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Bis(oxazoline)–ligand-mediated asymmetric [2,3]-Wittig rearrangement of benzyl ethers: reaction mechanism based on the hydrogen/deuterium exchange effect

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ABSTRACT

We have investigated the mechanism of chiral induction in the asymmetric [2,3]-Wittig rearrangement of allyl benzyl ether in the presence of a bis(oxazoline) chiral ligand [(*S*,*S*)-Box–*t*Bu] by comparing the reaction of both enantiomers of monodeuterated benzyl ether **1a**–*d*. As a result, we found that chirality was induced via enantioselective deprotonation followed by efficient chirality transfer of the resulting chiral benzyl carbanion with the inversion of stereochemistry. It was revealed that the chiral ligand facilitates selective deprotonation as well as prevents the chiral carbanion from racemization. Moreover, we examined the effect of the *o*-methoxy substituent on the benzene ring.

1. Introduction

The [2,3]-Wittig rearrangement is a useful method for stereoselectively constructing the carbon–carbon bond.[1] This rearrangement proceeds via the formation of a carbanion followed by [2,3]-sigmatropic rearrangement. Therefore, enantioselective formation of the chiral carbanion was expected to enable asymmetric [2,3]-Wittig rearrangement, which is a powerful tool to construct asymmetric carbons from achiral substrates. Considerable efforts have been devoted to develop the effective method.[2] In addition, the mechanistic research revealed that the chiral carbanion undergoes the [2,3]-sigmatoropic rearrangement with inversion of configuration.[3] During the course of these studies, it has been arguable whether the asymmetric induction occurs at the deprotonation step or the post-deprotonation step via the dynamic thermodynamic resolution or dynamic kinetic resolution.[4] Nakai[2a,b] and Kimachi[2h,i] have independently reported that the [2,3]-Wittig rearrangement of benzyl ethers proceeds via enantioselective deprotonation by using bis(oxazoline) (Box) and (−)-sparteine as an external chiral ligand, respectively. They assumed that chiral induction is caused by the asymmetric deprotonation by observing a decrease in the enantioselectivity of racemic α-monodeuterated benzyl ether compared with that of the non-deuterated substrate.

Their proof was based on the theory that enantiomeric excess (ee) will decrease in the α-monodeuterated substrate if chiral induction occurs at the deprotonation step. If chiral induction occurs at the post-deprotonation step, enantioselectivity will not change.[2a] However, the change in ee was small in their substrates because the enantioselectivity of the non-deuterated substrates was moderate.

In a preceding paper, we have reported the highly enantioselective [2,3]-Wittig rearrangement of allyl benzyl ethers using the chiral bis(oxazoline) ligand [(*S*,*S*)-Box-*t*Bu: **L1**].[5] Selectivity exceeded 85% ee except in the substrates with *o*-methoxybenzyl ether. The representative examples are shown in Scheme 1.[6]

We expected that if the hydrogen/deuterium exchange effect was considered in both the enantiomers of α-monodeuterated benzyl ether **1a**-*d*, the mechanism of chiral induction will be elucidated since the reaction of **1a** proceeded with high enantioselectivity (98% ee). Moreover, the reason for low selectivity in the benzyl ether bearing an *o*-methoxy substituent would be revealed using α-monodeuterated **1b**.

Herein, we report the results of the hydrogen/deuterium exchange effect on the asymmetric [2,3]-Wittig rearrangement and discuss how asymmetric induction occurs. Moreover, we discuss the effect of the *o*-methoxy substituent on the chiral induction of the carbanion.

