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Lewis Acid Mediated Reactions of Aldehydes with Styrene Derivatives: Synthesis of 1,3-Dihalo-1,3-diarylpropanes and 3-Chloro-1,3-diarylpropanols

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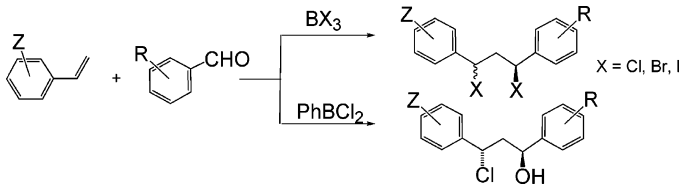
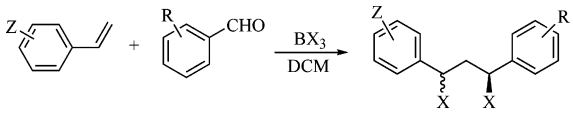


The reactions of aryl aldehydes with styrene derivatives, mediated by various boron Lewis acids, were investigated. 1,3-Dihalo-1,3-diarylpropanes were obtained in high yields with boron trihalides, while 3-chloro-1,3-diarylpropanols were obtained in good to excellent yields with phenylboron dichloride. Reactions involving nonenolizable aliphatic aldehydes, *trans*-cinnamaldehyde, and β-substituted styrenes were also investigated for the first time.

Introduction

The Lewis acid promoted addition of alkenes to carbonyl compounds is an important method for forming new carbon−carbon bonds.[1] Generally the reactions are catalyzed by Lewis acids, such as BF_3,[2a,b,f,3] $AlCl_3$,[4] $FeCl_3$,[4b,5] $SnCl_4$,[6c,e,4b,7] $TiCl_4$,[6c,8] $BiCl_3$,[9] and alkylaluminum chlorides.[2g,3c,10] Interestingly, BCl_3 has been reported to be an ineffective promoter of ene reactions between aldehydes and alkenes.[4b] During a study focused on boron halide mediated reactions,[11] we discovered that boron trihalides (BX_3) are very effective in promoting the addition of aryl aldehydes with styrene derivatives. The reactions produce diastereomeric mixtures (~1:1) of 1,3-dihalo-1,3-diarylpropanes (**1**) in excellent yields (Scheme 1).

SCHEME 1



X = Cl, Br, I

1

The preliminary results have been communicated[12] and a reaction mechanism (Scheme 2) proposed based on the isolation of 3-halo-1,3-diarylpropanols as side products.

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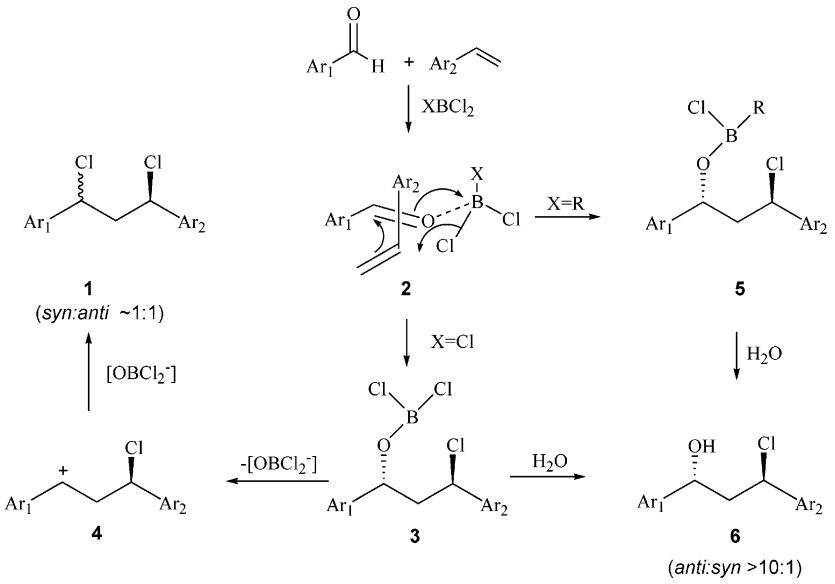
SCHEME 2. Proposed Reaction Mechanism



The reaction presumably proceeds through coordination of the carbonyl group to the boron trihalide followed by addition of the alkene to the activated carbonyl group to form **2**. Loss of the [$OBCl_2^-$] moiety from **3** would then generate cation **4**, which could then react with a chloride from the [$OBCl_2^-$] fragment to generate **1**. A similar intermediate has been observed in the $AlCl_3$-catalyzed ene reactions of aldehydes with aliphatic alkenes.[3c,4a] Supporting evidence for this mechanism is the isolation of 3-halo-1,3-diarylpropanols **6** when the reactions are quenched with water before completion.

