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Asymmetric Dearomatizing Spirolactonization of Naphthols Catalyzed by Spirobiindane-Based Chiral Hypervalent Iodine Species

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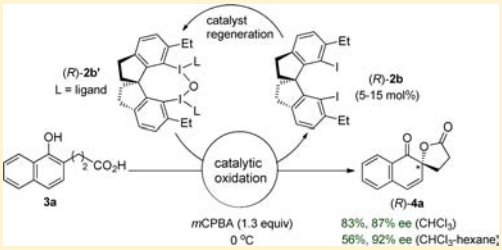
Supporting Information

ABSTRACT: This report details the development of a spirobiindane-based chiral hypervalent iodine reagent, especially focusing on its structural elucidation for effective asymmetric induction of the chiral spiro center during the oxidative dearomatizing spirolactonization of naphthols. In this study we synthesized a new series of *ortho*-functionalized spirobiindane catalysts and demonstrated that the enantioselectivity can be dramatically improved by the presence of the substituents *ortho* to the iodine atom. The structural elucidation of a spirobiindane-based hypervalent iodine catalyst has led to further improvement in the stereoselective construction of the spiro center during the oxidative dearomatizing spirolactonization of naphthols. Thus, catalytic oxidation with the highest reported level of enantioselectivity in hypervalent iodine chemistry has been achieved with also an excellent level of asymmetric induction (92% ee for substrate **3a**). As a result, this study, dealing with a series of modified iodine catalysts, can provide important clues about the transition state and reaction intermediate to help scientists understand the origin of the stereoselectivity. A plausible transition-state model and intermediate in the reaction for the stereoselective formation of spirolactone products are postulated by considering the *ortho*-substituent effect and the results of X-ray analysis. In this reaction model, the high enantiomeric excess obtained by using the spirobiindane catalysts could be well explained by the occupation of the equatorial site and extension of the surroundings around the hypervalent iodine bonds by the introduced *ortho*-substituent. Thus, this study would contribute to estimation of the chiral hypervalent iodine compounds in asymmetric reactions.



INTRODUCTION

Hypervalent iodine reagent has gained importance as a useful alternative to toxic heavy-metal oxidants, such as lead, thallium, mercury, etc., due to its low toxicity, high stability, and easy handling, in combination with a wide array of reactivities.[1] It is widely recognized as a valuable oxidant for performing environmentally benign reactions. Oxidations by some representative hypervalent iodine reagents—phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA)—have already been applied in many total syntheses of natural products and their pivotal intermediates,[2] in which the reagents are conventionally used as stoichiometric oxidants. From economic and environmental viewpoints, the recycling and catalytic utilization of hypervalent iodine reagents developed in recent years enhances their practical applications.[3]

In spite of the significant advances and usefulness of hypervalent iodine reagents as mild organo-oxidants in many synthetic reactions, asymmetric variants with control of the chiral hypervalent iodine compound have been rarely accomplished, and realization of a high enantioselectivity is still a challenge.[4−9] Early reports of the use of chiral hypervalent iodine compounds for asymmetric reactions are shown in Figure 1. These are classified by the two types of chiral molecules: those bearing a chiral leaving group attached to the iodine atom, and the compounds in which the chiral moiety is based on iodoarene backbones. The former type of compounds, having chirality at the leaving ligands, such as optically active carboxylic acids,[5a,b] sulfonic acids,[5c] and alcohols,[5d,e] were intensively investigated in early studies. Our research group also

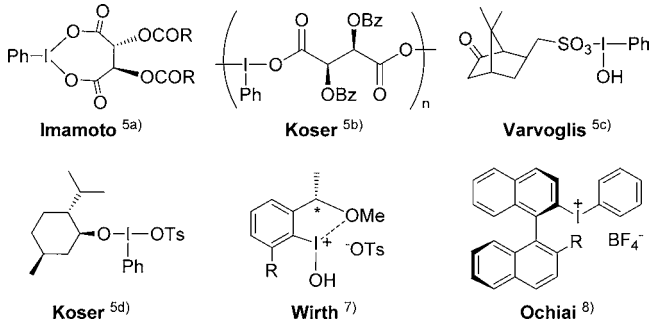


Figure 1. Chiral hypervalent iodine(III) reagents reported in early studies.

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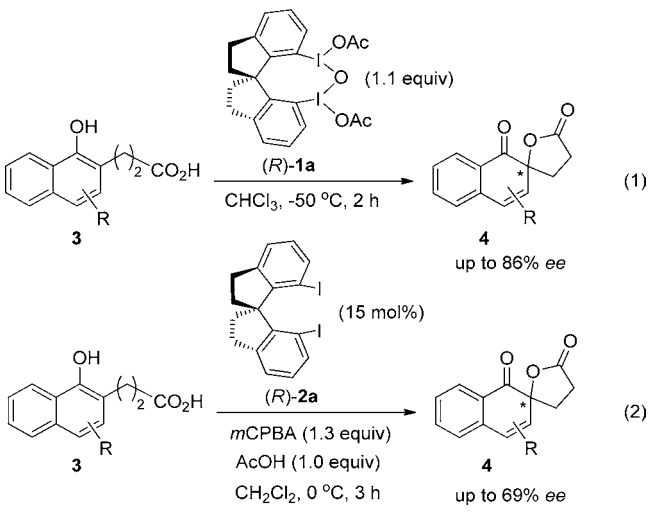
applied the strategy to the asymmetric oxidation of sulfides into sulfoxides and obtained moderate enantiomeric excess (ee) values.[6] However, oxidations mediated by hypervalent iodine reagents liberate the chiral ligands from the iodine during the early stages, and thus application of the system to other asymmetric oxidations was quite difficult.

