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Transition-Metal-Free Reactions of Boronic Acids: 1,3-Stereochemical Induction in the Substrate-Controlled Conjugate Addition

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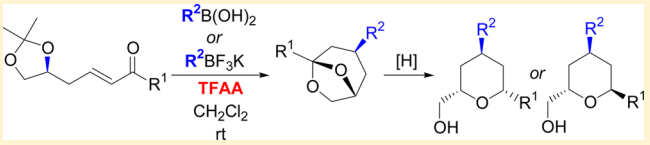
Supporting Information

ABSTRACT: The substrate-controlled 1,3-stereoselective conjugate addition of boronic acids and potassium trifluoroborates under metal-free conditions has been developed. This reaction affords bicyclic acetals, which have been used as key intermediates in the stereodivergent synthesis of polysubstituted tetrahydropyrans.

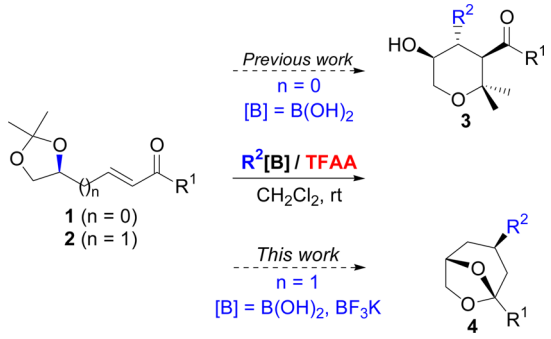


The formation of C−C bonds is a fundamental reaction in the construction of the carbon backbone of organic molecules. The conjugate addition of carbon-centered nucleophiles to electron-deficient alkenes constitutes one of the most relevant synthetic methods toward this end.[1] Control of the stereoselectivity is crucial in the development of these procedures. This has been achieved by using a variety of chiral ligands attached to transition metal catalysts and by organocatalytic procedures. Also, the use of covalently bound chiral inducers and the exploitation of 1,2-stereochemical induction are common strategies in the realm of conjugate additions to enantiopure acceptor substrates. Contrarily, 1,3-stereochemical induction using chiral-pool derived compounds as starting materials has been much less developed, despite its conceptual simplicity and practical usefulness in the preparation of important molecules such as drugs and natural products. This is particularly important with regard to conformationally flexible acyclic substrates, where stereocontrol is more challenging. Most of the reported examples[2,3] have been restricted to cuprates, simple organozinc reagents or carbon-stabilized nucleophiles, and suffer from modest stereoselectivities. In fact, catalyst control has been required in many of these cases to override poor substrate control and help to improve the stereoselectivity. The finding of other carbon-centered nucleophiles and reaction conditions that could enable 1,3-stereochemical induction fully under substrate control would be a highly attractive addendum to the synthetic arsenal.

Boronic acids[4] and potassium trifluororoborates[5] are attractive reagents for the synthesis of complex molecules due to their low toxicity, thermal stability, and wide compatibility with functional groups that are readily attacked by other organometallics. One of the handicaps of these reagents is their low nucleophilicity. This requires the inclusion of some type of extra activation in the synthetic procedures. Most frequently, transition metal catalysis has been used for this purpose. Comparatively, reactions in which boronic acids act as nucleophiles in conjugate addition reactions under metal-free conditions remain scarce.[6,7] This is a new rapidly expanding field of organoboron chemistry that has not been yet fully explored.

In the search for new reactions of boronic acids in the absence of metal catalysis, we have recently reported the 1,2-stereochemical induction in the tandem conjugate addition−acetal ring-opening of boronic acids to compounds **1** acids under trifluoroacetic anhydride (TFAA) activation (Scheme 1).[6a] In the present paper we have addressed the issue of 1,3-

Scheme 1. Metal-Free Conjugate Addition of Boronic Acids to Enones with a Pending Acetal Moiety



stereochemical induction using compounds **2** as starting materials. Boronic acids and potassium trifluoroborates have not been previously used in the context of substrate-controlled 1,3-stereochemical induction, despite their proven utility as carbon nucleophiles in stereoselective metal-catalyzed conjugate addition reactions.[8,9]

We have chosen for our study the δ-oxygen-substituted α,β-unsaturated carbonyl compounds **2**, which are easily prepared optically pure from the chiral pool. To the best of our knowledge, no conjugate additions of carbon-centered nucleophiles to these type of compounds have been previously reported.[10] On the basis of recent studies on conjugate addition reactions of alkenylboronic acids catalyzed by acylating

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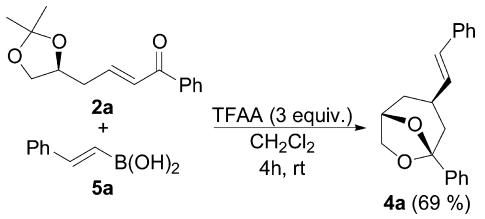
reagents,[7a] we first examined the reaction of ketone **2a** with (*E*)-styrylboronic acid (**5a**) (eq 1).

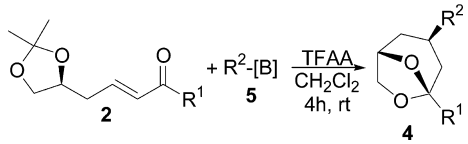


After optimization of reaction conditions, we found that this process was efficiently promoted by using TFAA (3.0 equiv) in CH_2Cl_2 under mild reaction conditions (4 h at rt). The 6,8-dioxa[3.2.1]bicycle **4a** was isolated exclusively as a single diastereomer,[11] with an *exo* relative disposition of the pending styryl chain.

