京都大学学術情報リポジトリ
KURENAI 紅
Kyoto University Research Information Repository

京都大学
KYOTO UNIVERSITY

Title	Synthesis of Tetrahydrobiphenylene via Pd(0)-Catalyzed C(sp^2)-H Functionalization
Author(s)	Tsukano, Chihiro; Suetsugu, Satoshi; Muto, Nobusuke; Takemoto, Yoshiji
Citation	Chemical and Pharmaceutical Bulletin (2017), 85(12): 1167-1174
Issue Date	2017-12-01
URL	http://hdl.handle.net/2433/235954
Right	許諾条件に基づいて掲載しています。
Type	Journal Article
Textversion	publisher

Kyoto University

Regular Article

Highlighted Paper selected by Editor-in-Chief

Synthesis of Tetrahydrobiphenylene *via* Pd(0)-Catalyzed C(sp^2)–H Functionalization

Chihiro Tsukano,* Satoshi Suetsugu, Nobusuke Muto, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University; Yoshida, Sakyo-ku, Kyoto 606–8501, Japan.
Received September 12, 2017; accepted October 4, 2017

Tetrahydrobiphenylene consists of cyclobutene fused with benzene and cyclohexene rings. In this paper, a direct method for synthesizing tetrahydrobiphenylenes based on a palladium (Pd)(0)-catalyzed C(sp^2)–H functionalization was investigated. The developed method was applied to the synthesis of several tetrahydrobiphenylenes having an oxygen functionality at the ring juncture. The derivatization of a tetrahydrobiphenylene is also reported.

Key words C–H functionalization; tetrahydrobiphenylene; palladium

Biphenylenes, which have a structure consisting of a cyclobutadiene fused with two benzene rings (Chart 1), have been extensively studied to date.[1)] This class of compounds possesses an interesting aromaticity[2)] and the aryl–aryl C–C bond can be cleaved to give metallocyclic complexes.[3–5)] In contrast, the synthesis of partially hydrogenated biphenylenes, including tetrahydro- and hexahydrobiphenylenes has received little attention, despite these compounds showing interesting bioactivity. Caubère and colleagues have reported that di- and tetrahydrobiphenylenes showed cytotoxicity against human lymphoblasts and L1210 murine leukemia cell lines.[6–8)] For the synthesis of hexahydrobiphenylenes, a facial [2+2] cycloaddition of benzyne with an enamide[9)] and an enolate[10)] has been reported under strong base conditions (Chart 1). The resultant hexahydrobiphenylenes could be converted to tetrahydrobiphenylenes under dehydration conditions.[10,11)] Epoxidation of biphenylenes has also been reported for the synthesis of tetrahydro- and hexahydrobiphenylenes.[12)] However, these reported methods require harsh conditions and have only been applied to limited substrates. Additionally, there are no reports of direct methods to construct tetrahydrobiphenylenes. Thus, there is a need to improve the current synthetic methods for application to a wider range of substrates.

In recent decades, transition metal catalyzed C–H functionalization has been the focus of many groups as it can be used as a direct method for constructing molecules.[13–20)] Methods for the formation of benzocyclobutenes based on intramolecular C–H functionalization have been developed by the Catellani, Baudoin, Wolfe, and Martin groups.[21–27)] Recently, we have investigated Pd(0)-catalyzed benzylic C(sp^3)–H functionalization for the synthesis of various heterocycles and tetrahydro-*2H*-fluorenes.[28–41)] In the synthesis of oxindoles, C(sp^3)–H activation was favorable over competitive C(sp^2)–H activation because of the presence of the sp^2 nitrogen linkage[29)] (Chart 2a). In contrast, two methyl groups were required for the synthesis of tetrahydro-*2H*-fluorene through C(sp^3)–H activation in the presence of the sp^3 carbon linkage (Chart 2b).[39)] These results indicated that molecular flexibility is important for selectivity in this reaction. In this context, we attempted cyclization of a substrate having a C–H bond at the *ortho* position of the benzene ring, and observed the formation of tetrahydrobiphenylene through C(sp^2)–H activation (Chart 2c). This reaction is potentially a direct synthetic method for the synthesis of tetrahydrobiphenylenes. The resultant tetrahydrobiphenylene can be derivatized into various hexahydrobiphenylenes because it contains several functional groups, including an olefin and allyl alcohol. In this report, we describe the development of a new synthetic method for tetrahydrobiphenylenes and derivatives.

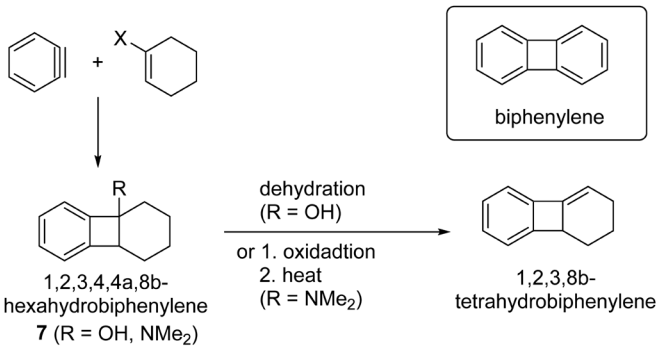


Chart 1. Reported Synthetic Method for 1,2,3,8*b*-Tetrahydrobiphenylene

Initially, we investigated the reaction conditions for the formation of tetrahydrobiphenylene **2a** from enol triflate **1a**.[42)] Treatment of **1a** with a catalytic amount of $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (1.1 equiv.), and PivOH (0.3 equiv.) in *N*,*N*-dimethylformamide (DMF) at 80°C gave tetrahydrobiphenylene **2a** in 75% yield along with dihydrobiphenylene **3a** (16%). The combination of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) resulted in a lower conversion rate and recovery of the starting material **1a** (Table 1, entries 1 and 2). We next examined several ligands for suppressing the formation of the byproduct **3a**. Use of an electron rich ligand, such as $(2\text{-furyl})_3P$, was not effective for suppression of the side reaction (entry 3). The reaction using bulky triaryl- and trialkyl-phosphine ligands, including $(o\text{-tolyl})_3P$, Ad_2PnBu, and $Cy_3P\cdot HBF_4$, hardly proceeded (entries 4–6), despite reports that bulky trialkylphosphine ligands were effective for C(sp^3)–H functionalization.[29)] Using 5 mol% of 1,1′-bis(diphenylphosphino)ferrocene (dppf), a bidentate ligand, resulted in poor conversion (entry 7). In sharp contrast, the reaction with 10 mol% of dppf proceeded smoothly to give the desired **2a**, suppressing the side reaction (entry 8). Dialkylbiarylphosphines, including

* To whom correspondence should be addressed. e-mail: tsukano@pharm.kyoto-u.ac.jp; takemoto@pharm.kyoto-u.ac.jp

