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Enantioselective Synthesis of Multisubstituted Biaryl Skeleton by Chiral Phosphoric Acid Catalyzed Desymmetrization/Kinetic Resolution Sequence

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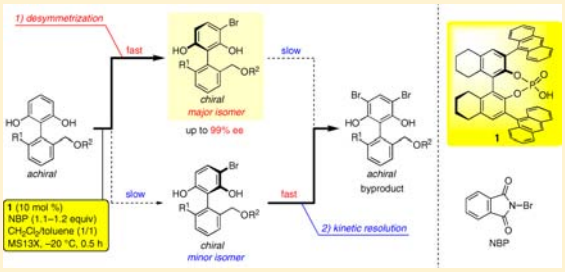
Supporting Information

ABSTRACT: Described herein is the enantioselective synthesis of multisubstituted biaryl derivatives by chiral phosphoric acid catalyzed asymmetric bromination. Two asymmetric reactions (desymmetrization and kinetic resolution) proceeded successively to afford chiral biaryls in excellent enantioselectivities (up to 99% ee). Both experimental and computational studies suggested that this excellent selectivity could be achieved via a highly organized hydrogen bond network among a substrate, a catalyst (chiral phosphoric acid), and a brominating reagent (*N*-bromophthalimide).



INTRODUCTION

Chiral biaryl skeletons are prevalent in useful organic molecules, such as biologically active compounds,[1] chiral ligands,[2] and chiral Brønsted acid catalysts.[3] In relation to this, much effort has been devoted to the development of new strategies for the construction of chiral biaryl scaffolds.[4]

Diastereo- or enantioselective coupling is the simplest and most straightforward method for the construction of chiral biaryl scaffolds.[5] The chemical yields of this method, however, are not always satisfactory due to the difficulty of connecting the two bulky aromatic moieties. From a practical point of view, Bringmann's asymmetric ring-opening strategy[6] is highly reliable and widely employed as a key step in the total synthesis of biologically active compounds, furnishing various tetrasubstituted biaryls with good to excellent enantioselectivities.[1e,7]

The desymmetrization of C_s-symmetric compounds has recently attracted much attention because it enables easy preparation of target molecules in a few steps. A wide range of important chiral substructures, such as chiral cyclohexenone[8] and *trans*-1,2-diamine,[9] have been synthesized with excellent selectivities. Nevertheless, to the best of our knowledge, this method has not been applied to the asymmetric construction of chiral biaryls except for the works of Hayashi,[10] Matsumoto,[11] and Alexakis group.[12] Although this method furnished chiral biaryls with excellent selectivities, the enantioselective synthesis of sterically encumbered, tetrasubstituted chiral biaryls remains a daunting task.[5,13]

We report herein the enantioselective construction of tetrasubstituted chiral biaryls by the desymmetrization strategy (asymmetric bromination strategy, Figure 1). This strategy consists of consecutive asymmetric transformations by means of chiral phosphoric acid: (1) desymmetrization of a C_s-symmetric biphenol moiety by chiral phosphoric acid catalyzed asymmetric bromination, and (2) chiral phosphoric acid induced kinetic resolution in the subsequent (second) bromination. The high selectivity in the first asymmetric reaction (desymmetrization) is further enhanced by the subsequent asymmetric reaction (kinetic resolution) to afford chiral biaryls with excellent selectivities (up to 99% ee).[14]

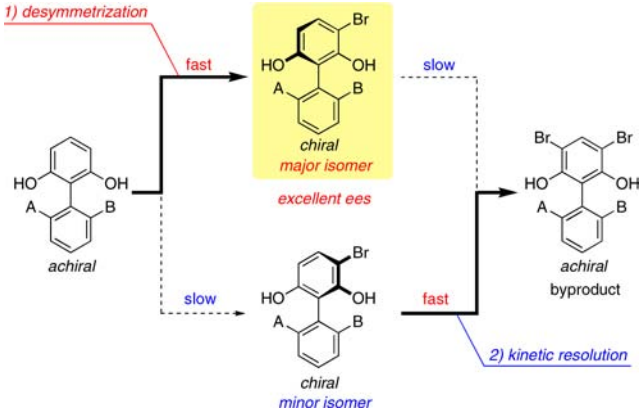


Figure 1. Sequential asymmetric bromination reaction.