It appears that a hypervalent iodine reagent based on a chiral ligand has not been effective for asymmetric induction in an extensive array of reactions. Therefore, the latter types of chiral compounds were recently explored with the aim of achieving extensive asymmetric oxidations. Wirth's research group has designed new molecules having a chiral moiety *ortho* to the iodine atom on the aromatic ring for the enantioselective oxygenation of ketones and alkenes (up to 65% ee value).[7] Ochiai and co-workers prepared chiral binaphthyl molecules having an iodine group and applied the salts to the asymmetric α-arylation of ketones (up to 53% ee).[8] These compounds, based on chiral iodoarene backbones, could expand the possibilities for hypervalent iodine reagents in extensive asymmetric oxidations, although there is still a requirement for improved enantioselectivities.

Over the past few decades, we have been engaged in the development of new reactions using hypervalent iodine reagents. In our continuous study of phenolic oxidations,[10] we have recently become interested in efficient construction of the *ortho*-spirolactone architecture as a potentially useful subunit for synthesizing some natural products.[11] It has been shown that the reactions that provided *ortho*-spirolactones well proceeded using reactive oxygen-bridged hypervalent iodine compounds.[12] To control the chiral spiro center in the products, we established in 2008 the first protocol for enantioselective *ortho*-spirocyclization of naphthols **3** bearing a carboxylic acid moiety as an intramolecular nucleophilic side chain by designing a novel chiral hypervalent iodine(III) compound **1a** based on the spirobiindane backbone (Scheme 1, eq 1).[13,14] Surprisingly, the reaction was found to proceed at an unprecedented excellent level for asymmetric induction (up to 86% ee value) in the field of hypervalent iodine-mediated transformations. The results are noteworthy because the use of other chiral iodoarenes (as in Figure 1) resulted in the formation of almost racemic spirolactones **4**. We also reported the catalytic use of the chiral hypervalent iodine compound combining the corresponding chiral iodoarene **2a** and stoichiometric *m*-chloroperbenzoic acid (*m*CPBA) as a co-oxidant (Scheme 1, eq 2). This is a landmark that proved the chiral iodine compound as a new entrance to asymmetric organocatalysis.[15]

Scheme 1. Dearomatizing *ortho*-Spirocyclization of Naphthols 3 Using Chiral Hypervalent Iodine Reagent 1a and Its Precursor 2a



Since our first report of the asymmetric dearomatization of naphthols, several asymmetric phenolic oxidations[16,17] as well as other transformations[18,19] have appeared in this area, employing new chiral hypervalent iodine compounds. With respect to our asymmetric spirolactonization and effective catalytic systems as model cases, Ishihara's group discovered in 2010 a new C_2-symmetric hypervalent iodine catalyst bearing two chiral lactate groups[20] at the *ortho* positions of the iodophenyl ring in their evaluation of catalysts for the reactions.[17] The new catalyst successfully provided the spirolactone product **4a** with up to 92% ee from the substrate **3a** by 10−15 mol% loadings with stoichiometric *m*CPBA.

In this paper, we report new results on the highly enantioselective organocatalytic spirolactonization of naphthols **3** based on the use of a chiral spirobiindane hypervalent iodine compound. Further elucidation of the chiral reagent's structure reveals that catalysts having a substituent at the *ortho* positions of the iodoarene rings are more effective and promise better stereocontrol for the enantioselective transformations. The excellent and remarkable utility of the *ortho*-substituted spirobiindane compound **2b** (*vide infra*) as an asymmetric catalyst in the presence of *m*CPBA as a co-oxidant is well demonstrated.

RESULTS AND DISCUSSION

Initial Investigation of the Catalytic Reaction Using Spirobiindane Iodoarene 2a. Recent progress in the field of hypervalent iodine-catalyzed oxidation has given it a significant position in synthetic chemistry.[3] In one of the pioneering studies, we reported an efficient *in situ* reoxidation hypervalent iodine(III) species from organoiodine(I) compounds,[21] and in 2005 we successfully established a general catalytic cycle for the oxidation of phenols and related compounds using *m*CPBA as a co-oxidant.[22] Based on previous results, we began the optimization of the catalytic conditions of the asymmetric spirolactonization using the original spirobindane catalyst (*R*)-**2a**. The optimizations were carried out with substrate **3a** and stoichiometric *m*CPBA in the presence of 15 mol% of the chiral iodoarene (*R*)-**2a** in several solvents (0.05 M concentration of substrate **3a**) at 0 °C.

As we expected, a remarkable solvent effect was observed even under the catalytic conditions, and the enantioselectivity was significantly affected by the solvent polarities, similar to the stoichiometric reactions.[13] Thus, less-polar solvents, chloroform, dichloromethane, and 1,2-dichloroethane, were used to afford the spirolactone **4a** with 47%, 66%, and 67% ee, respectively (for chemical yields 66%, 61%, and 57%, respectively, after 3 h), while the use of highly polar solvents, acetonitrile and 1,1,1,3,3,3-hexafluoro-2-propanol, gave the product **4a** with inferior and disappointing ee values (17% and 3% ee, respectively). With the aim of promoting the reaction rate, a higher concentration of the substrate **3a** was examined, but it did not improve the product yield. Subsequently, additives for the effective generation of the *in situ* reactive hypervalent iodine(III) species were also explored. Addition of 1 equiv of acetic acid to the reaction mixture of the

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substrate **3a**, stoichiometric *m*CPBA, and 15 mol% of (*R*)-**2a** in dichloromethane did not affect the ee value and gave only little improvement in the chemical yield (70% yield after 3 h, 65% ee; cf. the result in the absence of acetic acid mentioned above, 61% yield after 3 h, 66% ee). Finally, we checked the influence of the loading amount of (*R*)-**2a** on the yield and ee value. The use of 5 mol% of (*R*)-**2a** significantly decreased the chemical yield (16% yield after 12 h, 63% ee) at 0 °C, but when it was used at room temperature, a result comparable to that obtained with the higher catalyst loading (62% yield after 12 h, 61% ee for 5 mol% (*R*)-**2a**) was obtained after a prolonged reaction time. Therefore, the use of a lower amount of the catalyst still maintained the enantioselectivity but affected the chemical yield of the product **3a** to some extent.

