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Organocatalytic Chemo- and Regioselective Oxyarylation of Styrenes via a Cascade Reaction: Remote Activation of Hydroxyl Groups

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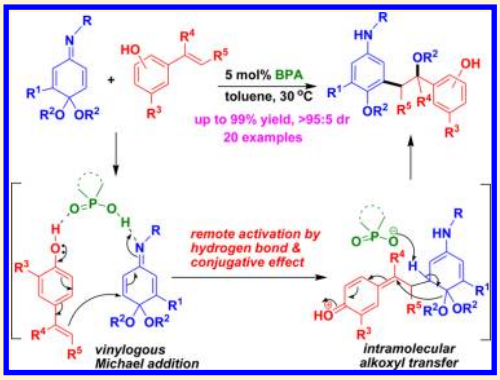
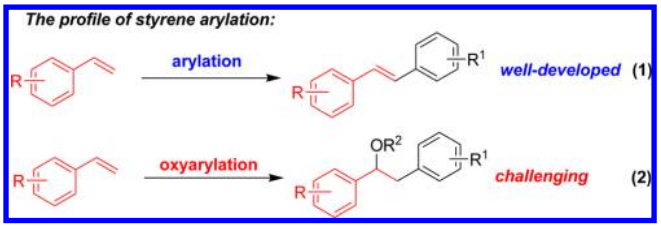
Supporting Information

ABSTRACT: The first organocatalytic oxyarylation of styrenes has been established through a cascade of vinylogous Michael addition/alkoxyl transfer reactions of *o*- or *p*-hydroxylstyrenes with quinone imine ketals. The process leads to a highly chemo- and regioselective oxyarylation of styrenes and provides access to *m*-alkylated anilines in generally high yields and excellent diastereoselectivity (up to 99% yield, >95:5 dr). An investigation of the reaction pathway revealed that the existence and position of the hydroxyl group of styrene played crucial roles in the cascade reaction, suggesting that the two reactants were simultaneously activated by binaphthyl-derived phosphoric acid via hydrogen bonding interactions and long-distance conjugative effects. In addition, the activating group of the hydroxyl functionality in the products can be easily removed or transformed, demonstrating the applicability and utility of this strategy in styrene oxyarylation and in the synthesis of styrene-based compounds.

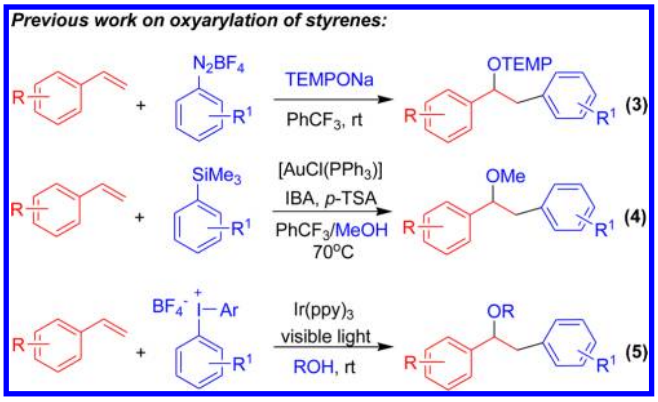


INTRODUCTION

Styrenes are a ubiquitous and fundamental chemical feedstock in organic, medicinal, and materials chemistry, and their functionalization is an important research field in both academia and industry.[1] In particular, the arylation of styrenes has been investigated intensively over the past few decades, resulting in well-developed procedures, including the Heck reaction[2] and metathesis[3] (eq 1). However, in contrast, the oxyarylation of styrenes has met with little success despite its great potential in generating a C−C bond and a C−O bond as well as a new stereocenter in a single transformation (eq 2).[4] The tendency of styrenes to polymerize makes their oxyarylation particularly challenging.[4b,5]



Some recent breakthroughs have, however, been made in the oxyarylation of styrenes. Studer et al.[4a] succeeded in a radical oxyarylation of styrenes employing aryl diazonium salts as radical precursors and TEMPONa as a reducing reagent (eq 3). Lloyd-Jones, Russell, and co-workers[4b] realized the methoxyarylation of styrenes using aryl silanes in the presence of a Au catalyst using 2-iodosobenzoic acid (IBA) as a terminal oxidant (eq 4). Very recently, Greaney et al.[4c] also reported a photoredox-catalyzed coupling of styrenes with aryl groups and alcohols under mild reaction conditions (eq 5). Despite these elegant works, the oxyarylation of styrenes, especially those exploiting organocatalysis, is still relatively underdeveloped and therefore highly desirable considering the importance of styrene functionalization and styrene-based chemicals.



Quinone imine ketals (QIKs)[6−8] have been recognized as electrophilic aryl group surrogates that react with various nucleophiles (eq 6)[6] and styrenes (eq 7).[7] This recognition suggested that QIK may be utilized as a latent functionalized aromatic ring to realize the oxyarylation of styrenes. However,

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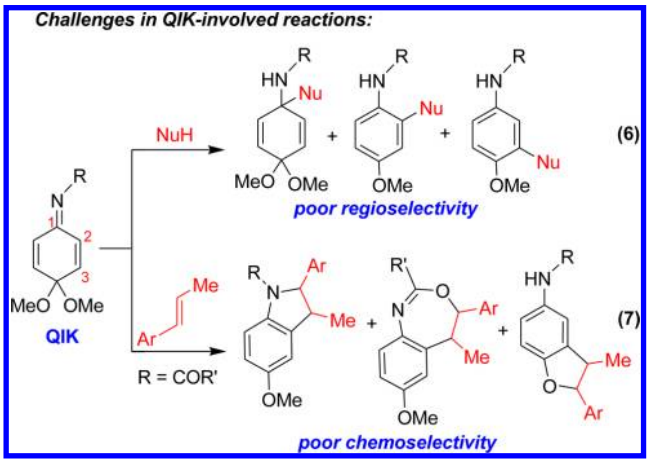
pioneering work into this concept has revealed several challenges in controlling the regioselectivity and chemoselectivity of QIK-involved reactions because of the existence of multiple electrophilic sites (C1−C3) in the QIK. Thus, facilitating the chemo- and regioselective oxyarylation of styrenes via reactions with QIK remains challenging.



Considering these challenges, and the great demand for the oxyarylation of styrenes, we designed a reaction for the organocatalytic oxyarylation of styrenes employing QIK as an aryl group precursor. Brønsted acids (BAs) are privileged organocatalysts that allow a variety of transformations via the activation of imino or carbonyl functionalities.[9] Because QIK contains an imine group, it could also be electrophilically activated by such an acid.[6a,7,8c−e] Nevertheless, styrenes lacking an activating group could not be motivated by a BA. Our previous success in BA-catalyzed reactions showed that double activation of both of the substrates greatly facilitates the reaction.[10] Therefore, we hypothesized that styrenes substituted with an *o*- or *p*-hydroxyl group could be activated by BAs through the formation of a hydrogen bond with the hydroxyl group, which would then undergo a vinylogous Michael addition to QIK (Scheme 1). Then, one alkoxyl group of transient intermediate **A** would attack the enone functionality, leading to the generation or restoration of two aromatic rings and thus completing the oxyarylation of the styrene. In this design, the hydroxyl group would impose a remote activation on the styrene double bond over a long distance. This activating group could then be removed using well-established procedures.[11] This approach also provides easy access to *m*-alkylated anilines, which cannot be obtained by simple Friedel−Crafts reactions of anilines.[12]

We report herein the first organocatalytic oxyarylation of styrenes through cascade reactions of *o*- or *p*-hydroxylstyrenes with quinone imine ketals. In the presence of a BA, the two substrates are simultaneously activated by hydrogen bonds over a long distance, resulting in a highly chemo- and regioselective domino sequence of vinylogous Michael addition and alkoxyl transfer. This procedure is a powerful approach to the oxyarylation of styrenes and *m*-alkylated anilines.