RESULTS AND DISCUSSION

Development of Sequential Asymmetric Bromination Reaction (Desymmetrization/Kinetic Resolution Se-

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quence). We initiated our study with the design of a substrate because the control of atropisomerism with an organocatalyst is still an underdeveloped and challenging area.[15] Generally, the high stability of the transition state structure and the high reactivity to induce a low-temperature reaction are indispensable to achieve excellent enantioselectivity. Under such circumstances, we envisaged that C_s-symmetric biaryl **A** with two hydroxy groups would be a suitable structural motif because of two reasons (Figure 2): (1) a hydrogen bond

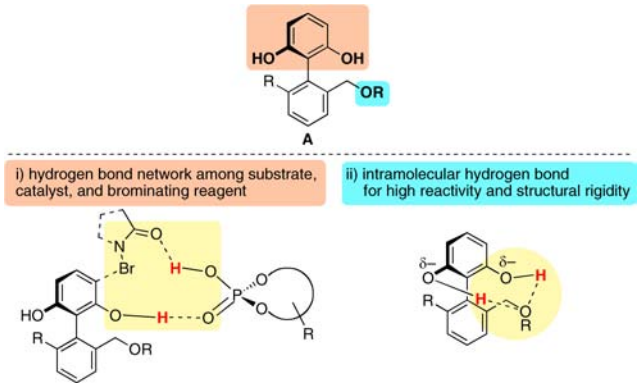

Figure 2. Design of the starting material.

network would be formed among the phenolic hydroxy group (substrate), phosphoric acid (catalyst), and the brominating reagent (such as NBS),[16] and (2) the intramolecular hydrogen bond between the phenolic hydroxy group and the OR group (light blue) would enhance not only reactivity but also structural rigidity.

The designed substrate provided another advantage: the facile connection of the two aryl portions. Due to the small size of the OR group, the Suzuki coupling of *o*-dialkoxy arylboronic acid and iodobenzene derivatives proceeded smoothly to afford the desired C_s-symmetric biphenol in good yield (not shown, see Supporting Information).

Hydrogenated phosphoric acid (*R*)-**1** bearing 9-anthryl groups turned out to be the most effective for the enantioselective bromination reaction of designed substrate **2a** (Figure 3a).[17,18] When a solution of **2a** in CH_2Cl_2/toluene (v/v = 1/1) was treated with 1.0 equiv of *N*-bromophthalimide (NBP) in the presence of **1** and MS13X, the desired asymmetric bromination reaction (desymmetrization) proceeded smoothly (within 0.5 h) to afford monobromide **3a** in excellent yield with satisfactory enantioselectivity (97%, 93% ee).[19,20] A further interesting feature of this methodology is its prominent kinetic resolution: treatment of *racemic*-**3a** with 0.50 equiv of NBP under the optimal conditions gave dibromide **4** in 45% yield, accompanied by unreacted **3a** in 49% yield in an optically active form (87% ee) in favor of the *R*-isomer, which is the major enantiomer in the desymmetrization reaction. The selectivity factor (*s*-value) was 31.5, which was sufficiently high for synthetic use.[21]

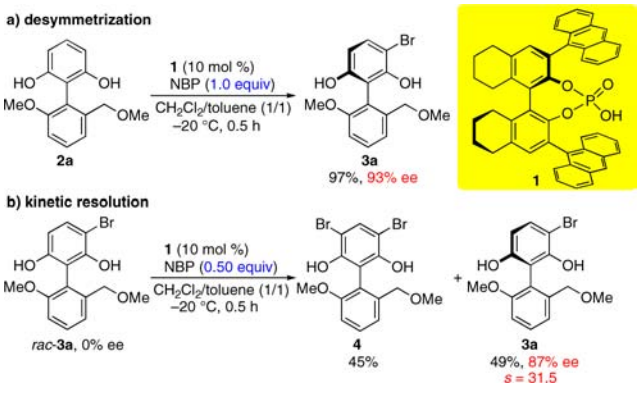

Figure 3. Desymmetrization and kinetic resolution.