In fact, adding water to quench the reaction can be utilized to prepare 3-halo-1,3-diarylpropanols **6**, but the reaction is somewhat difficult to control. We reasoned that replacement of one or two chlorides in BCl_3 with an organic group (R) might provide an efficient route to chloropropanol products **6**. Several $RBCl_2$ and R_2BCl derivatives were prepared and examined. We discovered that $PhBCl_2$ was the most effective reagent for preparing 3-chloro-1,3-diarylpropanols in excellent yields.[13]

The new reactions are not limited to aryl aldehydes and simple styrenes. We have found that β-substituted styrene derivatives work quite well and afford the corresponding 1,3-dihalo-1,3-diaryl-2-substituted propanes in good yields. The nonenolizable aliphatic aldehyde tribromoacetaldehyde also reacts with styrenes to produce the corresponding chloro alcohols. We wish to report details of these studies.

Results and Discussion

1. The BX_3-Mediated Reaction of Aldehydes with Styrene Derivatives. The reaction of benzaldehyde with styrene was chosen as the model system to optimize the reaction conditions with use of BCl_3 as the Lewis acid. When freshly distilled styrene was used, only polymerization occurred. However, polymerization can be totally eliminated by using commercially available styrene, which containes 4-*tert*-butylcatechol as a stabilizer. When reactions were carried out at room temperature, only chlorination of aryl aldehydes was observed.[11f,14] To avoid the chlorination reaction, the temperature was lowered to 0 °C. 1,3-Dichloro-1,3-diphenylpropane was isolated in good yield using methylene chloride as solvent; the product was found to consist of a 1:1 mixture of the syn/anti diasteromers.

Using the optimized reaction conditions, a series of substituted aryl aldehydes and styrenes were examined (Table 1). The reaction tolerates a variety of functional groups. The reactions of aldehydes containing electron-withdrawing groups are slower but produce high yields of the desired products.

Due to the facile bromination of aryl aldehydes by boron tribromide,[11f] reactions promoted by boron tribromide were carried out in methylene chloride at −40 °C. The corresponding 1,3-dibromo-1,3-diarylpropanes were obtained in good to excellent yields. Although reactions with boron triiodide proceeded well, the isolated yields of the products were low due to decomposition of the products during chromatography on silica gel. NMR analysis of the products revealed a nearly statistical distribution of the diastereoisomers. Generally the ^1H NMR resonances of the methine protons in the anti isomers appear at lower field than the methine protons in the syn isomers. The *R*,*R* and *S*,*S* racemate of 1,3-dibromo-1,3-di(4-fluorophenyl)propane (**1a*l***) has been isolated by crystallization and characterized by both NMR and X-ray crystallography (see the Supporting Information).

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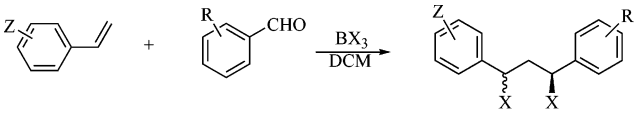
TABLE 1. BX_3-Mediated Reaction of Aryl Aldehydes with Styrenes to 1,3-Dihalo-1,3-diarylpropanes[a,b]



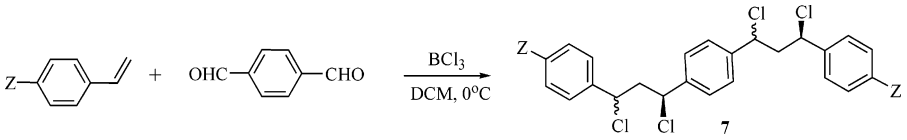
1

X=Cl, Br, I

entry	Z	R	X	product	yield (%)	entry	Z	R	X	product	yield (%)
1	H	H	Cl	**1a**	90	23	4-Me	4-Br	Cl	**1w**	82
2	H	4-F	Cl	**1b**	98	24	4-Me	2-F	Cl	**1x**	85
3	H	4-Cl	Cl	**1c**	97	25	4-Me	2-Cl	Cl	**1y**	83
4	H	4-Br	Cl	**1d**	89	26	4-Me	2-Br	Cl	**1z**	80
5	H	2-F	Cl	**1e**	97	27	4-Me	4-Me	Cl	**1aa**	79
6	H	2-Cl	Cl	**1f**	92	28	4-Me	2-Me	Cl	**1ab**	80
7	H	2-Br	Cl	**1g**	96	29	4-Me	4-NO_2	Cl	**1ac**	70
8	H	3-Br	Cl	**1h**	99	30	4-Me	4-CN	Cl	**1ad**	75
9	H	4-Me	Cl	**1i**	70	31	H	H	Br	**1ae**	75
10	H	2-Me	Cl	**1j**	74	32	H	4-F	Br	**1af**	98
11	H	4-CN	Cl	**1k**	80	33	H	4-Me	Br	**1ag**	60
12	H	4-NO_2	Cl	**1*l***	99	34	4-Me	4-F	Br	**1ah**	76
13	4-F	4-F	Cl	**1m**	98	35	4-Me	4-Cl	Br	**1ai**	74
14	4-F	4-Cl	Cl	**1n**	98	36	4-Me	4-Br	Br	**1aj**	70
15	4-F	4-Br	Cl	**1o**	96	37	4-Me	4-Me	Br	**1ak**	57
16	4-F	2-F	Cl	**1p**	99	38	4-F	4-F	Br	**1a*l***	96
17	4-F	2-Cl	Cl	**1q**	94	39	4-F	2-F	Br	**1am**	89
18	4-F	2-Br	Cl	**1r**	96	40	4-F	4-Br	Br	**1an**	76
19	4-F	4-Me	Cl	**1s**	95	41	4-F	3-Br	Br	**1ao**	90
20	4-F	2-Me	Cl	**1t**	96	42	H	H	I	**1ap**	35
21	4-F	4-NO_2	Cl	**1u**	98	43	4-F	H	I	**1aq**	30
22	4-Me	4-Cl	Cl	**1v**	80						

