Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900450

Link to VoR: http://dx.doi.org/10.1002/adsc.201900450

10.1002/adsc.201900450

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Palladium-Catalyzed Umpolung Type-II Cyclization of Allylic Carbonate-Aldehydes Leading to 3-Methylenecycloalkanol Derivatives

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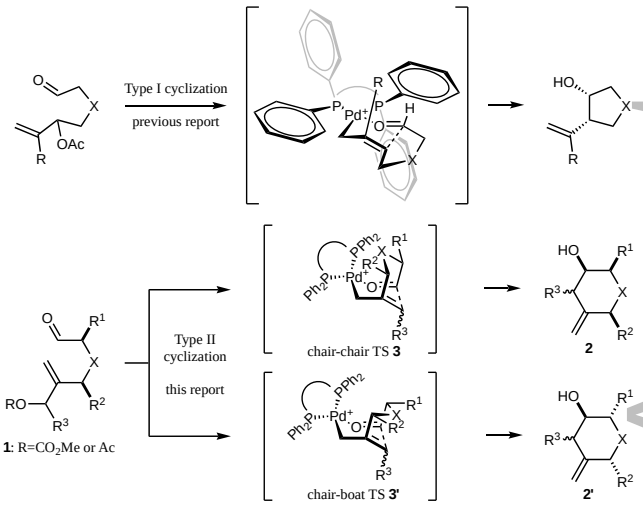
Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Palladium-catalyzed umpolung type-II cyclization of allylic carbonate-aldehydes leading to 3-methylenecycloalkanol derivatives was developed. The formate reductant was effective for the cyclization without causing a reduction of the η^3-allylpalladium intermediate. One-pot decarboxylative allylation of aldehyde-containing malonate with 2-[(acetyloxy)methyl]-2-propenyl methyl carbonate followed by the cyclization of the allyl acetate-aldehyde formed in situ was also achieved. The high diastereoselectivities observed in the cyclization of branched substrates indicates that a chair-chair transition state should be involved. Based on the presumed transition state, we could predict the enantioselectivity of the cyclization using SEGPHOS as a chiral diphosphine ligand and obtain optically active alcohols in up to 95:5 *er*.

Keywords: allylic carbonate; diastereoselectivity; enantioselectivity; one-pot; palladium; umpolung cyclization

An allylpalladium species usually generated by oxidative addition of an allylic acetate or carbonate to a palladium(0) catalyst is one of the most versatile intermediates in organic synthesis.[1] The allylpalladium exists in an equilibrium between an electrophilic η^3-complex and nucleophilic η^1-one which strongly biases toward the former. Therefore it is mainly utilized as an electrophile and an incorporation of chiral ligands enables the enantioselective allylation of various nucleophiles.[2] It is also possible to make use of the intermediate as a nucleophile,[3, 4] particularly in an intramolecular process, because the thermodynamically unstable η^1-complex is more effectively captured by an adjacent electrophile rather than external one. We have recently reported the palladium-catalyzed asymmetric umpolung type-I cyclization of allylic acetate-aldehydes using a combination of formate reductant[5] and commercially available chiral diphosphine ligands, i.e., SEGPHOS[6] or DM-SEGPHOS.[7, 8] In contrast to type-I metallo-carbonyl ene cyclization,[9] type-II one involving six-membered ring formation and its asymmetric variant has hardly been explored (Scheme 1).[10–14] Then, we direct our attention to the palladium-catalyzed umpolung type-II cyclization of allylic carbonate (or acetate)-aldehyde **1** to demonstrate the following three matters: 1) the reaction conditions to afford 3-methylenecyclohexanol derivatives **2** without causing both Tsuji-Trost reaction[15] and reduction of η^3-allylpalladium intermediate[16]; 2) diastereoselectivity to give important information about its uncertain transition state (chair-chair, chair-boat, etc.)[17–19]; 3) enantioselectivity, which has scarcely been achieved.