The results strongly suggest that sequential asymmetric reactions (desymmetrization/kinetic resolution) can provide chiral biaryls in excellent optical yields, i.e., the selectivity in the chiral phosphoric acid catalyzed desymmetrization (first asymmetric bromination) can be further improved by the second asymmetric bromination (kinetic resolution) with slight sacrifice of the chemical yield, as depicted in Figure 1.

As expected, the planned desymmetrization/kinetic resolution sequence worked well: subjection of **2a** and a slight excess of NBP (1.1 equiv) under the optimal conditions furnished monobromide **3a** with excellent enantioselectivity, accompanied by a slight loss of chemical yield (88%, 97% ee, entry 1 in Table 1). The substrate scope of this reaction is listed in Table 1. In all cases, good to excellent selectivities were achieved in desymmetrization (81−93% ee) and kinetic resolution (63−96% ee, *s*-value: 6.1−97.3), and the successive asymmetric bromination reaction realized excellent selectivities (≥91% ee). Benzyloxy analogue **3b** was obtained with complete enantioselectivity (99% ee, entry 2).[22,23] The electronic factor of the lower aromatic moiety was negligible in this transformation. Both substrates with electron-donating groups (methoxy and methyl) and the substrate with an electron-withdrawing group (fluoro) afforded corresponding monobromides (**3a**−**d**) with excellent selectivities (≥94% ee, entries 1−4). Excellent selectivities were also achieved when sterically encumbered, 2′,3′,6′-substituted substrates **2e** and **2f** were employed (≥96% ee, entries 5 and 6). Naphthyl-type substrates also participated in this reaction, affording **3g** and **3h** in 82% yield with 95% ee and in 90% yield with 95% ee, respectively (entries 7 and 8). This method was applicable to trisubstituted biaryls as well (entries 9−11). Various trisubstituted biaryls (**3i**−**k**) were obtained in excellent enantioselectivities (≥91% ee).[24]

The important feature of the present method is that the selectivity could be further enhanced by tuning the amount of the brominating reagent: e.g., excellent selectivity of 92% ee in **3i** (entry 9) was achieved by employing 1.2 equiv of NBP, whereas selectivity was 88% ee when the amount of NBP was reduced (1.1 equiv, 88% chemical yield). The absolute configurations of these products were surmised as depicted in Table 1 by analogy to **3c**, **3g**, and **3h**, whose absolute stereochemistries were unambiguously established by single-crystal X-ray analysis.[25]

Clarification of Transition State Model Based on Supporting Experiments and Computational Results. To clarify the reaction mechanism, additional experiments were conducted. The simple resorcinol moiety (upper aromatic part) and the alkoxy group at C6′-position in the lower aromatic part were found to be responsible for the excellent enantioselectivity (Figure 4a). 4-Methyl-substituted monobromide **3l** was obtained in good chemical yield (80%), but its selectivity was as low as 44% ee. The alkoxy group at C6′-position played a crucial role in the selectivity. In the case of substrate **2m** that had an ethyl group in place of a methoxymethyl group, the selectivity completely disappeared and corresponding mono-

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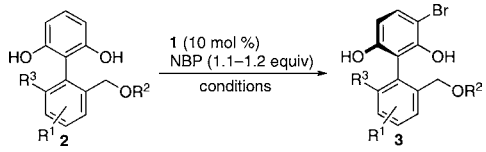
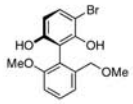
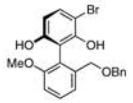
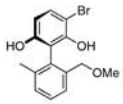
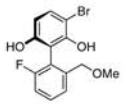
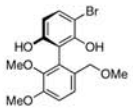
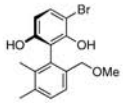
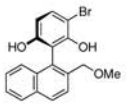
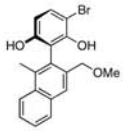
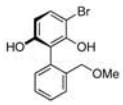
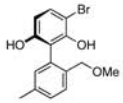
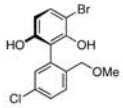
Table 1. Substrate Scope of the Sequential Bromination Reaction[a]



