Pergamon

Tetrahedron 57 (2001) 1663–1670

TETRAHEDRON

Alkylation of aromatic aldehydes with alkylboron chloride derivatives

George W. Kabalka,* Zhongzhi Wu and Yuhong Ju

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, TN 37996-1600, USA

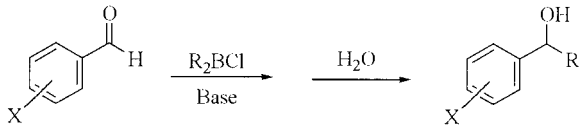
Received 13 September 2000; accepted 15 December 2000

Abstract—The reaction of aryl aldehydes with alkylboron chlorides has been investigated. Monoalkylboron dichlorides react with aryl aldehydes in hexane under reflux conditions to give a mixture of dichloroarylmethane and benzyl chloride. Under the same reaction conditions, dialkylboron chlorides lead to formation of a mixture of benzyl chloride and the chloroalkylation product. In the presence of a base such as 2,6-lutidine, the reactions of monoalkylboron dichlorides with aryl aldehydes yield small amounts of the desired alkylation products at room temperature. Dialkylboron chlorides react with aryl aldehydes in hexane in the presence of base to generate the corresponding arylalkylmethanols in good yields.

1. Introduction

Generally, only reactive alkylmetals such as the organomagnesium,[1–4] organolithium,[5] organozinc[6,7] and certain organotransition metal reagents[8–15] can be utilized to alkylate carbonyl compounds, one of the most important carbon–carbon bond forming reactions. Organoboranes do not normally react with carbonyl compounds in a Grignard-like fashion with the exception of allylborane and vinylborane reagents.[16–19] The few known alkylborane carbonyl alkylation reactions require reactive organoboranes,[20] free radical conditions,[21,22] or activation of the carbonyl groups.[23,24] However, a Grignard-like reaction involving organoborane reagents would possess a number of synthetic advantages including mild reaction conditions, stereochemical control and the fact that a large number of functional substituents are unaffected in most organoborane transformations.[25–30]

Boron halide derivatives have been used extensively in bond cleavage reactions[31] and as enolate reagents for use in the aldol reactions. Boron enolates are particularly useful in diastereoselective and enantioselective carbon–carbon bond formation.[32–34] However, organic boron halide reagents have not been used to alkylate carbonyl compounds. We recently reported the initial results of a study involving the alkylation of aryl aldehydes using alkylboron chloride derivatives to produce the corresponding alcohols in good yields (Scheme 1).[35] We now wish to report the results of a detailed study of this new reaction.



Scheme 1. Alkylation of aryl aldehydes.

2. Results and discussion

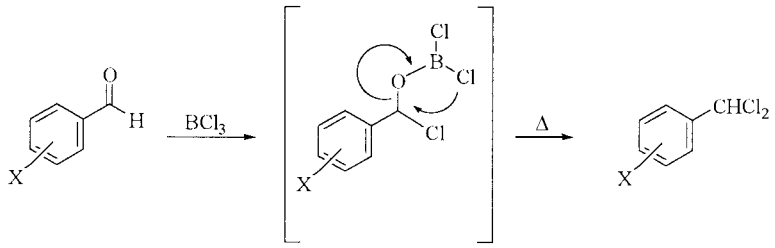
2.1. The reaction of alkylboron dichlorides with aryl aldehydes

Earlier, we reported a new method for converting aryl aldehydes into dichloroarylmethanes using boron trichloride.[36,37] The reaction appears to proceed via an alkoxyboron chloride intermediate (Scheme 2). It occurred to us that the use of an alkylboron derivative in place of boron trichloride could lead to a new alkylation reaction, which would provide a Grignard-like addition reaction. We thus examined the reaction of alkylboron dichloride reagents with aryl aldehydes but found that no reaction occurred in hexane solution at room temperature. However, a mixture of benzyl chloride and dichoromethylbenzene was formed when the reaction mixture was refluxed in hexane. This result indicates that, in addition to the formation of dichloroarylmethane, a reductive chlorination reaction occurs (Scheme 3). The formation of dichloroarylmethane presumably occurs via the pathway reported for reactions of BCl_3 with aryl aldehydes.[36] However, the generation of benzyl chloride could occur via two reaction pathways, as has been observed in the reaction of dialkylboron bromide with aryl aldehydes[38] (Scheme 3). The use of phenylboron dichloride (which has no transferable *beta*-hydrogens) results in the exclusive formation of dichloromethylbenzene.

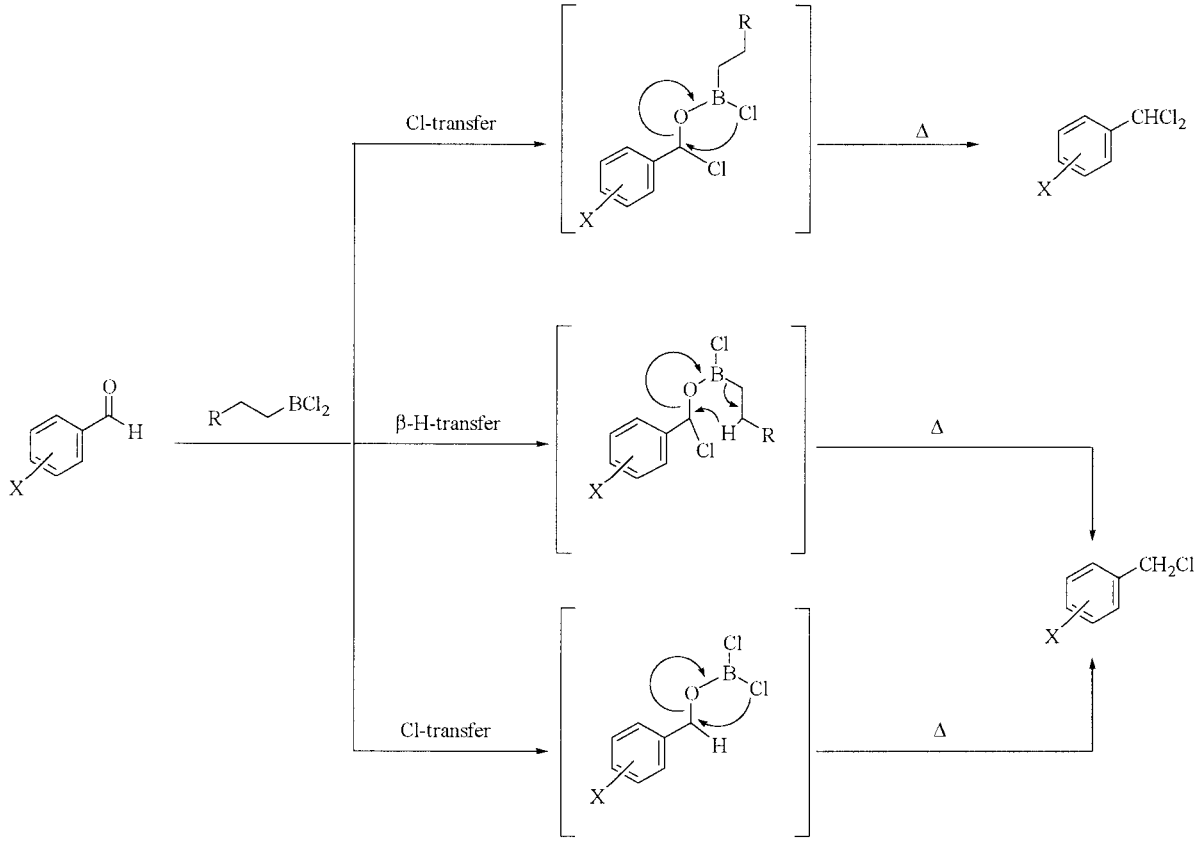
Keywords: boron and compounds; aldehydes; alcohols; alkylation.