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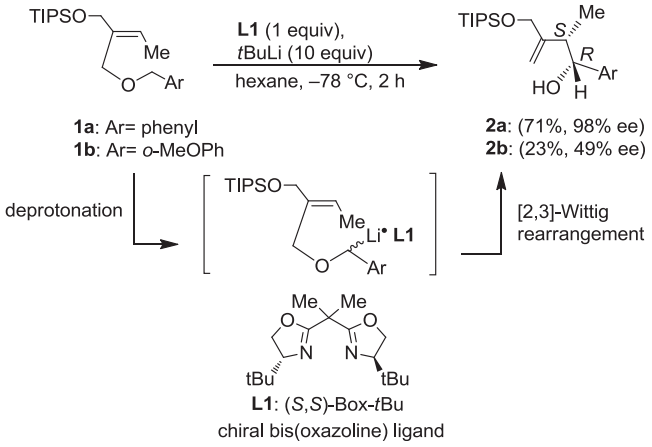
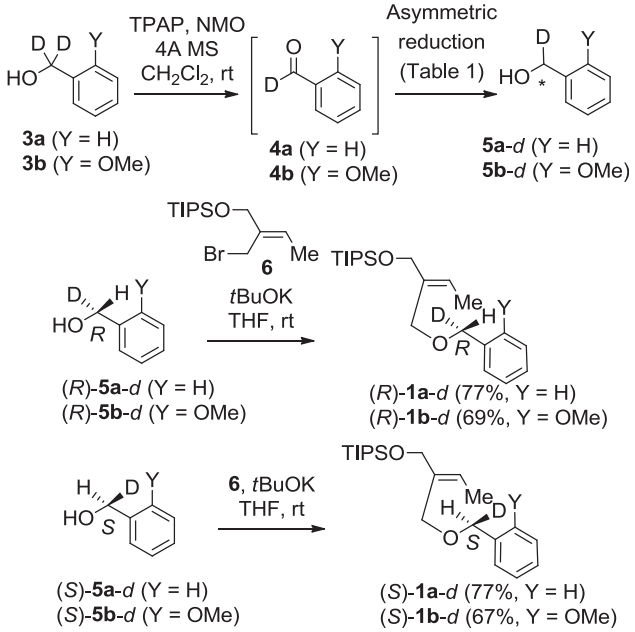


Scheme 1. Asymmetric [2,3]-Wittig rearrangement of **1a** and **1b**.

2. Results and discussion

We planned to examine the [2,3]-Wittig rearrangement using each of the enantiomeric isomers of α-monodeuterated benzyl ethers. Because the abstraction of deuterium is slower than that of hydrogen, the enantiomerically pure carbanion would be initially formed by selective deprotonation. If the rearrangement reaction was sufficiently faster than the racemization of the carbanion, the product would maintain high optical purity. By examining the relationship between the configuration of the carbanion and that of the product, it would be confirmed that the rearrangement proceeded in retention or inversion of the chiral carbanion. If racemization was faster than rearrangement, optical purity would decrease depending on the rate of racemization. In the presence of the chiral ligand, matching of the enantiomeric substrates and the chiral base would be confirmed by comparing the reaction of the enantiomers.

Both enantiomers of α-monodeuterated benzyl ethers **1a**-*d* and **1b**-*d* were synthesized as shown in Scheme 2. α,α-Dideuterated benzyl alcohol (**3a**)[7] was oxidized by tetrapropylammonium perruthenate (TPAP). The resulting α-deuterated benzaldehyde (**4a**) was unstable and was immediately subjected to asymmetric reduction using Corey's catalyst (2-Me-CBS).[8] Thus, α-monodeuterated benzyl alcohols (*R*)- and (*S*)-**5a**-*d* were obtained in 66% and 68% yield in two steps with 93% and 94% ee, respectively (Table 1, entries 1 and 2). Corresponding *o*-methoxybenzyl alcohols (*R*)- and (*S*)-**5b**-*d* were synthesized by TPAP oxidation of dideuterated *o*-methoxybenzyl alcohol (**3b**)[7] followed by asymmetric hydrogenation of purified α-deuterated *o*-methoxybenzaldehyde (**4b**) using BINAP-Ru (II) complex, developed by Takaya and co-workers.[9] By the addition of MeOH as the cosolvent, the asymmetric hydrogenation afforded (*R*)- and (*S*)-**5b**-*d* in good yield with 90% ee respevtively even under moderate H_2 pressure (0.4 MPa) (entries 3 and 4).



Scheme 2. Preparation of (*R*)- and (*S*)-benzyl ethers **1a**-*d* and **1b**-*d*.

The ee of these α-monodeuterated benzyl alcohols **5a**-*d* and **5b**-*d* was determined by ^{1}H NMR spectroscopy after conversion to Mosher esters. The absolute configuration of **5a**-*d* was determined by comparison with the reported specific rotation[10] and that of **5b**-*d* was assumed by Takeuchi's protocol using Mosher ester instead of CFTA ester.[11,12] These alcohols, (*R*)- and (*S*)-**5a**-*d*, were allylated with allylic bromide **6** using *t*BuOK as a base,[5] affording (*R*)- and (*S*)-**1a**-*d* in 77% yield. Similarly, α-monodeuterated *o*-methoxybenzyl alcohols (*R*)- and (*S*)-**5b**-*d* were also converted to the corresponding allylic ethers (*R*)- and (*S*)-**1b**-*d* in 69% and 67% yield, respectively.[13]