© 2017 The Pharmaceutical Society of Japan

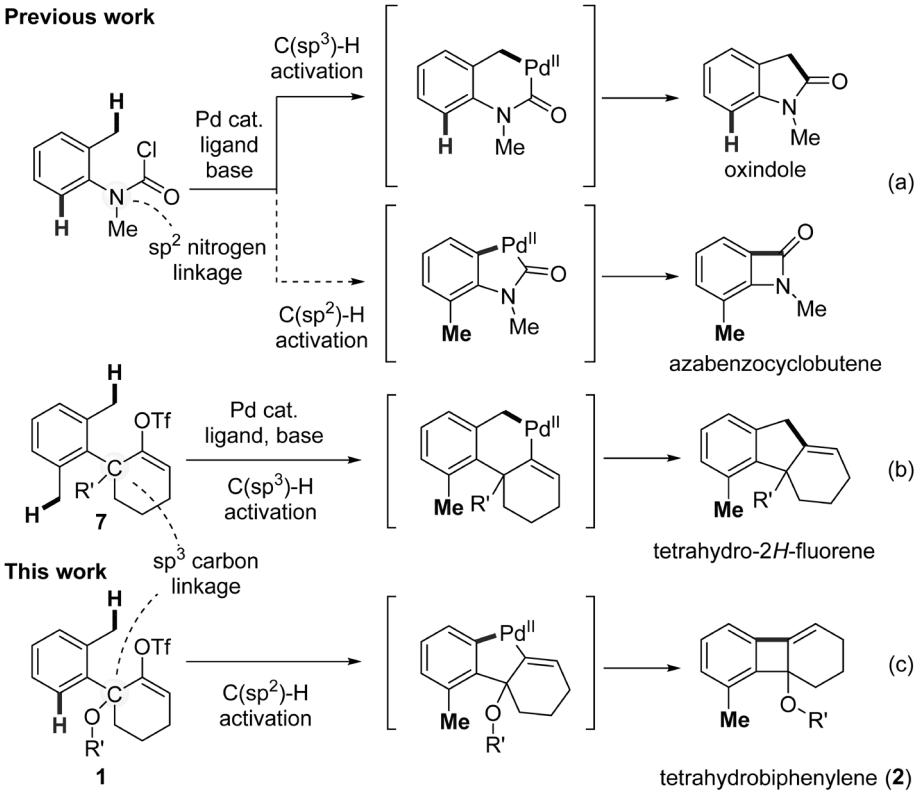
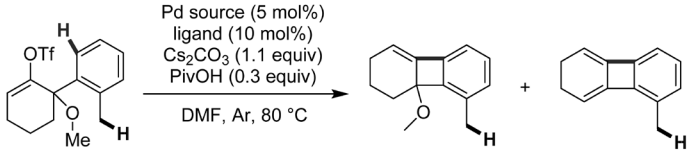


Chart 2. Synthesis of Oxindoles and Tetrahydro-*2H*-fluorenes through Pd(0)-catalyzed C(sp^3)–H Activation (a and b), and Tetrahydrobiphenylenes through C(sp^2)–H Activation (c)

Table 1. Investigation of Reaction Conditions for the Synthesis of Tetrahydrobiphenylene **2a**



Entry	Pd Source	Ligand	Base	Additive	Yield[a]		
					2a	**3a**	**1a**
1	$Pd(PPh_3)_4$	—	Cs_2CO_3	PivOH	75%	16%	—
2	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	PivOH	30%	4%	21%
3	$Pd(OAc)_2$	$(2\text{-furyl})_3P$	Cs_2CO_3	PivOH	50%	13%	—
4	$Pd(OAc)_2$	$(o\text{-tolyl})_3P$	Cs_2CO_3	PivOH	3%	3%	80%
5	$Pd(OAc)_2$	Ad_2PnBu	Cs_2CO_3	PivOH	—	—	85%
6	$Pd(OAc)_2$	$Cy_3P\cdot HBF_4$	Cs_2CO_3	PivOH	—	—	73%
7	$Pd(OAc)_2$	dppf[b]	Cs_2CO_3	PivOH	8%	1%	77%
8	$Pd(OAc)_2$	dppf	Cs_2CO_3	PivOH	84%	1%	—
9	$Pd(OAc)_2$	XPhos	Cs_2CO_3	PivOH	68%	10%	—
10	$Pd(OAc)_2$	SPhos	Cs_2CO_3	PivOH	93%	7%	—
11	$Pd(OAc)_2$	SPhos	Et_3N	PivOH	2%	—	77%
12	$Pd(OAc)_2$	SPhos	KOAc	PivOH	5%	4%	69%
13	$Pd(OAc)_2$	SPhos	Na_2CO_3	PivOH	—	—	81%
14	$Pd(OAc)_2$	SPhos	K_2CO_3	PivOH	40%	8%	—
15	$Pd(OAc)_2$	SPhos	Cs_2CO_3	None	60%	7%	—
16	$Pd(OAc)_2$	SPhos	Cs_2CO_3	AdOOH	69%	10%	—
17	$Pd(OAc)_2$	SPhos	Cs_2CO_3	CsOPiv	77%	19%	—
18	$Pd(OAc)_2$	SPhos	Cs_2CO_3	PivNHOH	—	—	89%

a) Isolated yield. *b*) 5 mol% of dppf was used. Piv=pivaloyl, Ad=1-adamantyl, Cy=cyclohexyl, dppf=1,1′-bis(diphenylphosphino)ferrocene, XPhos=dicyclohexyl(2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)phosphine, SPhos=dicyclohexyl(2′,6′-dimethoxy-[1,1′-biphenyl]-2-yl)phosphine.

dicyclohexyl(2′,4′,6′-triisopropyl-[1,1′-biphenyl]-2-yl)phosphine (XPhos) and dicyclohexyl(2′,6′-dimethoxy-[1,1′-biphenyl]-2-yl)-phosphine (SPhos), were also effective for this transformation (entries 9 and 10). Because SPhos gave the best yield (93%), it was used for the further investigation of bases and additives. When other organic (Et_3N) and inorganic (KOAc, Na_2CO_3, and K_2CO_3) bases were employed, the reaction hardly proceeded, or gave the desired product **2a** in low yields (entries 11–14). The addition of PivOH was not essential, but it gave a more improved yield, than the use of 1-adamantanecarboxylic acid (AdCOOH) or cesium pivalate (CsOPiv) (entries 15–17). Unexpectedly, PivNHOH, which was effective for benzylic C(sp^3)–H functionalization in the synthesis of oxindoles, completely suppressed the formation of the tetrahydrobiphenylene (entry 18). Therefore, the conditions using $Pd(OAc)_2$ (5 mol%), SPhos or dppf (10 mol%), Cs_2CO_3 (1.1 equiv), and PivOH (0.3 equiv) in DMF at 80°C were determined to be the best conditions for the synthesis of tetrahydrobiphenylenes.