* Corresponding author. Tel.: +1-865-974-3260; fax: +1-865-974-2997; e-mail: kabalka@utk.edu

0040–4020/01/$ - see front matter
PII: S0040-4020(00)01160-1



Scheme 2. Chlorination of aryl aldehydes via BCl_3.



Scheme 3. Reaction of aryl aldehydes with $RBCl_2$ under reflux conditions.

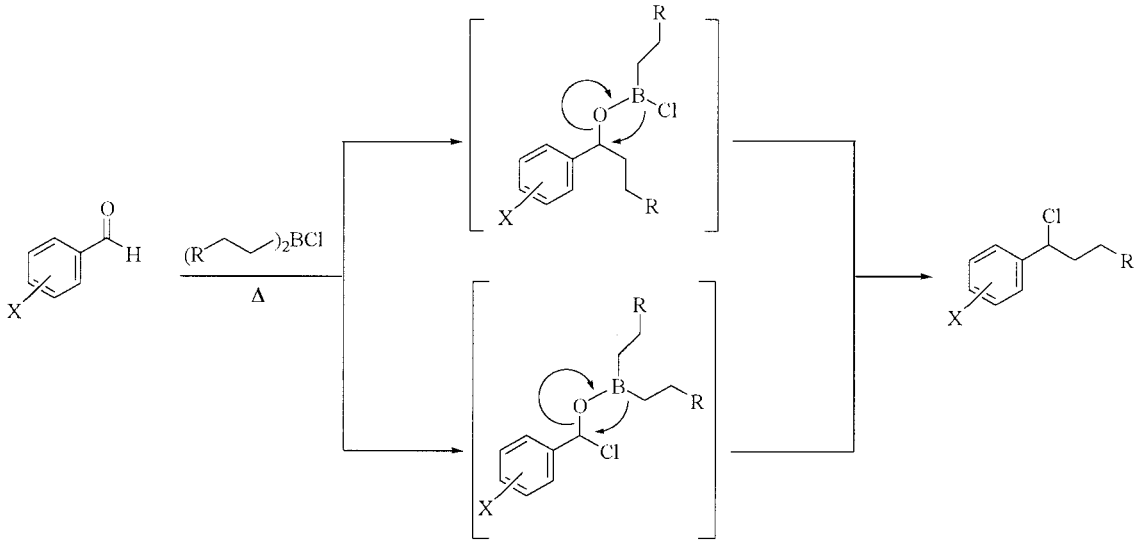
The reaction of *n*-butylboron dichloride with benzaldehyde leads to the formation of a small amount of the desired alkylation product if the reaction is carried out in the presence of a base such as triethylamine, quinuclidine or 2,6-lutidine. In the case of 2,6-lutidine, a 15% yield of 1-phenylpentanol can be isolated from the reaction mixture. Attempts to increase the yield of the alkylation product have been unsuccessful.

2.2. The reaction of dialkylboron chlorides with aryl aldehydes under reflux conditions

Since the reactions of alkylboron dichloride reagents with aryl aldehydes did not lead to significant yields of alkylation products, we studied the reactions of dialkylboron chloride derivatives with aldehydes. We first examined the reaction of dicyclohexylboron chloride with benzaldehyde in hexane at room temperature and found that no reaction occurred. The reaction was then carried out in hexane at reflux. Surprisingly, the chloroalkylation product, chlorocyclohexylphenylmethane, was formed along with benzyl chloride. However, the yield of the chloroalkylation product was modest (25% isolated yield). The formation of benzyl chloride was not unexpected and had been observed in the reaction of *n*-butylboron dichloride with aryl aldehydes. The formation of chloroalkylation product is unprecedented. Possible reaction pathways are presented in Scheme 4. Attempts to increase the yield of chloroalkylation products were unsuccessful.

2.3. The reaction of dialkylboron chlorides with aryl aldehydes in the presence of base

The reaction of dialkylboron chlorides with aryl aldehydes was then examined in the presence of various bases. Moderate to good yields of desired alkylation products,

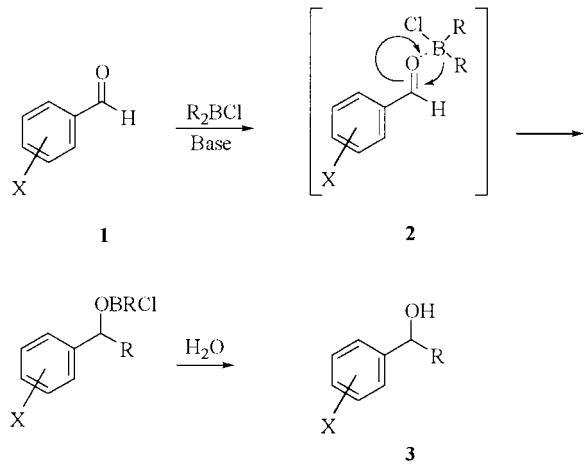


Scheme 4. Reaction of aryl aldehydes with R_2BCl under reflux conditions.