It is worth mentioning that this type of bicyclic acetals are key structures in certain natural products frameworks.[12] Also, they have attracted recent interest as agrochemicals[13] and as squalane synthase inhibitors,[14] apart from being interesting synthetic intermediates for the preparation of natural products.[15]

In order to investigate the scope of this transformation, we examined the reaction of **2a** with different boronic acids. The results are gathered in Table 1. We observed that this reaction

Table 1. Synthesis of 6,8-Dioxa[3.2.1]bicycles 4a[a]



entry	2	5	R^1	R^2–[B]	4 (yield %)[b]
1	**2a**	**5b**	Ph	(*E*)-*p*Me-C_6H_4—CH=CH-$B(OH)_2$	**4b** (64)
2	**2a**	**5c**	Ph	(*E*)-*p*F—C_6H_4—CH=CH-$B(OH)_2$	**4c** (61)
3	**2a**	**5d**	Ph	(*E*)-*p*Cl—C_6H_4—CH=CH-$B(OH)_2$	**4d** (66)
4	**2a**	**5e**	Ph	(*E*)-*p*CF_3—C_6H_4—CH=CH-$B(OH)_2$	**4e** (67)
5	**2a**	**5f**	Ph	(*E*)-Biphenyl-CH=CH-$B(OH)_2$	**4f** (59)
6	**2a**	**5g**	Ph	(*E*)-*p*MeO-C_6H_4—CH=CH-$B(OH)_2$	–
7	**2a**	**5h**	Ph	Ph-$B(OH)_2$	–
8	**2a**	**5i**	Ph	Ph-$B(OH)_2$	–
9	**2a**	**5j**	Ph	(*E*)-Ph—CH=CH-BF_3K	**4a** (70)
10	**2b**	**5a**	Me	(*E*)-Ph—CH=CH-$B(OH)_2$	–
11	**2c**	**5a**	H	(*E*)-Ph—CH=CH-$B(OH)_2$	–
12	**2b**	**5j**	Me	(*E*)-Ph—CH=CH-BF_3K	**4g** (71)
13	**2c**	**5j**	H	(*E*)-Ph—CH=CH-BF_3K	**4h** (52)

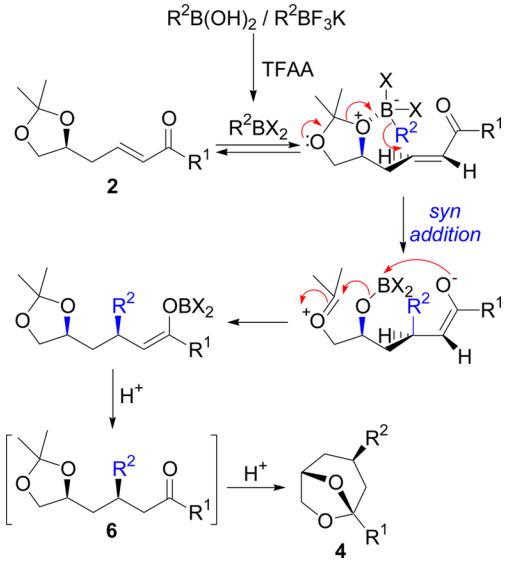
[a]Reaction conditions: **2** (0.13 mmol), **5** (0.26 mmol), TFAA (0.39 mmol, 3 equiv), CH_2Cl_2 (0.8 mL), 4 h, rt. [b]Isolated yield of **4** after column chromatography.

could be extended to other styrylboronic acids **5** substituted in the benzene ring with electron-withdrawing substituents (Table 1, entries 1–5). On the other hand, the reaction did not support the presence of a *p*-MeO group (Table 1, entry 6). Phenylboronic acid (Table 1, entry 7) did not react under these reaction conditions. Potassium vinyltrifluoroborates (Table 1, entry 8) were also good reagents for this type of transformation. However, no reaction was found for potassium phenyltrifluoroborate (Table 1, entry 9).

In addition, we examined the reaction of other substrates **2**. We found no reaction between the boronic acid **5a** and methylketone **2b** or aldehyde **2c** (Table 1, entries 10 and 11). However, we found that both transformations were possible when using instead the corresponding potassium trifluoroborate **5j** (Table 1, entries 12 and 13).

A reaction mechanism that accounts for the formation of compounds **4** and the observed stereochemistry is proposed in Scheme 2. Reaction of TFAA with a boronic acid may give a

Scheme 2. Proposed Mechanism



mono- or a diacylboronate[16] intermediate, where the Lewis acidity of the boron atom is enhanced with respect to that of the starting boronic acid. Similarly, potassium trifluoroborates are known to produce organodifluoroboranes under the influence of Lewis acids.[17] Therefore, we suggest the transient formation of an electron-deficient trivalent boron species (RBX_2) by the reaction of the starting boronic acid or potassium trifluoroborate with TFAA.[18] The enhanced Lewis acidity of the boron acid in these species enables coordination with the lone pair of the δ-oxygen of the acetal group,[6a,19] facilitated by the lone pair on the ε-oxygen. The intramolecular delivery (*syn*-addition) of the R^2 group from the boronate intermediate thus generated would finally afford the intermediate compounds **6** (not isolated), which rendered in situ the 6,8-dioxa[3.2.1]bicycles **4** by intramolecular transacetalization.

6,8-Dioxa[3.2.1]bicycles constitute useful materials for the stereodivergent synthesis of optically pure tetrahydropyrans,[20] a ubiquitous skeleton among pharmaceuticals and natural products. Considerable efforts have been made in recent times toward the stereoselective preparation of di- and trisubstituted tetrahydropyrans.[21] In this paper, we have used compounds **4** as key intermediates for the stereodivergent synthesis of trisubstituted tetrahydropyrans.