The optimized conditions were applied to the synthesis of several tetrahydrobiphenylenes **2b**–**k**. The substrate **1b**[42] having a methoxymethyl (MOM) group, instead of a methoxy group, was treated under the optimal conditions to give the cyclized product **2b** in 84% yield (Table 2, entry 1). The reaction of substrates **1c** and **d**, having bulkier ethyl and isopropyl substituents rather than the methyl group, gave the products **2c** and **d** in 99 and 90% yields, respectively (entries 2 and

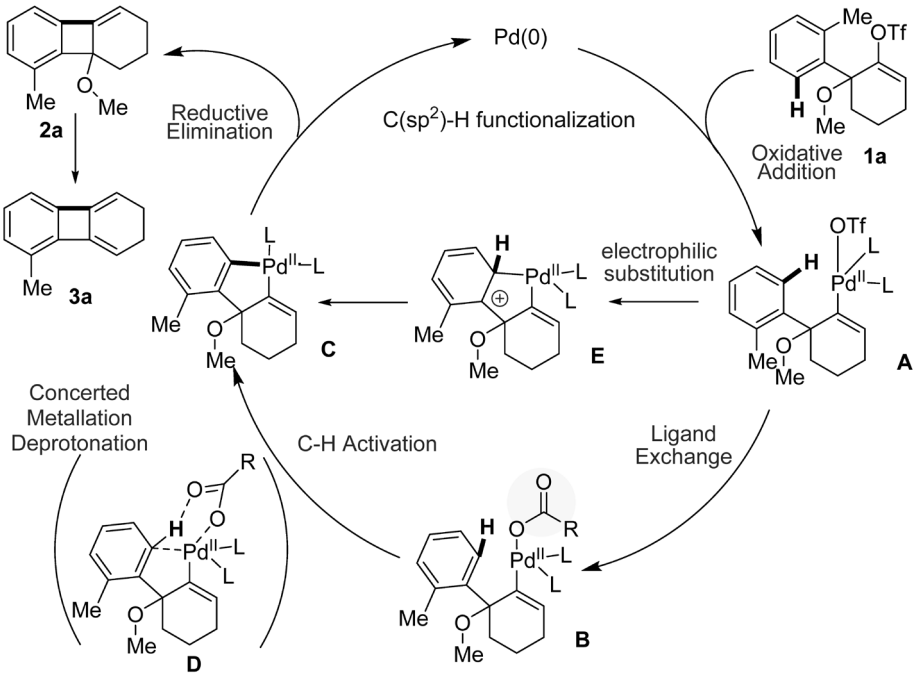
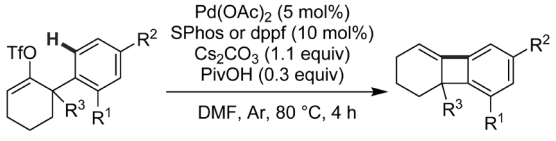


Chart 3. Proposed Reaction Mechanism for the Formation of Tetrahydrobiphenylene **2a**

Table 2. Scope and Limitations



Entry	Substrate	R^1	R^2	R^3	Product	Yield[a]	
						SPhos	dppf
1	**1b**	Me	H	OMOM	**2b**	84%	87%
2	**1c**	Et	H	OMOM	**2c**	99%	—[c]
3	**1d**	*i*Pr	H	OMOM	**2d**	90%	—[c]
4	**1e**	H	H	OMOM	**2e**	8%	22%
5	**1f**	Me	H	H	**2f**	0%[d]	—[c]
6	**1g**	Me	CO_2Me	OMOM	**2g**	82%	—[c]
7	**1h**	Me	OMe	OMOM	**2h**	26%	74%
8	**1i**	Me	Me	OMOM	**2i**	65%	77%
9	**1j**	Me	CF_3	OMOM	**2j**	54%[b]	87%
10	**1k**	Me	F	OMOM	**2k**	0%	78%

a) Isolated yield. *b*) The reaction time was 24 h. *c*) The reaction was not conducted. *d*) Starting material **1f** was recovered (47%).

3). On the other hand, when substrate **1e** having no substituent at the *ortho* position was employed, the yield of **2e** was dramatically decreased (entry 4). In the case of **1f**, having no MOM group, the cyclized product **2f** was not obtained (entry 5). These results indicated that steric repulsion between the R^1 and R^3 substituents could be important. In the case of substrates **1g**–**k** having substituents on the aromatic ring, the use of dppf, rather than SPhos, as a ligand was more effective. For example, while the reaction of **1g** having an ester group gave a satisfactory result using SPhos, the yields for the reactions of substrates **1h**–**j** decreased. In these cases, use of dppf improved the yields (entries 6–9). Additionally, tetrahydrobiphenylene **2k** could be only accessed using dppf. Interestingly, no correlation could be found between the yield and the electronic state of the aromatic ring. In these investigations, tetrahydro-*2H*-fluorenes derived *via* C(sp^3)–H activation were not observed.

The proposed reaction mechanism is shown in Chart 3. The oxidative addition of enol triflate **1a** to Pd(0) is followed by ligand exchange to give intermediate **B** through **A**. In comparison with our oxindole synthesis,[29] the intermediate **B** should be more flexible because of the presence of the sp^3 carbon at the ring juncture, and the Pd(II) center is close to an arene C(sp^2)–H bond, rather than a methyl C(sp^3)–H bond. Thus, C(sp^2)–H activation proceeds, rather than C(sp^3)–H activation, to give the palladacycle **C**. While electrophilic substitution to access intermediate **C** from **A** might be possible, it is unlikely to be the main pathway because no correlation between the yield and electronic state of the aromatic ring was observed. Finally, reductive elimination gives tetrahydrobiphenylene **2a**. Byproduct **3a** can be produced from the desired product through elimination of the methoxy group.

Because tetrahydrobiphenylene **2b** having an oxygen functionality at the ring juncture can be accessed by only our method, we also investigated the possibility of functional group transformation of this compound (Chart 4). The compound **2b** was unstable under acidic conditions; however, the MOM group was able to be removed by treatment with 80% aqueous acetic acid (AcOH) to give the allyl alcohol **4** in a moderate yield. Epoxidation of **2b** with 3-chloroperoxybenzoic acid (*m*CPBA) gave compound **5** in 55% yield in a stereoselective manner. Similarly, hydroboration of **2b** with thexylborane proceeded from only the β face to give the secondary alcohol **6** and tertiary alcohol **7** in 41 and 9% yields, respectively. The yields of these reactions were moderate presumably because of the instability of the starting material and products under the reaction conditions.

In summary, we have developed a new method for the synthesis of tetrahydrobiphenylenes based on a palladium (Pd)(0)-catalyzed C(sp^2)–H functionalization. Applying this method, several tetrahydrobiphenylenes **2a**–**e**, **g**–**k** having an oxygen functionality at the ring juncture could be accessed. We also investigated the reactivity of tetrahydrobiphenylene **2b**. These results provide insights into a new aspect of the chemistry of biphenylenes.