[a] Reactions carried out in dry DCM at 0 °C for BCl_3, −40 °C for BBr_3, and −70 °C for BI_3. [b] Isolated yields based on starting aldehydes.

SCHEME 3



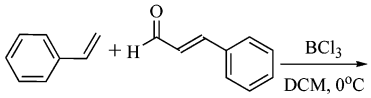
7a Z = H 92%; **7b** Z = Me 79%; **7c** Z = F 87%

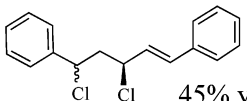
1,3-Dihalo-1,3-diarylpropanes are important intermediates in the preparation of arylcyclopropane,[15] pyrazolidine,[16] and centrohexaindane.[17] The bromo analogues can also be utilized in Suzuki coupling reactions.[18] 1,3-Dihalo-1,3-diarylpropanes are normally prepared by halogenation of the corresponding cyclopropanes[19] or 1,3-propanediols[20] which are not readily available. The boron trihalide mediated method reported here provides a simple and efficient procedure for the preparation of a variety of 1,3-dihalo-1,3-diarylpropanes with high regioselectivity.

In the presence of 2 equiv of boron trichloride, terephthaldicarboxaldehyde reacts with 2 equiv of a variety of styrenes smoothly (Scheme 3).

The *R*,*R*,*S*,*S*/*S*,*S*,*R*,*R* racemate of **7a** has been isolated by recrystallization and subjected to X-ray crystallographic analysis (see the Supporting Information). The ^{1}H NMR spectrum reveals that the resonances of the methine protons in the anti isomer appear at lower field than those in the syn isomer.

The BCl_3-mediated reaction of *trans*-cinnamaldehyde with styrene was also examined (eq 1). The isolated yield of desired product was modest.





(1)

45% yield

8

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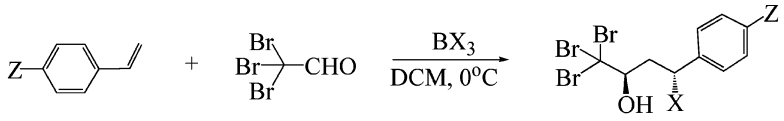
SCHEME 4



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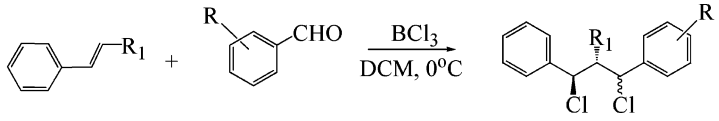
9a Z = H, X = Cl 93%; **9b** Z = Me, X = Cl 95%; **9c** Z = Me, X = Br 67%

SCHEME 5



10

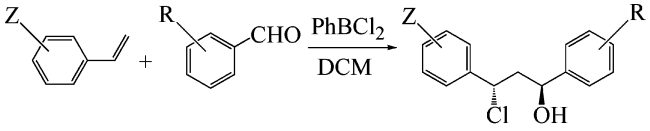
10a R_1 = Me, R = H 95%; **10b** R_1 = Me, R = 4-F 98%;
10c R_1 = Me, R = 4-Br 94%; **10d** R_1 = Ph, R = 4-Cl 86% **10e** R_1 = Ph, R = 4-Br 88%

Under the same reaction conditions, the nonenolizable aliphatic aldehyde tribromoacetaldehyde readily reacts with substituted styrenes. However, the reactions provide the corresponding 3-halopropanols, **9**, instead of the dihalide compounds (Scheme 4). The reaction is stereoselective with the anti isomer being the major product (anti/syn > 10:1).

Reactions of aryl aldehydes with β-substituted styrenes such as *trans*-β-methylstyrene and stilbene also proceed well. The desired 1,3-dihalo-1,3-diaryl-2-methylpropanes and 1,3-dihalo-1,3-diaryl-2-phenylpropanes were isolated in good yields (Scheme 5). The selectivity was confirmed by the X-ray crystallography (see the Supporting Information). However, the reaction with α-methylstyrene and 1,1-diphenylstyrene did not afford the anticipated 1,3-dihalides products.[21] Trisubstituted and tetrasubstituted styrenes were found to be unreactive.