Thus, reaction of compounds **4a–e** (R^1 = Ph) and **4g** (R^1 = Me) with Et_3SiH/BF_3 afforded the corresponding 2,4-*trans*-4,6-*trans*-2,4,6-trisubstituted tetrahydropyrans **7a–f** (Table 2, entries 1–6). Similar treatment of **4h** (R^1 = H) permitted

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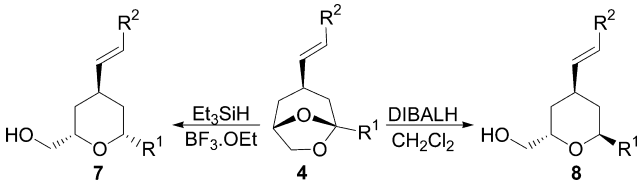
Table 2. Stereodivergent Synthesis of Tetrahydropyrans



entry	R^1	R^2	reaction conditions[a]	7, 8 (yield %)
1	Ph	Ph	A	**7a** (81)
2	Ph	*p*Me-C_6H_4	A	**7b** (77)
3	Ph	*p*F-C_6H_4	A	**7c** (71)
4	Ph	*p*Cl-C_6H_4	A	**7d** (77)
5	Ph	*p*CF_3–C_6H_4	A	**7e** (71)
6	Me	Ph	A	**7f** (66)
7	H	Ph	A	**7g** (77)
8	Ph	Ph	B	**8a** (63)
9	Me	Ph	B	**8b** (65)
10	H	Ph	B	**7g** (63)

[a]Reaction conditions A: **4** (0.06 mmol), BF_3·OEt (0.16 mmol), Et_3SiH (0.32 mmol), CH_2Cl_2 (1.8 mL), overnight, −40 °C → r.t. Reaction conditions B: **4** (0.062 mmol), DIBALH (1.5 M toluene, 0.49 mmol), CH_2Cl_2 (2 mL), overnight, 0 °C → r.t.

the synthesis of the 2,4-*trans*-disubstituted compound **7g** (Table 2, entry 7). On the other hand, reaction of **4a** or **4g** with DIBAL in CH_2Cl_2 gave rise to the 2,4-*cis*-4,6-*trans* isomers **8a,b** (Table 2, entries 8, 9). The disubstituted compound **7h** was again obtained from **4h** (Table 1, entry 10), although under these reaction conditions (DIBALH), the yield was lower than when Et_3SiH/BF_3 was used as reducer (Table 2, entry 7).

In conclusion, we have developed the substrate-controlled 1,3-stereoselective conjugate addition of alkenylboronic acids and potassium alkenyltrifluoroborates in the presence of trifluoroacetic anhydride (TFAA) under metal-free conditions, following a very simple experimental procedure. The reaction is highly stereoselective for the generation of 6,8-dioxa[3.2.1]-bicycles and constitutes a versatile method for the stereodivergent synthesis of optically pure di- and trisubstituted tetrahydropyrans.

EXPERIMENTAL SECTION

General Considerations. All commercially available reagents including anhydrous solvents were used without purification. Analytical thin-layer chromatography (TLC) was performed on commercial silica gel plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography (FC) was performed on silica gel F-60. Visualization was effected with ultraviolet light and ethanolic vanillin solution. NMR spectra were recorded on a 300 MHz spectrometer. Chemical shifts are given in ppm. ^1H NMR chemical shifts were referenced to the residual solvent signal; ^{13}C NMR chemical shifts were referenced to the deuterated solvent signal. Multiplicity was defined by DEPT 135 analysis. Data are presented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant J (Hz), integration.

General Procedure for the Preparation of Compounds 2. (*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethanol (500 mg, 3.42 mmol) was dissolved in 7.2 mL of anhydrous dichloromethane followed by slow addition of pyridinium chlorochromate (885 mg, 4.10 mmol) and powdered 4 Å molecular sieves (750 mg). The suspension was stirred vigorously overnight at room temperature. Hexane/ethyl acetate (1:1, 6.2 mL) was added to the reaction mixture that was then stirred for 30 min. The black suspension was filtered through a short flash silica gel column to remove excess PCC and its reduced forms. The organic solvents were evaporated to afford (*S*)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acetaldehyde (398 mg, 2.76 mmol, 81%) as a colorless oil.[22] To a stirred solution of this aldehyde (220 mg, 1.53 mmol) in 5 mL of THF was added the corresponding phosphonium ylide (1.68 mmol). The solution was stirred at reflux for 10 h and concentrated in vacuo. The crude product was chromatographed on silica gel (Hexane:AcOEt 7:3).

(S,E)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1-phenylbut-2-en-1-one ***2a.*** Following the general procedure, the reaction performed with (benzoylmethylene)-triphenylphosphorane (639 mg) afforded 280 mg (74%) of the title compound as a yellow solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (s, 3H), 1.37 (s, 3H), 2.43−2.63 (m, 2H), 3.57 (dd, *J* = 8.2 Hz, *J* = 6.7 Hz, 1H), 4.02 (dd, *J* = 8.2 Hz, *J* = 6.0 Hz, 1H), 4.22 (q, *J* = 6.3 Hz, 1H), 6.78−7.01 (m, 2H), 6.85−7.01 (m, 3H), 7.83−7.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.7, 27.0, 37.2, 69.0, 74.4, 109.5, 128.4, 128.7 (4C), 132.9, 144.2, 190.6. Anal. Calc. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.20; H, 7.40.

