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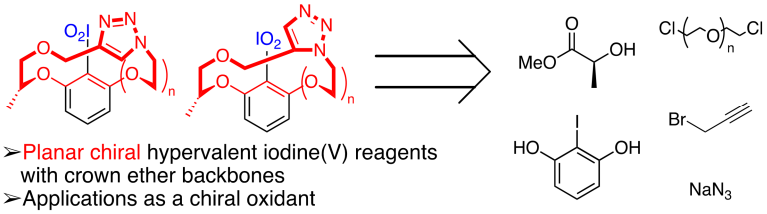

➢Planar chiral hypervalent iodine(V) reagents with crown ether backbones
➢Applications as a chiral oxidant

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ABSTRACT

Novel optically active hypervalent iodine(V) reagents with planar chiral crown ether backbones were synthesized using the intramolecular Huisgen reaction as a key step and L-methyl lactate as the source of chirality. The relative configurations of these reagents and stabilities of planar chiralities were determined by DFT calculations. These planar chiral reagents were applied to the hydroxylative dearomatization/[4+2]-dimerization reactions of phenols to afford bisthymol and biscarvacrol, a natural product, with moderate enantioselectivities.

1. Introduction

Chiral hypervalent iodine reagents have been studied because they can mediate characteristic molecular transformations enantioselectively (Figure 1).[1-3] In 2008, Kita *et al.* developed a chiral hypervalent iodine(III) reagent with a spiro skeleton **1**, which oxidatively spirolactonized 1-naphthol derivatives with enantioselectivities of up to 86% ee.[2d] In 2010, Ishihara, Uyanik *et al.* reported the first highly enantioselective catalytic Kita spirolactonization by employing a lactic-acid-derived C_2-symmetric chiral iodoarene **2b** with *m*CPBA as the stoichiometric co-oxidant, which provided the corresponding products in up to 92% ee.[3a] Following their elegant publication, the catalytic use of chiral hypervalent iodine(III) reagents was expanded to include diamination,[2g] aminofluorination,[2h] spirocyclization,[3c,3d,3i,3k] intramolecular double carbon-carbon bond formation,[3e] fluorination,[3f-3h] and hydroxylative dearomatization.[3m]

Hypervalent iodine(V) reagents are interesting chemical species because they can mediate characteristic transformations.[4] Chiral hypervalent iodine(V) reagent have also been studied; however, few successful examples have been reported.[5] In 2014, Pouységu, Quideau, and co-workers reported the first highly enantioselective chiral hypervalent iodine(V)-mediated oxidative dearomatization/dimerization reactions of substituted phenol derivatives, which produced *ortho*-quinol-based [4+2] cyclodimers in up to 94% ee when a bulky substituent was present in the *ortho* position (Scheme 1).[5e] Subsequently, they also developed a novel salen-type chiral iodane that was used in the asymmetric total synthesis of (–)-bacchopetiolone, which was formed in high yield and up to 82% ee.[5g] Recently, we developed an easy-to-synthesize lactic-acid-derived novel chiral hypervalent iodine(V) reagent **8**, which was applied to the asymmetric oxidative dearomatization of substituted phenol derivatives in combination with TFAA to give the dimerized products in up to 58% ee (Scheme 1).[5f] Despite the above-mentioned excellent examples, a new type of hypervalent iodine(V) reagent that delivers high product enantioselectivity and shows wide substrate scope needs to be developed.

Over the past few decades, planar chiral catalyst have been reported to show high asymmetric inducing abilities (Figure 2).[6,7] In 1997, Fu and co-workers developed a nucleophilic catalyst **9** based on a planar chiral ferrocene unit, which was applied to kinetically resolve secondary alcohols through the formation of acylated products in up to 99.7% ee (up to s = 52).[6a,7a,7b] Following their report, planar chirality has been used in the design of asymmetric catalysis to the present date. Recently, Lu, Zheng, and co-workers reported the syntheses and applications of the first planar chiral iodoarene **13** bearing a [2.2]paracyclophane unit, which was employed as a hypervalent iodine(III) precursor in the enantioselective fluorination of β-ketoesters to form the corresponding products in up to 92% ee (Scheme 2),[7g] and planar chiral crown ether units have been used in the design of chiral metal ligands and chiral-recognition reagents.[8,9] In 1992, Sawamura, Ito, and co-workers reported the development of a chiral ferrocene ligand with a crown ether moiety, which was applied to the asymmetric allylations of β-diketones with enantioselectivities of up to 75% ee.[8] Nevertheless, the applications of planar chiral catalyst remain limited.

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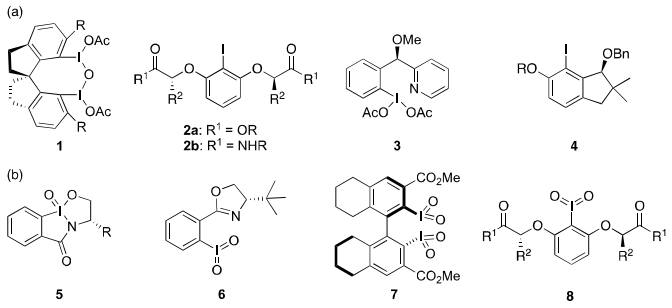
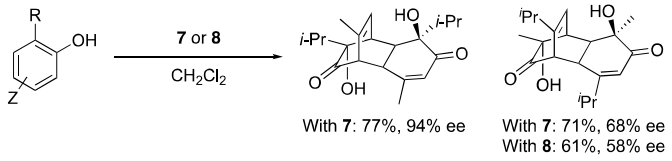


FIGURE 1 Examples of (a) chiral hypervalent iodine(III) reagents and their precursors, and (b) chiral hypervalent iodine(V) reagents.



SCHEME 1 The asymmetric hydroxylative dearomatization/[4+2]-dimerization cascade reactions of phenol derivatives mediated by chiral hypervalent iodine(V) reagents.

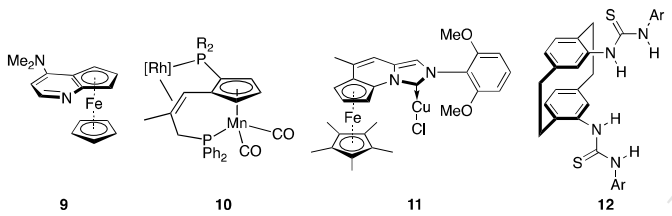
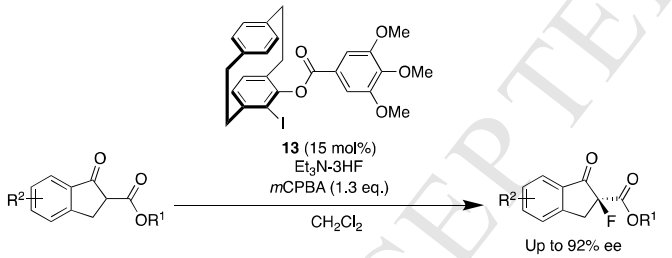
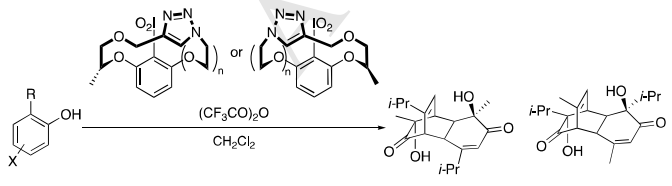


FIGURE 2 Planar chiral catalysts with high asymmetric inducing abilities.



SCHEME 2 Asymmetric fluorinations of β-ketoesters catalyzed by a planar chiral iodine reagent bearing a [2.2]paracyclophane unit.