We then confirmed the catalytic reaction for several 1-naphthol derivatives **3b–d** (Figure 2) under the standard

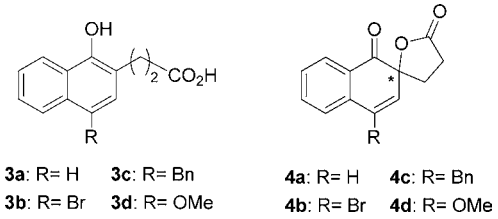
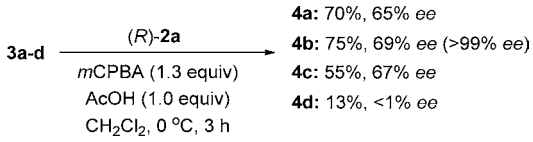


Figure 2. 4-Substituted derivatives of naphtholcarboxylic acids **3b–d** and their corresponding spirolactone products **4b–d**.

conditions, treating 15 mol% of (*R*)-**2a** and stoichiometric *m*CPBA in the presence of acetic acid in dichloromethane (Scheme 2). Reaction of the 4-substituted derivatives gave the

Scheme 2. Catalytic Asymmetric Spirocyclization of Naphthols 3a–d Using 15 mol% (*R*)-2a[a]



[a]The ee value in parentheses is that obtained after a single recrystallization.

corresponding spirolactones **4** in moderate to good yields and enantioselectivities, except for the substrate **3d**. In accord with the theoretical studies and experimental evidence for generation of phenoxenium ion during phenolic oxidations,[23] apparently the presence of the electron-donating group in substrate **3d** decreased the ee of the reaction. For a well-crystallized spirolactone such as **4b**, we could obtain for the first time[24] the enantiomerically pure spirolactone **4b** from the enantio-enriched sample after recrystallization.

It was revealed by this study that the chiral iodine compound **2a** offers a very moderate stereocontrol for the representative naphtholcarboxylic acids **3a–d** even under catalytic conditions, although there is a need for improved enantioselectivities. Thus, we next considered optimizing the structure of the spirobiindane catalyst **2a** to realize a highly selective asymmetric cyclization.

Design and Use of *ortho*-Functionalized Chiral Spirobiindane Iodoarene Catalysts. With the aim of designing an iodine catalyst that shows a higher enantioselectivity, we resumed our investigation of the possible structure of the spirobiindane catalyst in the hypervalent iodine state. In the catalyst (*R*)-**1′**, one side of the iodine atom of the reactive species is effectively shielded by the indane plane (Figure 3, left). Due to the rigid spirobiindane backbone of the catalyst, the conformation is almost maintained throughout the course of the reactions.

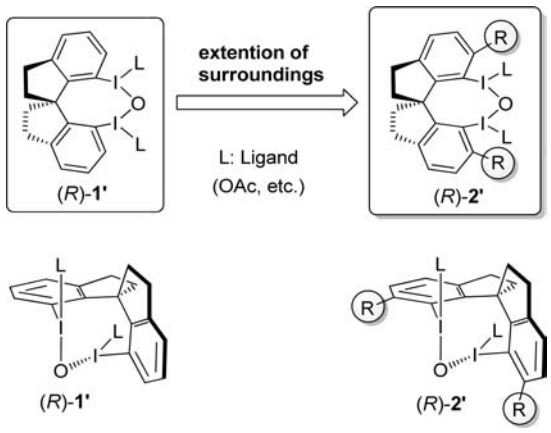


Figure 3. Extension of the equatorial surroundings around the iodine atom by *ortho*-substituent (*R*) to affect the chiral environment.

Previously, Wirth and co-workers reported that the introduction of an achiral substituent at the *ortho*-aryl ring position relative to the iodine atom improved the enantioselectivity in the α-oxygenation of ketones and dioxygenation of alkenes.[7b,c] They concluded that the enhanced enantioselectivity is due to a well-organized transition state in which the reactant is distributed more closely to the chiral environment, positioned in the axial space by an additional steric effect on the reaction sequence. In this scenario, introduction of an *ortho*-substituent at the equatorial position of the hypervalent iodine bonds also seems to produce some steric influence on the apically positioned ligand (L) and substrate **3** in the case of our chiral iodoarene catalyst (*R*)-**2a** (Figure 3, right), thus affecting the enantioselectivity. More extensively surrounding the iodine(III) atom by both the spirobiindane ring and a newly introduced *ortho*-substituent might positively affect the enantioselective performance during the reactions.

The *ortho*-functionalized chiral spirobiindane-based iodoarene catalysts have been developed from the diamine (*R*)-**5**,[14] a precursor of (*R*)-**2a** described in our previous report,[13] as a common intermediate in the synthetic sequences shown in Scheme 3. To prepare the spirobiindanes having *ortho*-alkyl groups, iodination of (*R*)-**6**, after introduction of an acetyl group into the *ortho* positions of the amines by the Houben–Hoesch-type reaction,[25] by the conventional protocol afforded (*R*)-**7**, which is a key compound in other *ortho*-functionalized derivatives. (*R*)-**7** was then transformed into the iodoarene (*R*)-**2b** having a linear alkyl substituent, while the ketone group of (*R*)-**7** was subjected to reduction by sodium tetrahydroborate ($NaBH_4$) to give the secondary alcohol (*R*)-**8** as the precursor of (*R*)-**2c–f**. The iodoarenes (*R*)-**2g–i** were readily prepared by controlled halogenation of the diamine (*R*)-**5**, followed by the same iodination procedure.