arylalkylmethanols, were obtained. In order to investigate the reaction mechanism, the reaction of 4-bromobenzaldehyde with dicyclohexylboron chloride was monitored by NMR spectroscopy. Dicyclohexylboron chloride (1 M hexane solution) was added to 4-bromobenzaldehyde in hexane at −30°C. The solvent was removed under reduced pressure to yield a yellow solid, which was then dissolved in benzene-d_6 for NMR analysis at room temperature. The characteristic ^1H and ^{13}C resonances for the aldehyde were absent in the resultant NMR spectra. Interestingly, no new resonances appeared in the ^1H and ^{13}C NMR spectra. Furthermore, upon addition of water (instead of a base), 4-bromobenzaldehyde was regenerated. These results suggest that 4-bromobenzaldehyde coordinates to dicyclohexylboron chloride. In a separate experiment, upon addition of Et_3N to the benzene-d_6 solution of the reaction mixture, a new doublet appeared at 5.11 ppm in the ^1H NMR and a new ^{13}C NMR resonance appeared at 83.4 ppm. Hydrolysis of this reaction mixture lead to the formation of the alkylation product cyclohexyl(4-bromophenyl)methanol. In a third NMR experiment, the benzene solution of the aldehyde and boron chloride was examined by ^{11}B NMR which revealed a resonance at 64.4 ppm (slightly upfield of the resonance at 78 ppm for dicyclohexylboron chloride) indicating a weak coordination of aldehyde with boron. Upon addition of Et_3N, the ^{11}B NMR signal shifted to 12.8 ppm, suggesting coordination of the amine to boron. However, the ^{11}B NMR data do not provide information about the reaction intermediate. On the basis of the NMR data, the alkylation of aldehydes presumably proceeds via coordination of the carbonyl to boron followed by migration of the alkyl group (Scheme 5).

The reaction of tri(*n*-butyl)borane with aryl aldehydes was then investigated at reflux in the presence of base. It was discovered that no alkylation reaction occurred under these conditions. The results suggest that the chloride atom plays a critical role in the alkylation reactions. Compared to trialkylboranes, chloroboranes are more electron-deficient and can coordinate more effectively to the carbonyl oxygen. It was noted that benzyl alcohols were also formed in small quantities along with the desired alkylated product in all the chloroborane reactions. Moreover, reduction of the aldehydes predominated if the more hindered boron reagents such as di(3-methyl-2-butyl)boron chloride, di(*exo*-norbornyl)boron chloride and DIP-chloride were utilized; these organoboranes have been widely used as an effective reducing reagent for carbonyl compounds.[39]

A series of aromatic aldehydes was subjected to the new alkylation reaction. Essentially all aldehydes examined were converted successfully to the corresponding arylalkylmethanols, Table 1. In the case of anisaldehyde, cleavage of the ether group did not occur.[31] Also, the cyano group was unaffected.[40] From the data in Table 1, it can be seen that boranes containing primary alkyl groups produce relatively low yields of the desired product compared to those containing secondary alkyl groups. Although it is not clear what leads to low yields for boranes containing primary alkyl groups, it could be a consequence of steric effects. We did find that the alkylation of aldehydes



Scheme 5. Alkylation of aryl aldehydes via R_2BCl in presence of base.

Table 1. Synthesis of 1-phenyl-1-alkanols via reaction of aromatic aldehydes with R_2BCl

Entry	X	R	Product	% Yield 3[a]
1	**1a** (H)	Cyclohexyl	**3a**	75
2	**1b** (4-F)	Cyclohexyl	**3b**	90
3	**1c** (4-Cl)	Cyclohexyl	**3c**	78
4	**1d** (2-Cl)	Cyclohexyl	**3d**	49
5	**1e** (4-Br)	Cyclohexyl	**3e**	76
6	**1f** (2-Me)	Cyclohexyl	**3f**	65
7	**1g** (4-Me)	Cyclohexyl	**3g**	78
8	**1h** (4-MeO)	Cyclohexyl	**3h**	83
9	**1i** (4-NC)	Cyclohexyl	**3i**	86
10	**1j** (Naphthyl)	Cyclohexyl	**3j**	27
11	**1k** (4-CHO)	Cyclohexyl	**3k**	66
12	**1l** (H)	Cyclopentyl	**3l**	65
13	**1m** (4-F)	Cyclopentyl	**3m**	78
14	**1n** (4-Cl)	Cyclopentyl	**3n**	70
15	**1o** (4-Me)	Cyclopentyl	**3o**	60
16	**1p** (H)	Norbornyl	**3p**	25
17	**1q** (4-Br)	Norbornyl	**3q**	28
18	**1r** (4-Me)	Norbornyl	**3r**	25
19	**1s** (H)	*s*-Butyl	**3s**	60
20	**1t** (4-F)	*s*-Butyl	**3t**	75
21	**1u** (4-Cl)	*s*-Butyl	**3u**	70
22	**1v** (4-Br)	*s*-Butyl	**3v**	79
23	**1w** (4-Me)	*s*-Butyl	**3w**	67
24	**1x** (2-Me)	*s*-Butyl	**3x**	20
25	**1y** (H)	1-Hexyl	**3y**	35
26	**1z** (4-F)	1-Hexyl	**3z**	70
27	**1aa** (4-Cl)	1-Hexyl	**3aa**	41
28	**1ab** (2-Cl)	1-Hexyl	**3ab**	30
29	**1ac** (4-Br)	1-Hexyl	**3ac**	40
30	**1ad** (4-Me)	1-Hexyl	**3ad**	30
31	**1ae** (2-Me)	1-Hexyl	**3ae**	25

[a] Isolated yields based on starting aldehydes.

via boranes containing primary alkyl groups was much slower than reactions involving boranes containing secondary alkyl groups. In one reaction, 4-bromobenzaldehyde was allowed to react with cyclohexyl(*n*-butyl)boron chloride. As anticipated, the major product was cyclohexyl(4-bromophenyl)methanol (58% isolated yield) (Scheme 6).

Although the role of base in the reaction is not clear, it could coordinate boron to increase steric crowding and thus induce the migration of an alkyl group. Alternatively, coordination of the base to the electron-deficient boron atom could increase the electron density on boron and facilitate the migration of the alkyl group. Table 2 contains a summary of the reaction of 4-bromobenzaldehyde with dicyclohexylboron chloride in the presence of a variety of bases. It can be seen that all bases result in the formation of the desired product. Bulky bases tend to produce higher yield of products, which is consistent with results noted earlier. Strong nucleophiles, such as *n*-butyllithium also lead to higher yields of products.