Scheme 1. Type-I and II Pallado-Carbonyl Ene Reactions

Prior to the development of the asymmetric cyclization, we ascertained whether the reaction conditions for the type-I cyclization using achiral diphosphine, i.e., 1,2-bis(diphenylphosphino)ethane (dppe), instead of SEGPHOS was applicable to the

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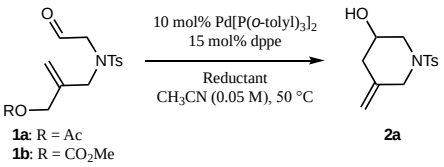
unexplored six-membered ring formation (Table 1). To our delight, the combination of formic acid and tributylamine also worked well for the cyclization of allylic acetate **1a** or carbonate **1b** tethered by *p*-toluenesulfonamide to afford **2a** in excellent yields (Entries 1 and 2). In the case of carbonate **1b**, the amine could be omitted owing to the basicity of the methoxide ion in situ formed from the leaving group (Entry 3).

Table 1. Effect of Leaving Groups and Reductant.

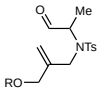
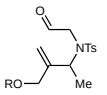
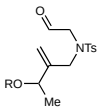
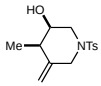
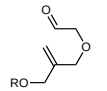
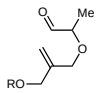
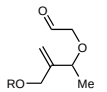
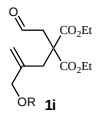
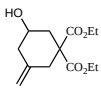
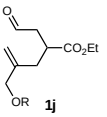
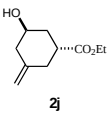
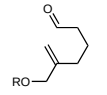
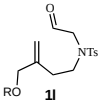
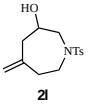
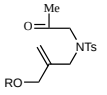
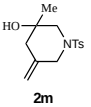
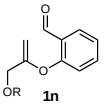
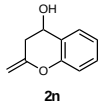
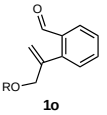
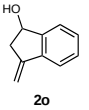


Entry	R	Reductant	Time (h)	Yield (%)[c]
1	Ac (**1a**)	HCO_2H-Bu_3N[a]	9	96
2	CO_2Me (**1b**)	HCO_2H-Bu_3N[a]	20	99
3	CO_2Me (**1b**)	HCO_2H[b]	8	84

[a] 3 equiv. [b] 1 equiv. [c] Isolated yield.

Next, substrate scope was explored (Table 2). Introduction of a methyl group at either α-position of *p*-toluenesulfonamide group led the exclusive formation of *trans*-adducts **2c** and **2d** (Table 2, Entries 1 and 2). As seen in the related compounds[20], NOESY spectra of these adducts with two *trans*-substituents at 5,6- and 2,5-positions showed that both of the substituents occupied pseudoaxial positions to prevent unfavorable gauche interactions between the methyl and *N*-tosyl groups (Figure 1). The reaction of secondary allylic carbonate **1e** resulted in the regio- and diastereoselective cyclization to give *cis*-adduct **2e** in high yield (Entry 3 and Figure 1). Oxygen-tethered substrates **1f–h** also underwent the reductive cyclization to give tetrahydro-5-methylene-2*H*-pyran-3-ols **2f–h** in excellent yields (Entries 4–6). Although the predominant formation of *cis*-substituted pyrans **2g** and **2h** seems to contrast with the stereoselectivity observed in the cyclization of sulfonamide-tethered substrates **1c** and **1d**, all of the hydroxyl groups are oriented in the common pseudoaxial positions in **2c**-**d** and **2g-h** to minimize the 1,3-diaxial interactions (Entries 1 vs. 5 and 2 vs. 6 and Figure 1).[21] In contrast to piperidin-3-ols **2c** and **2d**, *trans*-substituted pyrans **2g'** and **2h'** as minor diastereomers obtained from **1g** and **1h** adopted di-pseudoequatorial conformation (See Supporting Information).