2. The $PhBCl_2$-Mediated Reaction of Aldehydes with Styrene Derivatives. As noted earlier, 3-halopropan-1-ols can be obtained in moderate yield by quenching the BX_3 mediated reactions between aryl aldehydes and styrene with water. The resultant 3-halopropan-1-ols are useful intermediates in organic synthesis.[22] They can undergo a number of transformations, including halogenation, substitution, cyclization, and oxidation reactions, to generate mixed 1,3-dihalogenated diarylpropanes, cyclic ethers, and ketones. In view of the synthetic potential of 3-halopropan-1-ols, we investigated more efficient and practical methods for preparing the halogenated alcohols. We reasoned that replacement of one or two halides in BX_3 with an organic group might stabilize interemediate **5** and prevent C−O bond cleavage (Scheme 2). Hydrolysis of **5** would then produce the desired 3-halopropan-1-ol. Several $RBCl_2$ and R_2BCl reagents were prepared and used in the reaction. The reaction of 4-chlorobenzaldehyde with styrene in the presence of dicyclohexylboron chloride resulted only in reduction of the aldehyde via a β-hydride transfer. Boron dichloride reagents such as *n*-butylboron dichloride, *sec*-butylboron dichloride, *n*-hexylboron dichloride, cyclohexylboron dichloride, and cyclopentylboron dichloride also were found to be ineffective. However, phenylboron dichloride promoted the reaction; in CH_2Cl_2 at −10 °C, 3-chloro-1-(4-chlorophenyl)-3-phenylpropan-1-ol was isolated in 79% yield. Solvents such as hexane, toluene, and chloroform were examined but methylene chloride was found to be the most effective. Diethyl ether, THF, and dioxane simply underwent ether cleavage reactions.[23]

TABLE 2. $PhBCl_2$-Mediated Reaction of Aryl Aldehydes with Styrenes to 3-Chloro-1,3-diarylpropanols[a]



6

entry	Z	R	product	yield (%)[d]	entry	Z	R	product	yield (%)[d]
1	H	H	**6a**	76	9[c]	H	4-CN	**6i**	96
2	H	4-F	**6b**	87	10	H	4-CHO	**6j**	89
3	H	4-Cl	**6c**	79	11[c]	4-Cl	4-NO_2	**6k**	90
4	H	4-Br	**6d**	66	12	4-Cl	4-Cl	**6*l***	86
5[b]	H	4-Me	**6e**	57	13[c]	4-Me	4-NO_2	**6m**	99
6[b]	H	2-Me	**6f**	56	14[b]	4-Me	H	**6n**	75
7	H	2-F	**6g**	79	15[c]	4-Me	4-CN	**6o**	98
8[c]	H	4-NO_2	**6h**	97					

[a] Reactions carried out in dry DCM at −10 °C. [b] Reactions carried out in dry DCM at −20 °C. [c] Reactions carried out at room temperature. [d] Isolated yields based on starting aldehydes.

Using phenylboron dichloride, reactions of a series of substituted aryl aldehydes with substituted styrenes were examined (Table 2). Generally, reactions of styrenes and aldehydes containing electron-withdrawing groups require a higher reaction temperature (room temperature) but give higher yields of products. The reactions of

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(21) Although the reaction did not give the anticipated 1,3-dihalides or 3-halopropanol products, a reaction did occur but the structure of the product has not been identified.

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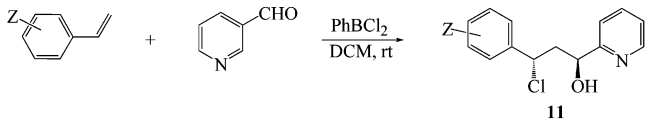
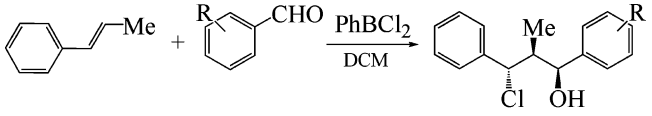
SCHEME 6



11

11a, Z = H, 90%; **11b**, Z = 4-F, 84%; **11c**, Z = 4-Cl, 90%; **11d**, Z = 2-Cl, 90%; **11e**, Z = 4-Me, 90%

TABLE 3. $PhBCl_2$-Mediated Reaction of Aryl Aldehydes with *trans*-β-Methylstyrene to Generate 3-Chloro-1,3-diaryl-2-methylpropanols[a]



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entry	R	product	yield (%)[e]	entry	R	product	yield (%)[e]
1[b]	4-F	**12a**	94	4[d]	4-NO_2	**12d**	95
2	4-Cl	**12b**	65	5[d]	4-CN	**12e**	97
3[c]	4-Me	**12c**	36	6[b]	2-F	**12f**	93

[a] Reactions carried out in dry DCM at −10 °C. [b] Reactions carried out at 0 °C. [c] Reactions carried out at −20 °C. [d] Reactions carried out at room temperature. [e] Isolated yields based on starting aldehydes.

styrenes and aldehydes containing electron-donating groups are faster but produce lower yields of the desired products.