(S,E)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-en-2-one ***2b.*** Following the general procedure, the reaction performed with 1-triphenylphosphoranylidene-2-propanone (280 mg) afforded 124 mg (84%) of the title compound as a pale yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3H), 1.39 (s, 3H), 2.23 (s, 3H), 2.42−2.51 (m, 2H), 3.56 (dd, *J* = 8.2 Hz, *J* = 6.6 Hz, 1H), 4.04 (dd, *J* = 8.2 Hz, *J* = 6.1 Hz, 1H), 4.21 (q, *J* = 6.1 Hz, 1H), 6.11 (dt, *J* = 16.1 Hz, *J* = 1.4 Hz, 1H), 6.75 (dt, *J* = 16.1 Hz, *J* = 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.6, 26.9, 27.0, 36.8, 68.8, 74.3, 109.5, 133.6, 143.0, 198.4. Anal. Calc. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.22; H, 8.70.

(S,E)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-but-2-enal ***2c.*** Following the general procedure, the reaction performed with (triphenylphosphoranylidene)acetaldehyde (636 mg) afforded 258 mg (80%) of the title compound as a pale yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 3H), 1.36 (s, 3H), 2.53 (td, *J* = 6.2 Hz, *J* = 1.5 Hz, 2H), 3.54 (dd, *J* = 8.2 Hz, *J* = 6.2 Hz, 1H), 4.04 (dd, *J* = 8.2 Hz, *J* = 6.2 Hz, 1H), 4.21 (q, *J* = 6.2 Hz, 1H), 6.13 (ddt, *J* = 15.6 Hz, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 6.79 (dt, *J* = 15.6 Hz, *J* = 7.0 Hz, 1H), 9.46 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.5, 26.9, 37.0, 68.8, 74.0, 109.6, 135.0, 153.1, 193.7. Anal. Calc. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.55; H, 8.32.

General Procedure for the Preparation of 6,8-Dioxa[3.2.1]-bicycles 4. To a stirred solution of boronic acid **5** (2.0 equiv) and the corresponding starting material **2** (1.0 equiv) in anhydrous CH_2Cl_2 (6 mL/mmol) was added trifluoroacetic anhydride (3.0 equiv). After stirring 4 h at rt, a saturated solution of Na_2CO_3 was added. The layers were separated, and the aqueous one was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed on silica gel (Hexane:AcOEt 8:2) to afford the title compounds.

(1S,3S,5S)-5-Phenyl-3-((E)-styryl)-6,8-dioxabicyclo[3.2.1]octane ***4a.*** Following the general procedure, reaction of **2a** (32 mg, 0.13 mmol) with *trans*-2-phenylvinylboronic acid **5a** (38 mg, 0.26 mmol) and TFAA (54 μL, 0.39 mmol) in CH_2Cl_2 (0.8 mL) yielded after flash chromatography (Hexane/AcOEt 8/2) **4a** (26 mg, 69%): ^1H NMR ($CDCl_3$, 500 MHz) δ 1.70−1.87 (m, 3H), 2.11 (dd, *J* = 13.3 Hz, *J* = 5.4 Hz, 1H), 2.95 (m, 1H), 3.96 (m, 1H), 4.05 (d, *J* = 6.9 Hz, 1H), 4.70−4.74 (m, 1H), 6.04 (dd, *J* = 15.9 Hz, *J* = 7.3 Hz, 1H), 6.36 (d, *J* = 15.9 Hz, 1H), 7.11−7.34 (m, 8H), 7.48−7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 33.3, 34.8, 42.8. 69.5, 75.0, 107.7, 125.2 (2C), 126.2 (2C), 127.4, 128.3 (2C), 128.5, 128.7 (2C), 129.2, 133.5, 137.5, 141.0. Anal. Calc. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.89. Found: C, 82.13; H, 6.80.

(1S,3S,5S)-3-((E)-4-Methylstyryl)-1-phenyl-6,8-dioxabicyclo[3.2.1]-octane ***4b.*** Following the general procedure, reaction of **2a** (33 mg, 0.13 mmol) with *trans*-2-(4-methylphenyl)vinylboronic acid **5b** (43 mg, 0.27 mmol) and TFAA (56 μL, 0.40 mmol) in CH_2Cl_2 (0.8 mL) yielded after flash chromatography (Hexane/AcOEt 8/2) **4b** (26 mg, 64%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66−1.88 (m, 3H), 2.10 (dd, *J* = 13.5 Hz, *J* = 5.5 Hz, 1H), 2.25 (s, 3H), 2.93 (m, 1H), 3.95 (m, 1H), 4.05 (d, *J* = 6.9 Hz, 1H), 4.69−4.76 (m, 1H), 5.98 (dd, *J* = 15.9 Hz, *J* = 7.4 Hz, 1H), 6.33 (d, *J* = 15.9 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 2H), 7.13−7.35 (m, 5H), 7.46−7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

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21.3, 33.3, 34.9, 42.9. 69.5, 75.0, 107.7, 125.2 (2C), 126.1 (2C), 128.3 (2C), 128.4, 129.0, 129.4 (2C), 132.4, 134.7, 137.1, 141.0. Anal. Calc. for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.38; H, 7.12.

