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A new method for alkylation of aromatic aldehydes using alkylboron chloride derivatives in the presence of oxygen

George W. Kabalka,* Zhongzhi Wu and Yuhong Ju

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

This paper is dedicated to Professor Herbert C. Brown, a pioneer in organoboron chemistry, on the occasion of his 90th birthday

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Abstract—Reactions of aromatic aldehydes with alkylboron chloride derivatives in the presence of oxygen have been investigated. Dialkylboron chlorides react with aryl aldehydes to produce arylalkylmethanols in good to excellent yields. Under the same reaction conditions, alkylboron dichlorides lead to the formation of arylalkyl chlorides.

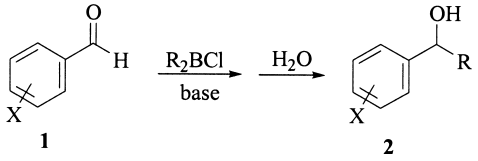
1. Introduction

The alkylation of carbonyl compounds by an organometallic reagent is an important method for assembling a variety of useful carbon skeletons. Generally, only reactive alkylmetals such as organomagnesium,[1] organolithium,[2] organozinc[3] and certain organotransition metal reagents[4–9] can be utilized to achieve this transformation. Allylborane, vinylborane and alkynylborane reagents have been used to successfully alkylate carbonyl compounds but saturated organoboranes are typically unreactive.[10–15] The earliest attempt to achieving a Grignard-like reaction using trialkylboranes resulted in the reduction of the aldehyde via a β-hydrogen elimination.[16] Although a general 1,2-addition of a trialkylborane to a carbonyl compounds has not been achieved, certain modifications in either the carbonyl compound or the trialkylborane have led to a few successful alkylation reactions.[17,18] Nevertheless, a Grignard-like reaction involving organoborane reagents would possess a number of advantages including mild reaction conditions, potential stereochemical control, and the fact that a large number of functional substituents are unaffected by most organoborane transformations.[19]

Alkylboron halide derivatives have been used extensively for the reduction of carbonyl compounds as well as for generating enolate reagents for aldol reactions.[20,21] This methodology has become one of the most important routes for diastereoselective, and enantioselective carbon–carbon bond formation.[22] We recently reported the successful alkylation of aryl aldehydes using dialkylboron chlorides in the presence of base (Scheme 1).[23] It was found that reagents containing secondary alkyl groups produce good yields of alkylation products whereas those containing primary alkyl groups produce low yields of desired products. Reduction predominates when hindered alkylboranes are utilized. Monoalkylboron chlorides failed to react with aldehydes under the same reaction conditions.

Organoboranes are known to undergo autoxidation in the presence of oxygen and the reaction has been used to prepare alcohols and alkyl hydroperoxides as well as to initiate free radical reactions.[24,25] Trialkylboranes readily react with α,β-unsaturated carbonyl compounds through a free radical 1,4-addition reaction in the presence of air[26] but they do not normally undergo 1,2-addition to saturated carbonyl compounds. Only formaldehyde was reported to react with trialkylboranes in the presence of air to produce alkylation products.[27] That reaction is believed to proceed via a free radical mechanism, since no alkylation occurs in the absence of oxygen.

We have examined the reaction of aryl aldehydes with a variety of alkylboron chlorides in the presence of oxygen and found that reactions involving dialkylboron chlorides occur more readily than the corresponding alkylation carried out in the absence of oxygen but in the presence of base. Alkylboron dichlorides also produce the alkylation products, arylalkyl chlorides, in the presence of oxygen. We



Scheme 1.

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

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

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Table 1. Synthesis of arylalkylmethanols via reactions of aryldehydes with R_2BCl in the presence of oxygen

Entry	X	R	Product	Yield (%)[a,b]
1	H (1a)	Cyclohexyl	(2a)	90
2	4-F (1b)	Cyclohexyl	(2b)	95
3	4-Cl (1c)	Cyclohexyl	(2c)	98
4	2-Cl (1d)	Cyclohexyl	(2d)	63
5	4-Br (1e)	Cyclohexyl	(2e)	95
6	4-Me (1f)	Cyclohexyl	(2f)	96
7	2-Me (1g)	Cyclohexyl	(2g)	88
8	4-OMe (1h)	Cyclohexyl	(2h)	98
9	Naphthyl (1i)	Cyclohexyl	(2i)	94
10	1,4-$(CHO)_2$ (1j)	Cyclohexyl	(2j)	84
11	4-CN (1k)	Cyclohexyl	(2k)	92[c]
12	H (1l)	Cyclopentyl	(2l)	92
13	4-F (1m)	Cyclopentyl	(2m)	99
14	4-Br (1n)	Cyclopentyl	(2n)	92
15	4-Me (1o)	Cyclopentyl	(2o)	91
16	H (1p)	Norbornyl	(2p)	76
17	4-Br (1q)	Norbornyl	(2q)	73
18	4-Me (1r)	Norbornyl	(2r)	75
19	H (1s)	*sec*-butyl	(2s)	65
20	4-F (1t)	*sec*-Butyl	(2t)	74
21	4-Cl (1u)	*sec*-Butyl	(2u)	67
22	4-Br (1v)	*sec*-Butyl	(2v)	70
23	4-Me (1w)	*sec*-Butyl	(2w)	71
24	2-Me (1x)	*sec*-Butyl	(2x)	55
25	H (1y)	*n*-Hexyl	(2y)	84[d]
26	4-Cl (1z)	*n*-Hexyl	(2z)	75[d]
27	4-Br (1aa)	*n*-Hexyl	(2aa)	64[d]
28	4-Me (1ab)	*n*-Hexyl	(2ab)	72[d]
29	2-Me (1ac)	*n*-Hexyl	(2ac)	81[d]

[a] Isolated yields based on starting aldehydes.
[b] Physical and spectroscopic data are consistent with literature values.[23]
[c] Two equivalents of borane were used.
[d] Significant quantities of the product containing the secondary alkyl group are formed.