The enantioselectivities of the *ortho*-functionalized iodoarenes (*R*)-**2b–i** in the dearomatizing spirocyclization were evaluated using naphtholcarboxylic acid **3a** as a reference substrate (Table 1). To our delight, newly prepared iodoarene

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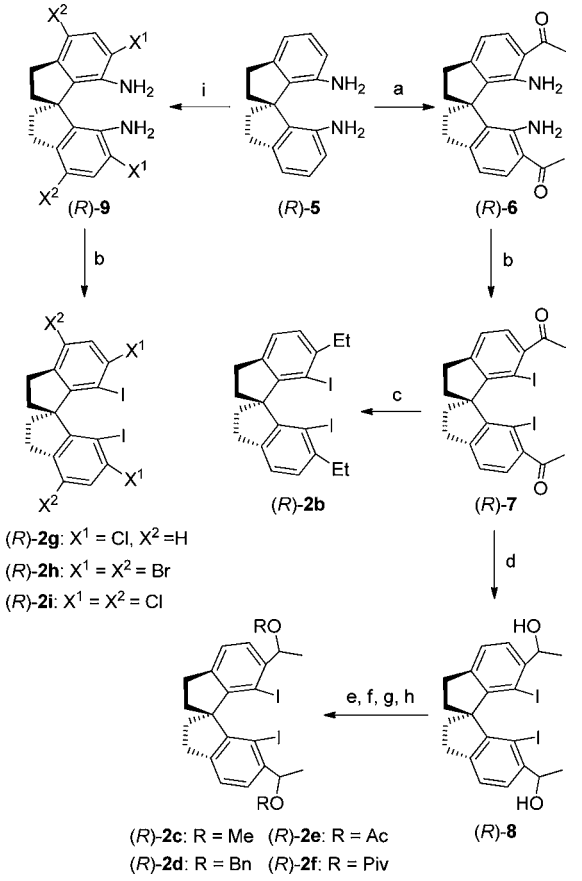
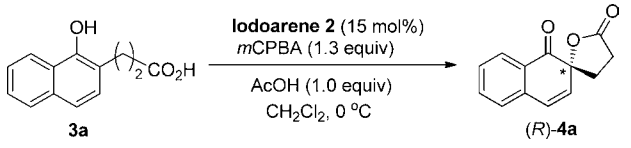
Scheme 3. Synthesis of *ortho*-Substituted Chiral Iodoarenes 2b–i[a]



[a]Reagents and conditions: (a) BCl_3, dichloromethane/acetonitrile, $ZnCl_2$, reflux, then HCl (aq) reflux. (b) $NaNO_2$, TFA, KI, H_2O. (c) CF_3SO_3H, Et_3SiH, dichloromethane. (d) $NaBH_4$, tetrahydrofuran (THF)/methanol. (e) NaH, MeI, THF. (f) NaH, BnBr, THF. (g) Ac_2O, NEt_3, cat. 4-DMAP, dichloromethane. (h) PivCl (Piv = pivaloyl), NEt_3, cat. 4-DMAP, dichloromethane. (i) NCS or NBS, dichloromethane.

Table 1. Screening of the *ortho*-Functionalized Spirobiindane Catalysts 2b–i



entry	*ortho*-substituted iodoarene (**2**)	time	yield, ee[a]
1[b,c]	(*R*)-**2b**	15 h	62%, 82% ee
2[c]	(*R*)-**2c**	46 h	51%, 80% ee
3	(*R*)-**2d**	18 h	42%, 72% ee
4	(*R*)-**2e**	40 h	45%, 77% ee
5	(*R*)-**2f**	10 h	52%, 75% ee
6[c]	(*R*)-**2g**	12 h	39%, 81% ee
7	(*R*)-**2h**	6 h	15%, 83% ee
8	(*R*)-**2i**	6 h	15%, 77% ee

[a]Determined by HPLC analysis using chiral separation column. [b]Reaction was performed at −10 °C. [c]Performed with 10 mol% of the catalysts. Compare these results with 70% yield of the product (+)-(*R*)-**4a** with 65% ee obtained with the original spirobiindane catalyst (*R*)-**2a** under the same conditions.

(*R*)-**2b** (10 mol%), having a linear alkyl substituent at the *ortho* position, could produce the spirolactone **4a** with a higher enantioselectivity (entry 1, 82% ee) in comparison to the original spirobiindane (*R*)-**2a** (65% ee). Similarly, a series of branched secondary groups in the iodoarenes (*R*)-**2c–f** improved the enantioselectivities,[26] among which the smallest substituent (R = Me; (*R*)-**2c**) showed the best result of 80% ee (entry 2). As the size of the substituent increased (R = Bn, Ac, and Piv; (*R*)-**2d–f**), spirolactone **4a** was obtained with slightly lower ee's between 72 and 78% (entries 3–5). As we expected, halogenated iodoarenes (*R*)-**2g–i** also gave better enantioselectivities,[27a] but the reactions were stopped within a few hours and the chemical yields dropped significantly (entries 6–8). This seemed to be the result of inefficient generation of the reactive iodine(III) species from the electron-deficient iodine atom of (*R*)-**2g–i** caused by the electron-withdrawing nature of the halogen groups.[3c,22] All the iodoarene catalysts (*R*)-**2b–i** are likely to produce the same enantiomer (*R*)-**4a** as the non-*ortho*-substituted one, (*R*)-**2a**, during the reactions.

Thus, (*R*)-**2b** was the best iodoarene catalyst in terms of both reactivity and enantioselectivity among those examined. To confirm the catalyst changes, the versatility and scope of the *o*-ethyl-substituted iodoarene (*R*)-**2b** in our dearomatizing spirolactonization were tested for various naphthol derivatives **3** under the catalytic conditions. Representative results are given in Table 2. Using chloroform as the solvent instead of dichloromethane, spirolactone **4a** was obtained with a slightly higher ee value, 87% (entry 1). A lower catalyst loading still permitted good enantioselectivities, but the reactions required higher concentrations and the addition of acetic acid (see eq 2). As the polarity of the solvent decreased upon addition of hexane, the selectivity further improved to 92% ee (entry 2). Catalytic oxidation of the 4-substituted naphthol derivatives **3b** and **3c** gave the corresponding spirolactones **4b** and **4c** with improved enantioselectivities (entries 3 and 4). In accord with our previous experience using the original chiral spirobiindane catalyst **2a** (*vide supra*), racemic spirolactone **4d** was obtained from the substrate **3d** with a methoxy substituent (entry 5). The present system was widely applicable for 3- (entry 7), 5- (entries 8–11), and 6-substituted (entries 12 and 13) naphtholcarboxylic acids **3f–l**, maintaining good ee values. However, the efficiency of the reaction as well as the stereoselectivity with the spirobiindane catalyst **2b** became significantly lower for substrate **3m**, having a *peri*-methyl group (entry 14, R^5 = Me). Hence, the substituent at the 8-position of the 1-naphthol **3m** might cause steric congestion between the spirobiindane ring of the catalyst **2** and the substrate **3m**, hindering organization of a plausible catalyst–substrate pair during the reaction.[28] After the reactions, most of the iodoarene **2b** (at least 90% used) could be recovered in a pure form by column chromatography, and when we reused the recovered catalyst **2b**, the reaction proceeded with the same level of yields and ee values.