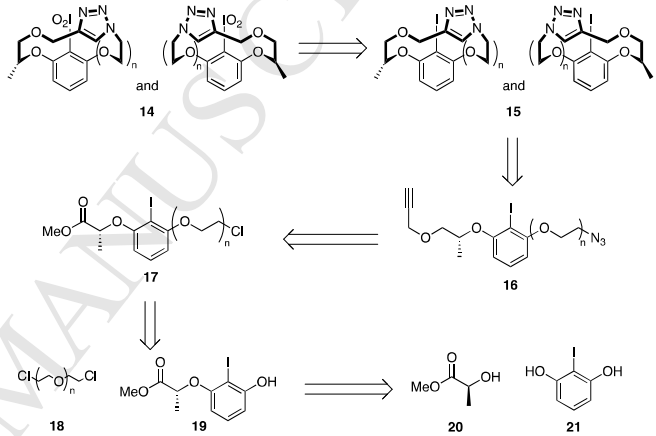


SCHEME 3 Applications of planar chiral hypervalent iodine(V) reagents with crown ether backbones (this work).

In this report, we describe the synthesis of the first planar chiral hypervalent iodine(V) reagents with crown ether backbones (Scheme 3). They are expected to make I(V)···O interactions between intramolecular iodyl moiety early studied by Ochiai *et al.*[10] and intermolecular hydroxy group of substrate,[11] which constructs an efficient asymmetric environment around the prochiral molecules. The construction of the macrocycle is achieved through the Huisgen reaction[12,13] as a key step; these reagents were then used in the asymmetric oxidative dearomatization reactions of phenol derivatives.

2. Results and discussion

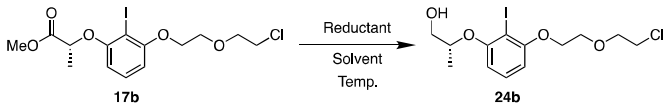
The retrosyntheses of the planar chiral hypervalent iodine(V) reagents are shown in Scheme 4. In this scheme, ester **19** is enantiospecifically formed from 2-iodoresorcinol (**21**) and optically pure (*S*)-methyl lactate using the Mitsunobu reaction, after which the long polyether chain is introduced to give **17**. The azide and alkyne moieties are then installed to form the Huisgen reaction precursor **16**, which is cyclized using the Huisgen reaction to generate the planar chiral iodoarene **15**. After separating both regioisomers of **15** by silica-gel column purification, they are converted into hypervalent iodine(V) reagents **14** by oxidation with DMDO.



SCHEME 4 Retrosynthesis of planar chiral hypervalent iodine(V) reagents bearing crown ether backbones.

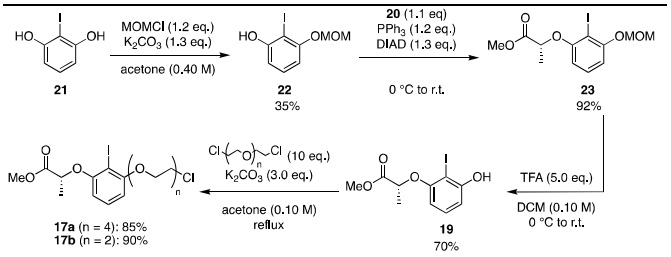
Accordingly, a hydroxyl group of 2-iodoresorcinol (**21**) was MOM-protected following the reported procedure (Scheme 5).[14] Chiral ester **23** was synthesized in 92% yield by the enantiospecific Mitsunobu reaction of **22** with the lactic-acid-derived chiral alcohol using DIAD and PPh_3. The MOM group of **23** was then removed in 70% yield by treatment with trifluoroacetic acid. The long polyether chain was introduced into **19** using K_2CO_3 and a dichloroalkyl polyether to form the corresponding products in 85% and 90% yields, respectively. The reduction of the methoxycarbonyl group of **17b** was next attempted (Table 1). First, $LiAlH_4$ was employed in THF at 0 °C to room temperature, but only the deiodinated product was obtained (Table 1, entry 1); hence the reaction conditions required optimization. The iodine atom was still lost at lower reaction temperatures (Table 1, entries 2–3), and the use of $^{i}Bu_2AlH$ also did not give any desired product even when conducted at –78 ºC with warming to room temperature (Table 1, entries 4–5). The desired iodide **24b** was formed in 10% yield when $NaBH_4$ was used in a mixed THF/MeOH solvent system.

TABLE 1 Optimizing the conditions for the reduction of **17b**

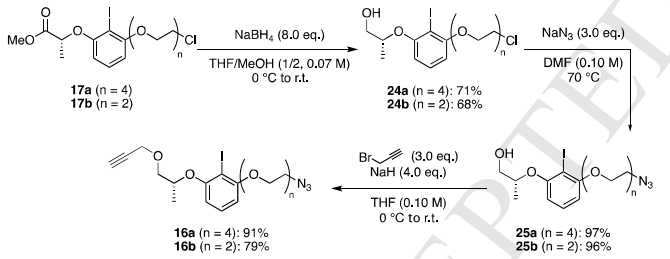


Entry	Reductant (eq.)	Solvent (M)	Temp.	Yield (%)[a]
1	$LiAlH_4$ (5.0)	THF (0.1)	0 ºC to r.t.	n.d.
2	$LiAlH_4$ (10)	THF (0.1)	0 ºC to r.t.	n.d.
3	$LiAlH_4$ (5.0)	THF (0.1)	−40 ºC	n.d.
4	*i*-Bu_2AlH (5.0)	Toluene (0.1)	−78 ºC to 0 ºC to r.t.	n.d.
5	*i*-Bu_2AlH (5.0)	Toluene (0.1)	−78 ºC	n.d.
6	$NaBH_4$ (5.0)	THF/MeOH (1/1) (0.1)	0 ºC to r.t.	10
7	$NaBH_4$ (8.0)	THF/MeOH (1/2) (0.07)	0 ºC to r.t.	68

[a]Yield of isolated product.



SCHEME 5 Synthesis of chiral polyethers **17**.



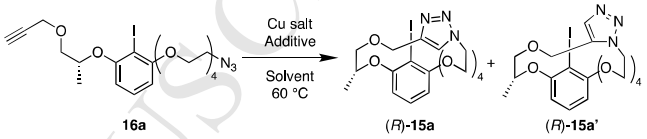
SCHEME 6 Syntheses of Huisgen reaction precursors **16**.

The reaction was finally carried out with 8.0 equivalents of 0.07 M $NaBH_4$ in 1:2 THF/MeOH to give **24b** in 68% yield (Scheme 6). In the same manner, **24a** was synthesized in 71% yield. The azide group was next introduced into **24** with NaN_3 in DMF to give **25a** and **25b** in 97% and 96% isolated yields, respectively, after which they were treated with propargyl bromide under basic condition in THF to afford the Huisgen reaction precursors **16a** and **16b** in 91% and 79% yields, respectively.

With the planar chiral precursors in hand, we used **16a** to optimize the conditions for the intramolecular Huisgen reaction (Table 2). Typical conditions using a copper salt in a mixed H_2O/^{t}BuOH solvent system were first employed (Table 2, entries 1–8),[13a] which resulted in full conversion but none of the desired product, which is due to loss of the iodine atom regardless of the presence or absence of the sodium L-ascorbate (NaAsc) ligand. A trace amount of the desired product was detected, but with low substrate conversion, when the same reaction was conducted in refluxing toluene in the absence of a catalyst (Table 2, entry 9).