All 3-halopropan-1-ols were characterized by elemental analysis and NMR spectroscopy. NMR data reveal that the reactions generate only one regioisomer with the aryl groups at the 1,3-positions. The reactions predominantly produce the anti-diastereoisomers (anti/syn > 10:1). The anti isomers exhibit two sets of resonances (doublets of doublets) for the diastereotopic benzylic protons between 5.8 and 5.0 ppm. The corresponding resonances for the syn isomers appear upfield between 4.8 and 4.5 ppm.

Heteroaromatic aldehydes such as 3-pyridinecarboxaldehyde also react with styrenes to generate 3-chloro-1-(3-pyridyl)-3-phenylpropanols in excellent yields (Scheme 6). However, the reactions are slow compared to the reactions of aryl aldehydes. Aliphatic aldehydes and alkenes do not undergo the desired reaction. Aliphatic aldehydes simply enolize. The reaction of aliphatic alkenes with aryl aldehydes produces mixtures of 1,3-dichloro compounds and ene-carbonyl adducts in very low yield.

Under similar conditions, the reaction of *trans*-β-methylstyrene with aryl aldehydes produces mainly *R*,*R*,*R*/*S*,*S*,*S* isomers (Table 3). For aryl aldehydes with electron-withdrawing groups, the reactions give excellent yields of products. The stereoselectivity was confirmed by NMR spectroscopy and supported by the X-ray crystallography of *R*,*R*,*R*/*S*,*S*,*S* racemate of **12e** (see the Supporting Information).

To gain insight into the mechanism, the reaction of styrene with 4-chlorobenzaldehyde was monitored by NMR spectroscopy. Styrene and phenylboron dichloride were placed in an NMR tube containing $CDCl_3$. The NMR data indicated that no haloboration occurred. 4-Chlorobenzaldehyde was then added to the mixture; the NMR spectrum was consistent with the formation of intermediate **5** (Scheme 2). Hydrolysis of **5** generated chloro alcohol **6**. In a separate experiment, a boron complex (as evidenced by a shift of the aldehyde proton from 9.98 δ to 9.37 δ in the ^1H NMR) was prepared by mixing 4-chlorobenzaldehyde with 1 equiv of phenylboron dichloride in $CDCl_3$. Styrene was then added to the complex, and the NMR spectrum revealed the formation of **5**. These observations support a mechanism involving an electrophilic addition of a complexed aldehyde to styrene in a concerted fashion (structure **2** in Scheme 2).

Conclusion

The reactions of aryl aldehydes with styrene derivatives mediated by boron Lewis acids were investigated. The products were dependent on the boron Lewis acids used. 1,3-Dihalo-1,3-diarylpropanes were obtained in high yields with use of boron trihalides, while 3-chloro-1,3-diarylpropanols were obtained with use of phenylboron dichloride.

Experimental Section

All glassware was dried in an oven heated to 100 °C for at least 12 h and then cooled prior to use. All solvents were distilled from appropriate drying agents prior to use. Reactions were magnetically stirred and monitored by TLC. Products were purified by flash chromatography, using silica gel (230−400 mesh, 60 Å). Boron trichloride (1.0 M methylene chloride solution) and phenylboron dichloride were used as received. Boron tribromide and triiodide were diluted to use as methylene chloride solutions (1.0 M). All aldehydes and styrenes were used as received.

All melting points are uncorrected. Nuclear Magnetic resonance (NMR) spectra were measured in $CDCl_3$ at 250 MHz (^1H) or at 62.9 MHz (^{13}C). Chemical shifts for ^1H and ^{13}C were referenced to TMS and $CDCl_3$.

Synthesis of 1,3-Dichloro-1,3-diphenylpropane (1a). Representative procedure for the synthesis of 1,3-dichloro-1,3-diarylpropanes: Benzaldehyde (4.0 mmol, 0.42 g) and styrene (4.0 mmol, 0.42 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to 0 °C in an ice bath, and boron trichloride (4.3 mmol, 4.3 mL of a 1.0 M CH_2Cl_2 solution) was added via a syringe. The reaction was allowed to stir at 0 °C for 2 h and then at room temperature for another 8 h, during which time the reaction solution turned purple. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by column chromatography (hexanes, silica gel) to yield 0.95 g (90% yield) of the desired product: colorless oil;[20c] ^1H NMR δ 7.36−7.30 (m, 10H), 5.20 (dd, *J* = 7.6, 7.5 Hz, 1H), 4.79 (dd, *J* = 7.8, 7.1 Hz, 1H), 3.03−2.91 (m, 0.5H), 2.74−2.63 (m, 1.5H); ^{13}C NMR δ 140.7, 140.1, 128.8, 128.6, 127.0, 60.7, 60.1, 49.6, 49.4.