On treatment of α-monodeuterated benzyl ethers (*R*)-**1a**-*d* and (*S*)-**1a**-*d* with an achiral base [*t*BuLi (10 equiv), THF, −78 °C],[14] the [2,3]-Wittig rearrangement proceeded to afford the rearranged products (1*R*,2*S*)-**2a**-*d* (52% ee) and (1*S*,2*R*)-**2a**-*d* (53% ee), respectively (Scheme 3). This suggests that C–C bond formation proceeded with the inversion of the initially formed carbanion because a chiral carbanion with high optical purity should be formed via the selective abstraction of the benzylic proton rather than deuterium, which was confirmed by the disappearance of the benzylic proton in the ^{1}H NMR spectral data of the rearranged product **2a**-*d*.[15] Because partial racemization to about 50% ee was observed in the products, the configuration of the carbanion was labile during the time course of the rearrangement reaction.

In contrast, in the presence of the chiral bis(oxazoline) ligand [**L1** (1 equiv), *t*BuLi (10 equiv), hexane, −78 °C], only (*R*)-**1a**-*d* afforded the product with 97% ee[16] along with the inversion of the stereogenic center. Only trace amount of [2,3]-Wittig rearranged product was obtained from (*S*)-**1a**-*d*, but the decomposition of the substrate occurred.

On the basis of the aforementioned results, we assumed the reaction mechanism of previously reported [2,3]-Wittig rearrangement of non-deuterated substrate **1a** as follows.[5] The *pro-S* proton of **1a** was abstracted predominately by the chiral base that was formed from *t*BuLi and (*S*,*S*)-Box-*t*Bu **L1**, and the resulting chiral carbanion underwent stereoinversive C–C bond formation. Furthermore, because no racemization was observed in (*R*)-**1a**-*d* by the use of the base/chiral ligand complex in contrast to the achiral base's case, the chiral ligand appears to prevent the racemization of the carbanion (Scheme 4).

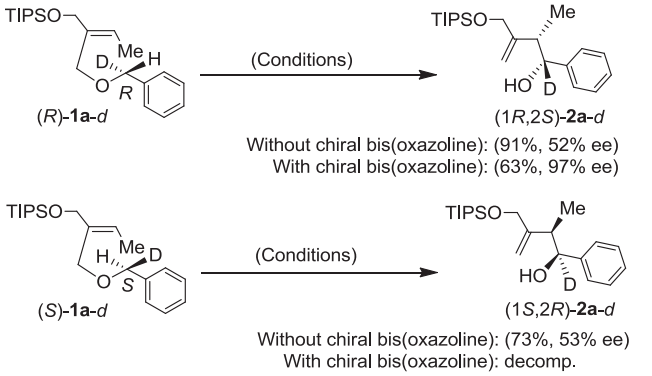
On the other hand, α-monodeuterated *o*-methoxybenzyl ether **1b**-*d* exhibited results that were significantly different from benzyl ether **1a**-*d*. The results are shown in Scheme 5. In the absence of the bis(oxazoline) **L1**, the selective abstraction of hydrogen instead of deuterium and the stereoinversion of the initially formed carbanion were observed in **1b**-*d* again, affording (1*R*,2*S*)-**2b**-*d* and (1*S*,2*R*)-**2b**-*d* from (*R*)- and (*S*)-**1b**-*d*, respectively, in moderate yields (67%–69%). However, the rate of racemization was higher than that of **1a**-*d* to give each the enantiomers of **2b**-*d* with 33% ee.

In the presence of **L1**, the yield from (*R*)-**1b**-*d* (24%–28%) was higher than that from (*S*)-**1b**-*d* (8%–11%) although the yield was low. The base/chiral ligand complex differentiated both the enantiomers (*R*)- and (*S*)-**1b**-*d* to some extent, but the differentiation was obviously low because even the mismatched substrate (*S*)-**1b**-*d* was deprotonated. Furthermore, the chiral ligand restricted the