Table 2. Reaction of 4-bromobenzaldehyde with dicyclohexylboron chloride in the presence of various bases

Entry	Base	Product	Yield (%)
1	Et_3N	**3e**	60
2	Quinuclidine	**3e**	74
3	Pyridine	**3e**	40
4	2,6-Lutidine	**3e**	76
5	DBU	**3e**	76
6	Bu^nLi	**3e**	72
7	Bu^tOK	**3e**	76

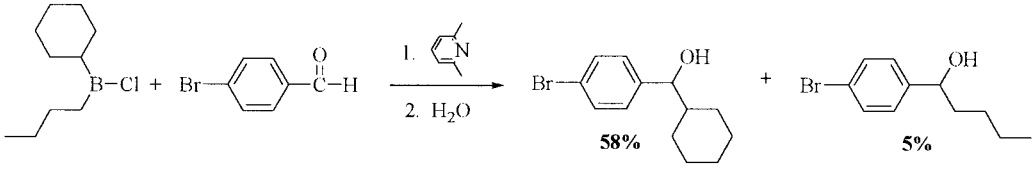
3. Conclusions

The new alkylation reaction provides a potentially useful alternative to traditional Grignard and organolithium reactions. The reaction occurs under mild reaction conditions and tolerates a variety of functional groups. It is limited to aldehydes that do not possess α-hydrogens due to the well-known enolization reactions that occur with dialkylboron halides. Benzyl alcohols are formed in small quantities along with the desired products; this reaction predominates if the more hindered organoboranes, such as diisopinocampheylboron chloride, dinorbornylboron chloride, and di-(3-methyl-2-butyl)boron chloride are utilized. Organoboron chlorides containing secondary alkyl groups tend to give higher yield of alkylation products. Bulkier bases also lead to higher yield of alkylated products.

4. Experimental

All glassware and equipment were dried in an oven heated to 250°C for at least 12 h and cooled under argon prior to use. All solvents were distilled from appropriate drying agents prior to use. Reactions were stirred magnetically and monitored by TLC. Products were purified by flash chromatography using silica gel (230–400 mesh, 60 Å, ICN Biomedical GmbH, Eschwege, Germany), with dichloromethane as eluent.

Dicyclohexylboron chloride (1.0 M hexane solution) and *n*-butyl dichloride (1.0 M hexane solution) were purchased from Aldrich Chemical Co. Dihexylboron chloride, di(*exo*-norbornyl)boron chloride, dicyclopentylboron chloride, and di-*sec*-butylboron chloride were prepared from $H_2BCl{\cdot}SMe_2$ and the corresponding alkenes (1-hexene, norbornylene, cyclopentene, *cis*-2-butene) according to the literature procedures.[40] Cyclohexyl(*n*-butyl)boron chloride was prepared via reaction of *n*-butylboron dichloride with cyclohexene and triethylsilane.[41] All aldehydes (Aldrich Chemical Co.) were dried and distilled under argon. Triethylamine, 2,6-lutidine, quinuclidine, and DBU were



Scheme 6. Alkylation of *p*-bromobenzaldehyde using cyclohexyl(*n*-butyl)boron chloride

dried and distilled prior to use. *n*-Butyllithium and lithium *t*-butoxide (Aldrich Chemical Co.) were used as received.

All melting points are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. NMR spectra were measured in $CDCl_3$ or C_6D_6 at 250 MHz (^1H) or at 62.9 MHz (^{13}C). In cases where more than one isomer formed, the NMR shifts of all isomers are reported. Chemical shifts are referenced to TMS. HR-EI-MS were obtained using a ZAB-EQ instrument.

4.1. Reaction of aryl aldehydes with alkylboron dichlorides in hexane

The reaction of *n*-butylboron dichloride with benzaldehyde is representative. Benzaldehyde (5.0 mmol, 0.53 g) was dissolved in hexane (10 mL) contained in a dry, argon-flushed, 50 mL round-bottomed flask. *n*-Butylboron dichloride (5.0 mmol, 5.0 mL of a 1.0 M hexane solution) was added via syringe and the solution was allowed to react at reflux for 3 h. Hydrolysis, separation of the organic layer and column chromatography afforded a mixture of dichlorotoluene and benzyl chloride (2:3 ratio).

4.2. Reaction of aryl aldehydes with dialkylboron chlorides

The reaction of dicyclohexylboron chloride with benzaldehyde is representative. Benzaldehyde (5.0 mmol, 0.53 g) was dissolved in hexane (10 mL) contained in a dry, argon-flushed, 50 mL round-bottomed flask. Dicyclohexylboron chloride (5.0 mmol, 5.0 mL of a 1.0 M hexane solution) was added via syringe, and the solution allowed to reflux for 4 h. Hydrolysis, separation of the organic layer and column chromatography afforded 0.12 g of benzyl chloride (15%) and 0.26 g of chlorocyclohexylphenylmethane (25%).[42] NMR data for chlorocyclohexylphenylmethane; ^1H NMR: δ 7.33–7.22 (m, 5H), 4.60 (d, J=8.41 Hz, 1H), 2.21–0.86 (m, 11H); ^{13}C NMR: δ 140.9, 128.3, 127.9, 127.5, 69.8, 45.7, 30.4, 30.3, 26.11, 25.9, 25.9.

4.3. Reaction of aryl aldehydes with alkylboron dichlorides in the presence of base

The reaction of *n*-butylboron dichloride with benzaldehyde is representative. Benzaldehyde (3.0 mmol, 0.32 g) was dissolved in hexane (10 mL) contained in a dry, argon-flushed, 50 mL round-bottomed flask. *n*-Butylboron dichloride (3.0 mmol, 3.0 mL of a 1.0 M hexane solution) was added via syringe and the solution allowed to stir for 10 h at room temperature. 2,6-Lutidine (3.0 mmol, 0.32 g) was then added and the mixture stirred at room temperature for 12 h. The reaction mixture was hydrolyzed, the organic layer separated and then dried over anhydrous $MgSO_4$. The desired product, 1-phenylpentanol,[43] was isolated by column chromatography in 15% yield.

4.4. General procedure for synthesis of alkylaryl alcohols

Benzaldehyde (3.0 mmol, 0.32 g) was dissolved in hexane (10 mL) contained in a dry, argon-flushed, 50 mL round-bottomed flask. Dicyclohexylboron chloride (3.0 mmol, 3.0 mL of a 1.0 M hexane solution) was added via syringe and the solution allowed to stir for 30 min at room temperature. 2,6-Lutidine (3.0 mmol, 0.32 g) was then added and the mixture stirred for 5 h. A precipitate was formed, which contained boron. Hydrolysis, as well as oxidation, of the remaining alkylboron group was accomplished by addition of hydrogen peroxide (0.5 mL of a 30% aqueous solution) and sodium hydroxide (3.0 mmol, 1.0 mL of a 3.0 M aqueous solution). [Alternatively, water could be added and the product isolated from the organic phase.] After separation of the organic layer, 0.43 g of the desired product (75% yield) was isolated by column chromatography.