RESULTS AND DISCUSSION

Our study of the organocatalytic oxyarylation of styrenes commenced with the reaction of quinone imine ketal (QIK) **1a** with *o*-hydroxylstyrene **2a** catalyzed by 5 mol % Brønsted acid (BA) **4** in toluene at 30 °C (Table 1). A preliminary screening of catalysts **4** revealed that the acidity of the BA played an important role in determining the overall reactivity (entries 1−6). Specifically, BAs **4a** and **4b**, which are weakly acidic, could not catalyze the desired reaction (entries 1 and 2, respectively), while BAs **4c** and **4d**, which are stronger acids, promoted the tandem reactions in moderate to good yields (entries 3 and 4, respectively). Using the racemic binaphthyl-derived phosphoric acid (BPA) **4e** delivered the target product **3aa** in a yield of 88% (entry 5). Exchanging racemic BPA **4e** for chiral BPA **4f** led to the same yield, but no enantioselective induction was observed (entry 6). Note that the BPA-catalyzed tandem reaction proceeded in a highly chemo- and regioselective manner, providing the sole product **3aa** without other chemo- or regioisomers. Because BPA **4e** is much more easily synthesized than BPA **4f**, the subsequent solvent evaluation was performed with catalyst **4e**. This evaluation showed that ethyl acetate (EtOAc), dichloromethane (DCM), and tetrahydrofuran (THF) were inferior to toluene in terms of reactivity (entries 7−9, respectively, vs entry 5). Finally, increasing the stoichiometric ratio of *o*-hydroxylstyrene **2a** led to improvements in yield (entries 10 and 11), and a mole ratio of 1:2 (**1a**:**2a**) delivered the model reaction in the highest yield of 99% (entry 10).

Scheme 1. Design of an Organocatalytic Oxyarylation Reaction for Styrenes

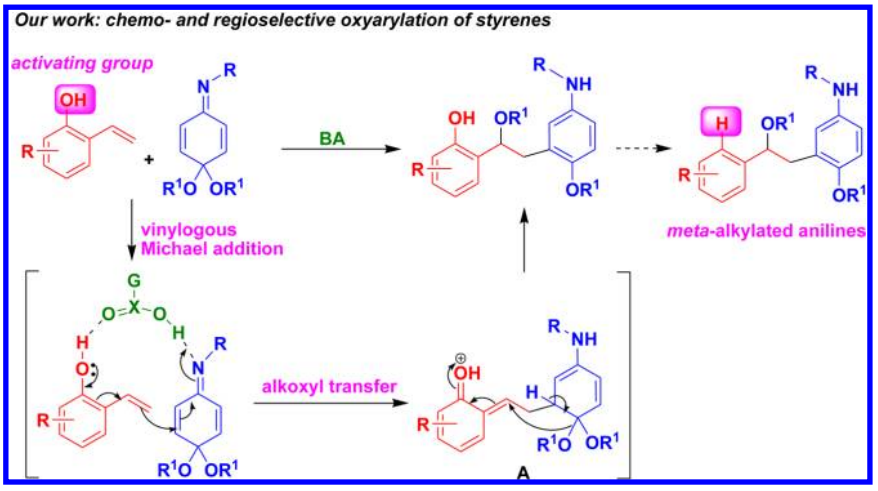


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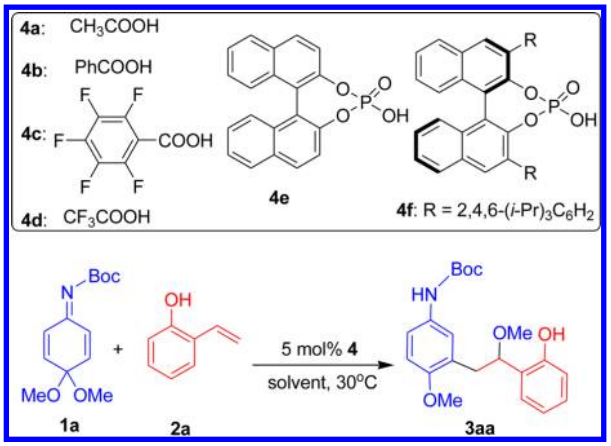
Table 1. Screening of Catalysts and Optimization of Reaction Conditions[a]



entry	4	solvent	1a:2a	yield (%)[b]
1	**4a**	toluene	1:1.5	–[c]
2	**4b**	toluene	1:1.5	–[c]
3	**4c**	toluene	1:1.5	41
4	**4d**	toluene	1:1.5	77
5	**4e**	toluene	1:1.5	88
6	**4f**	toluene	1:1.5	88 (<5% ee)[d]
7	**4e**	EtOAc	1:1.5	69
8	**4e**	DCM	1:1.5	74
9	**4e**	THF	1:1.5	50
10	**4e**	toluene	1:2	99
11	**4e**	toluene	1:2.5	95

[a]Unless indicated otherwise, the reaction was conducted at the 0.1 mmol scale in solvent (1 mL) at 30 °C for 12 h. [b]Isolated yields. [c]No reaction occurred. [d]The ee (enantiomeric excess) value was determined by HPLC.

With the optimal reaction conditions in hand, we investigated the substrate scope of QIKs via tandem vinylogous Michael addition and alkoxyl transfer reactions with *o*-hydroxylstyrene **2a** (Table 2). First, the effects of N-substituents on QIK were studied by employing different protecting groups, including Boc, Bz, Cbz, and Ac (entries 1–4, respectively). Among them, *N*-Boc-protected QIK exhibited the highest reactivity (entry 1), while *N*-Cbz-protected QIK (entry 2) yielded a higher reactivity than its *N*-Bz- and *N*-Ac-substituted counterparts (entries 3 and 4, respectively). This result indicated that the electronic nature of the protecting group imposed a delicate effect on reactivity. Then, a series of *N*-Boc QIKs, with either electronically poor or rich R^1 groups, were utilized in the reaction to generate the desired *m*-alkylated anilines in generally high yields (entries 5–8). Thus, the electronic nature of the R^1 group seemed to impose some influence on the reactivity because QIK substituted with an electron-donating methyl group facilitated the cascade reaction in a yield of 82%, which is higher than those obtained with electron-withdrawing analogues (entry 8 vs entries 5–7). More importantly, the two alkoxyl groups of the QIKs could be easily changed from methoxyl (entry 1) to ethoxyl, isopropoxyl, or butoxyl groups (entry 9, 10, or 11, respectively). Note that linear alkoxyl groups were superior to branched ones with regard to reactivity (entries 1, 9, and 11 vs entry 10). These examples demonstrate the efficiency and applicability of this strategy to the oxyarylation of styrenes. Furthermore, this strategy solves the problem of unchangeable alkoxyl groups that was evident in previous approaches (eqs 3 and 4).[4a,b] In some cases, chiral BPA **4f** was employed as a catalyst instead of racemic BPA **4e** to obtain higher yields (entries 4 and 6–11) because the former showed a higher catalytic activity than the latter. However, in most of these cases, the enantioselectivity was poor, with the exception of product **3ga**, which was generated with a moderate enantioselectivity of 55% enantiomeric excess (ee) (entry 7).