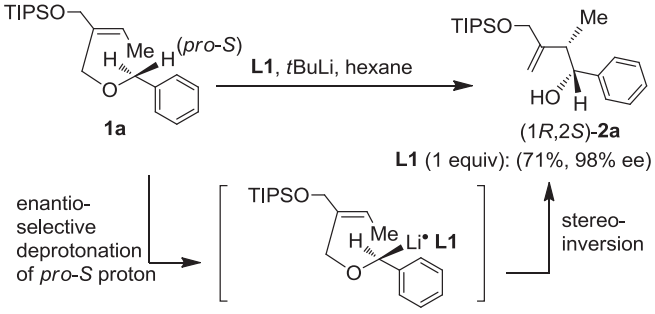
Table 1
Asymmetric reduction of α-deuterated benzaldehydes **4a** and **4b**

Entry	Aldehyde	Conditions	Yield [%][c]	ee [%][d]	Config.
1[a]	**4a**	(*S*)-2-Me–CBS (0.3 equiv), catecholborane (2.0 equiv), toluene–methylcyclohexane–CH_2Cl_2 (2:2:1), −78 °C	66	93	(*R*)-(−)
2[a]	**4a**	(*R*)-2-Me–CBS (0.3 equiv), catecholborane (2.0 equiv), toluene–methylcyclohexane–CH_2Cl_2 (2:2:1), −78 °C	68	94	(*S*)-(+)
3[b]	**4b**	(*S*)-2-Ru(OAc)$_2$(BINAP) (3 mol %), H_2 (0.4 MPa), THF/MeOH (4:1), 0.2 N HCl (15 mol %), 25 °C	83	90	(*R*)-(−)
4[b]	**4b**	(*R*)-2-Ru(OAc)$_2$(BINAP) (3 mol %), H_2 (0.4 MPa), THF/MeOH (4:1), 0.2 N HCl (15 mol %), 25 °C	85	90	(*S*)-(+)

[a] Crude aldehyde was used.
[b] Purified aldehyde was used.
[c] Yield from alcohol **3a** or **3b** in two steps.
[d] Determined by ^{1}H NMR spectroscopy after conversion to Mosher ester.



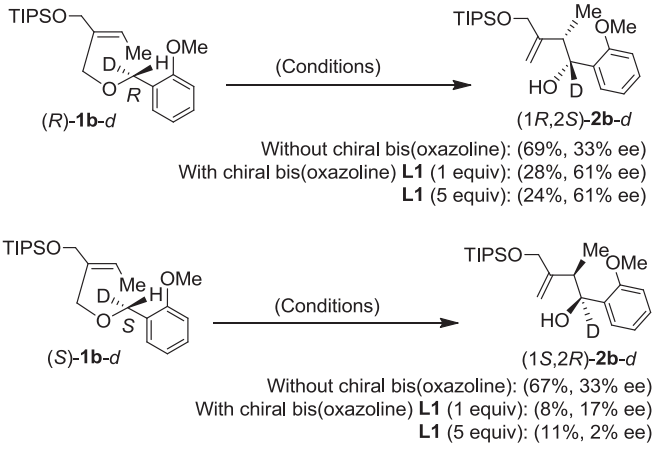
Scheme 3. Asymmetric [2,3]-Wittig rearrangement of (*R*)- and (*S*)-**1a**-*d*.



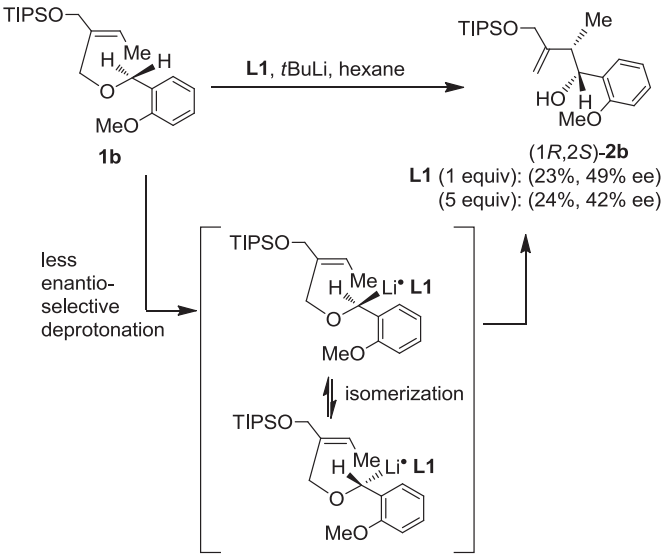
Scheme 4. Proposed mechanism of asymmetric [2,3]-Wittig rearrangement of **1a**.

racemization to some extent in (*R*)-**1b**-*d* (61% ee) but promoted the racemization (2%–17% ee) in its enantiomer (*S*)-**1b**-*d*.