Enantiomerically pure spirolactones (>99% ee) could be obtained in gram quantities after one-time recrystallization of the products **4** formed with the catalyst (*R*)-**2b**. Using the well-crystallized spirolactone **4b**, the absolute stereochemistry at the spiro carbon for the product (+)-**4b** was determined to be *R* by X-ray analysis (Figure 4).[29]

Based on these results regarding the extensive use of catalysts **2** and substrates **3**, we postulated a reasonable transition-state model for the formation of spirolactone products with the *R*-configuration caused by the catalyst (*R*)-**2b** as shown in

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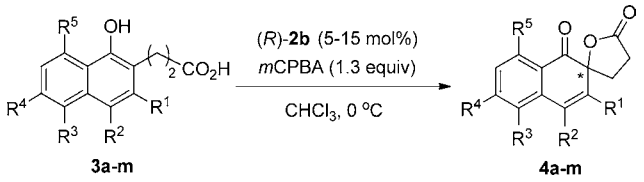
Table 2. Examples of the Asymmetric Spirocyclization Substrates 3a−m for *ortho*-Substituted Spirobiindane Catalyst (*R*)-2b[a]



entry	substrate	product	R^1	R^2	R^3	R^4	R^5	time	yield, ee[b]
1	**3a**	(+)-(*R*)-**4a**	H	H	H	H	H	8 h	83%, 87% ee
								12 h	60%, 87% ee[c]
								12 h	85%, 83% ee[c,d]
2[e]	**3a**	(+)-(*R*)-**4a**	H	H	H	H	H	10 h	56%, 92% ee
3[d]	**3b**	(+)-(*R*)-**4b**	H	Br	H	H	H	7 h	96%, 82% ee
4[e]	**3c**	(+)-**4c**	H	Bn	H	H	H	8 h	80%, 80% ee
5	**3d**	(±)-**4d**	H	OMe	H	H	H	8 h	16%, <1% ee
6[e]	**3e**	(+)-**4e**	H	Ph	H	H	H	8 h	64%, 83% ee
7[d]	**3f**	**4f**	Ph	H	H	H	H	8 h	66%, 90% ee
								10 h	88%, 86% ee[f]
8[d]	**3g**	**4g**	H	H	Ph	H	H	7 h	94%, 85% ee
9[d]	**3h**	**4h**	H	H	Br	H	H	7 h	70%, 80% ee
10	**3i**	**4i**	H	H	N_3	H	H	8 h	68%, 86% ee
11	**3j**	**4j**	H	H	OBn	H	H	8 h	52%, 84% ee
12	**3k**	**4k**	H	H	H	Ph	H	7 h	50%, 88% ee
13	**3l**	**4l**	H	H	H	N_3	H	8 h	67%, 87% ee
14	**3m**	**4m**	H	H	H	H	Me	7 h	20%, 40% ee

[a]Reactions were performed in chloroform with 10 mol% of (*R*)-**2b** at 0.02 M concentration of substrate **3**. [b]Determined by HPLC analysis using chiral separation column. [c]5 mol% catalyst (*R*)-**2b** was used. [d]1 equiv of acetic acid was added at higher concentration (0.05 M concentration of substrate **3**). [e]Reaction performed in a mixed solvent of chloroform/hexanes 1/1 with 15 mol% of the catalyst (*R*)-**2b**. [f]Chloroform/hexanes 1/1, −10 °C.

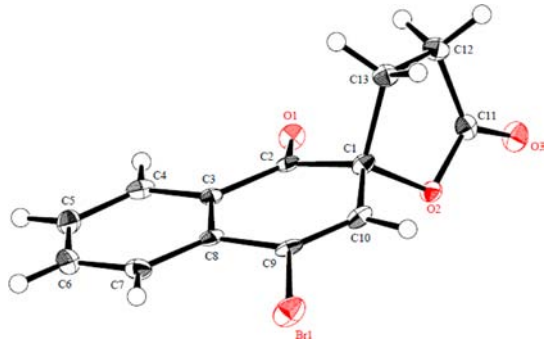
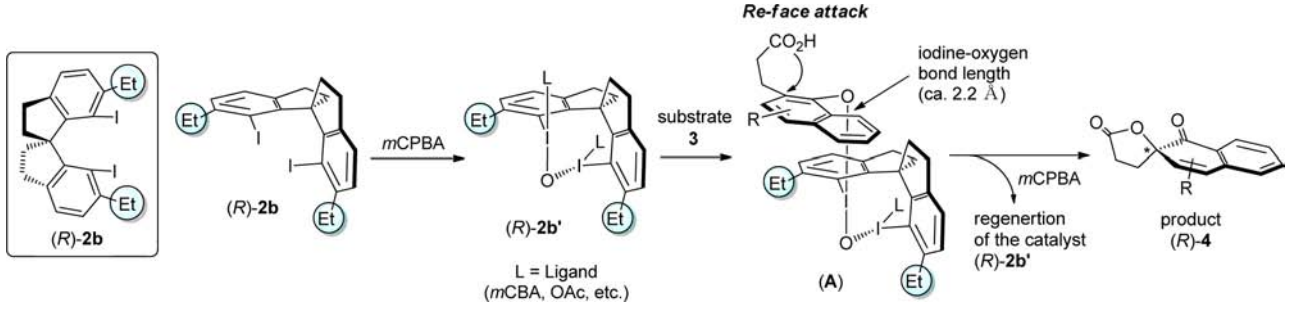


Figure 4. Crystal structure of the spirolactone product (+)-(*R*)-**4b** by X-ray analysis.