(1S,3S,5S)-3-((E)-4-Fluorostyryl)-1-phenyl-6,8-dioxabicyclo[3.2.1]-octane ***4c***. Following the general procedure, reaction of **2a** (31 mg, 0.13 mmol) with *trans*-2-(4-fluorophenyl)vinylboronic acid **5c** (42 mg, 0.25 mmol) and TFAA (52 μL, 0.38 mmol) in CH_2Cl_2 (0.8 mL) yielded after flash chromatography (Hexane/AcOEt 8/2) **4c** (24 mg, 61%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69−1.88 (m, 3H), 2.10 (dd, *J* = 13.4 Hz, *J* = 5.5 Hz, 1H), 2.92 (m, 1H), 3.96 (m, 1H), 4.05 (d, *J* = 7.0 Hz, 1H), 4.69−4.76 (m, 1H), 5.96 (dd, *J* = 15.9 Hz, *J* = 7.3 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.91 (t, *J* = 8.7 Hz, 2H), 7.16−7.36 (m, 6H), 7.45−7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.3, 34.8, 42.8. 69.5, 75.0, 107.7, 115.4, 115.7, 125.2 (2C), 127.6, 127.7, 128.0, 128.3 (2C), 128.5, 133.2, 141.0. Anal. Calc. for $C_{20}H_{19}FO_2$: C, 77.40; H, 6.17. Found: C, 77.44; H, 6.06.

(1S,3S,5S)-3-((E)-4-Chlorostyryl)-1-phenyl-6,8-dioxabicyclo[3.2.1]-octane ***4d***. Following the general procedure, reaction of **2a** (30 mg, 0.12 mmol) with *trans*-2-(4-chlorophenyl)vinylboronic acid **5d** (44 mg, 0.24 mmol) and TFAA (51 μL, 0.36 mmol) in CH_2Cl_2 (0.7 mL) yielded after flash chromatography (Hexane/AcOEt 8/2) **4d** (26 mg, 66%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69−1.88 (m, 3H), 2.10 (dd, *J* = 13.3 Hz, *J* = 5.5 Hz, 1H), 2.94 (m, 1H), 3.96 (m, 1H), 4.05 (d, *J* = 7.0 Hz, 1H), 4.68−4.76 (m, 1H), 6.02 (dd, *J* = 15.9 Hz, *J* = 7.3 Hz, 1H), 6.31 (dd, *J* = 15.9 Hz, *J* = 1.1 Hz, 1H), 7.14−7.36 (m, 7H), 7.45−7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.3, 34.7, 42.7. 69.5, 74.9, 107.7, 125.2 (2C), 127.4 (2C), 128.0, 128.3 (2C), 128.5, 128.8 (2C), 132.9, 134.2, 136.0, 140.9. Anal. Calc. for $C_{20}H_{19}ClO_2$: C, 73.50; H, 5.86. Found: C, 73.59; H, 5.79.

(1S,3S,5S)-1-Phenyl-3-((E)-4-(trifluoromethyl)styryl)-6,8-dioxabicyclo[3.2.1]-octane ***4e***. Following the general procedure, reaction of **2a** (33 mg, 0.12 mmol) with *trans*-2-(4-trifluoromethylphenyl)vinylboronic acid **5e** (57 mg, 0.27 mmol) and TFAA (56 μL, 0.40 mmol) in CH_2Cl_2 (0.8 mL) yielded after flash chromatography (Hexane/AcOEt 8/2) **4e** (32 mg, 66%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.71−1.91 (m, 3H), 2.12 (dd, *J* = 13.3 Hz, *J* = 5.4 Hz, 1H), 2.98 (m, 1H), 3.97 (m, 1H), 4.06 (d, *J* = 7.0 Hz, 1H), 4.70−4.79 (m, 1H), 6.15 (dd, *J* = 15.9 Hz, *J* = 7.2 Hz, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 7.16−7.39 (m, 5H), 7.44−7.55 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.4, 34.6, 42.6. 69.5, 74.9, 107.7, 125.2 (2C), 125.6, 125.7, 126.4 (2C), 128.0, 128.4 (2C), 128.5, 136.2, 140.9. Anal. Calc. for $C_{20}H_{19}F_3O_2$: C, 69.99; H, 5.31. Found: C, 70.06; H, 5.42.

(1S,3S,5S)-3-((E)-2-([1,1′-Biphenyl]-4-yl)vinyl)-1-phenyl-6,8-dioxabicyclo[3.2.1]-octane ***4f***. Following the general procedure, reaction of **2a** (27 mg, 0.11 mmol) with *trans*-2-(4-biphenyl)-vinylboronic acid **5f** (49 mg, 0.22 mmol) and TFAA (46 μL, 0.33 mmol) in CH_2Cl_2 (0.6 mL) yielded after flash chromatography (Hexane/AcOEt 8/2) **4f** (24 mg, 59%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.71−1.91 (m, 3H), 2.13 (dd, *J* = 13.5 Hz, *J* = 5.5 Hz, 1H), 2.96 (m, 1H), 3.97 (m, 1H), 4.07 (d, *J* = 6.9 Hz, 1H), 4.70−4.77 (m, 1H), 6.09 (dd, *J* = 15.9 Hz, *J* = 7.3 Hz, 1H), 6.40 (d, *J* = 15.9 Hz, 1H), 7.15−7.59 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 33.4, 34.8, 42.8. 69.5, 75.0, 107.7, 125.3 (2C), 126.6 (2C), 127.0 (2C), 127.4 (3C), 128.3 (2C), 128.5, 128.8, 128.9 (2C), 133.6, 136.5, 140.2, 140.9, 141.0. Anal. Calc. for $C_{26}H_{24}O_2$: C, 84.75; H, 6.57. Found: C, 84.82; H, 6.62.