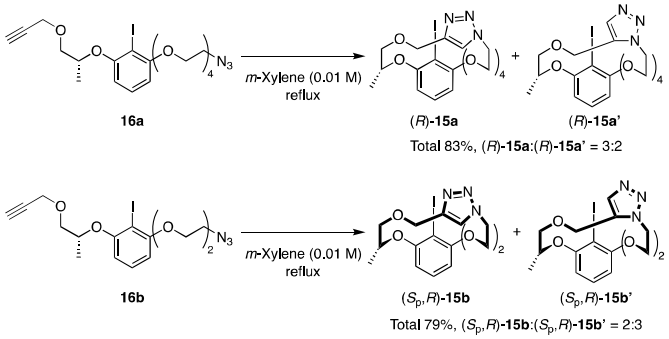
When, the Huisgen reaction was carried out in refluxing *m*-xylene, the desired planar chiral iodine reagent **15a** and **15a'** were obtained in 83% yield with a 3:2 regioisomeric ratio (rr) (Table 2, entry 10).[15] Compound **15b** and **15b'**, with the shorter polyether chain, was also prepared in the same manner as **15a** and **15a'** in 79% yield with a 3:2 rr (Scheme 7). The regioisomers of **15a** and **15b** failed to separate by column chromatography or recrystallization; hence the regioisomeric mixtures of chiral iodoarenes **15** were oxidized into the corresponding hypervalent iodine(V) reagents (Scheme 8). When **15a** was oxidized using dimethyldioxirane (DMDO), the chiral hypervalent iodine(V) reagents (*R*)-**14a** and (*R*)-**14a'** were isolated in 32% and 23% yields, respectively; (S_p,*R*)-**14b** and (S_p,*R*)-**14b'** were isolated in 4% and 15% yields from **15b**, respectively, using the same method. These low yields are ascribable to the high polarity of **14b** and **14b'**, which makes their recovery from silica gel difficult.

TABLE 2 Optimizing the conditions for the Huisgen reaction of **16a**

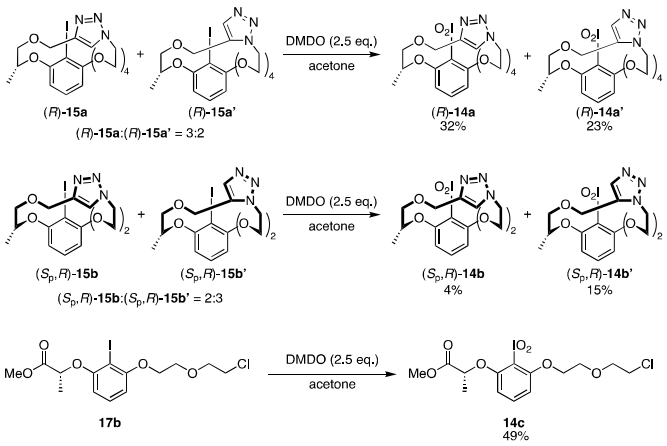


Entry	Cu salt (eq.)	Additive (eq.)	Solvent (M)	Total yield (%)[a]
1	$CuSO_4 \cdot 5H_2O$ (0.5)	–	H_2O/^{t}BuOH (1/1) (0.025)	n.d.
2	$CuSO_4 \cdot 5H_2O$ (0.5)	NaAsc (0.5)	H_2O/^{t}BuOH (1/1) (0.025)	n.d.
3	$CuSO_4 \cdot 5H_2O$ (0.5)	NaAsc (0.5)	H_2O/^{t}BuOH (1/1) (0.01)	n.d.
4	$CuSO_4 \cdot 5H_2O$ (1.0)	NaAsc (1.0)	H_2O/^{t}BuOH (1/1) (0.01)	n.d.
5	$CuSO_4 \cdot 5H_2O$ (1.0)	NaAsc (1.0)	H_2O/^{t}BuOH (3/2) (0.01)	n.d.
6	$CuSO_4 \cdot 5H_2O$ (1.0)	NaAsc (1.0)	H_2O/^{t}BuOH/THF (3/2/1) (0.01)	n.d.
7	$CuSO_4 \cdot 5H_2O$ (1.0)	NaAsc (1.0)	DMF (0.01)	n.d.
8	$CuSO_4 \cdot 5H_2O$ (0.2)	NaAsc (0.4)	DMF (0.005)	n.d.
9[b]	–	–	Toluene (0.01)	Trace
10[b]	–	–	*m*-Xylene (0.01)	83

[a]Yield of **15a** and **15a'** mixture after chromatographic purification. No isolable amount of diastereomers were observed.
[b]The reaction was carried out under reflux.



SCHEME 7 Huisgen reactions of **16**.



SCHEME 8 Synthesis of chiral hypervalent iodine(V) reagents **14**.

We next investigated the oxidation state of **14** (Figure 3). According to Katritzky and co-workers, the oxidation state of an iodine atom can be determined by comparing the ^{13}C-NMR chemical shift of its aromatic *ipso*-carbon atom (C_{ipso}-I^{III} or -I^{V}) with that prior to oxidation.[16] From their report, the ^{13}C-NMR chemical shift of the *ipso*-carbon atom of an I(III) species is shifted by around 15 ppm to lower field compared to that of the corresponding I(I) compound, and around 50 ppm for an I(V) compound. In the present case, although the corresponding I(I) species (*R*)-**15a** could not be isolated, the C_{ipso}-I ^{13}C-NMR chemical shift of (*R*)-**14a** is similar to that previously reported for the I(V) reagent **26**, which indicates that the oxidation state of the iodine in (*R*)-**14a** is five.

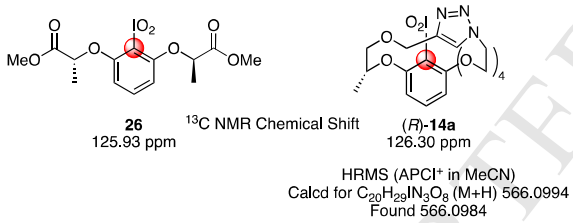


FIGURE 3 Oxidation state determination of **14a**.

Attempts to determine the absolute configuration of the chiral iodine(V) reagents by single-crystal X-ray crystallography failed because of their low crystallinities. Consequently, we calculated the total free energies of both diastereomers of **15** to determine which isomer is preferred. Accordingly, we optimized the geometries of both diastereomers of **15** by DFT calculation at the M05-2X/6-31G* level of theory (LANL2DZ[17] basis set for the iodine atom) in toluene using Gaussian 16[18] (Figure 4); these calculations reveal that (R_p,*R*)-**15a** is 0.15 kcal mol^{-1} more stable than (S_p,*R*)-**15a** in total free energy. Therefore, we conclude that the major diastereomer produced during the stereoselective Huisgen reaction of **16a** is (R_p,*R*)-**15a**, with the minor diastereomer being (S_p,*R*)-**15a**. The same DFT method was also applied to **15a'**, **15b**, and **15b'**, which revealed the different selectivity to that of **15a**. This reason seems to be the decrease of steric repulsion of methyl group on its asymmetric center with crown ether moiety compared with highly flexible **15a**. Additionally, we have calculated for the transition state structures at the epimerization of **15a'** and **15b'** by scanning their dihedral angles, which results are summarized in Figure 5. These results suggest **15b** and **15b'** with smaller crown ether backbones have enough high epimerization barrier for their planar chiralities, although, **15a** and **15a'** with larger crown ether backbones have smaller epimerization barrier. From above calculations, we concluded **15b** and **15b'** can keep their planar chiralties stably, on the other hand, the planar chirality of **15a** and **15a'** is not fixed even at room temperature. Because no changes were observed on ^{1}H-NMR analyses of recovered **15b** and **15b'** after the oxidation reaction shown in Scheme 10, the hypervalent iodine(V) reagent **14** are found to have the same stereochemistry to **15**.[19]