Scheme 4. Initially, catalyst (*R*)-**2b** was oxidized by *m*CPBA to give the reactive iodine(III) species (*R*)-**2b′**.[13] The apical approach and repositioning of the naphthol substrates **3** on the iodine(III) atom would occur from the less-hindered face of the spirobiindane ring of (*R*)-**2b′**. Thus, the catalytic species (*R*)-**2b′** could undergo ligand exchange[30] with the naphthol oxygen to give intermediate (**A**).[31] A similar intermediate having a hypervalent bond between the iodine(III) atom and naphtholic oxygen was previously isolated.[32] The presence of two iodine groups on the catalyst is important in order to restrict the substrate access and repositioning.[33] As such, the iodine groups can block access to substrate **3** from the major groove of the two spirobiindane planes and opposite apical position of the iodine(III) by forming an oxygen bridge. In intermediate (**A**), the pendant carboxylic acid would then preferentially attack the *ipso* position of the naphthol ring from the unshielded *Re*-face of substrate **3**, resulting in formation of the *R* enantiomer of the product **4** with good enantioselectivity, with the carboxylic acid in the naphthol plane of substrate **3** located away from the indane plane to avoid steric congestion of the just-formed lactone ring of the product **4**. One can expect a $\pi-\pi$ interaction

Scheme 4. Plausible Reaction Course and Transition-State Model for the Formation of the Product of *R* Configuration



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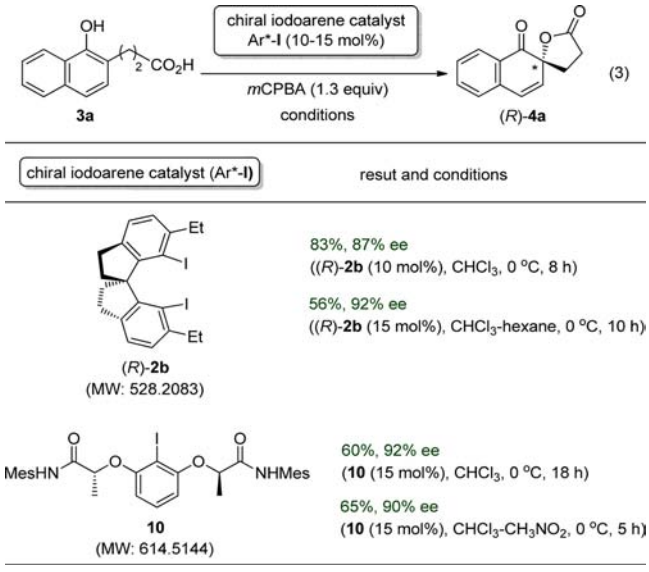
between the naphthol and equatorial indane rings of substrate **3** and catalyst (*R*)-**2b**′, but it seems unlikely in this case when considering the shorter bond length of the hypervalent iodine–oxygen atoms (2.0–2.2 Å)[34] compared to the typicallly required stacking distance for forceful interaction of two aromatic ring orbitals (around 3.5 Å). In fact, the opposite facial approach of the naphthalene ring of substrate **3** toward the catalyst (*R*)-**2b**′ should involve attack of the very crowded *Re*-face of the naphthalene by the carboxylic acid to form the observed product **4** with the *R* configuration, thus ruling out a $\pi-\pi$ interaction.[35] Therefore, introducing an ethyl group into the *ortho* position of the iodine atom of the spirobiindane catalyst **2b** can improve the selectivity without altering the stereochemistry of the products **4** by increasing the steric demand between the carboxylic side chains of the substrates **3** and the *ortho*-ethyl substituent of the catalyst as the result of extending the *Si*-face shielding of the naphthol ring of the substrates **3** in the intermediate (**A**). This transition-state model and formation of the intermediate are in accord with the unfavorable effect of the introduction of the 8-substituent of naphthol substrate **3m**, which shows a low enantioselectivity. The experimental results all match with the hypothesis regarding the reaction mechanism and intermediate.

After we accomplished the spirobiindane-catalyzed asymmetric oxidative dearomatization shown in eq 2,[13] Ishihara and co-workers reported in 2010 a new type of C_2-symmetric chiral hypevalent iodine catalyst **10** for the same reaction and catalytic conditions using *m*CPBA.[17] They concluded that the new catalyst **10** is a superior alternative to our original reagent **2a** in their own evaluation and comparison of the reaction selectivities. Indeed, it was reported that the product (*R*)-**4a** was obtained in 60% yield with 92% ee in chloroform and in 65% yield with 90% ee in a chloroform–nitromethane mixture using 15 mol% of the catalyst **10** (Scheme 5). In comparison, our modified reagent (*R*)-**2b** can afford the same product (*R*)-**4a** in a comparable yield and ee value, that is, 83% yield with 87% ee in chloroform,[27b] and 56% yield with 92% ee in a chloroform–hexane mixed solvent. Regarding the iodine content (20–30 mol% iodine) in the catalyst loading of **2a** (10–15 mol%), they also stated that their catalyst **10** well works even with a lower amount of catalyst loading (10–15 mol%), which is claimed as one of the significant merits of the new catalyst **10** over our catalyst. In our comparison of the required catalyst molecular weight, the used masses are not very different from each other ((*R*)-**2b**, MW = 528.2083; monoiodoarene catalyst **10**, MW = 614.5144). Besides, the favorable characteristics of our spirobiindane catalyst **2b** are as follows: (1) It is easy to handle and recover in a pure form by column chromatography (hexanes extraction) after the reactions due to the low polarity of the catalyst **2b** consisting of only carbon, hydrogen, and iodine elements (while the catalyst **10** is a highly polar compound). (2) The polarity difference between the nonpolar catalyst **2b** and polar product **4** also allows easy separation by column chromatography, and both enantiomers (*R*)- and (*S*)-**2b** are readily obtained, which could lead to utility of **2b** for flexible applications involving two enantiomers.