We suggest that low selectivity at the deprotonation step as well as the facile racemization at the post-lithiation step caused low enantioselectivity of the non-deuterated substrates with an *o*-methoxybenzyl group, such as **1b** (Scheme 6).[6] The racemization mechanism is ambiguous. However, considering that the replacement of the *o*-methoxy group with an *o*-ethyl group exhibited high enantioselectivity,[5] the *o*-methoxy group may cause low selective deprotonation by coordinating to the lithium cation of the base. Moreover, the substituent would disturb the lithiated substrate/chiral ligand complex by coordinating to the lithium cation.



Scheme 5. Asymmetric [2,3]-Wittig rearrangement of (*R*)- and (*S*)-**1b**-*d*.



Scheme 6. Proposed mechanism of asymmetric [2,3]-Wittig rearrangement of **1b**.

3. Conclusion

We investigated the hydrogen/deuterium exchange effect to elucidate the reaction mechanism of chiral induction on the

carbanion. As a result, we concluded that the bis(oxazoline) chiral ligand plays an important role in the highly enantioselective deprotonation as well as the prevention of racemization before the [2,3]-Wittig rearrangement. On the other hand, low enantioselectivity observed in the *o*-methoxybenzyl substrates was revealed to be caused by poor differentiation of deprotonation as well as destabilization of the chiral carbanion.

4. Experimental section

4.1. General information and materials

Optical rotations were measured by using a JASCO P-1020 digital polarimeter. ^{1}H, ^{2}D and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 400, 61 and 100 MHz, respectively, with a JEOL JNM-AL-400 spectrometer. Chemical shifts of ^{1}H NMR are expressed in parts per million downfield from tetramethylsilane as an internal standard (δ=0). Chemical shifts of ^{2}D and ^{13}C NMR are expressed as ppm in $CDCl_3$ as an internal standard (δ=7.26 and 77, respectively). The following abbreviations are used: broad=br, singlet=s, doublet=d, triplet=t, quartet=q, and multiplet=m. IR absorption spectra (FT: diffuse reflectance spectroscopy) were recorded with KBr powder with a JASCO FT-6300 IR spectrophotometer, and only noteworthy absorptions (cm^{-1}) are listed. Mass spectra were obtained with a JEOL GC-Mate II mass spectrometer. Synthesis of compounds **1a**, **1b**, **2a**, and **2b** have been reported in the previous paper.[5a] Purification of the crude products was carried out by flash column chromatography. Fuji Silysia Silica Gel BW-300 was used as an adsorbent for column chromatography. For preparative TLC (PTLC), Silica gel 60 F_{254} (Merck) was used. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of Ar or N_2. All organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure with rotary evaporator.

*4.1.1. (R)-α-Deuteriobenzyl alcohol [(R)-**5a**-d].* TPAP (56 mg, 0.16 mmol) was added to a mixture of α,α-dideuteriobenzyl alcohol **3a** (1.76 g, 16.0 mmol), 4 A molecular sieves (8.0 g), and NMO (2.88 g, 24.0 mmol) in CH_2Cl_2 (56 mL) with stirring at rt under Ar and the whole was stirred at the temperature for 16 h. After diluted with CH_2Cl_2, the mixture was filtered through a pad of Celite and the filtrate was washed with 10% HCl, water, saturated $NaHCO_3$, and brine prior to drying (Na_2SO_4) and solvent evaporation. The crude was used without further purification because of instability of the product for air oxidation to give benzaldehyde-α-*d* **4a** (1.70 g) as a gray oil. A 1 M THF solution of catecholborane (24.0 mL, 24.0 mmol) was added dropwise to a mixture of (*S*)-2-methyl-CBS-oxazaborolidine (1 M toluene solution) (4.96 mL, 4.96 mmol) and **4a** (1.70 g) in a mixed solvent of toluene–methylcyclohexane–CH_2Cl_2 (2 : 2: 1, v/v) (178 mL) with stirring at −78 °C. After the mixture was stirred for 3.5 h at this temperature, 4 M HCl in AcOEt (3 mL) and MeOH (19 mL) were added to the mixture. The mixture was washed with 1 M NaOH aqueous solution (30 mL) prior to drying ($MgSO_4$) and solvent evaporation. The residue was chromatographed on silica gel eluting with *n*-hexane/EtOAc (3:1) to give (*R*)-**5a**-*d* (1.15 g, 66% in two steps) as a colorless oil. $[\alpha]_D^{24}$ −1.35 (*c* 0.57, $CHCl_3$) [lit.[10] $[\alpha]_D^{25}$ −1.4 (*c* 3.0, $CHCl_3$)]; ^{1}H NMR: δ:1.70 (d, *J*=4.9 Hz, 1H), 4.68 (br s, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR: δ: 64.3 (*t*, $J_{(C,D)}$=21.5 Hz), 126.8 (2C), 127.3, 128.3 (2C), 140.7; IR (KBr) cm^{-1}: 3308, 2135, 1496; MS (EI) *m*/*z*: 109 $[M]^+$; HRMS (EI) *m*/*z*: calcd for C_7H_7DO: 109.0638, found: 109.0635$[M]^+$.