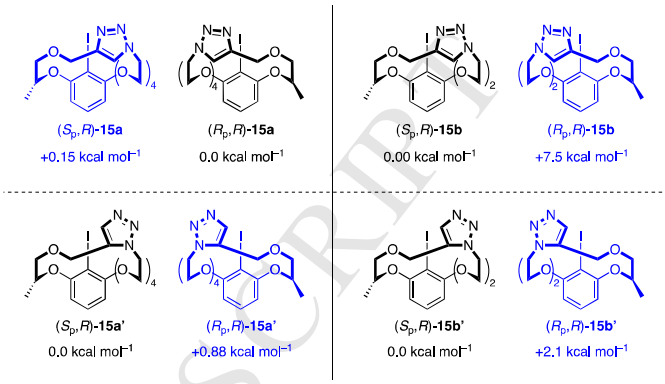
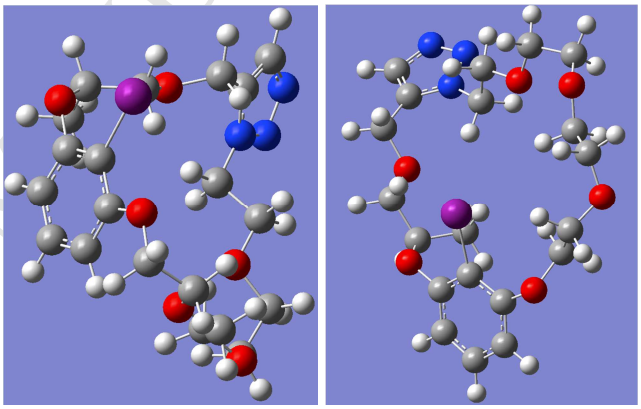
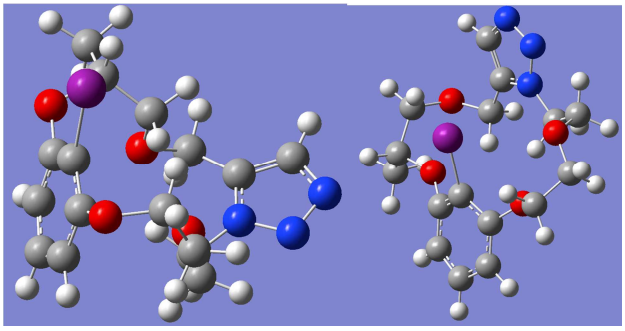


FIGURE 4 Calculational results for the diastereomers of **15**.



Basic structure of (R_p,*R*)-**15a'** 0 kcal mol^{-1} | Transition structure of **15a'** +8.9 kcal mol^{-1}



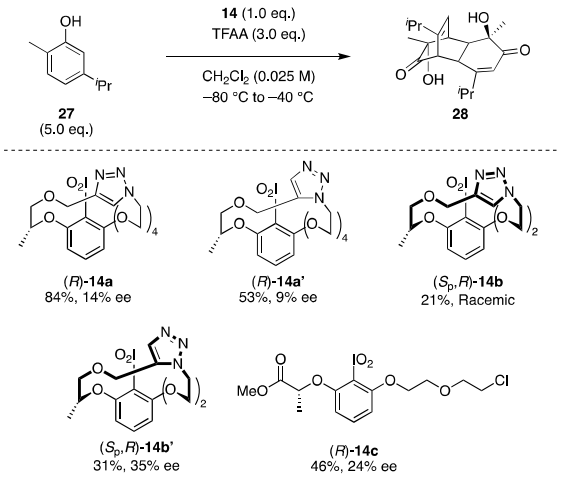
Basic structure of (S_p,*R*)-**15b'** 0 kcal mol^{-1} | Transition structure of **15b'** +32.7 kcal mol^{-1}

FIGURE 5 Calculational results for the transition structures of **15'**.

With the planar-chiral hypervalent iodine(V) reagents in hand, we applied them to the asymmetric oxidation-dimerization reactions of substituted phenol derivatives (Schemes 9 and 10), with carvacrol (**27**) employed as the first example (Scheme 9). The oxidation-dimerization reaction of **27** proceeded to form dimer **28**, a natural product isolated from *callitris macleayana*,[20]

in 84% yield and 14% ee when (*R*)-**14a** (bearing the longer polyether chain) was used with trifluoroacetic anhydride (TFAA) in dichloromethane at low temperature; **28** was obtained in 53% yield and 9% ee when (*R*)-**14a'** was used in this reaction. This result suggests that the **14a** with larger crown ether backbone constructs a more-efficient asymmetric environment than the **14a'**.

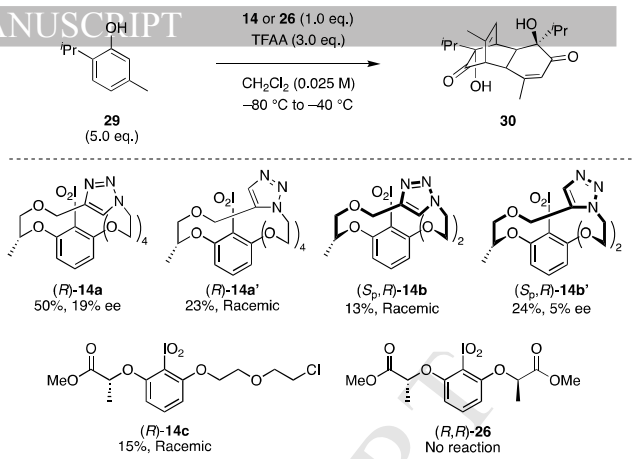
We next examined the use of the planar chiral hypervalent iodine(V) reagent **14b**, which possesses the smaller ether ring. In both cases, the yields of **28** were lower with **14b** than **14a**, which may be ascribable to the low activity associated with the sterically bulky ether ring. On the other hand, the ee of **28** was the highest (35% ee) when (S_p,*R*)-**14b'** was used, which suggests that the smaller ether ring more efficiently blocks the chiral face that leads to the formation of the minor enantiomer of **28**.



SCHEME 9 Asymmetric hydroxylative dearomatization/[4+2]-dimerizations of carvacrol (**27**).

Because our chiral reagents were found to promote the oxidation-dimerization reaction of carvacrol, they were applied to the oxidation of thymol (**29**), which is a regioisomer of carvacrol (Scheme 10). Previously, we applied the chiral-lactic-acid-derived hypervalent iodine(V) reagent (*R*,*R*)-**26** to the present reaction, with no success;[5f] when (*R*)-**14a** was used under the same conditions to oxidize carvacrol, the desired product was obtained in 50% yield with 19% ee. This result shows that **14** is more reactive than the previously reported reagent. Although the planar chiral hypervalent iodide (S_p,*R*)-**14b** with the longer ether chain provided **30** in 5% ee, both (*R*)-**14a'** and (S_p,*R*)-**14b** gave only low yields of racemic product.