run	product		desymmetrization[b]	kinetic resolution[b]	Sequential bromination[b]
1		**3a**	97%, 93% ee	49%, 87% ee, (s = 31.5)	88%, 97% ee
2		**3b**	91%, 87% ee	46%, 63% ee, (s = 6.1)	80%, 99% ee
3[c,d]		**3c**	93%, 88% ee	49%, 96% ee, (s = 97.3)	90%, 95% ee
4[d,e]		**3d**	94%, 92% ee	46%, 75% ee, (s = 10.0)	91%, 94% ee
5[f,g]		**3e**	97%, 93% ee	47%, 85% ee, (s = 19.0)	87%, 98% ee
6[g]		**3f**	96%, 87% ee	50%, 74% ee, (s = 14.7)	76%, 96% ee
7[e]		**3g**	91%, 90% ee	50%, 87% ee, (s = 40.7)	82%, 95% ee
8		**3h**	97%, 86% ee	50%, 63% ee, (s = 8.2)	90%, 95% ee
9[c,g]		**3i**	91%, 82% ee	46%, 66% ee, (s = 6.9)	82%, 92% ee
10[g]		**3j**	93%, 81% ee	48%, 83% ee, (s = 19.3)	82%, 91% ee
11[g]		**3k**	90%, 84% ee	46%, 71% ee, (s = 8.4)	81%, 93% ee

[a]Unless otherwise noted, all reactions were conducted with 0.1 mmol of biphenol **2** and NBP (1.1 equiv) in the presence of 10 mol % of **1** and MS13X in CH_2Cl_2/toluene (1.0 mL, v/v = 1/1) at −20 °C for 0.5 h. [b]Enantiomeric ratio was determined by the chiral stationary phase. [c]CH_2Cl_2 was employed as the reaction solvent. [d]At −40 °C. [e]4 mL of CH_2Cl_2 was employed. [f]4 mL of CH_2Cl_2/toluene (v/v = 1/1) was employed. [g]1.2 equiv of NBP was employed.

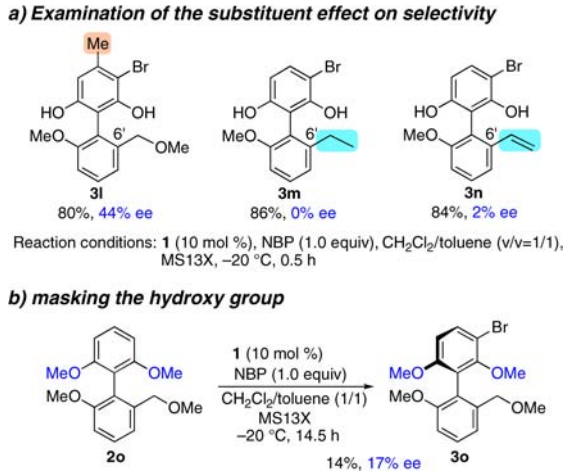


Figure 4. Examination for clarifying the transition state model.

bromide **3m** was obtained in racemic form (0% ee). The same situation was noted in vinyl (π-donor moiety) analogue **3n** (84%, 2% ee).

To confirm the importance of the hydrogen bond network, masked substrate (dimethoxy analogue) **2o** was subjected to the optimal reaction conditions (Figure 4b). Corresponding product **3o** was obtained in low yield (14%) even though the reaction was prolonged (14.5 h). In addition, the selectivity significantly dropped to 17% ee. The results strongly suggest the important role of the free hydroxy group in both reactivity and selectivity, and that this reaction proceeds via the expected hydrogen bond network: i.e., the Brønsted acidic part of the catalyst activates the carbonyl oxygen of NBP and the phosphoryl oxygen coordinates to the phenolic hydroxy group.[26,27]