*4.1.2. (S)-α-Deuteriobenzyl alcohol [(S)-**5a**-d].* The compound was synthesized in a similar manner that as described in (*R*)-**5a**-*d*. The spectral data was identified with those of the (*R*)-enantiomer. Colorless oil (66% in two steps). $[\alpha]_D^{24}$ +1.37 (*c* 0.57, $CHCl_3$) [lit.[10] $[\alpha]_D^{25}$ +1.4 (*c* 3.0, $CHCl_3$)].

*4.1.3. (R)-α-Deuterio-2-methoxybenzyl alcohol [(R)-**5b**-d].* TPAP (53 mg, 0.15 mmol) was added to a mixture of α,α-dideuterio-2-methoxybenzyl alcohol **3b** (2.09 g, 14.9 mmol), 4 A molecular sieves (7.5 g), and NMO (2.62 g, 22.4 mmol) in CH_2Cl_2 (50 mL) with stirring at rt under Ar and the whole was stirred at the temperature for 2.5 h. NMO (175 mg, 1.5 mmol) was added to the solution and the additional stirring was continued to 1.5 h. After diluted with CH_2Cl_2, the mixture was filtered through a pad of Celite and the filtrate was washed with 10% HCl, water, saturated $NaHCO_3$, and brine prior to drying ($MgSO_4$) and solvent evaporation. The crude was chromatographed on silica gel eluting with *n*-hexane/EtOAc (5:1) to give 2-methoxybenzaldehyde-α-*d* **4b** (1.79 g, 88%) as a colorless oil. (*S*)-Ru(OAc)$_2$(binap) (105 mg, 0.124 mmol) and aqueous 0.2 N HCl solution (3.1 mL, ca. 5 equiv to Ru) were added to a solution of **4b** (568 mg, 4.14 mmol) in THF/MeOH (4:1) (20 mL). The mixture was stirring at room temperature for 24 h under H_2 at 0.4 MPa. Then, the solution was poured to water and organic layer was separated. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel eluting with *n*-hexane/EtOAc (3:1→2:1) to give (*R*)-**5b**-*d* (558 mg, 97%) as a pale yellowish green oil. $[\alpha]_D^{22}$ −1.6 (*c* 3.14, $CHCl_3$); ^{1}H NMR δ: 2.30 (s, 1H), 3.87 (s, 3H), 4.67 (s, 1H), 6.89 (d, *J*=7.8 Hz, 1H), 6.95 (*t*, *J*=7.4 Hz, 1H), 7.26–7.31 (m, 2H); ^{13}C NMR δ: 55.2, 61.7 (*t*, $J_{(C,D)}$=22.3 Hz), 110.2, 120.6, 128.7, 128.9, 129.0, 157.4; IR (KBr) cm^{-1}: 3341, 2131, 1603, 1492; MS (EI) *m*/*z*: 139 $[M]^+$; HRMS (EI) *m*/*z*: calcd for $C_8H_9DO_2$: 139.0736, found: 139.0743 $[M]^+$.

*4.1.4. (S)-α-Deuterio-2-methoxybenzyl alcohol [(S)-**5b**-d].* The compound was synthesized in a similar manner that as described in (*R*)-**5b**-*d*. The spectral data was identified with those of the (*R*)-enantiomer. Pale yellowish green oil (85% in two steps). $[\alpha]_D^{22}$ +1.6 (*c* 3.14, $CHCl_3$).