Synthesis of 1,3-Dibromo-1,3-diphenylpropane (1ae). Representative procedure for the synthesis of 1,3-dibromo-1,3-diarylpropanes: Benzaldehyde (3.0 mmol, 0.32 g) and styrene (3.0 mmol, 0.31 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to −40 °C in a dry ice−ethyl acetate bath, and boron tribromide (3.2 mmol, 3.2 mL of a 1.0 M CH_2Cl_2 solution) was added via a syringe. The reaction was first allowed to stir at −40 °C for 2 h and then at room temperature for 2 h. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by flash column chromatography (silica gel, hexanes) to yield 0.80 g (75% yield) of the desired product: colorless oil;[19c] ^1H NMR δ 7.33−7.25

(m, 10H), 5.18 (t, J = 7.2 Hz, 1H), 4.79 (t, J = 7.7 Hz, 1H), 3.26−3.14 (m, 0.5H), 2.94−2.83 (m, 1.5H); ^{13}C NMR δ 140.9, 140.3, 128.9, 128.7, 127.4, 53.0, 51.8, 49.2, 49.1.

Synthesis of 1,3-Diiodo-1,3-diphenylpropane (1ap). Representative procedure for synthesis of 1,3-diiodo-1,3-diarylpropanes: Benzaldehyde (4.0 mmol, 0.42 g) and styrene (4.0 mmol, 0.42 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to −70 °C in a dry ice−acetone bath, and boron triiodide (4.3 mmol, 4.3 mL of a 1.0 M CH_2Cl_2 solution) was added via a syringe. The reaction was first allowed to stir at −70 °C for 3 h and then at room temperature for 2 h. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by column chromatography (silica gel, hexanes) to yield 0.63 g (35% yield) of the desired product: yellow oil; ^{1}H NMR δ 7.35−7.10 (m, 10H), 5.09 (t, J = 7.6 Hz, 1H), 4.97 (t, J = 7.6 Hz, 1H), 3.32−3.20 (m, 0.5H), 2.99 (t, J = 7.6 Hz, 1H), 2.29−2.68 (m, 0.5H); ^{13}C NMR δ 142.3, 142.0, 128.9, 128.3, 127.3, 127.2, 51.7, 51.3, 31.3, 30.9; HRMS calcd for $C_{15}H_{14}I_2$ 447.9185, found 447.9179.

Synthesis of 1,4-Di(1′,3′-dichloro-3′-phenylpropyl)benzene (7a). Representative procedure for synthesis of di-(1′,3′-dichloro-3′-phenylpropyl)benzene: Terephthaldicarboxaldehyde (2.0 mmol, 0.27 g) and styrene (4.0 mmol, 0.42 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to 0 °C in an ice bath, and boron trichloride (4.3 mmol, 4.3 mL of a 1.0 M CH_2Cl_2 solution) was added via a syringe. The reaction was first allowed to stir at 0 °C for 2 h and then at room temperature for another 10 h. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by column chromatography (hexanes, silica gel) to yield 0.83 g (92% yield) of the desired product: colorless crystals; mp 135−136 °C; ^{1}H NMR (*R*,*R*,*S*,*S*/*S*,*S*,*R*,*R* isomers) δ 7.40−7.34 (m, 14H), 5.24−5.18 (m, 4H), 2.65 (dd, J = 7.2, 6.7 Hz, 4H); ^{13}C NMR (*R*,*R*,*S*,*S*/*S*,*S*,*R*,*R* isomers) δ 141.3, 140.7, 128.9, 128.7, 127.5, 127.0, 60.6, 60.1, 49.6; ^{1}H NMR (*R*,*R*,*S*,*S*/*S*,*S*,*R*,*R* isomers) δ 7.38−7.22 (m, 14H), 4.84−4.72 (m, 4H), 3.01−2.89 (m, 2H), 2.72−2.61 (m, 2H); ^{13}C NMR (*R*,*R*,*S*,*S*/*S*,*S*,*R*,*R* isomers) δ 141.4, 140.5, 139.9, 128.9, 128.8, 127.6, 127.0, 59.9, 59.5, 49.3. Anal. Calcd for $C_{24}H_{22}Cl_4$: C, 63.74; H, 4.90. Found: C, 63.86; H, 4.95.