Table 2. Substrate Scope[a]

Entry	Substrate[b]	Product	Temp	Time	Yield[c]
1	 **1c**	 **2c**	50 °C	14 h	73%[d]
2	 **1d**	 **2d**	50 °C	13 h	92%[d]
3	 **1e**	 **2e**	50 °C	8 h	77%[d]
4	 **1f**	 **2f**	50 °C	5 h	91%
5	 **1g**	 **2g**[e]	50 °C	10 h	71% (*dr* 10:1)
6	 **1h**	 **2h**[e]	50 °C	5 h	84% (*dr* 4:1)
7	 **1i**	 **2i**	80 °C	8 h	95%
8	 **1j**	 **2j**	80 °C	9 h	89%[d]
9	 **1k**	 **2k**	80 °C	12 h	45%
10	 **1l**	 **2l**	50 °C	30 h	78%
11	 **1m**	 **2m**	100 °C	9 h	59%
12	 **1n**	 **2n**	50 °C	9 h	65%
13	 **1o**	 **2o**	100 °C	20 h	40%

[a] 1 equiv HCO_2H was used as a reductant. [b] R = CO_2Me (entries 1–11 and 13) and R = CO_2Et (entry 12). [c] Isolated yield. [d] A single diastereomer was obtained. [e] Only major isomer is shown.

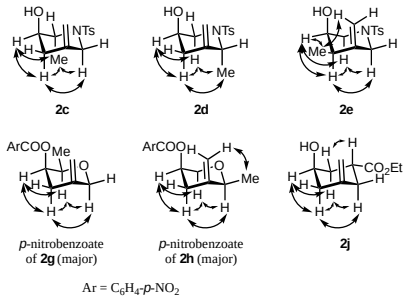
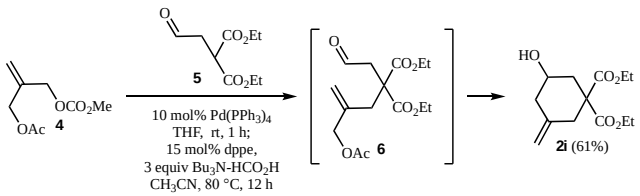


Figure 1. NOESY Correlations of **2c–e, j** and *p*-Nitrobenzoates of **2g** and **2h** (major isomer) and Their Conformations**.**

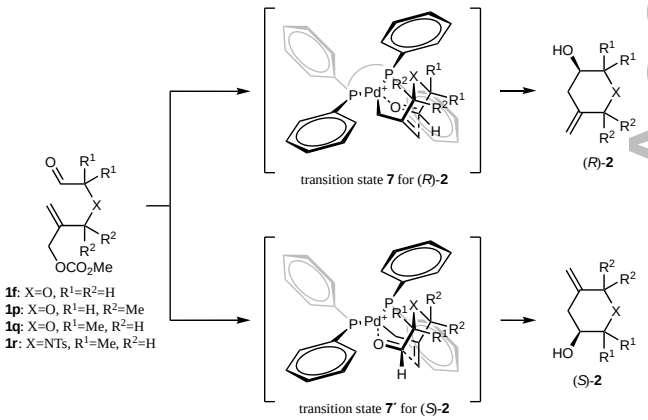
The cyclization of carbon-tethered ones **1i–k** required higher reaction temperature to complete conversion to give **2i–k** in moderate to excellent yields (Table 2, Entries 7–9). It is noteworthy that the product **2i** could also be obtained in good yield by one-pot sequence consisting of decarboxylative allylation of diethyl 2-oxoethylmalonate (**5**) with 2-[(acetyloxy) methyl]-2-propenyl methyl carbonate (**4**) under $Pd(PPh_3)_4$ catalysis in THF[22] followed by reductive cyclization of the allylic acetate-aldehyde intermediate **6** with the aid of diphosphine ligand and acetonitrile solvent (Scheme 2). The stereocenter in the tether carbon in **1j** induced perfect *trans*-diastereoselectivity leading to **2j** (Entry 8). These diastereoselectivities gave us information about the transition state as a hint for the asymmetric variant (vide infra). The reaction of homolog **1l** also proceeded well to give seven-membered ring **2l** in high yield (Entry 10).[23] Tertiary alcohol **2m** was obtained in moderate yield when ketone **1m** was heated at 100 °C under the similar reaction conditions (Entry 11).[24] The planar benzene tether in **1n** and **1o** seemed to cause lowering yields of six-membered heterocycle **2n** and five-membered carbocycle **2o** (Entries 12 and 13).