To gain further insight into the origin of the high enantioselectivity and the substituent effects of biaryls, theoretical calculations of the detailed transition state (**TS**) models were conducted. The bromination reaction consists of the nucleophilic attack of an aryl group on a brominating reagent and the subsequent proton transfer. It is widely accepted that the first nucleophilic attack is the rate-determining step and the subsequent proton transfer is a fast process.[28] The enantiotopic discrimination of the asymmetric bromination reaction of biaryls should be determined in the first step. On the basis of the bifunctional nature of the phosphoric acid[16] and the experimental results for masked substrate **2o**, cyclic TS through a two-point interaction at the Brønsted acidic and Lewis basic sites of the phosphoric acid was predicted.[29] Whereas one of the enantiotopic phenolic hydroxy groups of biaryl coordinates to the Lewis basic site of the catalyst (e.g., phosphoryl oxygen), the other phenolic hydroxy group intramolecularly coordinates to the OMe or CH_2OMe group. The Brønsted acidic site (e.g., proton) activates the brominating reagent (e.g., NBS)[30] through hydrogen bonding interaction. To elucidate the major factor contributing to the high enantioselectivity in this asymmetric bromination (desymmetrization), the possible TSs for both *R*- and *S*-products were addressed. Four possible TSs corresponding to two different conformations for the intramolecular hydrogen bonding in biaryl (**TS2**, **TS4**, OMe coordination; **TS1**, **TS3**, CH_2OMe coordination) and two different approaches to NBS (**TS1**, **TS2**, front of OMe; **TS3**, **TS4**, back of OMe) were investigated for each TS affording *R*- or *S*-product (**TSr** or **TSs**)

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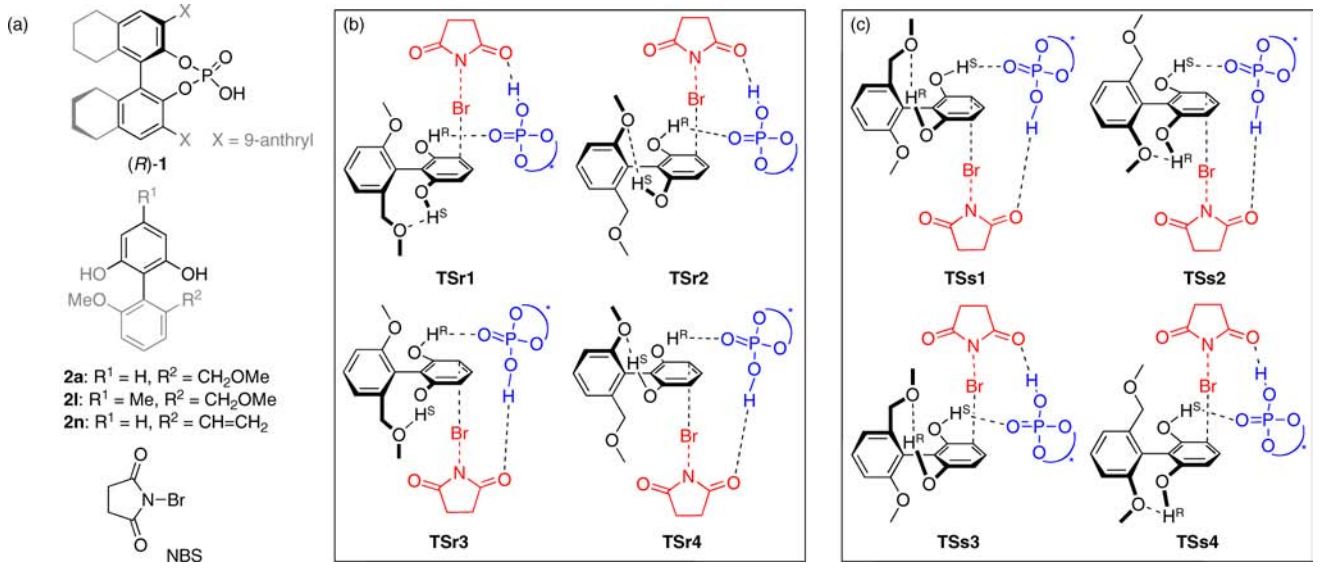

Figure 5. Examination for clarifying the transition state model.