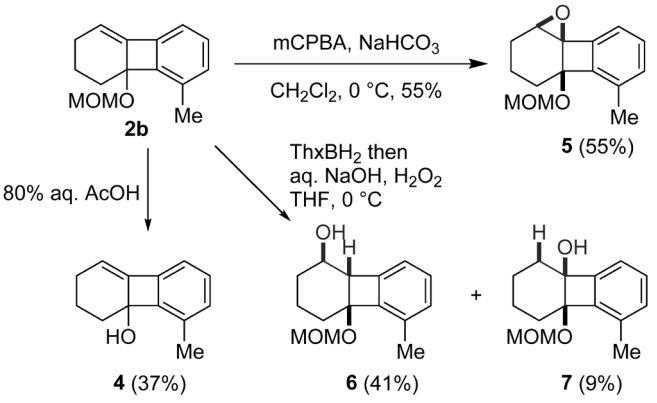


Chart 4. Derivatization of Tetrahydrobiphenylene **2b**

Experimental

General Experimental Details Unless otherwise noted, all the reagents were purchased from chemical companies and used without further purification. All non-aqueous reactions were carried out under a positive pressure of argon in over-dried glassware. Analytical TLC was performed using Silica gel 60 plates (Merck, Darmstadt, Germany). Silica gel column chromatography was performed using Kanto silica gel 60 (particle size 63–210 μm, Kanto, Tokyo, Japan) and Chromatorex BW-300 (Fuji silysia, Aichi, Japan). Proton NMR (^{1}H-NMR) spectra were recorded on a JNM-ECA 500 (JEOL, Tokyo, Japan) at 500 MHz or a JNM-AL 400 (JEOL) at 400 MHz. Chemical shifts were reported relative to Me_4Si (δ 0.00) in $CDCl_3$. Multiplicity was indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon NMR (^{13}C-NMR) spectra were recorded on a JNM-ECA 500 at 126 MHz or a JNM-AL 400 at 101 MHz. Chemical shifts were reported relative to $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a FT/IR-4100 Fourier-transform IR spectrometer (JASCO, Tokyo, Japan) attenuated total reflectance (ATR). Low and high resolution mass spectra were recorded on JMS-700 mass spectrometer (JEOL) for FAB-MS and a LCMS-IT-TOF (Shimadzu, Kyoto, Japan) for electrospray ionization (ESI)-MS.

Preparation of Enol Triflate 1a

2-Hydroxy-2-(*o*-tolyl)cyclohexan-1-one (**8**)

To a solution of 2-[(trimethylsilyl)oxy]cyclohex-2-en-1-one[43] (1.47 g, 7.97 mmol) in dry tetrahydrofuran (THF) (8.0 mL) was added *o*-tolylmagnesium bromide (8.90 mL, 0.9 M THF solution, 8.01 mmol, purchased from TCI) at room temperature under Ar. The reaction mixture was stirred at room temperature for 1.5 h, and then tetrabutylammonium fluoride (TBAF) (12.0 mL, 1.0 M in THF solution, 12.0 mmol, purchased from Aldrich) was added at the same temperature. The reaction mixture was stirred at room temperature for 2 h. The resultant mixture was diluted with Et_2O and saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O. The organic extracts were combined, washed with brine, and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/AcOEt=5/1) to give 2-hydroxy-2-(*o*-tolyl)cyclohexan-1-one (**8**) (1.53 g, 7.47 mmol, 94%) as a yellow oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.59 (1H, d, J=7.4 Hz), 7.29–7.23 (2H, m), 7.17 (1H, d, J=7.2 Hz), 4.48 (1H, s), 3.10 (1H, ddd, J=11.3, 6.1, 2.7 Hz), 2.51 (1H, m), 2.39 (1H, ddd, J=13.0, 13.0, 6.0 Hz), 2.14 (3H, s), 2.10 (1H, m), 1.87–1.74 (3H, m), 1.68 (1H, ddd, J=13.0, 13.0, 4.5 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 215.2, 138.0, 136.6, 132.6, 128.4, 127.0, 126.1, 81.5, 43.0, 39.0, 38.8, 30.3, 23.4, 20.7; IR (ATR) 3456, 2944, 2866, 1712, 1451, 1379, 1305, 1248,

1186, 1097, 1053, 1031 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227.1043. Found 227.1051.

2-Methoxy-2-(*o*-tolyl)cyclohexan-1-one (**9**)

To a solution of 2-hydroxy-2-(*o*-tolyl)cyclohexan-1-one (**8**) (391 mg, 1.91 mmol) in dry DMF (2 mL) was added a suspension of 60% sodium hydride (NaH) (111.2 mg, 2.78 mmol) in dry DMF (3 mL) slowly at 0°C. After stirring for 20 min at 0°C, the resultant mixture was treated with CH_3I (288 μL, 4.60 mmol). The reaction mixture was stirred at room temperature for 17 h. The resultant mixture was diluted with Et_2O and ice-water. The aqueous phase was extracted with Et_2O. The organic extracts were combined, washed with brine, and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/AcOEt=20/1 to 10/1 to 5/1) to give 2-methoxy-2-(*o*-tolyl)cyclohexan-1-one (**9**) (262 mg, 1.20 mmol, 63%) as a colorless oil.: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32 (1H, d, J=7.2 Hz), 7.24–7.18 (3H, m), 3.00 (3H, s), 2.85 (1H, m), 2.37–2.31 (3H, m), 2.20 (3H, s), 2.04–1.94 (2H, m), 1.87–1.77 (2H, m); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 210.0, 138.4, 135.6, 132.0, 128.1, 127.9, 125.4, 86.2, 50.0, 39.6, 36.4, 28.9, 21.6, 21.3; IR (ATR) 2940, 1722, 1485, 1308, 1252, 1207, 1150, 1132, 1099 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{14}H_{18}O_2Na$ $[M+Na]^+$ 241.1199. Found 241.1199.

1-Methoxy-2′-methyl-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-yl Trifluoromethanesulfonate (**1a**)

To a solution of 2-methoxy-2-(*o*-tolyl)cyclohexan-1-one (**9**) (207.2 mg, 0.949 mmol) in dry THF (1.9 mL) was added lithium diisopropylamide (LDA (6.2 mL, 0.17 M THF solution, 1.05 mmol, freshly prepared from iPr$_2$NH and nBuLi) at −78°C, and the resultant solution was stirred for 15 min. A solution of $PhNTf_2$ (373.5 mg, 1.10 mmol) in dry THF (2.0 mL) was added, and the reaction mixture was stirred at 0°C for 1 h. The resultant mixture was diluted with AcOEt and water. The aqueous phase was extracted with AcOEt. The organic extracts were combined, washed with brine, and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane) to give enol triflate **1a** (206.5 mg, 0.589 mmol, 62%) as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40 (1H, m), 7.20–7.16 (3H, m), 6.23 (1H, t, J=4.0 Hz), 3.43 (3H, s), 2.47 (3H, s), 2.43–2.19 (3H, m), 2.12 (1H, m), 1.82 (1H, m), 1.55 (1H, m); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 148.3, 138.6, 135.8, 132.7, 127.7, 125.4, 121.7, 119.7, 116.5, 80.3, 52.1, 34.3, 24.5, 20.9, 18.5; IR (ATR) 2944, 1457, 1413, 1248, 1206, 1143, 1089, 1065, 1040 cm^{-1}; HR-MS (FAB) *m/z* Calcd for $C_{15}H_{18}F_3O_4S$ $[M+H]^+$ 351.0878. Found 351.0873.