4.4.1. Cyclohexylphenylmethanol (3a). Colorless oil.[44] ^1H NMR: δ 7.36–7.23 (m, 5H), 4.35 (d, 1H, J=7.2 Hz), 1.90 (s, 1H), 2.01–0.94 (m, 11H). ^{13}C NMR: δ 143.6, 128.2, 127.4, 126.6, 79.4, 44.9, 29.3, 28.8, 26.4, 26.1, 26.0.

4.4.2. Cyclohexyl(4-fluorophenyl)methanol (3b). Colorless oil. ^1H NMR: δ 7.21–6.93 (m, 4H), 4.25 (d, 0.5H, J=4.4 Hz), 4.23 (d, 0.5H, J=4.4 Hz), 2.65 (s, 1H), 1.93–0.81 (m, 11H). ^{13}C NMR: δ 163.9, 160.0, 139.3, 139.2, 128.1, 128.0, 114.56, 114.6, 78.5, 44.9, 29.0, 28.8, 26.3, 25.9. Anal. Calcd for $C_{13}H_{17}OF$: C, 74.97; H, 8.23. Found: C, 74.85; H, 8.24.

4.4.3. Cyclohexyl(4-chlorophenyl)methanol (3c). White solid; mp 73–74°C (lit.[45]; 74–75°C). ^1H NMR: δ 7.27 (d, 2H, J=7.5 Hz), 7.17 (d, 2H, J=8.2 Hz), 4.28 (d, 1H, J=6.8 Hz), 2.31(s, 1H), 1.91–0.85 (m, 11H). ^{13}C NMR: δ 142.0, 132.9, 128.2, 127.9, 78.5, 44.9, 29.1, 28.6, 26.3, 25.9.

4.4.4. Cyclohexyl(2-chlorophenyl)methanol (3d). White solid; mp 85–86°C. ^1H NMR: δ 7.48–7.13 (m, 4H), 4.90 (d, 0.5H, J=3.7 Hz), 4.87 (d, 0.5H, J=3.7 Hz), 2.10 (d, 1H, J=3.7 Hz), 1.87–1.08 (m, 11H). ^{13}C NMR δ 141.1, 132.4, 129.3, 128.2, 128.1, 126.7, 74.9, 43.9, 29.4, 27.8, 26.3, 26.2, 26.0. Anal. Calcd for $C_{13}H_{17}OCl$: C, 69.48; H, 7.62. Found: C, 69.27; H, 7.67.

4.4.5. Cyclohexyl(4-bromophenyl)methanol (3e). White solid; mp 70–71°C (lit.[45] 71.5–72.5°C). ^1H NMR: δ 7.26 (d, 2H, J=6.9 Hz), 7.16 (d, 2H, J=7.0 Hz), 4.34 (d, 1H, J=6.9 Hz), 1.90 (s, 1H), 1.73–0.93 (m, 11H). ^{13}C NMR: δ 142.6, 131.2, 128.3, 121.1, 78.6, 45.0, 29.2, 28.6, 26.4, 26.2, 26.0.

4.4.6. Cyclohexyl(*o*-tolyl)methanol (3f). Colorless oil.[46] ^1H NMR: δ 7.38–7.08 (m, 4H), 4.60 (d, 1H, J=7.1 Hz), 2.29 (s, 3H), 1.99–1.03 (m, 12H). ^{13}C NMR: δ 142.0, 135.0, 130.2, 127.0, 126.2, 126.00, 75.0, 44.5, 29.5, 28.5, 26.3, 26.0, 19.4.

4.4.7. Cyclohexyl(*p*-tolyl)methanol (3g). White solid; mp 41–42°C (lit.[47] 41–42°C). ^1H NMR: δ 7.16 (d, 2H, J=8.3 Hz), 7.11 (d, 2H, J=8.3 Hz), 4.27 (d, 1H, J=7.0 Hz), 2.32 (s, 3H), 1.99 (s, 1H), 1.95–0.90 (m, 11H). ^{13}C NMR: δ 140.7, 136.9, 128.8, 126.5, 79.1, 44.8, 29.2, 28.9, 26.4, 26.00, 21.0.

4.4.8. Cyclohexyl(4-methoxyphenyl)methanol (3h). White solid; mp 81–82°C (lit.[48] 82–83°C). ^1H NMR: δ 7.21 (d, 2H, J=8.4 Hz), 6.86 (d, 2H, J=8.8 Hz), 4.29 (d,

1H, J=7.6 Hz), 3.80 (s, 1H), 2.02–1.03 (m, 12H). ^{13}C NMR: δ 158.9, 135.8, 127.7, 113.5, 79.0, 55.2, 44.9, 29.2, 29.1, 26.4, 26.1, 26.0.

4.4.9. Cyclohexyl(4-cyanophenyl)methanol (3i). White solid; mp 82–83°C. ^{1}H NMR: δ 7.61 (d, 2H, J=8.3 Hz), 7.41 (d, 2H, J=8.3 Hz), 4.48 (d, 0.5H, J=2.5 Hz), 4.45 (d, 0.5H, J=2.5 Hz), 2.17 (d, 1H, J=3.0 Hz), 1.85–0.94 (m, 11H). ^{13}C NMR: δ 148.9, 131.9, 127.3, 118.9, 110.9, 78.3, 45.0, 29.2, 28.1, 26.2, 26.0, 25.9. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.86; H, 7.97; N, 6.54.

4.4.10. Cyclohexyl(naphthyl)methanol (3j). Colorless oil.[49] ^{1}H NMR: δ 8.10–7.37 (m, 7H), 5.10 (d, 1H, J=6.2 Hz), 2.14 (s, 1H), 1.89–0.85 (m, 11H). ^{13}C NMR: δ 139.5, 133.8, 130.8, 128.8, 127.7, 125.7, 125.3, 125.2, 124.1, 123.6, 75.9, 44.3, 30.2, 28.2, 26.4, 26.3, 26.0.

