019**, *141*, 2228.

34 Even in case of R = H, a leaning toward the left and right in Zimmerman-Traxler transition states **10** and **10′**, respectively would favor **10**.

35 a) J. W. Faller, M. E. Thomsen, M. J. Mattina, *J. Am. Chem. Soc.* **1971**, *93*, 2642. b) J. W. Faller, M. T. Tully, K. J. Laffey, *J. Organomet. Chem.* **1972**, *37*, 193.

36 Regioselective carbopalladation of allenes usually produce C2-carbon-substituted π-allylpalladium(II): a) B. Cazes, *Pure Appl. Chem.* **1990**, *62*, 1867. b) S. Ma, *Pure Appl. Chem.* **2006**, *78*, 197. c) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701. d) R. W. Bates, V. Satcharoen, *Chem. Soc. Rev.* **2002**, *31*, 12. e) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067. f) G. Balme, E. Bossharth, N. Monteiro, *Eur. J. Org. Chem.* **2003**, 4101.

37 a) T. Bai, L. Xue, P. Xue, J. Zhu, H. H.-Y. Sung, S. Ma, I. D. Wiliams, Z. Lin, G. Jia, *Organometallics* **2008**, *27*, 2614. b) M. Yoshida, K. Matsuda, Y. Shoji, T. Gotou, M. Ihara, K. Shishido, *Org. Lett.* **2008**, *10*, 5183. c) T.-H. Huang, H.-M. Chang, M.-Y. Wu, C.-H. Chang, *J. Org. Chem.* **2002**, *67*, 99.

38 T. Hayashi, T. Hagihara, M. Konishi, M. Kumada, *J. Am. Chem. Soc.* **1983**, *105*, 7767.

