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Stereo- and regioselective synthesis of 1,3-diaryl-3-chloro-1-propanols via the reaction of aryl aldehydes with styrene and (*E*)-β-methylstyrene

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Abstract—Reactions of aryl aldehydes with styrene and (*E*)-β-methylstyrene in the presence of phenylboron dichloride regioselectively generate 1,3-diaryl-3-chloro-1-propanols and 1,3-diaryl-3-chloro-2-methyl-1-propanols in good to excellent yields with high stereoselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

Boron halides are versatile reagents in organic synthesis. They have been widely used for the cleavage of ethers,[1] halogenation of aryl aldehydes,[2] reduction of carbonyl compounds,[3] haloboration of alkynes[4] and as enolization reagents in aldol reactions.[5] We have been investigating carbon–carbon bond forming reactions utilizing boron halide reagents. Several new reactions have been developed including the alkylation[6] and dialkenylation of aryl aldehydes.[7] Although the haloboration of alkynes via boron halides[4] has been well documented, boron halides react with alkenes to give rise to mixtures of compounds.[8]

We recently discovered that aryl aldehydes react with styrenes in the presence of boron trihalides to produce 1,3-dihalo-1,3-diarylpropanes in excellent yields.[9] In these reactions we detected the formation of β-chloroalcohols but the yields were low. In a continuation of our ongoing studies, we investigated the reaction of aldehydes with alkenes in the presence of phenylboron dichloride and discovered that the reaction regioselectively produced *anti*-β-chloroalcohols in good to excellent yields (Tables 1–3). These β-chloroalcohols are potentially useful intermediates in organic synthesis because they can be subjected to a number of transformations such as halogenation, substitution, cyclization and oxidation reactions to generate mixed 1,3-dihalogenated diarylpropanes, cyclic ethers and ketones.

Initially, styrene was allowed to react with one equivalent of phenylboron dichloride in CH_2Cl_2 at room temperature to form haloboration intermediates.[8] Then, one equivalent 4-chlorobenzaldehdye was introduced at −10°C. The reaction solution turned yellow. After 1 h, the solution was hydrolyzed and 3-chloro-1-(4-chlorophenyl)-3-phenylpropanol was isolated in good yield. Alternatively, the reaction could be carried out by introducing phenylboron dichloride to a mixture of styrene and 4-chlorobenzaldehye in CH_2Cl_2 at −10°C. We noted that the freshly distilled styrene produced only polymerization products whereas commercially available styrene containing 4-*tert*-butylcatechol produced good yields of the desired product. The product chloroalcohols can be conveniently brominated using boron tribromide in CH_2Cl_2 at room temperature to form 1-bromo-3-chloro-1,3-diarylpropanes.

From the data in Tables 1 and 2,[10] it can be seen that the reactions of aldehydes and styrenes containing electron-withdrawing groups require a higher reaction temperature, but give higher yields of products. The reactions of aldehydes and styrenes containing electron-donating groups are faster but produce lower yields of the desired products due to the facile chlorination of the product alcohols to form 1,3-dichloro compounds.[9] Heteroaromatic aldehydes such as 3-pyridinecarboxaldehyde also react with styrenes to generate 3-chloro-1-(3-pyridyl)-3-phenylpropanols in excellent yields (Table 3). 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.

Keywords: boron and compounds; aldehydes; alkenes; alcohols; alkyl halides; aldol reaction.

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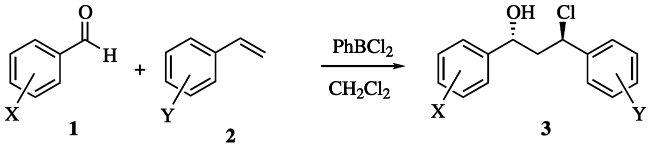
Table 1. Synthesis of 1,3-diaryl-3-chloro-1-propanols