4.4.11. 1,4-Benzenedi(cyclohexylmethanol) (3k). White solid; mp 153–154°C. ^{1}H NMR: δ 7.25(s, 4H), 4.35 (d, 2H, J=7.2 Hz), 2.00–0.88 (m, 24H). ^{13}C NMR: δ 142.8, 126.5, 79.2, 44.9, 29.3, 28.8, 26.4, 26.0. HR-EI-MS: Calcd for $C_{20}H_{26}$ $[M-2H_2O]^+$, 266.2035. Found: m/z 266.2046.

4.4.12. Cyclopentyl-phenylmethanol (3l). Colorless liquid;[50] ^{1}H NMR δ 7.34–7.25 (m, 5H), 4.38 (d, 1H, J=8.4 Hz), 2.56–1.15 (m, 10H); ^{13}C NMR δ 144.4, 128.3, 127.5, 126.4, 79.1, 47.6, 29.4, 25.5, 25.4.

4.4.13. Cyclopentyl-(4-fluorophenyl)methanol (3m). Colorless liquid; ^{1}H NMR δ 7.31–7.25 (m 2H), 7.03–6.96 (m, 2H), 4.35 (d, 1H, J=8.4 Hz), 2.20–1.02 (m, 10H); ^{13}C NMR δ 164.0, 160.1, 140.2, 128.1, 127.9, 115.2, 114.8, 78.4, 47.7, 29.4, 25.4, 25.3. HRMS: Calcd for $C_{12}H_{15}OF[M]^+$, 194.11. Found: m/z 194.111. Anal. Calcd for $C_{12}H_{15}OF$: C, 74.20; H, 7.78. Found: C, 74.21, H, 7.89.

4.4.14. Cyclopentyl-(4-chlorophenyl)methanol (3n). Colorless liquid;[50] ^{1}H NMR δ 7.26 (dd, 4H, J=8.7 Hz), 4.34 (d, 1H, J=8.3 Hz), 2.25 (s, 1H), 2.21–1.06 (m, 9H); ^{13}C NMR δ 142.8, 133.0, 128.3, 127.8, 79.2, 47.6, 29.3, 25.4 25.3.

4.4.15. Cyclopentyl-(*p*-tolyl)methanol (3o). Colorless liquid; ^{1}H NMR δ 7.17 (dd, 4H, J=8.1 Hz), 4.34 (d, 1H, J=8.5 Hz), 2.33 (s, 3H), 2.25–1.12 (m, 10H); ^{13}C NMR δ 141.5, 137.1, 128.9, 126.4, 78.9, 47.5, 29.4, 25.5, 25.4, 21.1 HRMS: Calcd for $C_{13}H_{18}O[M]^+$, 190.136. Found: m/z 190.137. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.92; H, 9.65.

4.4.16. 2-Norbornyl-phenylmethanol (3p). Colorless oil;[51] ^{1}H NMR δ 7.35–7.21 (m, 5H), 4.16 (d, 0.5H, J=9.6 Hz), 4.10 (d, 0.5H, J=10.0 Hz), 1.50–0.80 (m, 12H); ^{13}C NMR δ 144.5, 143.1, 128.2, 127.5, 127.4, 127.2, 126.8, 78.8, 49.9, 49.4, 38.7, 38.3, 35.8, 34.9, 34.2, 30.1, 29.9, 28.7.

4.4.17. 2-Norbornyl-(4-bromophenyl)methanol (3q). Colorless oil; ^{1}H NMR δ 7.47–7.42 (m, 2H), 7.20–7.16 (m, 2H), 4.18 (d, 0.6H, J=9.4 Hz), 4.10 (d, 0.4H, J=99 Hz), 2.48–0.84 (m, 12H); ^{13}C NMR δ 143.44, 142.1, 131.4, 128.9, 128.4, 121.4, 121.3, 78.2, 77.3, 50.2, 49.5, 38.8, 38.3, 36.9, 35.9, 35.4, 34.3, 30.1, 29.9, 28.6. HRMS: Calcd for $C_{14}H_{17}OBr[M]^+$, 280.046. Found: m/z 280.045. Anal. Calcd for $C_{14}H_{17}OBr$: C, 59.80; H, 6.09. Found: C, 59.99; H, 6.15.

4.4.18. 2-Norbornyl-(*p*-tolyl)methanol (3r). Colorless oil; ^{1}H NMR δ 7.244–7.10 (m, 4H), 4.16 (d, 0.4H, J=9.8 Hz), 4.10 (d, 0.6H, J=10.1 Hz), 2.33 (s, 3H), 2.51–0.85 (m, 12H); ^{13}C NMR δ 141.6, 140.1, 137.3, 137.1, 128.9, 127.2, 126.6, 78.7, 77.8, 50.0, 49.3, 38.8, 38.4, 37.0, 36.5, 35.4, 34.4, 30.0, 28.7, 21.1. HRMS: Calcd for $C_{15}H_{20}O[M]^+$, 216.151. Found: m/z 216.150. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.00; H, 9.43.

4.4.19. 2-Methyl-1-phenylbutan-1-ol (3s). Colorless oil.[52] ^{1}H NMR: δ 7.35–7.24 (m, 5H), 4.49 (d, 0.45 H, J=6.0 Hz), 4.40 (d, 0.55 H, J=7.3 Hz), 1.99 (s, 1H), 1.78–0.84 (m, 6H), 0.73(d, 3H, J=6.9 Hz). ^{13}C NMR: δ 143.9, 143.6, 128.1, 127.8, 127.3, 127.2, 126.7, 126.4, 78.7, 78.0, 41.9, 41.6, 25.8, 24.8, 15.0, 14.0, 11.6, 11.3.

4.4.20. 2-Methyl-1-(4-fluorophenyl)butan-1-ol (3t). Colorless oil. ^{1}H NMR: δ 7.22–6.90 (m, 4H), 4.42, (d, 0.40H, J=5.9 Hz), 4.34 (d, 0.60 H, J=6.9 Hz), 2.07 (s, 1H), 1.64–0.67 (m, 6H), 0.65 (d, 3H, J=6.8 Hz). ^{13}C NMR: δ 164.0, 163.9, 160.1, 160.0, 139.5, 139.3, 139.2, 128.3, 128.1, 127.9, 127.8, 115.0, 114.7, 78.0, 77.5, 42.0, 41.7, 25.7, 24.8, 14.9, 13.9, 11.6, 11.2. HR-EI-MS: Calcd for $C_{11}H_{13}F$ $[M-H_2O]^+$, 164.1001. Found: m/z 164.0996.