Preparation of Enol Triflate 1b

2-(Methoxymethoxy)-2-(*o*-tolyl)cyclohexan-1-one (**10**)

To a solution of 2-hydroxy-2-(*o*-tolyl)cyclohexan-1-one (**8**) (4.13 g, 20.2 mmol) in dry CH_2Cl_2 (100 mL) was added iPr$_2$NEt (35.0 mL, 201 mmol) and MOMCl (15.4 mL, 203 mmol). The reaction mixture was refluxed for 9 h. After cooling to room temperature, the resultant mixture was poured into H_2O and $CHCl_3$. The aqueous phase was extracted with $CHCl_3$. The organic extracts were combined, washed with brine, and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/AcOEt=5/1) to give 2-(methoxymethoxy)-2-(*o*-tolyl)cyclohexan-1-one (**10**) (4.25 g, 85%) as a pale yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.47 (1H, m), 7.27–7.23 (2H, m), 7.20 (1H, m), 4.48 (2H, dd, J=13.8, 7.0 Hz), 3.38 (3H, s), 2.77–2.69 (2H, m), 2.34 (1H, m), 2.25 (1H, m), 2.19 (3H, s), 2.00–1.82 (4H, m); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 209.8, 138.4, 135.2, 132.3, 128.5, 128.0, 125.7, 92.3, 87.1, 56.2, 39.9, 39.5, 29.2, 22.5, 21.2; IR (ATR) 2940, 1724, 1487, 1449, 1308, 1252, 1232, 1208, 1163, 1145, 1132, 1101, 1055, 1013 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1305. Found: 271.1305.

1-(Methoxymethoxy)-2′-methyl-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-yl Trifluoromethanesulfonate (**1b**)

To a solution of 2-(methoxymethoxy)-2-(*o*-tolyl)cyclohexan-1-one (**10**) (56.1 mg, 0.226 mmol) in dry THF (0.50 mL) was added a solution of LDA (1.50 mL, 0.17 M THF solution, 0.255 mmol, freshly prepared from iPr$_2$NH and nBuLi) at −78°C, and the resultant solution was stirred for 40 min. A solution of $PhNTf_2$ (88.4 mg, 0.247 mmol) in dry THF (0.5 mL) was added, and the solution was stirred at 0°C for 5 h. The resultant solution was diluted with AcOEt and water. The aqueous phase was extracted with AcOEt. The organic extracts were combined, washed with brine, and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane) to give enol triflate **1b** (62.8 mg, 0.165 mmol, 73%) as a yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.45 (1H, m), 7.20–7.16 (3H, m), 6.21 (1H, t, J=4.2 Hz), 5.07 (1H, d, J=7.6 Hz), 4.75 (1H, d, J=7.6 Hz), 3.51 (3H, s), 2.46 (3H, s), 2.42 (1H, m), 2.37–2.27 (2H, m), 2.15 (1H, m), 1.89 (1H, m), 1.61 (1H, m); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 148.0, 139.0, 135.2, 132.8, 127.7, 127.3, 125.6, 122.1, 119.8, 92.6, 80.2, 56.3, 36.4, 24.5, 21.2, 18.3; IR (ATR) 2947, 1484, 1457, 1416, 1249, 1212, 1147, 1045, 999, 932, 908 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{16}H_{19}F_3OSNa$ $[M+Na]^+$ 403.0798. Found 403.0792.

Synthesis of Tetrahydrobiphenylene 2

8*b*-Methoxy-8-methyl-1,2,3,8*b*-tetrahydrobiphenylene (**2a**)

To a stirred solution of enol triflate **1a** (28.1 mg, 0.0802 mmol), SPhos (3.3 mg, 0.0083 mmol), Cs_2CO_3 (28.7 mg, 0.0880 mmol), and PivOH (2.5 mg, 0.024.5 mmol) in DMF (0.40 mL) were added $Pd(OAc)_2$ (0.9 mg, 0.0040 mmol). The reaction was stirred at 80°C for 4 h. After cooling to room temperature, the resulting mixture was filtered through a pad of celite using Et_2O. The filtrate was washed with water and brine, and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% toluene/hexane) to give tetrahydrobiphenylene **2a** (18.0 mg, 93%) containing dihydrobiphenylene **3a** (1.4 mg, 7%) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.19 (t, 1H, J=6.0 Hz), 6.98 (d, 1H, J=6.0 Hz), 6.96 (d, 1H, J=6.4 Hz), 5.85 (dd, 1H, dd, J=3.8, 2.2 Hz), 3.17 (s, 3H), 2.39 (dd, 1H, J=18.4, 9.2 Hz), 2.28 (s, 3H), 2.24 (m, 1H), 2.17–2.09 (2H, m), 1.85 (m, 1H), 1.54 (m 1H); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 147.4, 147.4, 143.0, 134.0, 129.8, 128.7, 119.2, 115.7, 86.3, 52.6, 30.6, 29.7, 24.9, 18.9, 17.5; IR (ATR) 2933, 2896, 1474, 1455, 1435, 1349, 1330, 1229, 1158, 1119, 1072, 978 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{14}H_{17}O$ $[M+H]^+$ 201.1274. Found 201.1268.

Methoxymethoxy-8-methyl-1,2,3,8*b*-tetrahydrobiphenylene (**2b**)

Colorless oil, 253.4 mg, 87% yield (dppf); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.18 (1H, t, J=7.6 Hz), 6.98 (1H, d, J=7.6 Hz), 6.95 (1H, d, J=7.6 Hz), 5.83 (1H, dd, J=2.8, 4.8 Hz), 4.66 (1H, d, J=6.4 Hz), 4.62 (1H, d, J=6.8 Hz), 3.32 (3H, s),

2.45–2.38 (1H, m), 2.32–2.27 (4H, m), 2.22–2.11 (2H, m), 1.92–1.86 (1H, m), 1.58–1.50 (1H, m); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 147.5, 147.1, 143.2, 133.8, 129.9, 128.9, 118.5, 116.0, 92.9, 85.3, 55.4, 31.3, 24.8, 18.8, 17.4; IR (ATR) 2934, 1597, 1454, 1397, 1350, 1229, 1205, 1148, 1108, 1036, 963, 926, 882 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{15}H_{19}O_2$ $[M+H]^+$ 231.1380. Found: 231.1382.