(1R,3S,5S)-1-Methyl-3-((E)-styryl)-6,8-dioxabicyclo[3.2.1]octane ***4g***. Following the general procedure, reaction of **2b** (29 mg, 0.16 mmol) with potassium *trans*-β-styryltrifluoroborate **5i** (66 mg, 0.31 mmol) and TFAA (65 μL, 0.47 mmol) in CH_2Cl_2 (0.9 mL) yielded after flash chromatography (Hexane/AcOEt 8/2) **4g** (26 mg, 71%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 3H), 1.43−1.55 (m, 2H), 1.58−1.70 (m, 1H), 1.82 (dd, *J* = 13.4 Hz, *J* = 5.6 Hz, 1H), 2.76 (m, 1H), 3.78−3.90 (m, 2H), 4.49−4.58 (m, 1H), 5.98 (dd, *J* = 15.9 Hz, *J* = 7.4 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 7.06−7.38 (m, 5H); ^{13}C NMR (CDCl3, 75 MHz) δ 24.4, 33.0, 34.8, 42.0. 69.2, 74.6, 107.0, 126.2 (2C), 127.3, 128.7 (2C), 129.0, 133.7, 137.5. Anal. Calc. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.31; H, 7.95.

(1R,3S,5S)-3-((E)-Styryl)-6,8-dioxabicyclo[3.2.1]octane ***4h***. Following the general procedure, reaction of **2c** (33 mg, 0.19 mmol) with potassium *trans*-β-styryltrifluoroborate **5i** (82 mg, 0.39 mmol) and TFAA (81 μL, 0.58 mmol) in CH_2Cl_2 (1.2 mL) yielded after flash chromatography (Hexane/AcOEt 8/2) **4h** (22 mg, 52%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39−2.01 (m, 5H), 2.77 (m, 1H), 3.74 (m, 1H), 3.92 (d, *J* = 7.1 Hz, 1H), 4.46−4.56 (m, 1H), 5.51 (s, 1H), 5.98 (dd, *J* = 15.9 Hz, *J* = 7.4 Hz, 1H), 6.31 (d, *J* = 15.9 Hz, 1H), 7.06−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 35.4, 38.0, 68.5, 73.3, 101.4, 126.2 (2C), 127.4, 128.7 (2C), 129.0, 133.6, 137.4. Anal. Calc. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.62; H, 7.30.

General Procedure for the Preparation of Compounds 7 Using BF_3·Et_2O/Et_3SiH. To a stirred solution of the corresponding bicycle **4** (1.0 equiv) in anhydrous CH_2Cl_2 (28 mL/mmol) at −40 °C was added dropwise BF_3·Et_2O (2.5 equiv) and Et_3SiH (5.0 equiv) successively. After stirring overnight, a saturated solution of $NaHCO_3$ was added. The layers were separated, and the aqueous one was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed on silica gel (CH_2Cl_2:AcOEt 95:5) to afford the title compounds.

(2S,4S,6R)-6-Phenyl-4-((E)-styryl)tetrahydro-2H-pyran-2-yl)-methanol ***7a***. Following the general procedure, reaction of **4a** (19 mg, 0.07 mmol) with BF_3·Et_2O (20 μL, 0.16 mmol) and Et_3SiH (52 μL, 0.32 mmol) in CH_2Cl_2 (1.8 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **7a** (15 mg, 81%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64 (d, *J* = 13.4 Hz, 1H), 1.76 (ddd, *J* = 13.4 Hz, *J* = 11.8 Hz, *J* = 5.1 Hz, 1H), 1.85−1.92 (m, 2H), 2.88−2.96 (m, 1H), 3.54 (dd, *J* = 11.5 Hz, *J* = 7.0 Hz, 1H), 3.61 (dd, *J* = 11.5 Hz, *J* = 3.3 Hz, 1H), 3.88−3.99 (m, 1H), 4.66 (dd, *J* = 9.0 Hz, *J* = 5.0 Hz, 1H), 6.40−6.54 (m, 2H), 7.13−7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 34.2, 38.7, 66.6, 74.0, 75.1, 126.1 (2C), 126.2 (2C), 127.5, 127.7, 128.5 (2C), 128.8 (2C), 130.9, 132.4, 137.5, 143.0. Anal. Calc. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.71; H, 7.44.

(2S,4S,6R)-4-((E)-4-Methylstyryl)-6-phenyltetrahydro-2H-pyran-2-yl)methanol ***7b***. Following the general procedure, reaction of **4b** (21 mg, 0.07 mmol) with BF_3·Et_2O (22 μL, 0.17 mmol) and Et_3SiH (56 μL, 0.35 mmol) in CH_2Cl_2 (2.0 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **7b** (16 mg, 77%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.63 (d, *J* = 13.5 Hz, 1H), 1.75 (ddd, *J* = 13.5 Hz, *J* = 12.0 Hz, *J* = 5.1 Hz, 1H), 1.84−1.90 (m, 2H), 2.28 (s, 3H), 2.88−2.94 (m, 1H), 3.54 (dd, *J* = 11.5 Hz, *J* = 6.9 Hz, 1H), 3.61 (dd, *J* = 11.5 Hz, *J* = 3.2 Hz, 1H), 3.88−3.99 (m, 1H), 4.66 (dd, *J* = 9.2 Hz, *J* = 5.0 Hz, 1H), 6.40−6.45 (m, 2H), 7.03−7.34 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 31.7, 34.2, 38.7, 66.7, 74.0, 75.1, 126.0 (2C), 126.1 (2C), 127.6, 128.5 (2C), 129.5 (2C), 130.7, 131.3, 134.7, 137.3, 143.0. Anal. Calc. for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.88; H, 7.71.