4.2. General procedure of synthesis of substrates for [2,3]-Wittig rearrangement: (*R*,*E*)-1-[α-deuterio(benzyl)oxy]-2-(triisopropylsilyloxymethyl)but-2-en [(*R*)-1a-*d*]

*t*BuOK (438 mg, 3.90 mmol) was added to a solution of benzyl alcohol (*R*)-**5a**-*d* (963 mg, 3.00 mmol) and bromide **6** (357 mg, 3.30 mmol) in dry THF (20 mL) with stirring at rt under Ar. After the stirring was continued for 1 d, the reaction was quenched with saturated NH_4Cl. The mixture was partitioned between EtOAc and water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with water and brine prior to drying and solvent evaporation. The residue was chromatographed on silica gel with hexane/EtOAc (50:1) to give ether (*R*)-**1a**-*d* (812 mg, 77%) as a colorless oil. ^{1}H NMR δ: 0.90–1.20 (m, 21H), 1.69 (d, *J*=7.1 Hz, 3H), 4.09 (s, 2H), 4.25 (s, 2H), 4.45 (s, 1H), 5.80 (q, *J*=7.1 Hz, 1H), 7.23–7.37 (m, 5H); ^{13}C NMR δ: 12.0 (3C), 13.0, 10.0 (6C), 64.9, 65.5, 71.6 (t, $J_{(C,D)}$=21.5 Hz), 123.7, 127.5, 127.7 (2C), 128.3 (2C), 135.8, 138.5; IR (KBr) cm^{-1}: 2116, 1495; MS (FAB) *m*/*z*: 350 $[M+H]^+$; HRMS (FAB) *m*/*z*: calcd for $C_{21}H_{36}DO_2Si$: 350.2626, found: 350.2653 $[M+H]^+$.[17]

*4.2.1. (S,E)-1-[α-Deuterio(benzyl)oxy]-2-(triisopropylsilyloxymethyl) but-2-en [(S)-**1a**-d].* The procedure was same as that was described in the procedure of (*R*)-**1a**-*d*. Colorless oil (77%). The ^{1}H and ^{13}C NMR spectral data was identical to those of the (*R*)-enantiomer.[17]

*4.2.2. (R,E)-1-[α-Deuterio(2-methoxybenzyl)oxy]-2-(triisopropylsilyloxymethyl)but-2-en [(R)-**1b**-d].* Colorless oil (69%). ^{1}H NMR δ: 1.06–1.19 (m, 21H, TIPS), 1.71 (br d, *J*=6.9 Hz, 3H), 3.82 (s, 3H), 4.13

(s, 2H), 4.26 (br s, 2H), 4.49 (s, 1H), 5.80 (q, J=6.9 Hz, 1H), 6.86 (dd, J=8.1, 0.9 Hz, 1H), 6.94 (td, J=7.4, 0.9 Hz, 1H), 7.25 (td, J=8.1, 1.7 Hz, 1H), 7.37 (d, J=7.4, 1.7 Hz, 1H); ^{13}C NMR δ: 12.0 (3C), 13.0, 18.0 (6C), 55.3, 65.3, 65.5, 66.3 (t, $J_{(C,D)}$=21.5 Hz), 110.1, 120.4, 123.4, 127.0, 128.5, 128.9, 136.1, 157.1; IR (KBr) cm^{-1}: 2119, 1603, 1492; MS (FAB) m/z: 380 $[M+H]^+$; HRMS (FAB) m/z: calcd for $C_{22}H_{38}DO_3Si$: 380.2731, found: 380.2750 $[M+H]^+$.[17]

*4.2.3. (S,E)-1-[α-Deuterio(2-methoxybenzyl)oxy]-2-(triisopropylsilyloxymethyl)but-2-en [(S)-**1b**-d].* Colorless oil (67%). The ^{1}H and ^{13}C NMR spectral data were identified to those of the (*R*)-enantiomer.[17]

4.3. General procedure of [2,3]-Wittig rearrangement: (1*R*,2*S*)-1-deuterio-2-methyl-1-phenyl-3-(triisopropylsilyloxymethyl)but-3-en-1-ol [(1*R*,2*S*)-2a-*d*]