(Figure 5b,c). All calculations were performed with the Gaussian 03 package.[31] To reduce computational cost, geometries were fully optimized and characterized by frequency calculation using the ONIOM (M05-2X/6-31G*:HF/3-21G) method (black, higher level layer; gray, lower level layer, Figure 5a).[32−34] Single-point energy calculations were evaluated at the M05-2X/6-31G* level[35,36] for the ONIOM-optimized structures. Free energies were also computed for the gas phase.

Focusing on the 3,3′-substituent effect of **1**, the relative energy and the structural difference between the energetically lowest **TSr** and **TSs** were first investigated in the case of **2a** (Figure 6). In agreement with the experimental result, the lowest TS for *R*-product (**TSr1a**) is 4.1 kcal/mol lower in energy than the lowest TS for *S*-product (**TSs4a**). **TSr1a** has a similar structure to **TSs4a** with respect to the hydrogen bond network. The chiral pocket of **1** enforces the binding orientation of NBS and **2a** conformationally fixed by the intramolecular hydrogen bonding interaction. In the energetically disfavored **TSs4a**, the CH_2OMe group, which is bulkier than the OMe group, is located at the sterically demanding 9-anthryl group positioned in the upper left-hand quadrant and thereby leads to steric repulsive interaction (purple curved lines). Therefore, the major factor affecting the stereochemical outcome in this asymmetric bromination would be explained by the steric interaction between the 3,3′-positioned 9-anthryl group of **1** and the biaryl substituent group.

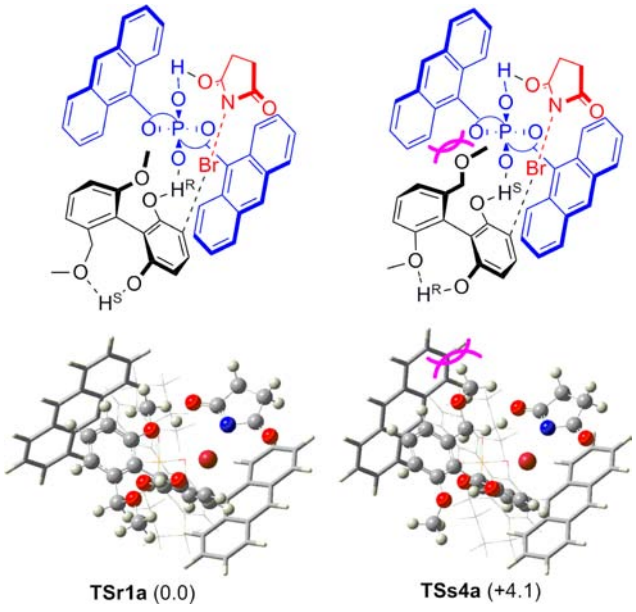

Figure 6. 3D structures of **TSr1a** and **TSs4a** and relative energies (kcal/mol) based on single-point energy calculations using M05-2X/6-31G* for the ONIOM (M05-2X/6-31G*:HF/3-21G)-optimized structures.

Next, we investigated the origin of the substituent effect of biaryls on the stereochemical outcome. Experiments showed that the enantioselectivity significantly decreased by using **2l** and **2n.** The small energy difference between the lowest **TSr** and **TSs** was responsible for the decrease in enantioselectivity. In the case of **2l**, the relative energy difference between the lowest **TSr** and **TSs** decreased to 1.1 kcal/mol (Figure 7a). **TSs3l** as the lowest **TSs** would be destabilized by the steric repulsion between the CH_2OMe group of **2l** and the 9-anthryl group of **1** positioned in the upper left-hand quadrant (purple curved lines). On the other hand, **TSr1l** would be also destabilized by the steric repulsion between the additional methyl group of **2l** and the 9-anthryl group of **1** positioned in the lower right-hand quadrant (purple curved lines). These steric effects resulted in the small energy difference of the diastereomeric transition structures in the case of **2l**. In a manner similar to **2l**, the 1.5 kcal/mol difference in energy between the lowest **TSr** and **TSs** was also obtained for **2n** (Figure 7b). In the case of **TSs4n** as the lowest **TSs**, the destabilization effect caused by the steric repulsion between the vinyl group of **2n** and the 9-anthryl group of **1** would be small because the vinyl group was smaller than the CH_2OMe group. On the other hand, the intramolecular hydrogen bonding of the biaryl unit disappeared in **TSr1n**. Therefore, **TSr1n** would be destabilized and the relative energy difference between the lowest **TSr** and **TSs** also decreased for **2n**. These calculation results rationally explained the substituent effects of the phosphoric acid catalyst at 3,3′-positions and the biaryls on the enantioselectivity.