4.4.21. 2-Methyl-1-(4-chlorophenyl)butan-1-ol (3u). Colorless oil.[53] ^{1}H NMR: δ 7.29 (d, 2H, J=8.6 Hz), 7.21 (d, 2H, J=8.4 Hz), 4.49 (d, 0.45 H, J=5.09 Hz), 4.39 (d, 0.55 H, J=6.7 Hz), 2.07 (s, 1H), 1.74–0.85 (m, 6H), 0.72 (d, 3H, J=6.8 Hz). ^{13}C NMR: δ 142.3, 141.9, 132.9, 132.7, 128.2, 128.0, 127.7, 78.0, 77.2, 41.9, 41.6, 25.7, 24.7, 14.9, 13.8, 11.6, 11.3.

4.4.22. 2-Methyl-1-(4-bromophenyl)butan-1-ol (3v). Colorless oil. ^{1}H NMR: δ 7.42 (d, 2H, J=8.3 Hz), 7.12 (d, 2H, J=8.1 Hz), 4.43 (d, 0.45 H, J=5.2 Hz), 4.34 (d,0.55 H, 6.1 Hz), 2.39 (d, 1H, J=2.5 Hz), 1.68–0.84 (m, 6H), 0.70 (d, 3H, J=6.7 Hz). ^{13}C NMR: δ 142.78, 142.7, 131.1, 128.3, 128.0, 121.0, 120.8, 77.9, 77.1, 41.8, 41.5, 25.7, 24.7, 14.8, 13.7, 11.6, 11.22. Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22. Found: C, 54.28; H, 6.24.

4.4.23. 2-Methyl-1-(*p*-tolyl)butan-1-ol (3w). Colorless oil.[54] ^{1}H NMR: δ 7.20 (d, 2H, J=9.2 Hz), 7.11 (d, 2H, J=8.2 Hz), 4.42 (d, 0.40 H, J=6.1 Hz), 2.32 (s, 3H), 2.03 (s, 1H), 1.74–0.83 (m, 6H), 0.71 (d, 3H, J=6.7 Hz). ^{13}C NMR: δ 140.9, 140.6, 136.9, 136.7, 128.7, 126.6, 126.3, 78.5, 78.0, 41.8, 41.5, 25.7, 24.9, 21.0, 15.9, 14.1, 11.6, 11.2.

4.4.24. 2-Methyl-1-(*o*-tolyl)butan-1-ol (3x). Colorless oil.[52] ^{1}H NMR: δ 7.44–7.10 (m, 4H), 4.79 (d, 0.55 h, J=5.5 Hz), 4.67 (d, 0.45 H, J=7.2 Hz), 2.33 (s, 1.5H), 2.31 (s, 1.5 H), 1.80–0.87 (m, 7H), 0.77 (d, 3H, J=6.8 Hz). ^{13}C NMR: δ 142.2, 135.1, 134.6, 130.2, 127.0, 126.9, 126.2, 126.1, 125.9, 74.8, 73.7, 41.1, 40.6, 26.4, 24.4, 19.4, 19.2, 15.4, 13.6, 11.9, 11.2.

4.4.25. 1-Phenylheptan-1-ol (3y). Colorless oil.[55] ^{1}H NMR: δ 7.34–7.21 (m, 5H), 4.57 (t, 1H, J=5.7 Hz), 2.40 (s, 1H), 1.77–0.84 (m, 13H). ^{13}C NMR: δ 144.9, 128.3, 127.3, 125.9, 74.5, 39.0, 31.7, 29.1, 25.7, 22.5, 14.0.

4.4.26. 1-(4-Fluorophenyl)heptan-1-ol (3z). Colorless oil. ^{1}H NMR: δ 7.30–6.96 (m, 4H), 4.58 (t, 1H, J=6.4 Hz), 2.38 (s, 1H), 1.72–0.84 (m, 13H). ^{13}C NMR: δ 164.00, 160.1, 140.6, 140.6, 127.5, 127.4, 115.2, 114.9, 73.9, 39.1, 31.7, 29.1, 25.7, 22.5, 14.0. Anal. Calcd for $C_{13}H_{19}OF$: C, 74.25; H, 9.11. Found: C, 74.31; H. 9.21.

4.4.27. 1-(4-Chlorophenyl)heptan-1-ol (3aa). Colorless oil.[56] ^{1}H NMR: δ 7.31 (d, 2H, J=8.0 Hz), 7.24 (d, 2H, J=8.4 Hz), 4.60 (t, 1H, J=6.4 Hz), 2.20 (s, 1H), 1.72–0.84 (m, 13H). ^{13}C NMR: δ 143.4, 133.0, 128.5, 127.2, 73.9, 39.1, 31.7, 29.1, 25.6, 22.5, 14.0.

4.4.28. 1-(2-Chlorophenyl)heptan-1-ol (3ab). Colorless oil. ^{1}H NMR: δ 7.53–7.13 (m, 4H), 5.08 (t, 1H, J=4.9 Hz), 2.41 (s, 1H), 1.73–0.84 (m, 13H). ^{13}C NMR: δ 142.4, 131.8, 129.3, 128.2, 127.0, 70.6, 37.6, 31.8, 29.1, 25.7, 22.6, 14.1. Anal. Calcd for $C_{13}H_{19}OCl$: C, 68.86; H, 8.44. Found: C, 68.61; H, 8.45.

4.4.29. 1-(4-Bromophenyl)heptan-1-ol (3ac). Colorless oil.[57] ^{1}H NMR: δ 7.43 (d, 2H, J=8.4 Hz), 7.16 (d, 2H, J=8.4 Hz), 4.56 (t, 1H, J=6.5 Hz), 2.35 (s, 1H), 1.70–0.84 (m, 13H). ^{13}C NMR: δ 143.8, 131.4, 127.6, 121.0, 73.9, 39.0, 31.7, 29.1, 25.6, 22.5, 14.0.

4.4.30. 1-(*p*-Tolyl)heptan-1-ol (3ad). Colorless oil.[58] ^{1}H NMR: δ 7.22 (d, 2H, J=8.0 Hz), 7.14 (d, 2H, J=8.0 Hz), 4.60 (t, 1H, J=6.5 Hz), 2.34 (s, 3H), 1.88 (s, 1H), 1.82–0.84 (m, 13H). ^{13}C NMR: δ 142.0, 137.1, 129.0, 125.8, 74.5, 39.0, 31.7, 29.2, 25.8, 22.6, 21.1, 14.0.