*t*BuLi (1.58 M in pentane, 0.80 mL, 1.27 mmol) was added to a solution of allyl benzyl ether (*R*)-**1a**-*d* (44.4 mg, 0.127 mmol) and (*S*,*S*)-Box-*t*Bu (37.4 mg, 0.127 mmol) in dry hexane (0.64 mL) with stirring at −78 °C under Ar. The stirring was continued for 2 h at this temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and allowed to warm to room temperature. The resulting mixture was extracted with EtOAc. The combined extracts were washed with saturated aqueous NH_4Cl, water, and brine prior to drying and solvent evaporation. The crude was purified by PTLC (SiO_2) with hexane/EtOAc (7:1) to give (1*R*,2*S*)-**2a**-*d* (28.0 mg, 63%) as a colorless oil (97% ee). $[\alpha]_D^{27}$ −11.7 (*c* 1.45, $CHCl_3$); ^{1}H NMR δ: 0.99 (d, J=7.1 Hz, 3H), 1.05–1.16 (m, 21H), 2.60 (q, J=7.1 Hz, 1H), 3.04 (s, 1H), 4.08 (d, J=12.9 Hz, 1H), 4.22 (d, J=12.9 Hz, 1H), 4.98 (br s, 1H), 5.20 (br s, 1H), 7.21–7.37 (m, 5H); ^{13}C NMR δ: 11.9 (3C), 12.5, 18.0 (6C), 44.8, 66.0, 75.5 (t, $J_{(C,D)}$=21.5 Hz), 112.6, 126.2 (2C), 126.9, 127.9 (2C), 142.9, 150.5; IR (KBr) cm^{-1}: 3411, 2129, 1651, 1603, 1494; MS (FAB) m/z: 350 $[M+H]^+$; HRMS (FAB) m/z: calcd for $C_{21}H_{36}DO_2Si$: 350.2626, found: 350.2612 $[M+H]^+$.

*4.3.1. (1R,2S)-1-Deuterio-1-(2-methoxyphenyl)-2-methyl-3-(triisopropylsilyloxymethyl)-but-3-en-1-ol [(1R,2S)-**2b**-d].* Colorless oil (61% ee). $[\alpha]_D^{26}$ −6.2 (*c* 0.46, $CHCl_3$); ^{1}H NMR δ: 1.01 (d, J=7.1 Hz, 3H), 1.06–1.16 (m, 21H), 2.65 (q, J=7.1 Hz, 1H), 3.00 (s, 1H), 3.83 (s, 3H), 4.10 (d, J=13.6 Hz, 1H), 4.19 (d, J=13.6 Hz, 1H), 5.02 (s, 1H), 5.20 (s, 1H), 6.85 (d, J=7.9 Hz, 1H), 6.94 (t, J=7.4 Hz, 1H), 7.21 (td, J=7.9 ,1.5 Hz, 1H), 7.40 (dd, J=7.4, 1.5 Hz, 1H); ^{13}C NMR δ: 12.0 (3C), 12.7, 18.0 (6C), 42.1, 55.2, 65.6, 71.8 (t, $J_{(C,D)}$=22.3 Hz), 110.1, 111.0, 120.4, 127.8, 127.8, 131.0, 151.3, 156.1; IR (KBr) cm^{-1}: 3423, 2163, 1650, 1602, 1491; MS (FAB) m/z: 380 $[M+H]^+$; HRMS (FAB) m/z: calcd for $C_{22}H_{38}DO_3Si$: 380.2731, found: 380.2744 $[M+H]^+$.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.03.059.

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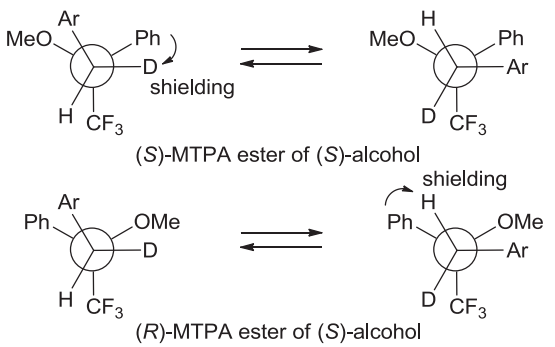

13. From the ^{1}H NMR spectral data, the deuterium exchange ratio of both enantiomers of **1a**-*d* and **1b**-*d* is high.
14. Ten equivalents of base were used to complete the [2,3]-Wittig rearrangement.
15. Hoppe reported the large H/D kinetic isotope effect on deprotonation; see: Hoppe, D.; Paetow, M.; Hintze, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 394–396.
16. Since ee of the substrate is estimated as 93% ee from that of (*R*)-**5a**-*d*, the ee of the resulting (1*R*,2*S*)-**2a**-*d* would be increased to 98% ee by kinetic resolution.
17. Specific rotation was considerably small to be measured with accuracy.