Scheme 2. One-Pot Reaction between **4** and **5** Leading to **2i.**

Based on the diastereoselectivity shown in Table 2, the cyclization would proceed through Zimmerman-Traxler chair-like transition state **3** (TS-**3**) where the other six-membered ring also exists in a chair conformation rather than a boat conformation (TS-**3'**) (Scheme 1). Except for toluenesulfonamide-tethered substrates **1c** and **1d**, the high diastereoselectivities can be rationalized by not only the methyl substituent in **1g** and **1h** but also the ethoxycarbonyl substituent in **1j** occupying pseudoequatorial positions in TS-**3** (Scheme 1 and Table 1, Entries 5, 6, and 8). In the case of **1c** and **1d**, the methyl substituent would be oriented in the pseudoaxial position of TS-**3** to avoid unfavorable gauche interactions between the methyl and *N*-tosyl groups. *Cis*-diastereoselective cyclization of **1e** should be derived from thermodynamically more stable *anti*-η^3-allypalladium.[25] Electron-withdrawing hetero atoms in the tether would increase the electrophilicity of the carbonyl groups by the inductive effect and accelerate the reaction. Rigid sp^2 aromatic ring in the tether moiety may cause the strain in the transition state leading to the low product yields.

Finally, we investigated the asymmetric type-II cyclization reaction with SEGPHOS ligand (Scheme 3 and Table 3). The reaction of oxygen-tethered substrate **1f** with (*S*)-SEGPHOS ligand instead of dppe led to the formation of **2f** in 70:30 *er* in favor of (*R*)-isomer (Table 3, Entry 1).[26] The moderate enantiomeric ratio of **2f** indicates that the activation energy of transition state **7** (TS-**7**) leading to (*R*)-**2** is slightly lower than that of TS-**7'** leading to (*S*)-**2** (Scheme 3). The difference in the activation energy between TS-**7** and **7'** can be enhanced by introduction of dialkyl groups at the allylic position as R^2, which generate more severe steric repulsion with the pseudoequatorial phenyl group on the right phosphorus atom in TS-**7'** rather than TS-**7**. As we expected, dimethyl-substituted substrate **1p** (R^1=H, R^2=Me) successfully underwent the enantioselective cyclization to afford (*R*)-**2p** in 95:5 *er* (Table 3, entry 2). On the other hand, the major enantiomer of the product was switched by shifting the position of geminal dimethyl groups to the α-position of carbonyl group in **1q** (R^1=Me, R^2=H) (Table 3, entry 3). The identical selectivity was also observed in the cyclization of sulfonamide-tethered substrate **1r** (Table 3, entry 4). The predominant formation of (*S*)-**2q** and (*S*)-**2r** should be ascribed to more severe steric repulsion between R^1 groups and the pseudo-equatorial phenyl group of SEGPHOS in TS-**7** rather than TS-**7'** (Scheme 3).



Scheme 3. (*S*)-SEGPHOS-Ligated Pd-Containing Transition States **7** and **7'** Leading to (*R*)- and (*S*)-**2**.

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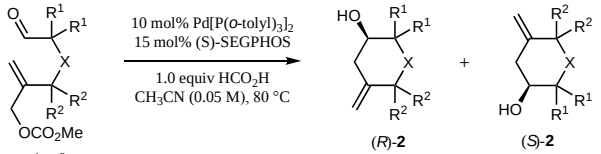
Table 3. Effect of Substituents on the Asymmetric Cyclization of **1f** and **1p–r**.