To determine the importance of planar chirality in the hypervalent iodine(V) reagent **14**, we synthesized the non-planar chiral reagent (*R*)-**14c** and compared its reactivity with those of **14a** and **14b** (Schemes 9 and 10). Accordingly, chiral ester **17b** was oxidized in 49% yield to the hypervalent iodine(V) reagent (*R*)-**14c** by DMDO, which was then used to oxidize carvacrol (**27**) and thymol (**29**). Although, (*R*)-**14c** was able to oxidize both substrates under the optimized condition, biscarvacrol (**28**) and bisthymol (**30**) were obtained in 46% yield with 24% ee, and 15% yield with racemate, respectively. These yields and enantioselectivities are lower than those mediated by planar chiral reagents **14a** and **14b**. On the basis of these observations, we conclude that the planar chirality of **14** assist its high reactivity and enantiofacial discriminating ability.



SCHEME 10 Asymmetric hydroxylative dearomatization/[4+2]-dimerizations of thymol (**29**).

Finally, we present a plausible reaction mechanism for the present transformations (Figure 6). First, the hypervalent iodine moiety is activated by TFAA to form **A**,[21] which is then nucleophilically attacked by the phenol derivative to form **C**. The oxonium moiety of **C** is deprotonated to form **D**, which undergoes intramolecular asymmetric oxidation to form **E**. The removal of the iodine reagent then produces *ortho*-quinol **F** that is dimerized through a stereospecific [4+2] cycloaddition reaction to give the corresponding product **28**.[4h]

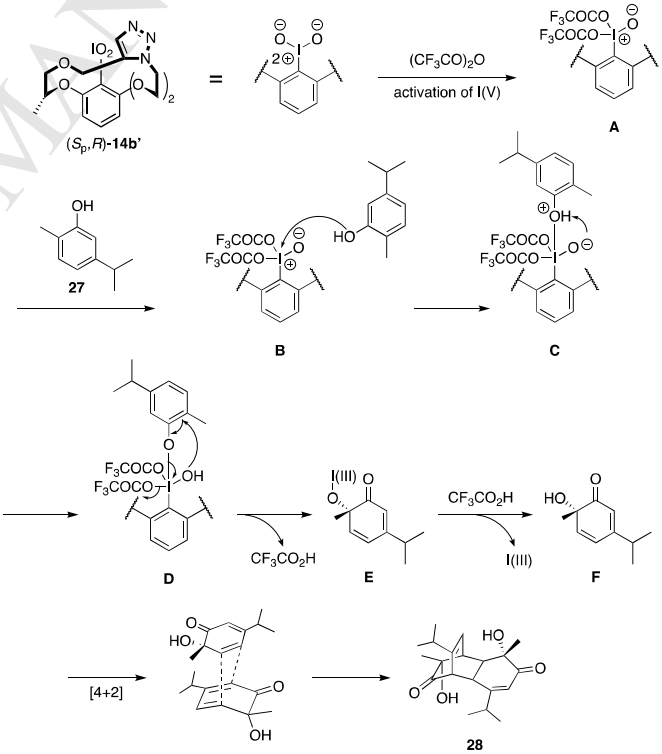


FIGURE 6 Plausible reaction mechanism.

A plausible mechanism that explains the asymmetric induction in the present transformation is shown in Figure 7. When carvacrol (**27**) was oxidized by our reagent, the highest enantioselectivity was observed using (S_p,*R*)-**14b'**, which contains a 16-membered ether ring; i.e., the smaller ring-containing reagent produced the product in higher enantioselectivity. The smaller crown ether ring appears to hydrogen bond more efficiently to the intramolecular iodyl moiety and hydroxy group of the substrate than the larger ring molecule, which makes the better asymmetric environment

around the prochiral carbon atom.[11] On the other hand, for the asymmetric oxidation of thymol (**29**), the 22-membered-ring-containing planar chiral reagent afforded better enantioselectivity, which is ascribable to the larger degree of steric repulsion between with the bulky isopropyl group at the *ortho*-position of thymol and (S_p,*R*)-**14b** with the smaller ring than with (*R*)-**14a**; hence, (*R*)-**14a** can efficiently transfer its asymmetric information.

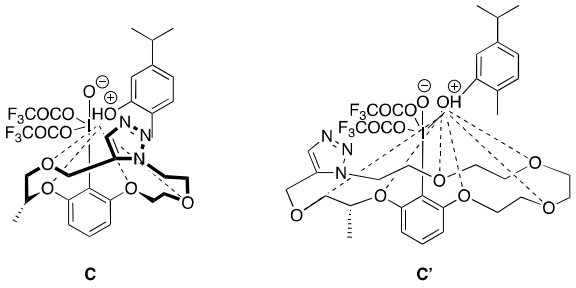


FIGURE 7 Plausible asymmetric induction mechanism for the asymmetric oxidation of carvacrol (**27**).

3. Conclusion

In conclusion, we developed the first planar chiral hypervalent iodine(V) reagents with crown ether backbones. The macrocycles were constructed using the Huisgen reaction as a key step. The stereochemistries of the planar chiral reagents were determined on the basis of DFT calculation of the Huisgen adducts, which revealed **14b** and **14b'** with smaller crown ether backbone had planar chirality stably. These reagents were applied to the asymmetric oxidative dearomatizations of phenol derivatives, which revealed that the prepared hypervalent iodides are potential asymmetric induction reagents. Further investigations into the applications of planar chiral crown ether skeletons to chiral catalyst are currently underway.

4. Experimental section

Instruments and materials

^{1}H-, ^{13}C-NMR spectra were recorded with JEOL JMN ECS400 FT NMR, JNM ECA500 FT NMR or Bruker AVANCEIII-400M, DPR-300 (^{1}H-NMR 300, 400, 500 MHz, ^{13}C-NMR 75, 100 or 125 MHz). ^{1}H-NMR spectra are reported as follows: chemical shift in ppm (δ) relative to the chemical shift of $CHCl_3$ at 7.26 ppm, integration, multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants (Hz). ^{13}C-NMR spectra reported in ppm (δ) relative to the central line of triplet for $CDCl_3$ at 77 ppm. ESI-MS spectra were obtained with Thermo Fisher, Exactive. Optical rotations were measured with JASCO P-2100 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU-1580 pump and UV-2075 UV/Vis detector). FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR-460 Plus). Mp was measured with AS ONE ATM-02. Column chromatography on SiO_2 and neutral SiO_2 was performed with Kanto Silica Gel 60 (40-50 μm). All reactions were carried out under Ar atmosphere unless otherwise noted. Commercially available organic and inorganic compounds were used without further purification. All dehydrated solvents were purchased from Wako Pure Chemical Industries, Ltd, and were used without further purification. DMDO was prepared through the reported procedure.[22]

2-Iodo-3-(methoxymethoxy)phenol (**22**)

To a stirred solution of 2-iodoresorcinol (**21**) (670 mg, 2.84 mmol, 1.0 equiv) and K_2CO_3 (510 mg, 3.69 mmol, 1.3 equiv) in acetone (7 mL) at room temperature was added MOMCl (0.28 mL, 3.41 mmol, 1.2 equiv) and the resulting mixture was stirred at the same temperature for 24 h. The reaction was quenched by addition of H_2O and extracted with EtOAc, dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane:EtOAc = 3:1, v/v) to give phenol **22** (278 mg, 0.994 mmol, 35% yield). The spectral data was matched with the reported value.[23]

Methyl (*R*)-2-(2-iodo-3-(methoxymethoxy)phenoxy)propanoate (**23**)

To a stirred solution of **22** (4.40 g, 15.7 mmol, 1.0 equiv), Ph_3P (4.93 g, 18.8 mmol, 1.2 equiv), and methyl L-(–)-lactate (1.80 g, 17.2 mmol, 1.1 equiv) in THF (78 mL) at 0 ºC was added DIAD (1.9 M toluene solution, 10.7 mL, 20.3 mmol, 1.3 equiv) and the resulting mixture was stirred at the room temperature for 72 h. After evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane:EtOAc = 3:1, v/v) to give chiral ester **23** (5.29 g, 14.5 mmol, 92% yield).