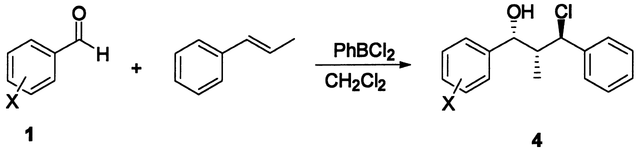


Entry	X	Y	*T* (°C)	Time (h)	*anti* (%)	Yield (%)[a,b] (**3**)
1	H	H	−10	1	83	76 (**3a**)
2	*p*-F	H	0	2	93	87 (**3b**)
3	*o*-F	H	0	2	80	79 (**3c**)
4	*p*-Cl	H	−10	1	84	79 (**3d**)
5	*o*-CH_3	H	−20	0.5	92	56 (**3e**)
6	CH_3O	H	−20	0.5	89	45 (**3f**)
7	*p*-CN	H	25	6	84	96 (**3g**)
8	*p*-NO_2	*p*-Cl	25	4	86	90 (**3h**)
9	H	*p*-Cl	−10	1	84	85 (**3i**)
10	*p*-Cl	*p*-Cl	−10	1.5	86	86 (**3j**)
11	*p*-CN	*p*-Cl	25	12	77	99 (**3k**)
12	*p*-NO_2	*p*-CH_3	25	6	87	99 (**3l**)
13	H	*p*-CH_3	−20	0.5	85	75 (**3m**)
14	*p*-CN	*p*-CH_3	25	8	90	98 (**3n**)

[a] Isolated yields based on the starting aldehydes.

[b] All compounds were characterized by elemental analysis and NMR spectroscopy.

Table 2. Synthesis of 1,3-diaryl-3-chloro-2-methyl-1-propanols



Entry	X	*T* (°C)	Time (h)	*anti* (%)[a]	Yield (%)[b,c] (**4**)
1	*p*-F	0	2	94	94 (**4a**)
2	*o*-F	0	2	92	95 (**4b**)
3	*p*-Cl	−10	1.5	89	65 (**4c**)
4	*p*-Br	−10	1	86	60 (**4d**)
5	*p*-Me	−20	0.5	90	36 (**4e**)
6	*p*-CN	25	48	98	97 (**4f**)
7	*p*-NO_2	25	24	95	95 (**4g**)

[a] *anti*-3-Chloro-1-hydroxy isomer (in all cases hydoxy and methyl are *syn*).

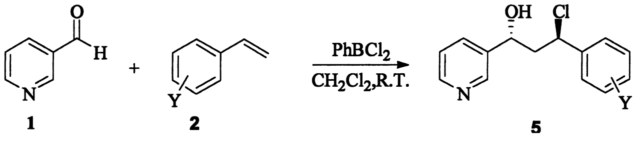
[b] Isolated yields based on the starting aldehydes.

[c] All compounds were characterized by elemental analysis and NMR spectroscopy.

The reaction of aliphatic alkenes with aryl aldehydes produces mixtures of 1,3-dichloro compounds and ene–carbonyl adducts in low yield. Boron chlorides such as *n*-butylboron dichloride, *sec*-butylboron dichloride, *n*-hexylboron dichloride, cyclohexylboron dichloride and cyclopentylboron dichloride were found to be ineffective. Solvents such as hexane, toluene, chloroform and CH_2Cl_2 were examined as reaction solvents. CH_2Cl_2 was found to be the most effective. Diethyl ether, THF and dioxane simply undergo ether cleavage reactions.[1]

In order to gain insight regarding the mechanism, the reaction of styrene and 4-chlorobenzaldehyde was monitored by NMR spectroscopy. Styrene and phenylboron dichloride were placed in a NMR tube containing $CDCl_3$. The NMR data indicated that no haloboration had occurred. 4-Chlorobenzaldehyde was then added to the reaction mixture; the NMR spectra revealed the rapid formation of β-chloroalkoxyborane intermediate **6** (Scheme 1). Hydrolysis of **6** generated chloroalcohol **3**. In a separate experiment, a boron complex was prepared by mixing 4-chlorobenzaldehyde with one equivalent of phenylboron dichloride in $CDCl_3$. Styrene was then added to the complex, and the reaction generated intermediate **6**. Based on these observations, the reaction presumably occurs via an electrophilic addition of the complexed aldehyde to styrene, in a concerted mechanism (Scheme 1). A similar mechanism has been reported for Lewis acid promoted ene–carbonyl reactions.[11]