Next, the generality of the reaction for *o*-hydroxylstyrenes **2** was explored by reactions with QIK **1a** under optimal conditions. As shown in Table 3, this protocol was acceptable over a wide range of *o*-hydroxylstyrenes **2** with various, electronically distinct substituents linked to the phenyl ring. The desired products of oxyarylation were generated in generally high yields (57–99%, entries 1–7). Basically, substrates **2a–h**, which bear electron-neutral or -donating groups on their aromatic rings, were beneficial to the desired tandem reaction (entries 1–4). The exception was **2c**, which bears a bulky *tert*-butyl group (entry 3). Moreover, the electronically poor *o*-hydroxylstyrenes **2e–g** also served as suitable substrates in the oxyarylation reactions with good yields (60–74%, entries 5–7, respectively). Even α-methyl *o*-hydroxylstyrene **2h** was a suitable reaction partner and afforded oxyarylation product **3ah** with a quaternary stereocenter in a considerable yield of 70% (entry 8). Notably, in the presence of chiral BPA **4f**, (*E*)-β-methyl *o*-hydroxylstyrene **2i**, a type of nonterminal olefin, was able to participate in the tandem reaction and gave the desired product **3ai** in an acceptable yield of 52%, considerable enantioselectivity of 72% ee, and an excellent diastereoselectivity of >95:5 dr (entry 9). These examples, and in particular the reactions with disubstituted olefins, greatly expanded the scope of our strategy but also demonstrated the chemo-, regio-, and stereospecific nature of this oxyarylation process.

To obtain insight into the reaction pathway and the activation mode of BPA **4e** on the various substrates, several control experiments were performed under optimized reaction conditions (Scheme 2). First, *o*-methoxylstyrene **2j** was employed as a substrate instead of *o*-hydroxylstyrene **2a** in a reaction with QIK **1a** (eq 8). No reaction (N.R.) occurred, which indicates that the hydroxyl group plays a crucial role in the as-designed cascade reaction. Second, *m*- and *p*-hydroxylstyrenes (**2k** and **2l**, respectively) were used as reactants in the same reaction. *m*-Hydroxylstyrene **2k** gave only trace amounts of product (eq 9), while *p*-hydroxylstyrene **2l** generated the target product **3aj** in an excellent yield of 92% (eq 10). These results suggest that the position of the hydroxyl group was essential to the success of the reaction, and that hydrogen bonding of the hydroxyl group with BPA was not enough to guarantee the desired tandem reaction. The success of *p*-hydroxylstyrene **2l** in generating the desired product demonstrates that the hydroxyl group remotely activates the styrene double bond over a long distance via conjugative effects. This hydrogen bond therefore facilitates the first step in the vinylogous Michael addition to QIK. To verify the second step of the tandem reaction (i.e., the transfer of an alkoxyl group through an intramolecular rather than intermolecular pathway), a control experiment was performed using two different QIKs, **1a** and **1k** (1:1 mole ratio), to react with 2 equiv of *o*-hydroxylstyrene **2a** (eq 11). As expected, two corresponding products **3aa** and **3ka** were produced with no crossover products, verifying the proposed intramolecular alkoxyl transfer pathway.

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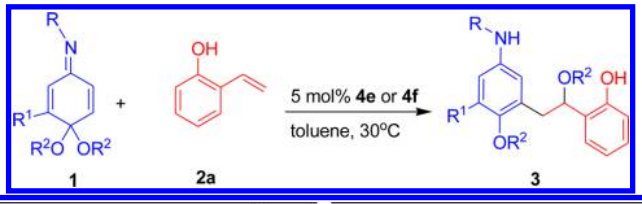
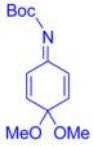
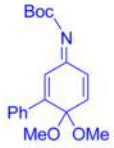
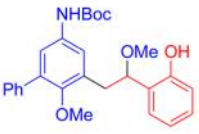
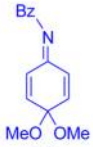
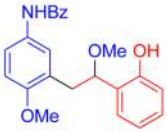
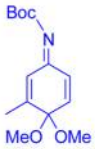
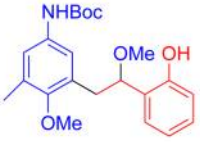
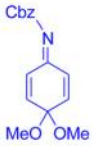
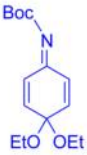
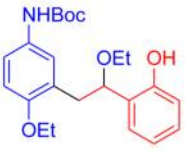
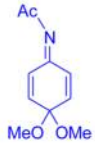
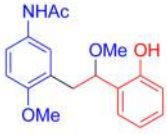
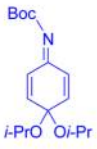
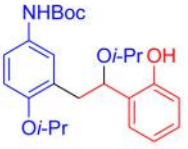
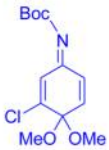
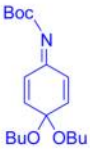
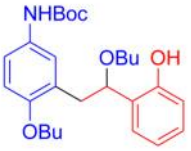
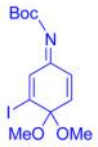
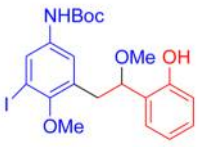
Table 2. Substrate Scope of QIKs 1[a]



entry	1	3	yield (%)[b]	entry	1	3	yield (%)[b]
1	 **1a**	 **3aa**	99	7[c]	 **1g**	 **3ga**	72 (55% *ee*)[d]
2	 **1b**	 **3ba**	52	8[c]	 **1h**	 **3ha**	82 (<5% *ee*)[d]
3	 **1c**	 **3ca**	64	9[c]	 **1i**	 **3ia**	62 (16% *ee*)[d]
4[c]	 **1d**	 **3da**	46 (<5% *ee*)[d]	10[c]	 **1j**	 **3ja**	42 (<5% *ee*)[d]
5	 **1e**	 **3ea**	69	11[c]	 **1k**	 **3ka**	75 (14% *ee*)[d]
6[c]	 **1f**	 **3fa**	55 (<5% *ee*)[d]				

[a]Unless indicated otherwise, the reaction was conducted at the 0.1 mmol scale and catalyzed by racemic BPA **4e** in toluene (1 mL) at 30 °C for 12 h. The **1**:**2a** mole ratio was 1:2. [b]Isolated yields. [c]Chiral BPA **4f** was employed as the catalyst. [d]The ee value was determined by HPLC.

In accordance with these control experiments, a possible reaction mechanism was deduced. Scheme 3 uses *p*-hydroxylstyrene **2l** as an example to illustrate the remote activation of the hydroxyl group on the styrene double bond via hydrogen bonding and conjugative effects. BPA **4e** acts as a bifunctional catalyst to activate both *p*-hydroxylstyrene **2l** and QIK **1a** at the same time through hydrogen bonding interactions, thereby initiating a vinylogous Michael addition. Subsequent hydrogen elimination and an intramolecular alkoxyl transfer take place simultaneously under the catalysis of the BPA anion, which acts as a base, resulting in the experimentally observed chemo- and regioselective oxyarylation product **3al**.