1f: X=O, R^1=R^2=H
1p: X=O, R^1=H, R^2=Me
1q: X=O, R^1=Me, R^2=H
1r: X=NTs, R^1=Me, R^2=H

Entry	**1**	**2**	Time (h)	Isolated yield (%)	*Er* (*R*):(*S*)[a]
1	**1f**	**2f**	19	49	70:30
2	**1p**	**2p**	8	83	95:5
3	**1q**	**2q**	72	74	27:73
4	**1r**	**2r**	36	60	12:88

[a] Enantiomeric ratio (*er*) was determined by chiral HPLC.

In summary, we developed palladium-catalyzed umpolung type-II cyclization of allylic carbonate-aldehydes leading to 3-methylenecycloalkanol derivatives. The high diastereoselectivities observed in the cyclization of branched substrates indicates that a chair-chair transition state should be involved. Based on the presumed transition state, we designed some substrates for its asymmetric variant using SEGPHOS as a chiral diphosphine ligand, which were converted into optically active alcohols in up to 95:5 *er*.

Experimental Section

General procedure for umpolung cyclization of allylic carbonate-carbonyls 1b–o (Table 1 and 2)

To a test tube containing a solution of **1b**–**o** (1.0 equiv) in anhydrous CH_3CN (0.05 M) were added $Pd[P(o\text{-tolyl})_3]_2$ (10 mol%), dppe (15 mol%) and HCO_2H (1.0 equiv) under argon. The resulting mixture was sealed with a screw cap and stirred at the temperature for the time described in Table 1 and 2. Then the mixture was concentrated *in vacuo*. The residue was purified by preparative TLC or silica gel chromatography to afford **2b–o**.

General procedure for one-pot Tsuji-Trost reaction and umpolung cyclization between 4 and 5 (Scheme 2)

To a test tube containing a solution of **4** (18.6 mg, 0.099 mmol) and **5** (20.0 mg, 0.099 mmol) in anhydrous THF (2.0 mL) was added $Pd(PPh_3)_4$ (11.5 mg, 0.010 mmol) under argon. The resulting mixture was sealed with a screw cap and stirred at room temperature for 1 h. To the mixture were added dppe (5.9 mg, 0.015 mmol), HCO_2H-Bu_3N (11.2 µL/ 70.5 µL, 0.30 mmol) and anhydrous CH_3CN (2.0 mL). The resulting mixture was stirred at 80 °C for 12 h and then treated with water. 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 silica gel chromatography (14% EtOAc/hexane) to afford **2i** (15.5 mg, 0.060 mmol, 61%).

General procedure for asymmetric umpolung cyclization of allylic carbonate-aldehydes 1f·p–r (Table 3)

To a test tube containing a solution of **1f·p–r** (1.0 equiv) in anhydrous CH_3CN (0.05 M) were added $Pd[P(o\text{-tolyl})_3]_2$ (10 mol%), (*S*)-SEGPHOS (15 mol%), and HCO_2H (1.0 equiv) under argon. The resulting mixture was sealed with a screw cap and stirred at 80 °C for the time described in Table 3. Then the mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography (11% Et_2O/hexane) for **2f·p·q** or preparative TLC (20% EtOAc/toluene, developed 2 times) for **2r** to afford **2f·p–r**. Except for **2r**, the enantiomeric ratio (*er*) of the products was determined by chiral HPLC after conversion of the products to their *p*-nitrobenzoates (*p*-NO_2BzCl, Et_3N, DMAP and DCM). The absolute configurations were determined by modified Mosher's method[27] using major and minor diastereomers of (*R*)-MTPA esters, which were obtained by condensation of the products (DCC, DMAP and DCM) with (*R*)-Mosher's acid and subsequent separation with preparative TLC. In the case of **2r**, the enantiomeric ratio was directly determined by chiral HPLC and the absolute configuration was determined by modified Mosher's method using major diastereomers of its (*R*)- and (*S*)-MTPA esters.

Acknowledgements

This work was partly supported by The Research Foundation for Pharmaceutical Sciences, SUNTRY 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.

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10.1002/adsc.201900450

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Palladium-Catalyzed Umpolung Type-II Cyclization of Allylic Carbonate-Aldehydes Leading to 3-Methylenecycloalkanol Derivatives

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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