Scheme 5. Yield and Enantioselectivity by Reported Hypervalent Iodine Catalysts in Our Dearomatizing Spirocyclization of Simple Naphthol 3a (Eq 3)[a]



[a]Mes = mesityl.

CONCLUSIONS

We have demonstrated the theoretical elucidation of our spirobiindane-based iodoarene catalyst **2** and synthesized a series of *ortho*-functionalized catalysts. Evaluation of these catalysts for the asymmetric dearomatizing spirolactonization of naphtholcarboxylic acid **3a** indicates that the enantioselectivity is improved by the presence of the *ortho* substituents. Additionally, based on the results of an X-ray analysis, we have proposed a reasonable transition-state model for the formation of the (*R*)-spirolactone product **4** from the (*R*)-**2a** spirobiindane catalyst, which is in good agreement with the results of the reactions performed for various naphthol derivatives **3**. Our chiral iodoarene compounds based on the spirobiindane structure can realize the highest level of asymmetric induction for the catalytic reaction in hypervalent iodine chemistry. In fact, an enantioselectivity of up to 92% ee for simple substrate **3a** has been achieved using the elucidated spirobiindane catalyst **2b**. Recently, our dearomatizing reaction conditions and the catalytic systems have been applied to further catalyst screening by others.[16,17] Consequently, the findings of this research study will contribute to the design and discovery of effective chiral hypervalent iodine catalysts for organic synthesis.

EXPERIMENTAL SECTION

General. Melting point (mp) was measured by using a Stuart SMP3 melting point apparatus with AC input 100 V. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JMN-400 or -300 spectrometer operating at 400 or 300 MHz (100 or 75 MHz for ^{13}C NMR) at 25 °C with tetramethylsilane (δ = 0.0 ppm) as an internal standard. The NMR data are reported as follows: chemical shift in ppm (δ), integration, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), and coupling constant (Hz). Infrared (IR) spectra were obtained using a Hitachi 270-50 spectrometer; absorptions are reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed by the Elemental Analysis Section of Osaka University and Osaka University Pharmaceutical Sciences. Analytical thin-layer chromatography (TLC) was performed on MERCK silica gel, grade 60 F_{254}. The spots and bands were detected by irradiation with UV light (254, 365 nm) and/or by staining with 5% phosphomolybdic acid followed by heating. Column chromatography for isolation of the products **4** was carried out on Merck silica gel 60 (230–400 mesh). Naphtholcarboxylic acid

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3a was prepared by hydrolysis of 3,4-dihydro-2*H*-naphtho[1,2-*b*]pyran-2-one.[36a] Other substituted derivatives (**3b**−**m**) were prepared from the corresponding naphthols according to literature procedures.[36b] Unless otherwise noted, all other chemicals for the reactions and chromatography in this study were obtained from commercial suppliers and used as received without further purification.

Preparation of *ortho*-Substituted Iodoarene Compound 2b. Enantiopure 1,1′-spirobiindane-7,7′-diamine **5** was obtained according to the literature.[14c] To a solution of (*R*)-**5** (1.0 g, 4.0 mmol) in 1,2-dichloroethane (80 mL), boron trichloride in dichloromethane (1.0 M solution, 40 mL, 40 mmol) was added under nitrogen at 0 °C, and the mixture was stirred for 40 min. At the same temperature, zinc(II) chloride (2.7 g, 20 mmol) and acetonitrile (3 mL) were added. The mixture was stirred for 15 min at room temperature and then refluxed at 80 °C for 20 h. After the mixture cooled to room temperature, 10% aqueous hydrogen chloride was added, and then the mixture was refluxed at 80 °C for 30 min. After cooling to ambient temperature, the reaction mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the crude (*R*)-6,6′-diacetyl-7,7′-diamino-1,1′-spirobiindane (*R*)-**6** (1.22 g, 3.64 mmol) in 91% yield, which was used for a further transformation.

The obtained (*R*)-**6** (251 mg, 0.75 mmol) was dissolved in 10 mL of trifluoroacetic acid under nitrogen. Sodium nitrite (207 mg, 3 mmol) was added to the solution, which was stirred for 30 min at 0 °C. The reaction mixture was added to a solution of potassium iodide (1.0 g, 6 mmol) in water (15 mL) at room temperature, and it was stirred for an additional 15 min, and then for 18 h at 50 °C. Ice−water was added, and the reaction mixture was extracted with dichloromethane. The organic phase was washed with dilute aqueous sodium thiosulfate and saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was subjected to column chromatography (eluent *n*-hexane/ethyl acetate 10/1) on silica gel to give (*R*)-6,6′-diacetyl-7,7′-diiodo-1,1′-spirobiindane (*R*)-**7** (242 mg, 0.435 mmol, 58% yield) as a white powder.

The diiodide (*R*)-**7** (834 mg, 1.50 mmol) was dissolved in 15 mL of dichloromethane at 0 °C, and trifluoromethanesulfonic acid (0.13 mL, 1.5 mmol) in dichloromethane (15 mL) was slowly added. A solution of triethylsilane (1.8 mL, 11.3 mmol) in dichloromethane (15 mL) was then added. After being stirred for 15 h, the reaction mixture was poured into saturated aqueous sodium hydrogen carbonate, extracted with dichloromethane, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was subjected to column chromatography on silica gel (eluent *n*-hexane) to give (*R*)-6,6′-diethyl-7,7′-diiodo-1,1′-spirobiindane (*R*)-**2b** (634 mg, 1.20 mmol, 80% yield).