Preliminary derivations of oxyarylation product **3aa** were conducted to explore the potential of this methodology. As shown in Scheme 4, the hydroxyl activating group in compound **3aa** can be easily removed to create product **6** by Pd/C-catalyzed deoxygenation[11] of aryl triflate **5** in 82% yield, which shows that our approach can be used to oxyarylate various styrenes. In addition, triflate **5** of compound **3aa** is available for cross-coupling reactions as demonstrated by the formation of product **7** in a high yield of 88%. This further exhibits the synthetic utility of the hydroxyl group in compounds **3**. Furthermore, the bromination of compound **3aa** regioselectively occurred at the *ortho* position of the NHBoc group to

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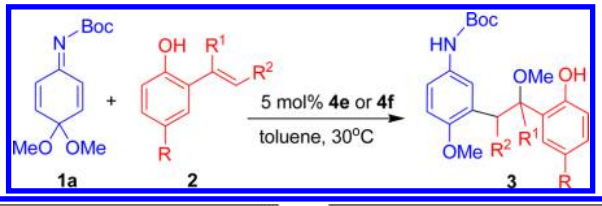
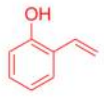
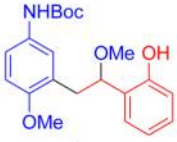
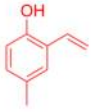
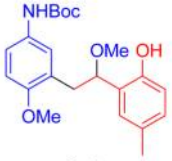
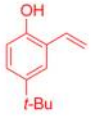
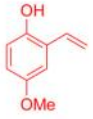
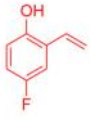
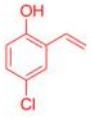
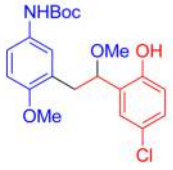
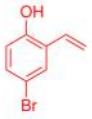
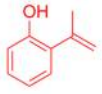
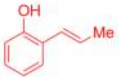
Table 3. Substrate Scope of *o*-Hydroxylstyrenes 2[a]



entry	2	3	yield (%)[b]
1	 **2a**	 **3aa**	99
2	 **2b**	 **3ab**	85
3	 **2c**	 **3ac**	57
4	 **2d**	 **3ad**	70
5	 **2e**	 **3ae**	60
6	 **2f**	 **3af**	60
7[c]	 **2g**	 **3ag**	74 (13% *ee*)[d]
8	 **2h**	 **3ah**	70
9[c]	 **2i**	 **3ai**	52 (72% *ee*)[d] (>95:5 *dr*)[e]

[a]Unless indicated otherwise, the reaction was conducted at the 0.1 mmol scale and was catalyzed by racemic BPA **4e** in toluene (1 mL) at 30 °C for 12 h. The **1a**:**2** mole ratio was 1:2. [b]Isolated yields. [c]Chiral BPA **4f** was employed as a catalyst. [d]The ee value was determined by HPLC. [e]The dr was determined by ^{1}H NMR.

afford product **8**, albeit in a moderate yield of 58%. Nevertheless, this transformation not only provides an alternative approach to synthesizing this type of compound, as opposed to using 2-substituted QIKs, but also offers opportunities for further derivations based on the aryl halide.

CONCLUSIONS

We have demonstrated the first organocatalytic oxyarylation of styrenes via a cascade of vinylogous Michael addition and alkoxyl transfer reactions of *o*- or *p*-hydroxylstyrenes with quinone imine ketals. In the presence of a binaphthyl-derived phosphoric acid, the two types of substrates were simultaneously activated via hydrogen bonds and conjugative effects over a long distance, ultimately resulting in the highly chemo- and regioselective oxyarylation of styrenes and providing access to *m*-alkylated anilines. This approach combines the merits of organocatalysis and cascade reactions to generate a C−C bond and a C−O bond as well as a new stereocenter in a single transformation. Furthermore, the reaction tolerates a wide range of substrates and provides the target products in generally high yields and excellent diastereoselectivity (up to 99% yield, >95:5 dr). The hydroxyl functionality as a remote activating group can be easily removed to perform further transformations, which demonstrates the applicability and utility of this strategy in styrene oxyarylation and the synthesis of styrene-based compounds.

EXPERIMENTAL SECTION

General Information. NMR spectra were measured at 400 and 100 MHz. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS spectra were recorded on a LTQ-Orbitrap mass spectrometer (ionization mode,

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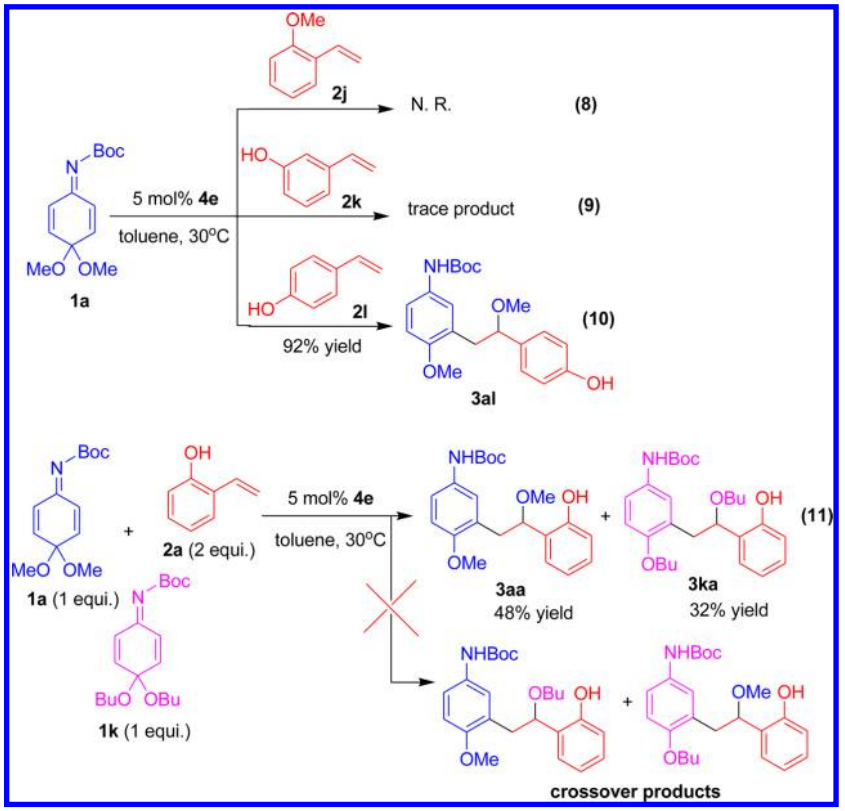
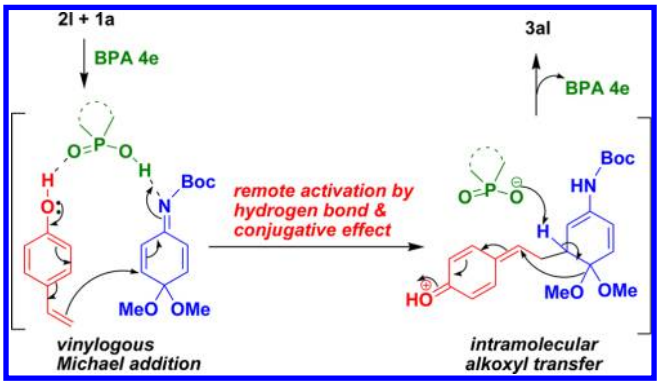
Scheme 2. Control Experiments for Exploring the Reaction Pathway



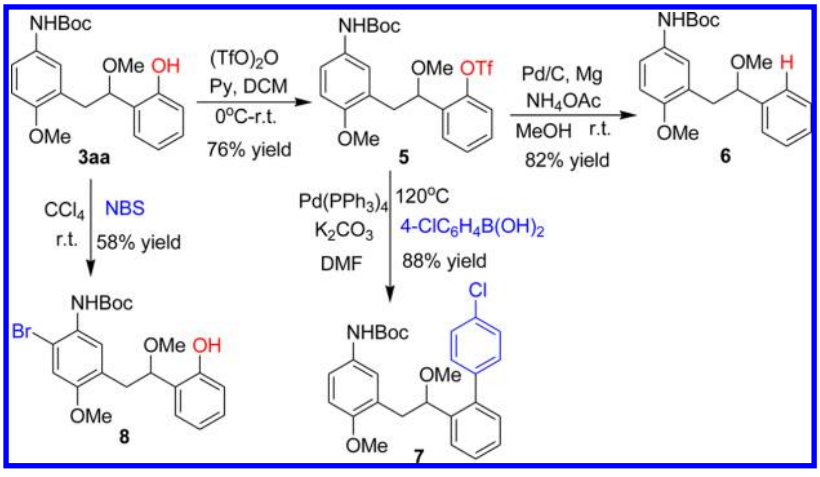
Scheme 3. Proposed Reaction Pathway and Activation Mode