(2S,4S,6R)-4-((E)-4-Fluorostyryl)-6-phenyltetrahydro-2H-pyran-2-yl)methanol ***7c***. Following the general procedure, reaction of **4c** (27 mg, 0.09 mmol) with BF_3·Et_2O (26 μL, 0.21 mmol) and Et_3SiH (70 μL, 0.43 mmol) in CH_2Cl_2 (2.4 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **7c** (19 mg, 71%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62 (d, *J* = 13.4 Hz, 1H), 1.75 (ddd, *J* = 13.4 Hz, *J* = 12.0 Hz, *J* = 5.2 Hz, 1H), 1.84−1.92 (m, 2H), 2.86−2.94 (m, 1H), 3.54 (dd, *J* = 11.3 Hz, *J* = 6.9 Hz, 1H), 3.61 (dd, *J* = 11.3 Hz, *J* = 2.3 Hz, 1H), 3.86−3.97 (m, 1H), 4.65 (t, *J* = 6.3 Hz, 1H), 6.33−6.48 (m, 2H), 6.96 (t, *J* = 8.5 Hz, 2H), 7.15−7.36 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.6, 34.2, 38.6, 66.6, 74.0, 75.1, 115.5, 115.8, 126.1 (2C), 127.6, 127.6, 127.7, 128.5 (2C), 129.7, 132.1, 132.2, 133.6, 133.7, 142.9, 160.7, 164.0. Anal. Calc. for $C_{20}H_{21}FO_2$: C, 76.90; H, 6.78. Found: C, 76.81; H, 6.91.

(2S,4S,6R)-4-((E)-4-Chlorostyryl)-6-phenyltetrahydro-2H-pyran-2-yl)methanol ***7d***. Following the general procedure, reaction of **4d** (21 mg, 0.06 mmol) with BF_3·Et_2O (20 μL, 0.16 mmol) and Et_3SiH (52 μL, 0.32 mmol) in CH_2Cl_2 (1.8 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **7d** (16 mg, 77%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.63 (d, *J* = 13.4 Hz, 1H), 1.76 (ddd, *J* = 13.4 Hz, *J* = 12.4 Hz, *J* = 5.3 Hz, 1H), 1.85−1.92 (m, 2H), 2.86−2.96 (m, 1H), 3.48−3.68 (m, 2H), 3.85−4.02 (m, 1H), 4.64 (t, *J* = 6.6 Hz, 1H), 6.35−6.52 (m, 2H), 7.04−7.36 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.5, 34.2, 38.5, 66.6, 74.0, 75.1, 126.1 (2C), 127.4 (3C), 127.7,

128.5 (2C), 128.9 (2C), 129.7, 133.1, 136.0, 142.9. Anal. Calc. for $C_{20}H_{21}ClO_2$: C, 73.05; H, 6.44. Found: C, 72.91; H, 6.56.

(2S,4S,6R)-6-Phenyl-4-((E)-4-(trifluoromethyl)styryl)tetrahydro-2H-pyran-2-yl)methanol ***7e***. Following the general procedure, reaction of **4e** (16 mg, 0.04 mmol) with $BF_3{\cdot}Et_2O$ (14 μL, 0.11 mmol) and Et_3SiH (37 μL, 0.22 mmol) in CH_2Cl_2 (1.3 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **7e** (12 mg, 71%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (d, *J* = 13.6 Hz, 1H), 1.78 (ddd, *J* = 13.6 Hz, *J* = 11.8 Hz, *J* = 5.1 Hz, 1H), 1.86−1.95 (m, 2H), 2.89−3.00 (m, 1H), 3.55 (dd, *J* = 11.5 Hz, *J* = 6.9 Hz, 1H), 3.62 (dd, *J* = 11.5 Hz, *J* = 3.4 Hz, 1H), 3.86−3.97 (m, 1H), 4.64 (t, *J* = 6.7 Hz, 1H), 6.49 (d, *J* = 16.1 Hz, 1H), 6.59 (dd, *J* = 16.1 Hz, *J* = 5.8 Hz, 1H), 7.15−7.34 (m, 5H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.4, 34.3, 38.4, 66.6, 74.1, 75.1, 125.6, 125.7, 125.8, 126.1(2C), 126.4 (2C), 127.8, 128.5 (2C), 129.2, 129.8, 135.3, 141.0, 142.8. Anal. Calc. for $C_{21}H_{21}F_3O_2$: C, 69.60; H, 5.84. Found: C, 69.72; H, 5.73.

(2S,4S,6S)-6-Methyl-4-((E)-styryl)tetrahydro-2H-pyran-2-yl)-methanol ***7f***. Following the general procedure, reaction of **4g** (21 mg, 0.09 mmol) with $BF_3{\cdot}Et_2O$ (27 μL, 0.23 mmol) and Et_3SiH (72 μL, 0.45 mmol) in CH_2Cl_2 (2.5 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **7f** (14 mg, 66%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, *J* = 6.13 Hz, 3H), 1.46−1.70 (m, 4H), 2.70−2.84 (m, 1H), 3.44 (dd, *J* = 11.3 Hz, *J* = 7.2 Hz, 1H), 3.53 (dd, *J* = 11.3 Hz, *J* = 3.2 Hz, 1H), 3.70−3.81 (m, 2H), 6.26−6.45 (m, 2H), 7.07−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.3, 31.7, 34.0, 38.3, 66.6, 69.0, 73.4, 126.1 (2C), 127.4, 128.7 (2C), 130.4, 132.9, 137.6. Anal. Calc. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.68; H, 8.51.