(+)-(*R*)-6,6′-Diethyl-7,7′-diiodo-1,1′-spirobiindane (2b, (*R*)-Enantiomer). Colorless solid, mp 105−106 °C, $[\alpha]^{25}_{D}$ +21.0 (*c* 1.09, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (6H, t, J = 7.6 Hz), 2.18−2.24 (2H, m), 2.41−2.69 (2H, m), 2.70−2.80 (4H, m), 2.98−3.10 (4H, m), 7.07 (2H, d, J = 7.6 Hz), 7.16 (2H, d, J = 7.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.0, 30.1, 34.4, 36.9, 66.9, 123.5, 124.4, 126.7, 126.8, 142.8, 143.8 ppm; IR (KBr) 2967, 2902, 2253, 1815, 1792, 1454, 1454, 1385, 1384, 1095, 912, 745 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{22}I_2$ $[M]^+$, 527.9811, found 527. 9813.

Typical Procedure for Dearomatizing Spirolactonization by *ortho*-Substituted Iodoarene Catalyst 2b. To a stirred solution of (*R*)-6,6′-diethyl-7,7′-diiodo-1,1′-spirobiindane (*R*)-**2b** (26.4 mg, 0.050 mmol) in chloroform (25 mL), the wet *m*-chloroperbenzoic acid (ca. 69% purity including ∼25% water, 163 mg, 0.65 mmol) was added at room temperature. The mixture was cooled to 0 °C for 10 min, and 3-(1-hydroxy-2-naphthyl)propionic acid **3a** (108 mg, 0.50 mmol) was then added. The mixture was stirred for 8 h at the same temperature, while the reaction progress was monitored by TLC. After the reaction was completed, saturated aqueous sodium hydrogen carbonate was added to the mixture. The organic layer was separated, and the aqueous phase was extracted with dichloromethane several times. The combined organic extract was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by column chromatography on silica gel (eluent *n*-hexane/ethyl acetate 8/1) to give (+)-(*R*)-spiro[tetrahydrofuran-2,2′-(1′*H*-naphthalene)]-1′,5-dione **3a** (89 mg, 0.42 mmol) in 83% yield. The ee of the product was determined by HPLC analysis using a chiral separation column.

Use of the (*S*) enantiomer of the catalyst **2b** could preferentially afford as product the opposite enantiomer, (−)-(*S*)-**4a**, in a comparable yield and ee.

Determination of the Enantioselectivity of the Reactions. The ee values of all the spirolactone products **4** obtained using the spirobiindane catalyst (*R*)-**2b** were measured by HPLC analyses using a JASCO DM-2010 multiwavelength detector. The chiral columns included Chiralcel OD and OD-H, and Chiral-pac IA (Daicel Chemical Industries, Ltd., 0.46 × 25 cm). The separation conditions are summarized as follows for each compound.

*Spiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4a**).* The ee value was determined by HPLC, OD-H chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, t(major, *R* isomer) = 16.07 min, t(minor, *S* isomer) = 21.37 min.)

*4′-Bromospiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4b**).* By HPLC, OD-H chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 0.7 mL/min, 25 °C, λ = 235 nm, t(major) = 26.79 min, t(minor) = 31.76 min.

*4′-Benzylspiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4c**).* OD chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 1.0 mL/min, 25 °C, λ = 235 nm, t(major) = 22.56 min, t(minor) = 52.23 min.

*4′-Methoxyspiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4d**).* OD-H chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 0.7 mL/min, 25 °C, λ = 230 nm, t = 26.47, 33.87 min.

*4′-Phenylspiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4e**).* OD-H chiral column, eluent: *n*-hexane/isopropanol: 90/10, flow rate: 0.8 mL/min, 25 °C, λ = 230 nm, t(minor) = 33.97 min, t(major) = 43.13 min.

*3′-Phenylspiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4f**).* OD-H chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 1.0 mL/min, 25 °C, λ = 230 nm, t(minor) = 13.80 min, t(major) = 18.98 min.

*5′-Phenylspiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4g**).* IA chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 0.9 mL/min, 25 °C, λ = 230 nm, t(minor) = 12.35 min, t(major) = 13.93 min.

*5′-Bromospiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4h**).* OD-H chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 0.8 mL/min, 25 °C, λ = 230 nm, t(major) = 24.48 min, t(minor) = 29.51 min.

*5′-Azidospiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4i**).* OD-H chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 0.8 mL/min, 25 °C, λ = 230 nm, t(major) = 28.73 min, t(minor) = 33.11 min.

*5′-Benzyloxyspiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4j**).* IA chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 0.9 mL/min, 25 °C, λ = 230 nm, t(minor) = 22.34 min, t(major) = 27.16 min.

*6′-Phenylspiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4k**).* OD-H chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 0.9 mL/min, 25 °C, λ = 230 nm, t(major) = 30.83 min, t(minor) = 36.41 min.

*6′-Azidospiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4l**).* OD-H chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 1.0 mL/min, 25 °C, λ = 235 nm, t(major) = 18.50 min, t(minor) = 22.67 min.

*8′-Methylspiro[tetrahydrofuran-2,2′-(1′H-naphthalene)]-1′,5-dione (**4m**).* OD-H chiral column, eluent *n*-hexane/isopropanol 85/15, flow rate 0.9 mL/min, 25 °C, λ = 230 nm, t(major) = 20.08 min, t(minor) = 23.80 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details and detailed spectroscopic data for new materials and products, including ^{1}H and ^{13}C NMR

spectra, and CIF file for (+)-**4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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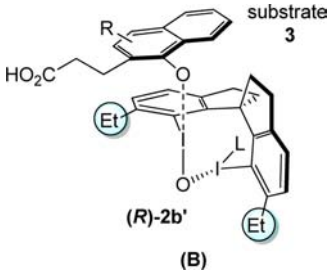
(35) Intermediate (**B**), shown here, seems to be unfavorable and should involve attack of the carboxylic group from the catalyst side. In this intermediate, the ethyl group must act negatively during the *Re*-face attack and enantioselectivity; thus it is ruled out.



(B)

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