ESI+). Enantiomeric excesses (ee) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral columns used for the determination of the enantiomeric excess by chiral HPLC were Chiralpak IC and AD-H columns. Analytical grade solvents for the column chromatography and commercially available reagents were used as received. Toluene was dried and distilled prior to use. Substrates **1** and **2** were synthesized according to the literature methods.[8e,13]

General Procedure for the Synthesis of Oxyarylation Product 3 via Cascade Reactions. After catalyst **4e** or **4f** (0.005 mmol) had been weighed to a reaction tube, the solution of hydroxylstyrenes **2** (0.2 mmol) in toluene (0.5 mL) was added to the tube and stirred. Then, the solution of quinone imine ketals **1** (0.1 mmol) in toluene (0.5 mL) was added to the stirred mixture and the new mixture stirred at 30 °C for 12 h. After the reaction had been stopped, the reaction mixture was directly purified via flash column

Scheme 4. Derivations of Oxyarylation Product 3aa



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chromatography on silica gel (flushed by a 10% Et_3N/petrol ether mixture in advance) to afford pure products **3**.

*tert-Butyl {3-[2-(2-hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**3aa**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 10:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 99% (37.0 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.29 (s, 1H), 7.20−7.10 (m, 1H), 7.00−6.83 (m, 2H), 6.80−6.69 (m, 3H), 6.29 (s, 1H), 4.64−4.43 (m, 1H), 3.73 (s, 3H), 3.34 (s, 3H), 3.15−3.08 (m, 1H), 3.04−2.97 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 153.7, 131.0, 128.9, 128.4, 126.6, 124.7, 119.4, 116.6, 110.6, 85.0, 57.5, 55.6, 37.0, 28.3; IR (KBr) 3648, 3110, 2930, 2337, 1700, 1507, 1238, 1161, 756 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{27}NO_5 + Na)^+$ requires m/z 396.1781, found m/z 396.1789.

*N-{3-[2-(2-Hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}-benzamide (**3ba**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 10:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 52% (19.6 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.87 (d, J = 7.2 Hz, 2H), 7.81 (s, 1H), 7.69−7.63 (m, 1H), 7.59−7.53 (m, 1H), 7.49 (t, J = 7.4 Hz, 2H), 7.23−7.14 (m, 2H), 6.94−6.88 (m, 1H), 6.88−6.74 (m, 3H), 4.65−4.54 (m, 1H), 3.79 (s, 3H), 3.37 (s, 3H), 3.24−3.13 (m, 1H), 3.12−3.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 154.7, 135.0, 131.6, 130.6, 128.9, 128.7, 128.4, 127.0, 126.7, 124.7, 123.8, 120.2, 119.5, 116.6, 110.6, 84.9, 57.5, 55.6, 36.9; IR (KBr) 3649, 3614, 3291, 2930, 2361, 1651, 1504, 1234, 1080, 704 cm^{-1}; ESI FTMS exact mass calcd for $(C_{23}H_{23}NO_4 + Na)^+$ requires m/z 400.1519, found m/z 400.1510.

*Benzyl {3-[2-(2-hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**3ca**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 2:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 64% (26.0 mg); red oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.59−7.28 (m, 6H), 7.22−7.10 (m, 1H), 7.01−6.84 (m, 2H), 6.82−6.69 (m, 3H), 6.54 (s, 1H), 5.19 (s, 2H), 4.71−4.41 (m, 1H), 3.74 (s, 3H), 3.34 (s, 3H), 3.23−3.09 (m, 1H), 3.08−2.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 136.2, 128.9, 128.6, 128.4, 128.3, 128.2, 126.7, 124.6, 119.4, 116.6, 110.6, 85.0, 57.5, 55.6, 36.9; IR (KBr) 3303, 2933, 2832, 2357, 1707, 1504, 1225, 1808, 753 cm^{-1}; ESI FTMS exact mass calcd for $(C_{24}H_{25}NO_5 + Na)^+$ requires m/z 430.1625, found m/z 430.1628.

*N-{3-[2-(2-Hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}-acetamide (**3da**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 2:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 46% (14.5 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.79−7.60 (m, 1H), 7.52−7.45 (m, 2H), 7.23 (s, 1H), 6.98 (d, J = 2.6 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 6.81−6.75 (m, 2H), 4.62−4.47 (m, 1H), 3.74 (s, 3H), 3.33 (s, 3H), 3.18−3.08 (m, 1H), 3.04−2.95 (m, 1H), 2.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 155.3, 154.5, 132.0, 128.9, 128.4, 126.6, 123.6, 120.1, 119.4, 116.6, 110.5, 84.9, 57.5, 55.6, 36.9, 24.3; IR (KBr) 3671, 3641, 3271, 3270, 2926, 2360, 1740, 1504, 1381, 1233, 1085, 755 cm^{-1}; ESI FTMS exact mass calcd for $(C_{18}H_{21}NO_4 + Na)^+$ requires m/z 338.1363, found m/z 338.1364; ee, <5%, determined by HPLC (Daicel Chirapak AD-H, 95:5 hexane/2-propanol, flow rate of 1.0 mL/min, 30 °C, 254 nm); t_R = 42.327 min, t_R = 47.277 min.

*tert-Butyl {3-chloro-5-[2-(2-hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**3ea**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 10:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 69% (28.0 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.49 (s, 1H), 7.22−7.14 (m, 1H), 6.96−6.72 (m, 4H), 6.40 (s, 1H), 4.57−4.48 (m, 1H), 3.75 (s, 3H), 3.33 (s, 3H), 3.22−3.13 (m, 1H), 3.00−2.91 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 152.5, 150.0, 134.5, 133.1, 129.2, 128.4, 127.9, 124.3, 119.8, 116.9, 85.4, 60.8, 57.6, 37.2, 28.3; IR (KBr) 3474, 3413, 2978, 2934, 2362, 1701, 1526, 1483, 1240, 1159, 1085, 756 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{26}ClNO_5 + Na)^+$ requires m/z 430.1392, found m/z 430.1416.

*tert-Butyl {3-[2-(2-hydroxyphenyl)-2-methoxyethyl]-5-iodo-4-methoxyphenyl}carbamate (**3fa**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 10:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 55% (27.7 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.85 (s, 1H), 7.26−7.15 (m, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.94−6.90 (m, 1H), 6.89−6.86 (m, 1H), 6.85−6.79 (m, 1H), 6.36 (s, 1H), 4.66−4.53 (m, 1H), 3.75 (s, 3H), 3.35 (s, 3H), 3.30−3.16 (m, 1H), 3.05−2.89 (m, 1H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 153.9, 152.5, 135.3, 132.2, 129.2, 128.4, 124.4, 119.8, 116.9, 91.6, 85.3, 61.1, 57.6, 37.9, 28.3; IR (KBr) 3650, 3294, 2928, 2337, 1828, 1700, 1491, 1427, 1368, 1115, 731 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{26}INO_5 + Na)^+$ requires m/z 522.0753, found m/z 522.0739; ee, <5%, determined by HPLC (Daicel Chirapak AD-H, 92:8 hexane/2-propanol, flow rate of 1.0 mL/min, 30 °C, 254 nm); t_R = 8.553 min, t_R = 10.797 min.