(2S,4S)-4-((E)-Styryl)tetrahydro-2H-pyran-2-yl)methanol ***7g***. Following the general procedure, reaction of **4h** (12 mg, 0.06 mmol) with $BF_3{\cdot}Et_2O$ (17 μL, 0.14 mmol) and Et_3SiH (45 μL, 0.28 mmol) in CH_2Cl_2 (1.6 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **7g** (10 mg, 77%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.52−1.73 (m, 2H), 1.83−2.00 (m, 2H), 2.69−2.76 (m, 1H), 3.48−3.58 (m, 2H), 3.60−3.80 (m, 3H), 6.29−6.42 (m, 2H), 7.09−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.0, 32.3, 33.4, 63.4, 65.8, 73.3, 126.2 (2C), 127.4, 128.7 (2C), 130.4, 132.6, 137.6. Anal. Calc. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.14; H, 8.42.

General Procedure for the Preparation of Compounds 7g and 8 Using DIBALH. To a stirred solution of the corresponding bicycle **4** (1.0 equiv) in CH_2Cl_2 (30 mL/mmol) at 0 °C was added dropwise DIBALH (1.5 M toluene, 8.0 equiv). After stirring overnight at rt, a saturated solution of $NaHCO_3$ was added. The layers were separated, and the aqueous one was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was chromatographed on silica gel (CH_2Cl_2:AcOEt 95:5) to afford the title compounds.

(2S,4S)-4-((E)-Styryl)tetrahydro-2H-pyran-2-yl)methanol ***7g***. Following the general procedure, reaction of **4h** (12 mg, 0.06 mmol) with DIBAL (1.5 M toluene, 0.33 mL, 0.49 mmol) in CH_2Cl_2 (2 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **7g** (8 mg, 63%). NMR data matched those previously obtained in the reaction of **4h** with $BF_3{\cdot}Et_2O$ and Et_3SiH in CH_2Cl_2. Anal. Calc. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.12; H, 8.25.

(2S,4S,6S)-6-Phenyl-4-((E)-styryl)tetrahydro-2H-pyran-2-yl)-methanol ***8a***. Following the general procedure, reaction of **4a** (18 mg, 0.06 mmol) with DIBAL (1.5 M toluene, 0.33 mL, 0.49 mmol) in CH_2Cl_2 (2 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **8a** (12 mg, 63%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41−1.56 (m, 1H), 1.71−1.82 (m, 2H), 1.93 (d, *J* = 13.5 Hz, 1H), 2.53−2.68 (m, 1H), 3.49 (dd, *J* = 10.8 Hz, *J* = 4.0 Hz, 1H), 4.13 (t, *J* = 10.8 Hz,, 1H), 4.18−4.28 (m, 1H), 4.64 (dd, *J* = 11.6 Hz, *J* = 2.0 Hz, 1H), 6.00 (dd, *J* = 16.0 Hz, *J* = 6.8 Hz, 1H), 6.34 (d, *J* = 16.0 Hz, 1H), 7.08−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.5, 34.8, 40.0, 61.1, 72.0, 73.9, 126.1 (2C), 126.2 (2C), 127.4, 127.8, 128.6 (2C), 128.7 (2C), 129.0, 134.0, 137.4, 142.7. Anal. Calc. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.72; H, 7.41.

(2S,4S,6R)-6-Methyl-4-((E)-styryl)tetrahydro-2H-pyran-2-yl)-methanol ***8b***. Following the general procedure, reaction of **4g** (23 mg, 0.10 mmol) with DIBAL (1.5 M toluene, 0.53 mL, 0.80 mmol) in CH_2Cl_2 (3 mL) yielded after flash chromatography (CH_2Cl_2:AcOEt 95:5) **8a** (15 mg, 65%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (d, *J* = 6.1 Hz, 3H), 1.68 (dd, *J* = 11.0 Hz, *J* = 5.4 Hz, 2H), 1.76 (dm, *J* = 13.3 Hz, 2H), 2.40−2.56 (m, 1H), 3.46 (dm, *J* = 7.3 Hz, 1H), 3.74−3.86 (m, 1H), 4.05 (d, *J* = 10.4 Hz, 1H), 4.07−4.12 (m, 1H), 6.06 (dd, *J* = 15.9 Hz, *J* = 6.8 Hz, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 7.17−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.3, 31.4, 34.4, 39.6, 61.1, 65.5, 73.3, 126.2 (2C), 127.4, 128.70 (2C), 128.72, 134.4, 137.5. Anal. Calc. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.66; H, 8.51.

(2S,4S,6R)-6-Phenyl-4-((E)-styryl)tetrahydro-2H-pyran-2-yl)-methyl benzoate ***9a***. To a solution of **7a** (9.8 mg, 0.033 mmol) in anhydrous CH_2Cl_2 (2 mL) was added BzCl (4 μL, 0.04 mmol), Et_3N (5 μL, 0.033 mmol) and DMAP (0.4 mg, 0.003 mmol). The reaction mixture was stirred overnight at rt. The resulting solution was filtered through a Celite plug and the filtrate was concentrated. The residue was purified by flash cromatography (Hexane:AcOEt, 8:2) to yield **9a** (11.5 mg, 87%): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80−1.95 (m, 4H), 2.91−3.00 (m, 1H), 4.12−4.23 (m, 1H), 4.29−4.43 (m, 2H), 4.70 (dd, *J* = 10.6 Hz, *J* = 3.5 Hz, 1H), 6.43−6.56 (m, 2H), 7.08−7.52 (m, 13H), 7.96−8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.4, 34.2, 38.4, 68.0, 71.6, 75.0, 126.0 (2C), 126.3 (2C), 127.4, 127.5, 128.4 (2C), 128.5 (2C), 128.8 (2C), 129.9 (2C), 130.4, 131.0, 132.2, 133.1, 137.4, 143.0, 166.7. Anal. Calcd. for $C_{27}H_{26}O_3$: C, 81.38; H, 6.58. Found: C, 81.45; H, 6.44.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra for all compounds. 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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