Synthesis of *trans*-3,5-Dichloro-1,5-diphenylpent-1-ene (8). *trans*-Cinnamaldehyde (3.0 mmol, 0.40 g) and styrene (3.0 mmol, 0.31 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to 0 °C in an ice bath, and boron trichloride (3.2 mmol, 3.2 mL of a 1.0 M CH_2Cl_2 solution) was added via a syringe. The reaction was first allowed to stir at 0 °C for 3 h and then at room temperature for 12 h. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by flash column chromatography (silica gel, hexanes) (0.39 g, 45%): colorless oil; ^{1}H NMR δ 7.36−7.12 (m, 10H), 6.13−5.90 (m, 2H), 4.74 (dd, J = 8.9, 6.0 Hz, 0.5H), 4.56 (dd, J = 9.3, 5.3 Hz, 0.5H), 3.64−3.47 (m, 1H), 2.58−2.29 (m, 2H); ^{13}C NMR δ 141.5, 141.2, 141.0, 140.9, 136.1, 135.3, 128.9, 128.8, 128.7, 128.5, 127.6, 127.4, 127.2, 127.1, 126.9, 118.9, 118.5, 61.1, 60.9, 45.3, 44.9. Anal. Calcd for $C_{17}H_{16}Cl_2$: C, 70.11; H, 5.54. Found: C, 70.41; H, 5.54.

Synthesis of 1,1,1-Tribromo-4-chloro-4-phenylbutan-2-ol (9a). Representative procedure for synthesis of 1,1,1-tribromo-4-chloro-4-phenylbutan-2-ol: Tribromoacetaldehyde (2.0 mmol, 0.56 g) and styrene (2.0 mmol, 0.21 g) were dissolved in methylene chloride (12 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to 0 °C in an ice bath, and boron trichloride (2.2 mmol, 2.2 mL of a 1.0 M CH_2Cl_2 solution) was added via a syringe. The reaction was first allowed to stir at 0 °C for 3 h and then at room temperature for another 8 h. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by column chromatography (hexanes/EtOAc, silica gel) to yield 0.78 g (93% yield) of the desired product: wax; ^{1}H NMR (2*R*,4*R*/2*S*,4*S* isomers) δ 7.47−7.25 (m, 5H), 5.26 (dd, J = 11.8, 11.7 Hz, 1H), 4.49−4.43 (m, 1H), 3.03−2.88 (m, 1H), 2.27−2.18 (m, 1H); ^{13}C NMR (2*R*,4*R*/2*S*,4*S* isomers) δ 141.1, 128.8, 128.6, 126.7, 81.8, 60.1, 53.4, 42.6; ^{1}H NMR (2*R*,4*S*/2*S*,4*R* isomers) δ 7.47−7.26 (m, 5H), 5.18 (dd, J = 11.4, 11.2 Hz, 1H), 3.52−3.31 (m, 1H), 3.06−2.91 (m, 1H), 2.62−2.58 (m, 1H); ^{13}C NMR (2*R*,4*S*/2*S*,4*R* isomers) δ 139.7, 129.0, 128.8, 127.3, 81.5, 59.1, 53.2, 42.2. Anal. Calcd for $C_{10}H_{10}Br_3ClO$: C, 28.51; H, 2.39. Found: C, 28.70; H, 2.12.

Synthesis of 1,3-Dichloro-1,3-diphenyl-2-methylpropane (10a). Representative procedure for synthesis of 1,3-dichloro-1,3-diphenyl-2-methylpropane: benzaldehyde (4.0 mmol, 0.42 g) and β-methylstyrene (4.0 mmol, 0.47 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to 0 °C in an ice bath, and boron trichloride (4.3 mmol, 4.3 mL of a 1.0 M CH_2Cl_2 solution) was added by syringe. The reaction was first allowed to stir at 0 °C for 2 h and then stirred at room temperature for another 5 h. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by column chromatography (hexane, silica gel) to yield 1.06 g (95% yield) of the desired product: colorless crystals; mp 71−72 °C. ^{1}H NMR (1*R*,3*R*/1*S*,3*S* isomers) δ 7.37−7.28 (m, 10H), 4.75 (d, J = 6.3 Hz, 2H), 2.63−2.50 (m, 1H), 1.22 (d, J = 6.4 Hz, 3H); ^{13}C NMR (1*R*,3*R*/1*S*,3*S* isomers) δ 140.0, 128.6, 128.2, 127.2, 66.0, 49.9, 11.0; ^{1}H NMR (other two pairs of diastereomers) δ 7.48−7.23 (m, 10H), 5.91 (s, 0.8H), 5.01 (d, J = 7.2 Hz, 0.4H), 4.95 (d, J = 10.2 Hz, 0.8H), 2.89−2.81 (m, 0.2H), 2.60−2.48 (m, 0.8H), 0.74 (d, J = 7.0 Hz, 0.6H), 0.64 (d, J = 6.7 Hz, 2.4H); ^{13}C NMR (other two pairs of diastereomers) δ 140.0, 138.2, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 127.7, 127.2, 66.6, 65.4, 64.8, 49.3, 49.1, 10.8. Anal. Calcd for $C_{16}H_{16}Cl_2$: C, 68.83; H, 5.78. Found: C, 68.70; H, 5.92.