*tert-Butyl {5-[2-(2-hydroxyphenyl)-2-methoxyethyl]-6-methoxy-[1,1′-biphenyl]-3-yl}carbamate (**3ga**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 10:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 72% (32.3 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.65−7.50 (m, 2H), 7.51−7.40 (m, 2H), 7.39−7.30 (m, 2H), 7.25−7.18 (m, 1H), 7.07 (s, 1H), 6.99−6.89 (m, 2H), 6.87−6.78 (m, 1H), 6.45 (s, 1H), 4.79−4.60 (m, 1H), 3.41 (s, 3H), 3.32−3.23 (m, 4H), 3.13−2.91 (m, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.9, 151.8, 138.5, 135.1, 133.8, 131.9, 129.0, 128.9, 128.4, 128.2, 127.2, 124.7, 119.7, 116.8, 85.7, 60.4, 57.6, 37.2, 28.3; IR (KBr) 3730, 3294, 2977, 2932, 2361, 1700, 1538, 1376, 1239, 1158, 1080, 755, 698 cm^{-1}; ESI FTMS exact mass calcd for $(C_{27}H_{31}NO_5 + Na)^+$ requires m/z 472.2095, found m/z 472.2108; ee, 55%, determined by HPLC (Daicel Chirapak AD-H, 92:8 hexane/2-propanol, flow rate of 1.0 mL/min, 30 °C, 254 nm); t_R = 9.670 min (major), t_R = 10.937 min (minor).

*tert-Butyl {3-[2-(2-hydroxyphenyl)-2-methoxyethyl]-4-methoxy-5-methylphenyl}carbamate (**3ha**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 10:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 82% (31.6 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.25−7.17 (m, 2H), 6.99−6.76 (m, 4H), 6.33 (s, 1H), 4.72−4.51 (m, 1H), 3.66 (s, 3H), 3.36 (s, 3H), 3.25−3.12 (m, 1H), 3.02−2.90 (m, 1H), 2.30 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 152.9, 152.8, 133.7, 131.4, 131.2, 129.0, 128.4, 124.8, 119.7, 116.8, 85.8, 60.4, 57.6, 37.0, 28.4, 16.4; IR (KBr) 3731, 3674, 3313, 2977, 2943, 2361, 1700, 1539, 1239, 1153, 1085, 753 cm^{-1}; ESI FTMS exact mass calcd for $(C_{22}H_{29}NO_5 + Na)^+$ requires m/z 410.1922, found m/z 410.1926; ee, <5%, determined by HPLC (Daicel Chirapak AD-H, 92:8 hexane/2-propanol, flow rate of 1.0 mL/min, 30 °C, 254 nm); t_R = 8.873 min, t_R = 11.613 min.

*tert-Butyl {4-ethoxy-3-[2-ethoxy-2-(2-hydroxyphenyl)ethyl]-phenyl}carbamate (**3ia**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 62% (24.8 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.26 (s, 1H), 7.24−7.07 (m, 1H), 6.97−6.85 (m, 2H), 6.78−6.70 (m, 3H), 6.29 (s, 1H), 4.85−4.50 (m, 1H), 4.04−3.79 (m, 2H), 3.66−3.49 (m, 1H), 3.50−3.35 (m, 1H), 3.25−3.07 (m, 1H), 3.06−2.96 (m, 1H), 1.51 (s, 9H), 1.40 (t, J = 6.9 Hz, 3H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 153.1, 130.7, 128.7, 128.2, 126.9, 119.3, 116.6, 111.5, 83.3, 65.5, 63.8, 37.3, 28.4, 15.0, 14.9; IR (KBr) 3612, 3338, 2976, 2928, 2360, 1698, 1507, 1236, 1161, 1069, 754 cm^{-1}; ESI FTMS exact mass calcd for $(C_{23}H_{31}NO_5 + Na)^+$ requires m/z 424.2094, found m/z 424.2088; ee, 16%, determined by HPLC (Daicel Chirapak AD-H, 92:8 hexane/2-propanol, flow rate of 1.0 mL/min, 30 °C, 254 nm); t_R = 7.893 min (minor), t_R = 11.473 min (major).

*tert-Butyl {3-[2-(2-hydroxyphenyl)-2-isopropoxyethyl]-4-isopropoxyphenyl}carbamate (**3ja**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 42% (18.0 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.33 (s,

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1H), 7.19−7.08 (m, 1H), 6.92−6.84 (m, 1H), 6.84−6.70 (m, 4H), 6.23 (s, 1H), 4.85−4.68 (m, 1H), 4.60−4.47 (m, 1H), 3.70−3.54 (m, 1H), 3.14−2.98 (m, 1H), 2.99−2.87 (m, 1H), 1.50 (s, 9H), 1.40−1.30 (m, 6H), 1.11 (d, J = 6.2 Hz, 3H), 0.97 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 153.2, 130.7, 128.7, 128.2, 126.9, 125.4, 119.2, 116.7, 83.6, 69.9, 67.8, 31.5, 28.3, 19.4, 19.1; IR (KBr) 3649, 3332, 2961, 2932, 2361, 1724, 1507, 1389, 1238, 1163, 1078, 755 cm^{-1}; ESI FTMS exact mass calcd for $(C_{25}H_{35}NO_5 + Na)^+$ requires m/z 452.2407, found m/z 452.2381; ee, <5%, determined by HPLC (Daicel Chirapak AD-H, 92:8 hexane/2-propanol, flow rate of 1.0 mL/min, 30 °C, 254 nm); t_R = 5.890 min, t_R = 7.073 min.

*tert-Butyl {4-butoxy-3-[2-butoxy-2-(2-hydroxyphenyl)ethyl]-phenyl}carbamate (**3ka**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 75% (34.5 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.28 (s, 1H), 7.20−7.11 (m, 1H), 6.96−6.83 (m, 2H), 6.81−6.67 (m, 3H), 6.25 (s, 1H), 4.68−4.53 (m, 1H), 3.97−3.85 (m, 2H), 3.59−3.45 (m, 1H), 3.39−3.28 (m, 1H), 3.23−3.07 (m, 1H), 3.04−2.94 (m, 1H), 1.89−1.73 (m, 2H), 1.63−1.53 (m, 2H), 1.50 (s, 9H), 1.49−1.45 (m, 2H), 1.30−1.23 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 151.8, 130.5, 128.6, 127.9, 127.9, 126.2, 119.2, 116.8, 113.0, 80.6, 71.3, 70.0, 38.3, 28.3, 22.6, 22.2, 21.1; IR (KBr) 3742, 3614, 3310, 2959, 2930, 2361, 1701, 1508, 1390, 1238, 1163, 754 cm^{-1}; ESI FTMS exact mass calcd for $(C_{27}H_{39}NO_5 + Na)^+$ requires m/z 480.2720, found m/z 480.2720; ee, 14%, determined by HPLC (Daicel Chirapak AD-H, 98:2 hexane/2-propanol, flow rate of 1.0 mL/min, 30 °C, 254 nm); t_R = 15.983 min (minor), t_R = 17.460 min (major).

*tert-Butyl {3-[2-(2-hydroxy-5-methylphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**3ab**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 85% (32.9 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.31 (s, 1H), 7.02−6.92 (m, 2H), 6.84−6.74 (m, 2H), 6.65 (d, J = 1.7 Hz, 1H), 6.37 (s, 1H), 4.56−4.44 (m, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 3.17−3.07 (m, 1H), 3.05−2.97 (m, 1H), 2.22 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 153.0, 131.0, 129.4, 128.8, 128.6, 126.9, 124.6, 116.4, 110.6, 85.0, 57.5, 55.7, 37.2, 28.4, 20.4; IR (KBr) 3705, 3647, 3443, 2360, 2336, 1698, 1507, 1389, 1237, 1162, 815 cm^{-1}; ESI FTMS exact mass calcd for $(C_{22}H_{29}NO_5 + Na)^+$ requires m/z 410.1938, found m/z 410.1917.