Colorless solid, Mp 45-47ºC; ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.18 (t, *J* = 8.3 Hz, 1H), 6.74 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.39 (dd, *J* = 8.3, 1.0 Hz, 1H), 5.26 (d, *J* = 7.0 Hz, 1H), 5.24 (d, *J* = 7.0 Hz, 1H), 4.78 (q, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 3.51 (s, 3H), 1.71 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 172.16, 157.97, 157.66, 129.67, 108.48, 106.94, 94.97, 80.64, 74.22, 56.46, 52.37, 18.61; HRMS (ESI$^+$ in MeCN) calcd for $C_{12}H_{16}O_5I$ (M+H) 367.0037 found 367.0030; IR (KBr) 3469, 3086, 2957, 2820, 1936, 1737, 1458, 1248, 921, 638 cm^{-1}; $[\alpha]_D^{20}$ = –10.46 (*c* = 0.43, $CHCl_3$).

Methyl (*R*)-2-(3-hydroxy-2-iodophenoxy)propanoate (**19**)

To a stirred solution of **23** (5.24 g, 14.3 mmol, 1.0 equiv) in CH_2Cl_2 (143 mL) at 0 ºC was slowly added TFA (5.47 mL, 71.6 mmol, 5.0 equiv) and the resulting mixture was stirred at the room temperature for 5 h. The reaction was quenched by addition of H_2O and extracted with CH_2Cl_2, dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane:EtOAc = 4:1, v/v) to give phenol **19** (3.23 g, 10.0 mmol, 70% yield).
Colorless solid, Mp 65-67ºC; ^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.13 (t, *J* = 8.2 Hz, 1H), 6.68 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.24 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.48 (s, 1H), 4.78 (q, *J* = 6.8 Hz, 1H), 3.76 (s, 3H), 1.70 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 172.01, 157.09, 156.42, 130.08, 108.64, 104.66, 79.37, 74.00, 52.41, 18.58; HRMS (ESI$^+$ in MeCN) calcd for $C_{10}H_{12}O_4I$ (M+H) 322.9775 found 322.9771; IR (KBr) 3418, 2999, 2949, 2847, 1913, 1727, 1458, 1223, 1061, 773 cm^{-1}; $[\alpha]_D^{20}$ = –24.64 (*c* = 0.53, $CHCl_3$).

General procedure for the alkylation of **19**.

To a stirred solution of **19** (1.0 equiv) in acetone (0.1 M) at room temperature was added K_2CO_3 (3.0 equiv) and corresponding alkyl dichloride (10.0 equiv) and the resulting mixture was refluxed for 48 h. After filtration and evaporation of the solvent

under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane:EtOAc = 4:1, v/v) to give chiral ester **17**. Spectroscopic data of **17a** and **17b** are given below.

Methyl (*R*)-2-(3-(2-(2-(2-(2-(2-chloroethoxy)ethoxy)ethoxy)ethoxy)-2-iodophenoxy)propanoate (**17a**)

Light yellow oil, 1.16 g, 2.24 mmol, 85% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.18 (t, *J* = 8.3 Hz, 1H), 6.51 (d, *J* = 8.3 Hz, 1H), 6.36 (d, *J* = 8.3 Hz, 1H), 4.78 (q, *J* = 6.8 Hz, 1H), 4.17 (dd, *J* = 5.3, 4.8 Hz, 2H), 3.93 (dd, *J* = 6.0, 4.8 Hz, 2H), 3.82-3.84 (m, 2H), 3.74-3.77 (m, 5H), 3.68-3.71 (m, 6H), 3.62 (t, *J* = 5.9 Hz, 2H), 1.70 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 172.17, 159.17, 158.04, 129.66, 106.36, 106.19, 79.93, 74.23, 71.34, 71.25, 70.80, 70.67, 70.62, 69.50, 69.37, 52.34, 42.72, 18.60 HRMS (ESI$^-$ in MeCN) calcd for $C_{18}H_{25}O_7ClI$ (M−H) 515.0339 found 515.0355; IR (NaCl) 2872, 1756, 1734, 1587, 1457, 1253, 1134, 1021, 767, 668 cm^{-1}; $[\alpha]_D^{20}$ = –10.51 (*c* = 1.42, $CHCl_3$).

Methyl (*R*)-2-(3-(2-(2-chloroethoxy)ethoxy)-2-iodophenoxy)propanoate (**17b**)

Light yellow oil, 432 mg, 1.01 mmol, 90% yield
^{1}H-NMR (300 MHz, CHLOROFORM-D) δ 7.19 (t, *J* = 8.3 Hz, 1H), 6.51 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.36 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.78 (q, *J* = 6.8 Hz, 1H), 4.18 (dd, *J* = 5.3, 4.2 Hz, 2H), 3.95-3.99 (m, 4H), 3.75 (s, 3H), 3.68 (t, *J* = 5.7 Hz, 2H), 1.70 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 172.15, 159.06, 158.06, 129.69, 106.44, 106.12, 79.89, 74.22, 71.98, 69.54, 69.45, 52.35, 43.06, 18.60; HRMS (ESI$^+$ in MeCN) calcd for $C_{14}H_{19}O_5ClI$ (M+H) 428.9960 found 428.9952; IR (NaCl) 2952, 2873, 1755, 1587, 1463, 1252, 1210, 1134, 1021, 766 cm^{-1}; $[\alpha]_D^{20}$ = –12.84 (*c* = 1.29, $CHCl_3$).

General procedure for the reduction of **17**.

To a stirred solution of **17** (1.0 equiv) in THF/MeOH = 1/2 (0.07 M) at 0 ºC was added $NaBH_4$ (8.0 equiv) and the resulting mixture was stirred at room temperature for 24 h. The reaction was quenched by addition of H_2O and extracted with EtOAc, dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane:EtOAc = 3:1, v/v) to give chiral alcohol **24**. Spectroscopic data of **24a** and **24b** are given below.

(*R*)-2-(3-(2-(2-(2-(2-chloroethoxy)ethoxy)ethoxy)ethoxy)-2-iodophenoxy)propan-1-ol (**24a**)

Light yellow oil, 673 mg, 1.38 mmol, 71% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.22 (t, *J* = 8.3 Hz, 1H), 6.55 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.50 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.48-4.55 (m, 1H), 4.18 (dd, *J* = 5.1, 4.6 Hz, 2H), 3.94 (dd, *J* = 5.4, 4.6 Hz, 2H), 3.82-3.84 (m, 2H), 3.74-3.77 (m, 4H), 3.68-3.71 (m, 6H), 3.62 (t, *J* = 5.9 Hz, 2H), 1.35 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 159.04, 157.90, 129.76, 107.54, 105.76, 81.05, 71.34, 71.23, 70.80, 70.67, 70.61, 69.50, 69.31, 66.20, 42.72, 16.09 (One carbon peak is overlapped with other one); HRMS (ESI$^-$ in MeCN) calcd for $C_{17}H_{25}O_6ClI$ (M−H) 487.0390 found 487.0411; IR (NaCl) 3453, 2873, 1586, 1461, 1296, 1252, 1092, 1019, 766, 666 cm^{-1}; $[\alpha]_D^{20}$ = –28.35 (*c* = 0.58, $CHCl_3$).