4.4.31. 1-(*o*-Tolyl)heptan-1-ol (3ae). Colorless oil.[59] ^{1}H NMR: δ 7.47–7.10 (m, 4H), 4.91 (t, 1H, J=5.6 Hz), 2.33 (s, 3H), 1.81 (s, 1H), 1.75–0.84 (m, 13H). ^{13}C NMR: δ 143.1, 134.4, 130.1, 127.0, 126.2, 125.1, 70.7, 38.1, 31.8, 29.2, 26.0, 22.6, 19.0, 14.0.

4.5. Reaction of dicyclohexylboron chloride with 4-bromobenzaldehyde in the presence of bases

Cyclohexyl-(4-bromophenyl)methanol (**3e**) was prepared by the procedure described earlier using triethylamine, 2,6-lutidine, quinuclidine, DBU, *n*-butyllithium and *t*-butoxide lithium as bases, and the yield of the desired product is summarized in Table 2.

Acknowledgements

We wish to thank the US Department of Energy and the Robert H. Cole Foundation for support of this research.

References

1. Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*, Prentice-Hall: New York, 1954.
2. Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18.
3. Larock, R. C. *Comprehensive Organic Transformations*, VCH: New York, 1989 (pp 553–567).
4. Sweeny, J. B. In *Comprehensive Organic Functional Group Transformations*, Katrizky, A. R., Meth-Cohn, O., Rees, C. W., Ley, S. V., Eds.; Pergamon: Cambridge, 1995; Vol. 2, pp 37.
5. Wakefield, B. J. *Organolithium Method*, Academic: New York, 1988.
6. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.
7. Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* **1974**, *12*, 103.
8. Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1.
9. Kauffmann, T.; Hamsen, A.; Beirich, C. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 144.
10. Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem. Int.* **1982**, *21*, 135.
11. Kauffmann, T.; Abel, T.; Schreer, M.; Wingbermuhle, D. *Tetrahedron* **1987**, *43*, 2021.
12. Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723.
13. Kauffmann, T.; Hopp, G.; Laarmann, B. *Tetrahedron Lett.* **1990**, *31*, 511.
14. Fukuzawa, S.; Tsuchimoto, T.; Tanai, T. *Chem. Lett.* **1994**, 1981.
15. Kataoka, Y.; Makihira, I.; Utsunomiya, M.; Tani, K. *J. Org. Chem.* **1997**, *62*, 8540.
16. Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806.
17. Brown, H. C.; Randad, R. A.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.
18. Jacob, P.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 579.
19. Batey, R. A.; Mackay, D. B.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075.
20. Mikhailov, B. M.; Baryshnikova, T. K.; Shashkov, A. S. *J. Organomet. Chem.* **1981**, *219*, 301.
21. Kabalka, G. W. *Intra-Sci. Chem. Rep.* **1973**, *7*, 57.
22. Miyaura, N.; Itoh, M.; Suzuki, A.; Brown, H. C.; Midland, M. M.; Jacob, I. I. I. P. *J. Am. Chem. Soc.* **1972**, *94*, 6549.
23. Kabalka, G. W.; Maddox, J. T.; Bogas, E.; Kelly, S. W. *J. Org. Chem.* **1997**, *62*, 3688.
24. Okada, K.; Hosoda, Y.; Oda, M. *Tetrahedron Lett.* **1986**, *27*, 6213.
25. Brown, H. C.; Kramer, G. W.; Ley, A. B.; Midland, M. M. *Organic Syntheses via Boranes*, Wiley-Interscience: New York, 1975 (p 11).
26. Eleveld, M. B.; Hogevven, H. *Tetrahedron Lett.* **1984**, *25*, 5187.
27. Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455.
28. Mazalerrat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585.
29. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823.
30. Joshi, N. N.; Srebnik, M.; Brown, H. C. *Tetrahedron Lett.* **1989**, *30*, 5551.
31. Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.
32. Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
33. Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics in Stereochemistry*, Vol. 2; Wiley: New York, 1982 (p 1).
34. Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2 (239pp).
35. Kabalka, G. W.; Wu, Z.; Trotman, S. E.; Gao, X. *Org. Lett.* **2000**, *2*, 255.
36. Kabalka, G. W.; Wu, Z. *Tetrahedron Lett.* **2000**, *41*, 579.

37. Lansinger, J. M.; Ronald, R. C. *Synth. Commun.* **1979**, *9*, 341.
38. Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* **2000**, *41*, 5161.
39. Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16.
40. Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499.
41. Souindarajan, R.; Matteson, D. S. *Organometallics* **1995**, *14*, 4157.
42. Coleman, J. P.; Shah-Malak, F. I.; Utley, J. H. P. *J. Chem. Soc. B* **1970**, 666.
43. Kabalka, G. W.; Li, N.-S.; Yu, S. *Tetrahedron Lett.* **1995**, *36*, 8545.
44. Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *11*, 3278.
45. Huitric, A. C.; Kumler, W. D. *J. Am. Chem. Soc.* **1956**, *78*, 1147.
46. Cervinka, O.; Belovsky, O. *Collect. Czech. Chem. Commun.* **1967**, *32*, 4149.
47. Kristic, V.; Muskatirovic, M. *Liebigs Ann. Chem.* **1980**, *11*, 1637.
48. Szmuszkovicz, J.; Skaletzky, L. L. *J. Org. Chem.* **1967**, *32*, 3300.
49. Barcus, R. L.; Hadel, L. M.; Johnston, L. J.; Platz, M. S.; Savino, T. G.; Scaiano, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 3928.
50. Geigy Chem. Corp. US 34,448,200; 1963; *Chem. Abstr.* **1969**, *71*, 60981.
51. Kasper, F.; Muller, H.-G. *J. Prakt. Chem.* **1966**, *34*, 283.
52. Blanch, A. I.; Fernandez, G. F.; Perez, O. R.; Plumet, J. *An. Quim.* **1978**, *74*, 70.
53. Owen, J. R.; Saunders Jr., W. H. *J. Am. Chem. Soc.* **1966**, *88*, 5809.
54. Kabalka, G. W.; Maddox, J. T.; Bogas, E. *J. Org. Chem.* **1994**, *59*, 5530.
55. Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.
56. Eprova, Ltd., GB 1,014,668; **1965**; *Chem Abstr. 62*, 14635f.
57. Franks, S.; Hartley, F. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2233.
58. Buu-Hoi, N. P.; Xuong, N. D.; Diep, B. K. *J. Org. Chem.* **1961**, *26*, 1673.
59. Nicolaus, R. *Ann. Chim (Rome)* **1953**, *43*, 488.