Synthesis of 3-Chloro-1,3-diphenylpropanol (6a). Representative procedure for synthesis of 3-chloro-1,3-diphenylpropanols: benzaldehyde (4.0 mmol, 0.42 g) and styrene (4.0 mmol, 0.42 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to −10 °C, and phenylboron dichloride (4.3 mmol, 4.3 mL of a 1.0 M CH_2Cl_2 solution) was added by syringe. The reaction was first allowed to stir at −10 °C for 4 h and then stirred at room temperature for another 4 h. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by column chromatography (hexane/EtOAc, silica gel) to yield 0.75 g of the desired product: colorless oil; ^{1}H NMR (*R*,*R*/*S*,*S* isomers) δ 7.38−7.21 (m, 10H), 7.01−6.95 (m, 2H), 5.20 (dd, J = 9.8, 9.7 Hz, 1H), 5.09 (dd, J = 8.8, 8.7 Hz, 1H), 2.44 (s, 1H), 2.33−2.27 (m, 2H); ^{13}C NMR (*R*,*R*/*S*,*S* isomers) δ 143.8, 141.6, 128.6, 128.5, 128.3, 127.8, 126.9, 125.7, 71.2, 51.9, 60.5, 48.8. Anal. Calcd for $C_{15}H_{15}ClO$: C, 73.02; H, 6.13. Found: C, 73.07; H, 6.24.

Synthesis of 3-Chloro-1-(3-pyridinyl)-3-phenylpropanol (11a). Representative procedure for synthesis of 3-chloro-1-(3-pyridinyl)-3-phenylpropanols: 3-Pyridinecarboxaldehyde (4.0 mmol, 0.43 g) and styrene (4.0 mmol, 0.42 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under argon atmosphere. Phenylboron dichloride (4.3 mmol, 4.3 mL of a 1.0 M CH_2Cl_2 solution) was added by syringe. The reaction mixture was stirred at room temperature for several hours, using TLC

to monitor the reaction. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by column chromatography (hexane/EtoAc, silica gel) to yield 0.89 g of the desired product: yellow wax; ^{1}H NMR (*R*,*R*/*S*,*S* isomers) δ 9.26 (s, 1H), 8.28−8.18 (dd, J = 15.0, 8.1 Hz, 1H), 7.75 (t, J = 7.2 Hz, 1H), 7.38−7.24 (m, 5H), 5.35−5.25 (m, 1H), 5.01 (t, J = 7.5 Hz, 0.5 H), 4.81 (dd, J = 8.7, 8.5 Hz, 0.5 H), 2.89 (s, 1H), 2.74−2.62 (m, 0.5 H), 2.46−2.23 (m, 1.5H); ^{13}C NMR (*R*,*R*/*S*,*S* isomers) δ 143.7, 143.5, 143.3, 142.7, 142.3, 142.1, 141.6, 141.4, 140.4, 139.6, 129.0, 128.8, 128.6, 127.0, 126.8, 126.0, 68.6, 68.2, 59.7, 59.3, 46.4, 46.1. Anal. Calcd for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.98; H, 5.43; N, 5.58.

Synthesis of 3-Chloro-1-(4-fluorophenyl)-2-methyl-3-phenylpropanol (12a). Representative procedure for synthesis of 3-chloro-1-(4-cyanophenyl)-1-hydroxy-2-methyl-3-phenylpropanol: 4-Cyanobenzaldehyde (4.0 mmol, 0.52 g) and *trans*-β-methylstyrene (4.0 mmol, 0.47 g) were dissolved in methylene chloride (20 mL) at room temperature in a dry flask maintained under a nitrogen atmosphere. The solution was cooled to 0 °C in an ice bath, and boron trichloride (4.3 mmol, 4.3 mL of a 1.0 M CH_2Cl_2 solution) was added via a syringe. The reaction was first allowed to stir at 0 °C for 2 h and then at room temperature for 24 h. Water (20 mL) was added and the product extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous magnesium sulfate and the product isolated by column chromatography (methylene chloride, silica gel) to yield 1.11 g (97% yield) of the desired product: colorless oil; ^{1}H NMR (*R*,*R*,*R*/*S*,*S*,*S* isomers) δ 7.33−7.26 (m, 7H), 7.01−6.95 (m, 2H), 5.52 (s, 1H), 5.00 (d, J = 10.8 Hz, 1H), 2.53 (s, 1H), 2.37−2.20 (m, 1H), 0.50 (d, J = 7.0 Hz, 3H); ^{13}C NMR (*R*,*R*,*R*/*S*,*S*,*S* isomers) δ 163.7, 159.1, 140.6, 139.1, 128.6, 128.1, 127.5, 127.1, 127.0, 115.1, 114.8, 71.9, 64.7, 48.1, 9.9. Anal. Calcd for $C_{16}H_{16}FClO$: C, 68.94; H, 5.79. Found: C, 68.85; H, 5.62.

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Supporting Information Available: Experimental data of all compounds as well as X-ray crystallographic data of compounds **1a*l***, **7a**, **10a**, and **12e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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