8-Ethyl-methoxymethoxy-1,2,3,8*b*-tetrahydrobiphenylene (**2c**)

Colorless oil, 34.6 mg, 99% yield (SPhos); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.22 (1H, t, *J*=7.6 Hz), 7.00 (2H, dd, *J*=7.6, 4.7 Hz), 5.84–5.83 (1H, m), 4.61 (2H, dd, *J*=11.9, 6.7 Hz), 3.32 (3H, s), 2.66–2.61 (2H, m), 2.44–2.42 (1H, m), 2.30–2.27 (1H, m), 2.20–2.17 (2H, m), 1.90–1.89 (1H, m), 1.58–1.56 (1H, m), 1.24 (3H, t, *J*=7.6 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 147.7, 146.3, 143.4, 140.5, 130.1, 127.5, 118.4, 116.1, 92.7, 85.4, 55.5, 32.2, 25.4, 24.8, 18.8, 14.7; IR (ATR) 2937, 1748, 1472, 1107, 1039 cm^{-1}; HR-MS (ESI) *m/z* calcd for $C_{16}H_{20}O_2Na$: $[M+Na]^+$ 267.1361. Found 267.1356.

8-Isopropyl-methoxymethoxy-1,2,3,8*b*-tetrahydrobiphenylene (**2d**)

Pale yellow oil, 31.4 mg, 90% yield (SPhos); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.25–7.22 (1H, m), 7.03–7.01 (2H, m), 5.84–5.83 (1H, m), 4.62 (1H, d, *J*=6.6 Hz), 4.54 (1H, d, *J*=6.6 Hz), 3.33 (3H, s), 2.96–2.90 (1H, m), 2.44–2.43 (1H, m), 2.30–2.28 (1H, m), 2.20–2.18 (2H, m), 1.91–1.90 (1H, m), 1.61–1.55 (1H, m), 1.26 (6H, dd, *J*=8.0, 7.2 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 147.8, 145.6, 145.2, 143.5, 130.1, 125.9, 118.2, 116.0, 92.3, 85.4, 55.5, 32.9, 31.6, 24.7, 23.5, 23.1, 18.9; IR (ATR) 2957, 1147, 1105, 1031 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{17}H_{22}O_2Na$: $[M+Na]^+$ 281.1517. Found 281.1512.

Methyl-methoxymethoxy-4-methyl-4*b*,5,6,7-tetrahydrobiphenylene-2-carboxylate (**2g**)

Yellow oil, 31.1 mg, 82% yield (SPhos); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.72 (1H, s), 7.64 (1H, s), 5.94–5.93 (1H, m), 4.66 (1H, d, *J*=6.9 Hz), 4.61 (1H, d, *J*=6.9 Hz), 3.90 (3H, s), 3.29 (3H, s), 2.46–2.41 (1H, m), 2.34 (3H, s), 2.31–2.28 (1H, m), 2.22–2.14 (2H, m), 1.92–1.91 (1H, m), 1.54–1.51 (1H, m); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 167.3, 152.4, 147.5, 142.1, 133.9, 131.7, 130.7, 120.4, 117.1, 93.0, 84.9, 55.5, 52.1, 31.1, 24.8, 18.6, 17.3; IR (ATR) 2949, 1722, 1415, 1207, 1042 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{17}H_{20}O_4Na$: $[M+Na]^+$ 311.1259. Found 311.1254.

6-Methoxy-methoxymethoxy-8-methyl-1,2,3,8*b*-tetrahydrobiphenylene (**2h**)

Colorless oil, 33.0 mg, 74% yield (dppf); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.84 (2H, d, *J*=8.0 Hz), 7.58 (1H, d, *J*=8.0 Hz), 6.25–6.24 (1H, m), 5.09 (1H, d, *J*=7.7 Hz), 4.76 (1H, d, *J*=8.0 Hz), 3.91 (3H, s), 3.52 (3H, s), 2.49–2.45 (4H, m), 2.37–2.28 (2H, m), 2.12–2.07 (1H, m), 1.91–1.89 (1H, m), 1.63–1.61 (1H, m); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 161.5, 148.3, 142.7, 139.1, 135.3, 118.0, 115.7, 101.0, 92.7, 84.4, 55.37, 55.33, 31.5, 24. 7, 18.8, 17.5; IR (ATR) 2936, 1596, 1475, 1138, 1040 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{16}H_{20}O_3Na$: $[M+Na]^+$ 283.1310. Found 283.1305.

Methoxymethoxy-6,8-dimethyl-1,2,3,8*b*-tetrahydrobiphenylene (**2i**)

Colorless oil, 20.6 mg, 77% yield (dppf); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.83 (1H, s), 6.79 (1H, s), 5.79–5.78 (1H, m), 4.66 (1H, d, *J*=6.9 Hz), 4.62 (1H, d, *J*=6.9 Hz), 3.33 (3H, s), 2.42–2.40 (1H, m), 2.31 (3H, s), 2.26–2.24 (4H, m), 2.20–2.12 (2H, m), 1.89–1.86 (1H, m), 1.53–1.50 (1H, m); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 147.6, 144.1, 143.0, 139.9, 133.5, 129.8, 117.9, 116.6, 92.8, 84.8, 55.4, 31.4, 24. 7, 21.9, 18.7, 17.3; IR (ATR) 2933, 1591, 1453, 1151, 1029 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{16}H_{20}O_2Na$: $[M+Na]^+$ 267.1361. Found 267.1356.

8*b*-(Methoxymethoxy)-8-methyl-6-(trifluoromethyl)-1,2,3,8*b*-tetrahydrobiphenylene (**2j**)

Yellow oil, 34.8 mg, 87% yield (dppf); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.23 (2H, s), 5.96 (1H, dd, *J*=4.5, 2.4 Hz), 4.66 (1H, d, *J*=6.9 Hz), 4.61 (1H, d, *J*=6.9 Hz), 3.31 (3H, s), 2.45 (1H, m), 2.35 (3H, s), 2.30 (1H, ddd, *J*=12.6, 4.2, 2.4 Hz), 2.24–2.14 (2H, m), 1.92 (1H, m), 1.51 (1H, ddd, *J*=13.0, 13.0, 4.2 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 150.8, 147.6, 142.0, 134.6, 132.1 (q, *J*=31.2 Hz), 125.8 (q, *J*=3.5 Hz), 124.2 (q, *J*=272.8 Hz), 121.1, 113.0 (q, *J*=3.5 Hz), 92.9, 84.9, 55.5, 31.1, 24.9, 18.6, 17.4; IR (ATR) 2948, 2889, 1327, 1307, 1201, 1160, 1127, 1042 cm^{-1}; HR-MS (FAB) *m/z* Calcd for $C_{16}H_{17}F_3O_2Na$: $[M+Na]^+$ 321.1078. Found 321.1077.

6-Fluoro-methoxymethoxy-8-methyl-1,2,3,8*b*-tetrahydrobiphenylene (**2k**)

Pale yellow oil, 36.3 mg, 78% yield (dppf); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.70–6.67 (2H, m), 5.87–5.86 (1H, m), 4.65 (1H, d, *J*=6.9 Hz), 4.61 (1H, d, *J*=6.9 Hz), 3.31 (3H, s), 2.47–2.40 (1H, m), 2.28–2.27 (4H, m), 2.21–2.14 (2H, m), 1.92–1.88 (1H, m), 1.53–1.47 (1H, m); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 165.2, 163.2, 148.4 (d, *J*=6.7 Hz), 142.3 (d, *J*=35.2 Hz), 136.3 (d, *J*=6.7 Hz), 119.7, 115.9 (d, *J*=19.1 Hz), 103.7 (d, *J*=18.2 Hz), 92.7, 84.2, 56.4, 31.4, 24.8, 18.8, 17.4; IR (ATR) 2939, 1586, 1467, 1348, 1107, 1030 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{15}H_{17}FO_2Na$: $[M+Na]^+$ 271.1110. Found 271.1105.