*tert-Butyl {3-{2-[5-(tert-butyl)-2-hydroxyphenyl]-2-methoxyethyl}-4-methoxyphenyl)carbamate (**3ac**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 3:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 57% (24.3 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.28 (s, 1H), 7.23−7.11 (m, 1H), 6.87−6.73 (m, 3H), 6.59 (d, J = 2.4 Hz, 1H), 6.26 (s, 1H), 4.51 (t, J = 7.1 Hz, 1H), 3.74 (s, 3H), 3.42 (s, 3H), 3.29−3.16 (m, 1H), 3.02−2.86 (m, 1H), 1.52 (s, 9H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 152.9, 141.8, 131.0, 126.6, 125.6, 125.4, 123.5, 115.9, 110.6, 85.6, 57.5, 55.7, 36.9, 33.8, 31.6, 31.4, 28.4; IR (KBr) 3673, 3649, 3297, 2960, 2361, 1701, 1505, 1234, 1162, 821, 733 cm^{-1}; ESI FTMS exact mass calcd for $(C_{25}H_{35}NO_5 + Na)^+$ requires m/z 452.2407, found m/z 452.2395.

*tert-Butyl {3-[2-(2-hydroxy-5-methoxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**3ad**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 3:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 70% (26.9 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.28 (s, 1H), 6.94 (s, 1H), 6.89−6.64 (m, 3H), 6.36 (d, J = 3.0 Hz, 1H), 6.33 (s, 1H), 4.50−4.40 (m, 1H), 3.74 (s, 3H), 3.66 (s, 3H), 3.32 (s, 3H), 3.16−3.05 (m, 1H), 3.05−2.92 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 152.6, 149.1, 131.0, 126.7, 125.5, 117.1, 114.1, 113.6, 110.6, 84.7, 57.5, 55.7, 55.7, 37.0, 28.3; IR (KBr) 3647, 3612, 3341, 2976, 2934, 2360, 1699, 1457, 1235, 1034, 811, 731 cm^{-1}; ESI FTMS exact mass calcd for $(C_{22}H_{29}NO_6 + Na)^+$ requires m/z 426.1887, found m/z 426.1889.

*tert-Butyl {3-[2-(5-fluoro-2-hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**3ae**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 60% (23.6 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.26 (s, 1H), 6.97 (s, 1H), 6.88−6.72 (m, 3H), 6.52 (dd, J = 8.7, 2.8 Hz, 1H), 6.32 (s, 1H), 4.50−4.44 (m, 1H), 3.74 (s, 3H), 3.33 (s, 3H), 3.12−3.04 (m, 1H), 3.04−2.96 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 155.0, 153.6, 151.3, 151.2, 131.1, 126.3, 117.5, 117.40, 115.2, 115.0, 114.6, 114.4, 110.6, 84.4, 57.7, 55.6, 36.9, 28.4; IR (KBr) 3650, 3306, 2929, 2361, 1700, 1512, 1236, 1162, 1082, 814, 771 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{26}FNO_5 + Na)^+$ requires m/z 414.1687, found m/z 414.1649.

*tert-Butyl {3-[2-(5-chloro-2-hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**3af**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 60% (24.3 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.24 (s, 1H), 7.11 (dd, J = 8.6, 2.6 Hz, 1H), 7.00 (s, 1H), 6.85−6.70 (m, 3H), 6.32 (s, 1H), 4.49−4.43 (m, 1H), 3.73 (s, 3H), 3.32 (s, 3H), 3.10−3.03 (m, 1H), 3.03−2.96 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 153.6, 131.0, 128.7, 127.9, 126.5, 126.2, 124.1, 118.0, 110.6, 84.5, 57.7, 55.6, 37.1, 28.4; IR (KBr) 3648, 3618, 3331, 2930, 1261, 1699, 1512, 1390, 1235, 1161 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{26}ClNO_5 + Na)^+$ requires m/z 430.1392, found m/z 430.1393.

*tert-Butyl {3-[2-(5-bromo-2-hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**3ag**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 74% (33.6 mg); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.25 (dd, J = 8.8, 2.6 Hz, 2H), 7.00 (s, 1H), 6.91 (d, J = 2.4 Hz, 1H), 6.85−6.65 (m, 2H), 6.31 (s, 1H), 4.49−4.41 (m, 1H), 3.73 (s, 3H), 3.32 (s, 3H), 3.09−3.03 (m, 1H), 3.03−2.98 (m, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 153.6, 131.6, 131.0, 130.8, 127.1, 126.2, 118.6, 111.4, 110.6, 84.4, 57.7, 55.6, 37.1, 28.4; IR (KBr) 3731, 3649, 3298, 2929, 2361, 1700, 1508, 1238, 1161, 815, 761 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{26}BrNO_5 + Na)^+$ requires m/z 474.0886, found m/z 474.0892; ee, 13%, determined by HPLC (Daicel Chirapak AD-H, 92:8 hexane/2-propanol, flow rate of 1.0 mL/min, 30 °C, 254 nm); t_R = 11.920 min (minor), t_R = 21.507 min (major).

*tert-Butyl {3-[2-(2-hydroxyphenyl)-2-methoxypropyl]-4-methoxyphenyl}carbamate (**3ah**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 70% (27.1 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 7.33 (s, 1H), 7.23−7.13 (m, 1H), 6.92−6.87 (m, 1H), 6.86−6.81 (m, 1H), 6.79−6.66 (m, 3H), 6.40 (s, 1H), 3.61 (s, 3H), 3.20 (d, J = 10.3 Hz, 4H), 3.10 (d, J = 13.3 Hz, 1H), 1.53 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 154.2, 130.7, 129.2, 127.9, 127.4, 125.6, 119.2, 116.6, 110.6, 83.4, 55.5, 50.7, 39.7, 28.4, 20.6; IR (KBr) 3552, 3413, 2979, 1714, 1616, 1505, 1367, 1243, 1161, 622 cm^{-1}; ESI FTMS exact mass calcd for $(C_{22}H_{29}NO_5 + Na)^+$ requires m/z 410.1938, found m/z 410.1931.

*tert-Butyl {3-[1-(2-hydroxyphenyl)-1-methoxypropan-2-yl]-4-methoxyphenyl}carbamate (**3ai**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 52% (20.1 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.26 (s, 1H), 7.23−7.15 (m, 1H), 7.06 (d, J = 2.2 Hz, 1H), 6.91−6.83 (m, 2H), 6.80 (t, J = 7.6 Hz, 2H), 6.36 (s, 1H), 4.42 (d, J = 8.7 Hz, 1H), 3.76 (s, 3H), 3.73−3.65 (m, 1H), 3.27 (s, 3H), 1.51 (s, 9H), 1.05 (d, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 153.7, 132.5, 131.3, 130.1, 129.0, 123.3, 119.1, 116.8, 111.2, 89.3, 57.6, 55.9, 28.4, 17.1; IR (KBr) 3611, 2975, 2933, 2360, 1698, 1505, 1368, 1241, 1161, 1066, 810, 756 cm^{-1}; ESI FTMS exact mass calcd for $(C_{22}H_{29}NO_5 + Na)^+$ requires m/z 410.1938, found m/z 410.1918; ee, 72%, determined by HPLC (Daicel Chirapak IC, 95:5 hexane/2-propanol, flow rate of 1.0 mL/min, 30 °C, 254 nm); t_R = 10.010 min (major), t_R = 11.637 min (minor).