(*R*)-2-(3-(2-(2-chloroethoxy)ethoxy)-2-iodophenoxy)propan-1-ol (**24b**)

Light yellow oil, 209 mg, 0.523 mmol, 68% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.22 (t, *J* = 8.3 Hz, 1H), 6.56 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.50 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.48-4.55 (m, 1H), 4.19 (dd, *J* = 5.1, 4.4 Hz, 2H), 3.94-3.98 (m, 4H), 3.75-3.77 (m, 2H), 3.68 (t, *J* = 5.8 Hz, 2H), 2.15 (s, 1H), 1.35 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 158.92, 157.91, 129.78, 107.62, 105.68, 80.98, 77.33, 71.96, 69.53, 69.38, 66.18, 43.03, 16.06; HRMS (ESI$^-$ in MeCN) calcd for $C_{13}H_{17}O_4ClI$ (M−H) 398.9866 found 398.9878; IR (NaCl) 3433, 2931, 1585, 1455, 1377, 1247, 1088, 920, 765, 666 cm^{-1}; $[\alpha]_D^{20}$ = –37.17 (*c* = 1.24, $CHCl_3$).

General procedure for the azidation of **24**.

To a stirred solution of **24** (1.0 equiv) in DMF (0.1 M) at room temperature was added NaN_3 (3.0 equiv) and the resulting mixture was stirred at 70 ºC for 24 h. The reaction was quenched by addition of H_2O and saturated NH_4Cl *aq.* and extracted with Et_2O, dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane:EtOAc = 2:1, v/v) to give chiral azide **25**. Spectroscopic data of **25a** and **25b** are given below.

(*R*)-2-(3-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)-2-iodophenoxy)propan-1-ol (**25a**)

Colorless oil, 562 mg, 1.13 mmol, 97% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.21 (t, *J* = 8.3 Hz, 1H), 6.55 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.50 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.48-4.55 (m, 1H), 4.18 (dd, *J* = 5.4, 4.4 Hz, 2H), 3.93 (dd, *J* = 5.4, 4.4 Hz, 2H), 3.81-3.84 (m, 2H), 3.75-3.77 (m, 2H), 3.65-3.72 (m, 8H), 3.37 (t, *J* = 5.1 Hz, 2H), 2.19 (s, 1H), 1.34 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 158.98, 157.86, 129.71, 107.50, 105.70, 80.99, 77.32, 71.18, 70.76, 70.64, 70.61, 69.97, 69.44, 69.25, 66.13, 50.63, 16.06; HRMS (APCI$^+$ in MeCN) calcd for $C_{17}H_{26}O_6N_3I$ (M+) 495.0866 found 495.0864; IR (NaCl) 3446, 2925, 2871, 2108, 1586, 1457, 1252, 1092, 934, 766 cm^{-1}; $[\alpha]_D^{20}$ = –25.49 (*c* = 0.92, $CHCl_3$).

(*R*)-2-(3-(2-(2-azidoethoxy)ethoxy)-2-iodophenoxy)propan-1-ol (**25b**)

Colorless oil, 204 mg, 0.501 mmol, 96% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.14 (t, *J* = 8.3 Hz, 1H), 6.48 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.43 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.40-4.47 (m, 1H), 4.11 (dd, *J* = 5.4, 4.1 Hz, 2H), 3.87 (dd, *J* = 5.4, 4.1 Hz, 2H), 3.79 (dd, *J* = 5.6, 4.6 Hz, 2H), 3.67-3.69 (m, 2H), 3.35 (t, *J* = 5.0 Hz, 2H), 2.30 (s, 1H), 1.27 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 158.85, 157.83, 129.75, 107.54, 105.63, 80.91, 77.31, 70.63, 69.46, 69.35, 66.08, 50.82, 16.01; HRMS (APCI$^+$ in MeCN) calcd for $C_{13}H_{19}O_4N_3I$ (M+H) 408.0415 found 408.0409; IR (NaCl) 3420,

2931, 2871, 2108, 1586, 1457, 1252, 1092, 932, 765 cm^{-1}; $[\alpha]_D^{20}$ = –30.56 (*c* = 1.30, $CHCl_3$).

General procedure for the propargylation of **25**.

To a stirred solution of NaH (4.0 equiv) in THF (0.01 M) was added **25** (1.0 equiv) in THF at room temperature and the resulting mixture was cooled to 0 ºC. The mixture was added propargyl bromide (3.0 equiv) and the resulting solution was stirred at room temperature for 4 h. The reaction was quenched by addition of H_2O at 0 ºC and extracted with EtOAc, dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel, hexane:EtOAc = 2:1, v/v) to give Huisgen precursors **16**. Spectroscopic data of **16a** and **16b** are given below.

(*R*)-1-(2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethoxy)-2-iodo-3-((1-(prop-2-yn-1-yloxy)propan-2-yl)oxy)benzene (**16a**)

Light brown oil, 519 mg, 0.974 mmol, 91% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.20 (t, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 6.48 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.54-4.62 (m, 1H), 4.28 (d, *J* = 2.4 Hz, 2H), 4.17 (dd, *J* = 5.4, 4.5 Hz, 2H), 3.93 (dd, *J* = 5.4, 4.5 Hz, 2H), 3.82-3.84 (m, 2H), 3.78 (dd, *J* = 10.3, 6.0 Hz, 1H), 3.65-3.72 (m, 9H), 3.38 (t, *J* = 5.0 Hz, 2H), 2.45 (t, *J* = 2.4 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 159.03, 158.25, 129.54, 107.58, 105.53, 80.94, 79.68, 75.31, 74.53, 72.96, 71.20, 70.79, 70.67, 70.64, 69.98, 69.47, 69.27, 58.88, 50.65, 17.11; HRMS (APCI$^+$ in MeCN) calcd for $C_{20}H_{29}O_6N_3I$ (M+H) 534.1096 found 534.1094; IR (NaCl) 3284, 2930, 2869, 2109, 1586, 1457, 1251, 1099, 1019, 766 cm^{-1}; $[\alpha]_D^{20}$ = –17.05 (*c* = 1.38, $CHCl_3$).

(*R*)-1-(2-(2-azidoethoxy)ethoxy)-2-iodo-3-((1-(prop-2-yn-1-yloxy)propan-2-yl)oxy)benzene (**16b**).

Light brown oil, 173 mg, 0.173 mmol, 79% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.20 (t, *J* = 8.3 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 6.49 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.55-4.62 (m, 1H), 4.28 (d, *J* = 2.4 Hz, 2H), 4.18 (dd, *J* = 5.1, 4.4 Hz, 2H), 3.95 (dd, *J* = 5.1, 4.4 Hz, 2H), 3.86-3.88 (m, 2H), 3.68-3.80 (m, 2H), 3.42 (t, *J* = 5.1 Hz, 2H), 2.45 (t, *J* = 2.4 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 158.92, 158.24, 129.59, 107.64, 105.49, 80.87, 79.66, 75.29, 74.54, 72.93, 70.67, 69.51, 69.40, 58.86, 50.88, 17.09; HRMS (APCI$^+$ in MeCN) calcd for C16H21O4N3I (M+H) 446.0571 found 446.0572; IR (NaCl) 3288, 2931, 2869, 2109, 1586, 1457, 1250, 1099, 1020, 764 cm^{-1}; $[\alpha]_D^{20}$ = –5.11 (*c* = 2.61, $CHCl_3$).

General procedure for the Huisgen reaction of **16**.