Removal of MOM Group of Compound 2b Compound **2b** (30.3 mg, 0.132 mmol) was dissolved in 80% aq. AcOH (1.3 mL). The solution was stirred at room temperature for 10 h, and 50°C for 16 h. After cooling to room temperature, the resulting solution was diluted with EtOAc, washed with satd. aq. $NaHCO_3$, and dried over Na_2SO_4. After filtration and concentration under reduced pressure, the residue was purified by silica gel column chromatography (10–20% EtOAc/hexane) to give compound **4** (9.0 mg, 37%) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.18 (1H, t, *J*=7.5 Hz), 7.00 (1H, d, *J*=7.5 Hz), 6.97 (1H, d, *J*=7.5 Hz), 5.78 (1H, dd, *J*=4.6, 2.3 Hz), 2.42 (1H, m), 2.31 (3H, s), 2.29–2.10 (4H, m), 1.90 (1H, m), 1.62 (1H, ddd, *J*=12.6, 12.6, 4.3 Hz); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 150.5, 147.1, 145.0, 132.8, 129.8, 129.2, 117.7, 116.7, 80.9, 31.0, 25.0, 18.5, 17.1; IR (ATR) 3380, 3042, 2938, 2866, 1596, 1453, 1375, 1102, 1036, 984 cm^{-1}; HR-MS (ESI) *m/z* Calcd for $C_{13}H_{15}O$: $[M+H]^+$ 187.1117. Found 187.1115.

Epoxydation of Compound 2b To a solution of compound **2b** (84.0 mg, 0.365 mmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (66.2 mg, 0.788 mmol) and *m*CPBA (77% purity, 90.5 mg, 0.403 mmol) at 0°C. The resultant mixture was stirred at 0°C overnight. The resulting mixture was diluted with EtOAc, and washed with satd. aq. $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% EtOAc/hexane) to give compound **5** (49.6 mg, 55%) as a colorless oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28 (1H, t, *J*=7.8 Hz), 7.15 (1H, d, *J*=7.8 Hz), 7.01 (1H, d, *J*=7.8 Hz), 4.82 (1H, d, *J*=6.7 Hz), 4.71

(1H, d, J=6.7 Hz), 3.55 (1H, d, J=2.3 Hz), 3.37 (3H, s), 2.34 (3H, s), 2.30–2.18 (2H, m), 1.80–1.68 (2H, m), 1.56–1.43 (2H, m); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 146.2, 145.0, 133.8, 130.8, 130.4, 119.0, 93.2, 86.7, 67.4, 58.4, 55.8, 32.2, 25.8, 17.6, 16.3; IR (ATR) 2938, 1610, 1465, 1151, 1116, 1034 cm^{-1}; HR-MS (ESI) m/z Calcd for $C_{15}H_{18}O_3Na$: $[M+Na]^+$ 269.1148. Found 269.1134.

Hydroboration of Compound 2b To a solution of compound **2b** (30.0 mg) in dry THF (1 mL) was added thexylborane solution (0.5 M in THF, 0.39 mL, 0.195 mmol, prepared from $BH_3 \cdot SMe_2$ (2.0 M in THF, 1.25 mL) and 2,3-dimethyl-2-butene (0.30 mL)) at 0°C. The resultant mixture was stirred at 0°C for 110 min. The solution was treated with 3 M aq. NaOH (0.39 mL) followed by 30% aq. H_2O_2, and stirred at room temperature for 2.5 h. The resulting mixture was diluted with EtOAc, and washed with satd. aq. NH_4Cl and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (25–40% EtOAc/hexane) to give compound **7** (2.9 mg, 9%) and then compound **6** (13.8 mg, 41%) as a colorless oil: compound **6**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.19 (1H, t, J=7.5 Hz), 7.03 (1H, d, J=7.5 Hz), 6.96 (1H, d, J=7.5 Hz), 4.84 (1H, d, J=7.2 Hz), 4.75 (1H, d, J=7.2 Hz), 4.26 (1H, ddd, J=4.6, 4.6, 4.6 Hz), 3.68 (1H, d, J=4.6 Hz), 3.44 (3H, s), 2.34 (1H, m), 2.25 (3H, s), 1.93 (1H, m), 1.77 (1H, m), 1.63–1.58 (2H, m), 1.25 (1H, m); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 144.9, 142.7, 133.3, 129.5, 129.0, 119.6, 92.7, 83.2, 69.7, 56.4, 55.5, 30.4, 27.8, 17.1, 16.8; IR (ATR) 3423, 2936, 1729, 1612, 1450, 1349, 1146, 1031 cm^{-1}; HR-MS (ESI) m/z Calcd for $C_{15}H_{20}O_3Na$: $[M+Na]^+$ 271.1305. Found 271.1280; compound **7**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28 (1H, t, J=7.5 Hz), 7.12 (1H, d, J=7.5 Hz), 7.10 (1H, d, J=7.5 Hz), 4.84 (1H, d, J=6.4 Hz), 4.71 (1H, d, J=6.4 Hz), 4.41 (1H, s), 3.33 (3H, s), 2.28 (3H, s), 2.12–2.09 (2H, m), 2.05–1.93 (2H, m), 1.66–1.49 (3H, m), 1.10 (1H, m), 0.96 (1H, m); ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 150.5, 141.3, 135.1, 130.4, 130.1, 119.7, 93.4, 90.8, 80.6, 55.6, 30.9, 29.1, 17.7, 17.2, 16.7; IR (ATR) 3435, 2940, 1728, 1608, 1467, 1344, 1148, 1040 cm^{-1}; HR-MS (ESI) m/z Calcd for $C_{15}H_{20}O_3Na$: $[M+Na]^+$ 271.1305. Found 271.1286.