*tert-Butyl {3-[2-(4-hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**3al**):* flash column chromatography

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eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 92% (34.2 mg); red oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.20−7.04 (m, 2H), 6.88 (d, J = 1.9 Hz, 1H), 6.83−6.67 (m, 3H), 6.37 (s, 1H), 6.20 (s, 1H), 4.43−4.29 (m, 1H), 3.74 (s, 3H), 3.18 (s, 3H), 3.11−2.99 (m, 1H), 2.95−2.80 (m, 1H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 153.9, 133.4, 130.7, 128.9, 128.0, 127.9, 127.5, 115.6, 115.1, 110.7, 83.0, 56.5, 55.7, 50.7, 38.9, 28.4; IR (KBr) 3741, 3648, 3306, 2976, 2361, 1698, 1512, 1367, 1241, 1161, 811, 729 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{27}NO_5 + Na)^+$ requires m/z 396.1781, found m/z 396.1781.

Procedure for the Synthesis of Compound 5. To the solution of compound **3aa** (374 mg, 1 mmol) in dichloromethane (10 mL) was added pyridine (237 mg, 3 mmol). Then, the solution of Tf_2O (423 mg, 1.5 mmol) in dichloromethane (5 mL) was added dropwise to the reaction mixture at 0 °C, which was stirred overnight at room temperature. After the completion of the reaction indicated by TLC, water (5 mL) was added to the reaction mixture, which was further extracted by dichloromethane and dried by anhydrous Na_2SO_4. The resultant organic layer was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel (flushed with a 10% Et_3N/petrol ether mixture in advance) to afford pure products **5** (384 mg, 76% yield).

*2-(2-{5-[(tert-Butoxycarbonyl)amino]-2-methoxyphenyl}-1-methoxyethyl)phenyl trifluoromethanesulfonate (**5**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 12:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 76% (384 mg); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.48 (m, 1H), 7.43−7.23 (m, 3H), 7.20 (d, J = 8.1 Hz, 1H), 6.87 (s, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.32 (s, 1H), 4.96−4.69 (m, 1H), 3.70 (s, 3H), 3.19 (s, 3H), 3.06−2.98 (m, 1H), 2.96−2.87 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 142.9, 130.5, 126.0, 124.2, 123.8, 123.7, 121.1, 116.0, 105.5, 52.3, 50.5, 33.7, 23.6; IR (KBr) 3647, 3589, 3443, 2922, 2851, 2360, 1699, 1645, 1510, 1391, 1232, 1161, 755 cm^{-1}; ESI FTMS exact mass calcd for $(C_{22}H_{26}F_3NO_7S + Na)^+$ requires m/z 528.1274, found m/z 528.1277.

Procedure for the Synthesis of Compound 6. Methanol (2 mL) was added to the mixture of compound **5** (25.3 mg, 0.05 mmol), Mg (12 mg, 0.5 mmol), 10% Pd/C (32 mg), and ammonium acetate (120 mg, 1.55 mmol). After the mixture had been stirred at room temperature overnight and the completion of the reaction indicated by TLC, the reaction mixture was filtered, and the filtrate was concentrated under the reduced pressure to give the residue, which was then added to water (5 mL), extracted by ethyl acetate, and dried by anhydrous Na_2SO_4. The resultant organic layer was again concentrated under reduced pressure to give pure products **6** (15 mg, 82% yield).

*tert-Butyl [4-methoxy-3-(2-methoxy-2-phenylethyl)phenyl]carbamate (**6**):* reaction time, 12 h; yield, 82% (15.0 mg); yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 3H), 7.27−7.21 (m, 3H), 6.87 (d, J = 2.3 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 6.26 (s, 1H), 4.45−4.35 (m, 1H), 3.72 (s, 3H), 3.18 (s, 3H), 3.08−2.99 (m, 1H), 2.95−2.85 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 142.2, 130.8, 128.1, 127.4, 127.3, 126.7, 110.6, 83.3, 56.8, 55.6, 39.2, 28.4; IR (KBr) 3420, 2964, 2929, 1699, 1649, 1509, 1389, 1262, 1161, 1097, 822, 699 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{27}NO_4 + Na)^+$ requires m/z 380.1832, found m/z 380.1830.

Procedure for the Synthesis of Compound 7. Under an argon atmosphere, DMF (1.5 mL) was added to the mixture of compound **5** (25.3 mg, 0.05 mmol), 4-chlorophenylboronic acid (11.7 mg, 0.075 mmol), K_2CO_3 (13.8 mg, 0.1 mmol), and $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol). After the mixture had been stirred at 120 °C for 4 h and the completion of the reaction indicated by TLC, water (5 mL) was added to the reaction mixture, which was extracted by ethyl acetate and dried by anhydrous Na_2SO_4. The resultant organic layer was concentrated under reduced pressure to give the residue, which was purified through column chromatography on aluminum oxide to afford pure products **7** (20.2 mg, 88% yield).

*tert-Butyl {3-[2-(4′-chloro[1,1′-biphenyl]-2-yl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**7**):* flash column chromatography eluent (Al_2O_3), 4:1 petroleum ether/ethyl acetate; reaction time, 4 h; yield, 88% (20.2 mg); yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74−7.59 (m, 1H), 7.56−7.37 (m, 1H), 7.37−7.23 (m, 4H), 7.15−7.00 (m, 1H), 6.87 (d, J = 8.0 Hz, 2H), 6.62 (d, J = 8.7 Hz, 2H), 6.19 (s, 1H), 4.52 (t, J = 6.8 Hz, 1H), 3.49 (s, 3H), 3.10 (s, 3H), 3.06−2.95 (m, 1H), 2.92−2.73 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 141.0, 139.6, 139.4, 132.7, 130.8, 129.3, 128.1, 127.9, 127.0, 126.6, 126.5, 110.4, 78.2, 56.3, 55.2, 38.8, 29.7, 28.4; IR (KBr) 3672, 3648, 3362, 2925, 2857, 2361, 2337, 1720, 1538, 1508, 1233, 1164, 835, 766 cm^{-1}; ESI FTMS exact mass calcd for $(C_{27}H_{30}ClNO_4 - H)^-$ requires m/z 466.1779, found m/z 466.1780.

Procedure for the Synthesis of Compound 8. CCl_4 (1 mL) was added to the mixture of compound **3aa** (18.7 mg, 0.05 mmol) and NBS (9.8 mg, 0.055 mmol). After the mixture had been stirred at room temperature overnight and the completion of the reaction indicated by TLC, the reaction mixture was concentrated under reduced pressure to give the residue, which was purified through flash column chromatography on silica gel (flushed with a 10% Et_3N/petrol ether mixture in advance) to afford pure product **8** (13.0 mg, 58% yield).

*tert-Butyl {2-bromo-5-[2-(2-hydroxyphenyl)-2-methoxyethyl]-4-methoxyphenyl}carbamate (**8**):* flash column chromatography eluent (flushed with a 10% Et_3N/petrol ether mixture in advance), 8:1 petroleum ether/ethyl acetate; reaction time, 12 h; yield, 58% (13.0 mg); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.28 (s, 1H), 6.92 (s, 1H), 6.80−6.69 (m, 2H), 6.68−6.52 (m, 1H), 6.28 (s, 1H), 4.56 (t, J = 7.0 Hz, 1H), 3.70 (d, J = 1.2 Hz, 3H), 3.34 (d, J = 1.5 Hz, 3H), 3.19−3.06 (m, 1H), 3.05−2.92 (m, 1H), 1.51 (d, J = 1.4 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 147.0, 127.4, 126.2, 122.8, 121.8, 121.5, 115.7, 105.9, 105.8, 79.6, 52.9, 50.8, 32.0, 23.6; IR (KBr) 3737, 3647, 3275, 2930, 2360, 2336, 1700, 1508, 1229, 1161, 882, 774 cm^{-1}; ESI FTMS exact mass calcd for $(C_{21}H_{26}BrNO_5 - H)^-$ requires m/z 450.0910, found m/z 450.0936.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data (including ^1H and ^{13}C NMR and HPLC spectra) for all products **3** and **5**−**8**. 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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