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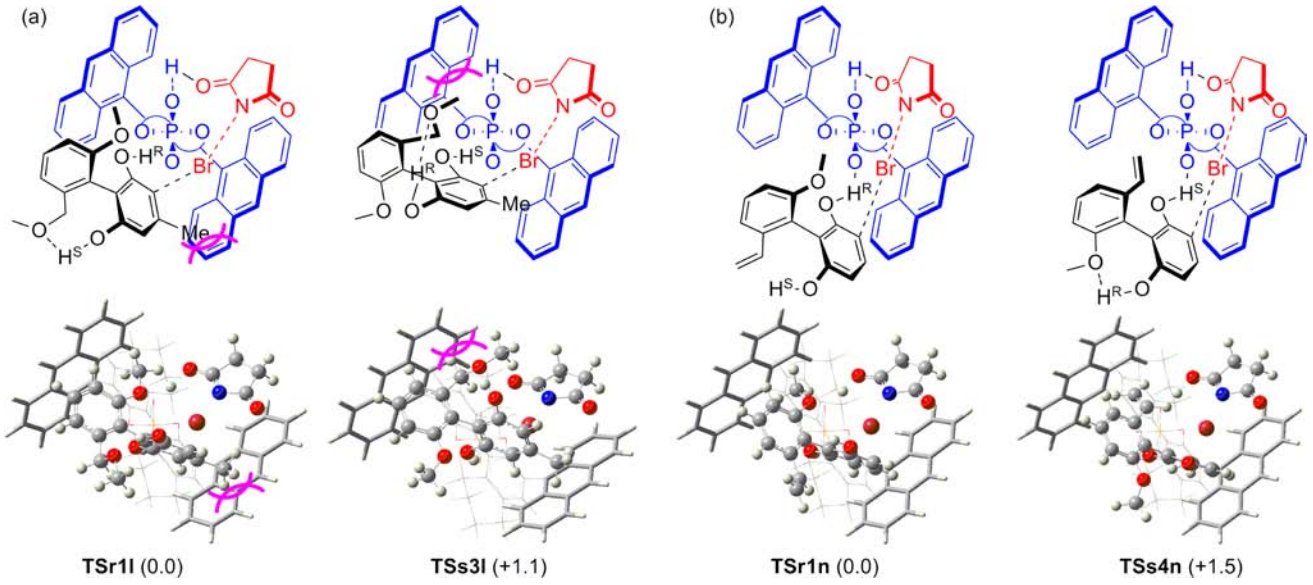

Figure 7. 3D structures and relative energies (kcal/mol) based on single-point energy calculations using M05-2X/6-31G* for the ONIOM(M05-2X/6-31G*:HF/3-21G)-optimized structures of (a) **TSr1l** and **TSs3l** and (b) **TSr1n** and **TSs4n**.

In summary, we have developed a strategy for the enantioselective construction of sterically encumbered biaryls, which involves the chiral phosphoric acid catalyzed asymmetric bromination of C_s-symmetric biphenols. The interesting feature of the present strategy is the combination of two chiral transformations (desymmetrization/kinetic resolution). A range of substrates were employed in this transformation, i.e., various biphenyl derivatives with electron-donating and -withdrawing groups, and some arylnaphthalenes afforded monobrominated biaryls with excellent enantioselectivities (up to 99% ee). The experimental and computational results suggest that the highly organized hydrogen bond network among the substrate, the catalyst, and the brominating reagent plays a key role in attaining the excellent selectivities. Further investigations of its application to natural product synthesis are under way in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical and spectroscopic data for new compounds, copies of NMR and HPLC spectra, and crystallographic data for **s53**, **3g**, and **3h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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