The solution of **16** (1.0 equiv) in *m*-xylene (0.01 M) was stirred at 140 ºC for 24 h. After evaporation of the solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel, EtOAc:MeOH = 9:1, v/v) to give the regioisomeric mixture of planar chiral iodoarene **15a**, **15a'** and **15b**, **15b'** in 83% and 79% total yields, which was used next step without further purification.

General procedure for the oxidation of **15**.

The solution of DMDO (0.010-0.058 M in acetone) was added to the mixture of iodoarenes **15** and **15'**, which was stirred for 1 h. After the evaporation of solvent under reduced pressure, the residue was purified by preparative TLC (MeCN:MeOH = 3:1-1:1).

(*R*)-**14a**

Colorless oil, 97.4 mg, 0.183 mmol, 32% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.57 (s, 1H), 7.42 (t, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.19 (d, *J* = 13.6 Hz, 1H), 4.90 (d, *J* = 13.6 Hz, 1H), 4.55-4.68 (m, 3H), 4.26-4.34 (m, 2H), 3.57-3.90 (m, 14H), 1.44 (d, *J* = 6.3 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 159.06, 158.60, 135.58, 135.52, 132.43, 126.30, 109.25, 107.68, 76.61, 73.97, 70.67, 70.62, 70.52, 70.40, 70.18, 69.01, 68.56, 64.34, 46.63, 15.34
HRMS (APCI$^+$ in MeCN) calcd for $C_{20}H_{29}O_8N_3I$ (M+H) 566.0994 found 566.0984; IR (NaCl) 3461, 2922, 2871, 1586, 1464, 1360, 1253, 1096, 754, 664 cm^{-1}; $[\alpha]_D^{20}$ = +0.44 (*c* = 1.27, $CHCl_3$).

(*R*)-**14a'**

Colorless oil, 72.1 mg, 0.135 mmol, 23% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 8.33 (s, 1H), 7.36 (t, *J* = 8.3 Hz, 1H), 6.67 (d, *J* = 8.3 Hz, 2H), 4.89 (d, *J* = 12.8 Hz, 1H), 4.66 (d, *J* = 12.8 Hz, 1H), 4.64-4.59 (m, 1H), 4.52-4.56 (m, 2H), 4.23-4.38 (m, 2H), 3.58-3.98 (m, 14H), 1.45 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 159.22, 158.14, 143.85, 135.56, 126.74, 125.89, 110.33, 108.42, 77.20, 76.90, 71.29, 70.86, 70.74, 70.34, 69.73, 69.00, 64.62, 49.89, 16.82 (One peaks are overlapped with other one); HRMS (APCI$^+$ in MeCN) calcd for $C_{20}H_{29}O_8N_3I$ (M+H) 566.0994 found 566.0981; IR (NaCl) 3464, 2920, 2870, 1584, 1470, 1355, 1250, 1090, 941, 774 cm^{-1}; $[\alpha]_D^{20}$ = –27.10 (*c* = 0.37, $CHCl_3$).

(S_p,*R*)-**14b**

Colorless oil, 4.94 mg, 0.0111 mmol, 4% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.47 (s, 1H), 7.38 (t, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 8.3 Hz, 1H), 4.93 (d, *J* = 12.0 Hz, 1H), 4.69-4.77 (m, 2H), 4.38-4.43 (m, 3H), 4.27 (td, *J* = 10.1, 7.4 Hz, 1H), 3.96-4.05 (m, 3H), 3.81-3.88 (m, 1H), 3.70-3.75 (m, 1H), 3.65 (d, *J* = 10.1 Hz, 1H), 1.46 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 160.57, 158.73, 135.58, 133.61, 133.43, 127.82, 111.39, 111.30, 78.04, 75.24, 70.94, 69.22, 68.09, 60.74, 45.74, 17.16; HRMS (APCI$^+$ in MeCN) calcd for $C_{16}H_{21}O_6N_3I$ (M+H) 478.0470 found 478.0461; IR (NaCl) 3450, 2979, 2925, 2871, 1584, 1463, 1228, 1085, 1007, 758 cm^{-1}; $[\alpha]_D^{20}$ = +1.14 (*c* = 0.53, $CHCl_3$).

(S_p,*R*)-**14b'**

Colorless oil, 18.1 mg, 0.0407 mmol, 15% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.97 (s, 1H), 7.28 (t, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 5.05 (d, *J* = 12.3 Hz, 1H), 4.70 (ddd, *J* = 12.9, 9.2, 1.6 Hz, 1H), 4.56-4.63 (m, 1H), 4.37-4.48 (m, 4H), 4.10-4.16 (ddd, *J* = 12.9, 9.2, 1.6 Hz, 1H), 3.80-3.89 (m, 2H), 3.73-3.77 (m, 1H), 3.53 (dd, *J* = 10.8, 3.1 Hz, 1H), 3.38 (dd, *J* = 10.8, 3.1 Hz, 1H),

1.50 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 159.67, 157.38, 143.24, 135.02, 126.17, 125.10, 110.28, 108.97, 70.21, 69.67, 68.30, 66.45, 64.75, 53.40, 49.61, 17.42; HRMS (APCI$^+$ in MeCN) calcd for $C_{16}H_{21}O_6N_3I$ (M+H) 478.0470 found 478.0462; IR (NaCl) 3459, 3151, 2981, 2869, 1584, 1463, 1231, 1084, 930, 764 cm^{-1}; $[\alpha]_D^{20}$ = –6.69 (*c* = 1.90, $CHCl_3$).

Methyl (*R*)-2-(3-(2-(2-chloroethoxy)ethoxy)-2-iodylphenoxy)propanoate ((*R*)-**14c**)

Colorless oil, 26.7 mg, 0.0581 mmol, 49% yield
^{1}H-NMR (400 MHz, CHLOROFORM-D) δ 7.41 (t, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 4.89 (q, *J* = 6.9 Hz, 1H), 4.31 (dd, *J* = 4.9, 4.5 Hz, 2H), 3.98-4.01 (m, 4H), 3.77 (s, 3H), 3.71 (dd, *J* = 6.1, 4.9 Hz, 2H), 1.71 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (101 MHz, CHLOROFORM-D) δ 171.92, 160.05, 157.67, 135.85, 125.78, 109.60, 108.46, 76.31, 72.00, 70.27, 68.90, 53.05, 43.60, 18.43; HRMS (APCI$^+$ in MeCN) calcd for $C_{14}H_{19}O_7ClI$ (M+H) 460.9859 found 460.9848; IR (NaCl) 3461, 3073, 2953, 1754, 1575, 1471, 1258, 1078, 765, 659 cm^{-1}; $[\alpha]_D^{20}$ = –41.59 (*c* = 1.03, $CHCl_3$).

General procedure for asymmetric hydroxylative phenol dearomatization/[4+2]-dimerization cascade reaction.

To a stirred solution of phenol derivatives (5.0 equiv) in CH_2Cl_2 (0.025 M) at room temperature was slowly added chiral I(V) reagent (1.0 equiv) in CH_2Cl_2 and the resulting mixture was stirred at –80 ºC for 10 min. TFAA (3.0 equiv) was slowly added at the same temperature and slowly warm to –40 ºC and stirred for 24 h. The reaction was quenched by addition of saturated $NaHCO_3$ *aq*. and extracted with CH_2Cl_2, dried over Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the yield of product was determined by ^{1}H-NMR using benzyl phenyl ether as internal standard. Pure HPLC sample was prepared by preparative TLC purification of residue (silica gel, hexane:EtOAc = 3:1, v/v). The ee of product was determined by HPLC analysis under the reported condition.[5e] The spectroscopic data was matched with the reported value.[5e]

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at xx.