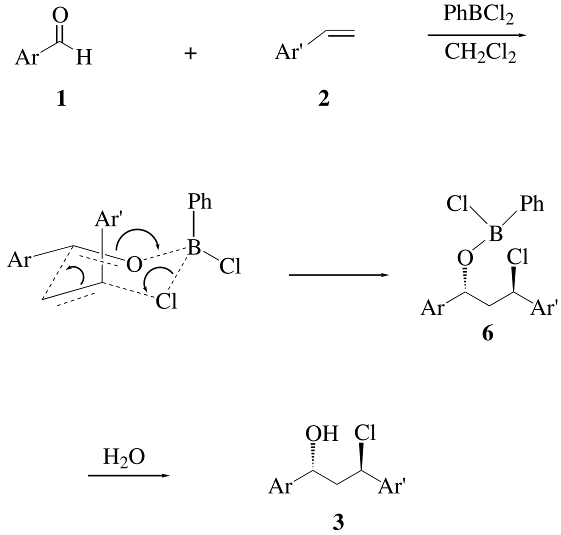
Table 3. Synthesis of 3-chlorlo-3-aryl-1-(3-pyridinyl)-1-propanols



Entry	Y	Time (h)	*anti* (%)	Yield (%)[a,b] (**5**)
1	H	20	88	90 (**5a**)
2	*p*-F	30	92	84 (**5b**)
3	*p*-Cl	24	91	85 (**5c**)
4	*o*-Cl	24	95	91 (**5d**)
5	*p*-Me	10	88	64 (**5e**)

[a] Isolated yields based on starting aldehydes.

[b] All compounds were characeterized by elemental analysis and NMR spectroscopy.



Scheme 1.

All products 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. In addition, the reactions predominantly produced the *anti*-diastereoisomers. For styrenes, the *R*,*R*/*S*,*S*-isomers were the major products whereas the (*E*)-β-methyl styrenes produced mainly *R*,*R*,*R*/*S*,*S*,*S*-isomers (Table 2). The *anti*-isomers, exhibit two sets of resonances (doublets of doublets) for the diastereotopic benzylic protons in the range of 5.80–5.00 δ. The corresponding resonances for the *syn*-isomers appear upfield in the range of 4.80–4.50 δ. A single crystal of compound **4f** was analyzed by X-ray crystallography. The X-ray structure analysis confirmed the NMR assignment.

In conclusion, we have discovered a new reaction of styrenes with aryl aldehydes in the presence of phenylboron dichlorides. The reactions stereo- and regioselectively generate a series of useful 1,3-diaryl-3-chloro-1-propanols and 3-chloro-1,3-diaryl-2-methyl-1-propanols in excellent yields. Efforts to utilize boron bromides and iodides, to promote new condensation reactions are currently underway.

Acknowledgements

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10. *Representative procedure for the synthesis of 1,3-diaryl-3-chloro-1-propanols*: Benzaldehyde (4.0 mmol, 0.42 g) and styrene (4.0 mmol, 0.42 g) were dissolved in CH_2Cl_2 (10 mL) at room temperature in a dry round-bottomed flask under a nitrogen atmosphere. The solution was cooled to −10°C in a dry-ice bath, and phenylboron dichloride (4.0 mmol, 0.64 g) was added via syringe. The solution gradually turned yellow. After stirring at −10°C for 1 h, the solution was hydrolyzed and extracted with hexanes. The organic layer was separated, dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and the product isolated by column chromatography (silica gel, CH_2Cl_2) to afford 0.75 g (76%) of **3a** as a colorless liquid; ^1H NMR ($CDCl_3$, 250 MHz) *anti*-isomers: δ 7.38–7.21 (m, 10H), 5.20 (dd, 1H, $J=9.7$, 4.5 Hz), 4.99 (dd, 1H, $J=8.8$, 4.4 Hz), 2.44 (s, 1H), 2.33–2.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 143.8, 141.6, 128.6, 128.3, 127.8, 126.9, 125.7, 71.2, 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%.
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