Acknowledgments We thank Mrs. T. Kimura, T. Sakaguchi, Y. Tokuhiro, and Ms. N. Kato for checking reproducibility and spectra data. This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant No. JP17H05051), the Platform Project for Supporting Drug Discovery and Life Science Research from Japan Agency for Medical Research and Development (AMED). We thank Victoria Muir, Ph.D., from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

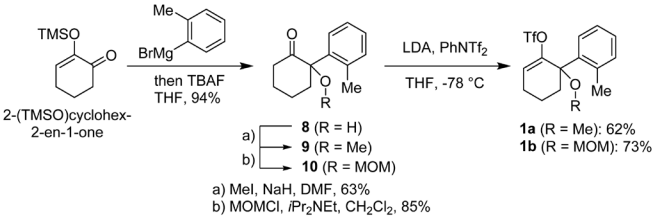
Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

References and Notes

1) Lothrop W. X., *J. Am. Chem. Soc.*, **63**, 1187–1191 (1941).
2) Toda F., Garratt P., *Chem. Rev.*, **92**, 1685–1707 (1992).
3) Perthuisot C., Edelbach B. L., Zubris D. L., Simhai N., Iverson C. N., Müller C., Satoh T., Jones W. D., *J. Mol. Catal. A*, **189**, 157–168 (2002).
4) Darmon J. M., Stieber S. C. E., Sylvester K. T., Fernández I., Lobkovsky E., Semproni S. P., Bill E., Wieghardt K., DeBeer S., Chirik P. J., *J. Am. Chem. Soc.*, **134**, 17125–17137 (2012).
5) Breunig J. M., Gupta P., Das A., Tussupbayev S., Diefenbach M., Bolte M., Wagner M., Holthausen M. C., Lerner H.-W., *Chem. Asian J.*, **9**, 3163–3173 (2014).
6) Graf-Christophe S. C., Kuehm-Caubère C. P., Renard P., Pfeiffer B., Pierre A., Leonce S., Caubère P., *Bioorg. Med. Chem. Lett.*, **10**, 2589–2591 (2000).
7) Christophe S., Kuehm-Caubère C., Renard P., Pfeiffer B., Caubère P., *Tetrahedron Lett.*, **39**, 9431–9434 (1998).
8) Carre M.-C., Youlassani A., Caubere P., Saint-Aubin-Floch A., Blanc M., Advenier C., *J. Med. Chem.*, **27**, 792–799 (1984).
9) Keyton D. J., Griffin G. W., Kuehne M. E., Bayha C. E., *Tetrahedron Lett.*, **10**, 4163–4168 (1969).
10) Zouaoui M. A., Mouaddib A., Jamart-Gregoire B., Ianelli S., Nardelli M., Caubere P., *J. Org. Chem.*, **56**, 4078–4081 (1991).
11) Caubere P., Mourad M. S., *Tetrahedron*, **30**, 3439–3445 (1974).
12) Kumaraswamy S., Jalisatgi S. S., Matzger A. J., Miljanic O. S., Vollhardt K. P. C., *Angew. Chem. Int. Ed.*, **43**, 3711–3715 (2004).
13) Zhang Y.-H., Shi G. F., Yu J.-Q., "Comprehensive Organic Synthesis II (Second Edition)," Vol. 3, ed. by Knochel P., Molander G. A., Elsevier, the Netherlands, 2014, pp. 1101–1209.
14) He J., Wasa M., Chan K. S. L., Shao Q., Yu J. Q., *Chem. Rev.*, **117**, 8754–8786 (2017).
15) Roudesly F., Oble J., Poli G., *J. Mol. Catal. A.*, **426**, 275–296 (2017).
16) Chen Z., Wang B., Zhang J., Yu W., Liu Z., Zhang Y., *Org. Chem. Front.*, **2**, 1107–1295 (2015).
17) Rouquet G., Chatani N., *Angew. Chem. Int. Ed.*, **52**, 11726–11743 (2013).
18) Wencel-Delord J., Dröge T., Liu F., Glorius F., *Chem. Soc. Rev.*, **40**, 4740–4761 (2011).
19) Ackermann L., *Chem. Rev.*, **111**, 1315–1345 (2011).
20) Lyons T. W., Sanford M. S., *Chem. Rev.*, **110**, 1147–1169 (2010).
21) Catellani M., Ferioli L., *Synthesis*, **1996**, 769–772 (1996).
22) Baudoin O., Herrbach A., Gueritte F., *Angew. Chem. Int. Ed.*, **42**, 5736–5740 (2003).
23) Chaumontet M., Piccardi R., Audic N., Hitce J., Peglion J. L., Clot E., Baudoin O., *J. Am. Chem. Soc.*, **130**, 15157–15166 (2008).
24) Rousseaux S., Davi M., Sofack-Kreutzer J., Pierre C., Kefalidis C. E., Clot E., Fagnou K., Baudoin O., *J. Am. Chem. Soc.*, **132**, 10706–10716 (2010).
25) Baudoin O., *Acc. Chem. Res.*, **50**, 1114–1123 (2017).
26) Bertrand M. B., Wolfe J. P., *Org. Lett.*, **9**, 3073–3075 (2007).
27) Alvarez-Bercedo P., Flores-Gaspar A., Correa A., Martin R., *J. Am. Chem. Soc.*, **132**, 466–467 (2010).
28) Tsukano C., *Chem. Pharm. Bull.*, **65**, 409–425 (2017).
29) Tsukano C., Okuno M., Takemoto Y., *Angew. Chem. Int. Ed.*, **51**, 2763–2766 (2012).
30) Nanjo T., Tsukano C., Takemoto Y., *Org. Lett.*, **14**, 4270–4273 (2012).
31) Tsukano C., Okuno M., Takemoto Y., *Chem. Lett.*, **42**, 753–755 (2013).
32) Nanjo T., Yamamoto S., Tsukano C., Takemoto Y., *Org. Lett.*, **15**, 3754–3757 (2013).
33) Zhao L., Tsukano C., Kwon E., Takemoto Y., Hirama M., *Angew. Chem. Int. Ed.*, **52**, 1722–1725 (2013).
34) Tsukano C., Muto N., Enkhtaivan I., Takemoto Y., *Chem. Asian J.*, **9**, 2628–2634 (2014).
35) Tsukano C., Okuno M., Nishiguchi H., Takemoto Y., *Adv. Synth. Catal.*, **356**, 1533–1538 (2014).
36) Nanjo T., Tsukano C., Takemoto Y., *Synlett*, **25**, 1473–1477 (2014).
37) Suetsugu S., Nishiguchi H., Tsukano C., Takemoto Y., *Org. Lett.*, **16**, 996–999 (2014).
38) Tsukano C., Yamamoto S., Takemoto Y., *Chem. Pharm. Bull.*, **63**,

710–719 (2015).
39) Suetsugu S., Muto N., Horinouchi M., Tsukano C., Takemoto Y., *Chemistry*, **22**, 8059–8062 (2016).
40) Nanjo T., Tsukano C., Takemoto Y., *Chem. Pharm. Bull.*, **64**, 1384–1392 (2016).
41) Zhao L., Tsukano C., Kwon E., Shirakawa H., Kaneko S., Takemoto Y., Hirama M., *Chemistry*, **23**, 802–812 (2017).
42) Enol triflate **1a** was prepared from 2-(trimethylsilyloxy)cyclohex-2-en-1-one in three steps, including nucleophilic addition of a Grignard reagent and triflation as shown below. Also see in Experimental. Other enol triflates **1b**–**k** were prepared in a similar manner using the corresponding Grignard reagents.



43) Fujiwara T., Tsuruta Y., Arizono K.-i., Takeda T., *Synlett*, **1997**, 962–964 (1997).