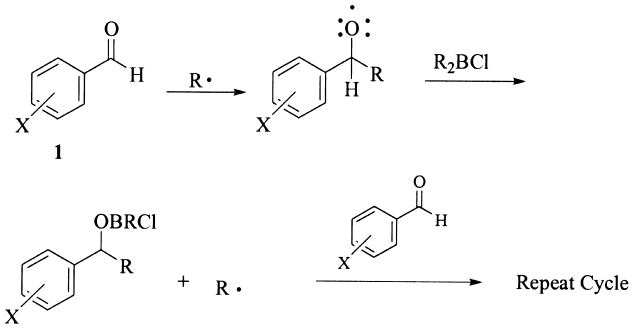
wish to report the results of our study of the alkylation reactions of aryl aldehydes using alkylboron chlorides.

2. Results and discussion

2.1. The reaction of dialkylboron chlorides with aryl aldehydes in the presence of oxygen

We first examined the reaction of dicyclohexylboron chloride with benzaldehyde in hexane at room temperature in the presence of oxygen. Surprisingly, the reaction occurs rapidly at room temperature and produces the desired alkylation product, cyclohexylphenylmethanol, in excellent yield. The reaction appears to be general for all aryl aldehydes studied (Table 1). The reaction proceeds most efficiently at 0°C but partial reduction occurs when the reaction is carried out at room temperature. In contrast to alkylation reactions carried out in the absence of oxygen,[23] organoboranes containing primary and hindered alkyl groups produce good yields of alkylation products.

In an effort to probe the mechanism of the reaction, dicyclohexylboron chloride (1 M in hexane) was added to 4-bromobenzaldehyde in hexane at −30°C. The solvent was removed in vacuo to yield a yellow solid which was then re-dissolved in benzene-d_6 for NMR analysis. Interestingly, the characteristic ^1H and ^{13}C resonances of the aldehyde group were absent in the NMR spectra, and no new resonances were observed. Furthermore, upon addition of water, 4-bromobenzaldehyde was regenerated. This suggests that 4-bromobenzaldehyde reversibly coordinates to dicyclohexylboron chloride. In a separate experiment, after oxygen was introduced to a benzene solution of the yellow solid, a new doublet appeared at 5.11 ppm in the ^1H NMR and a corresponding resonance appeared at 83.4 ppm in the ^{13}C NMR. Hydrolysis of the reaction mixture led to the formation of the desired alkylation product, (4-bromophenyl)cyclohexylmethanol.



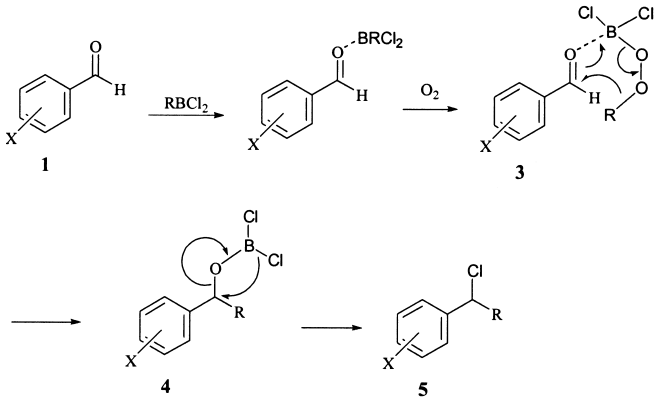
Scheme 2.

The alkylation reaction is rapid but no alkylation occurs in the presence of radical scavenger such as galvinoxyl. In addition, when both primary and secondary alkyl groups are present, as is generally the case when alkyl boron halides are formed via hydroboration, the secondary group reacts preferentially. These observations support the postulation that the reaction is occurring via a radical pathway, such as the one outlined in Scheme 2. A similar pathway was reported for the reaction of trimethylboron with formaldehyde.[27] It is also possible that the reaction involves complexation of the alkylboron halide with carbonyl group prior to radical attack.[26g]

2.2. The reaction of alkylboron dichlorides with aryl aldehydes in the presence of oxygen

Since only one alkyl group in dialkylboron chloride is transferred to the carbonyl carbon, the reaction would be more efficient if monoalkylboron dichlorides could be utilized. Thus, we examined the reaction of alkylboron dichlorides with aryl aldehydes in the presence of oxygen. Interestingly, instead of alkylarylmethanols, the reaction produces the chloroalkylation products exclusively at room temperature. We also noted that a small quantity of benzyl chloride formed along with the desired alkylation products, an observation we made earlier.[23,28] α,α-Dichlorotoluenes are also formed in small quantities if reactions are carried out at the higher temperature.[29]

In contrast to the reaction of di(*n*-hexyl)boron chloride with aromatic aldehydes, isomeric products arising from migration of a secondary alkyl group are not observed in the reaction of *n*-butylboron dichloride with aryl aldehydes. This suggests that the reaction of monoalkylboron dichlorides may proceed via a different pathway, NMR spectroscopy was used to monitor a representative reaction. Benzaldehyde was mixed with one equivalent of *n*-butylboron dichloride in benzene-d_6 and the ^1H and ^{13}C



Scheme 3.

resonances of carbonyl group were no longer observable. In addition, no new resonances related to carbonyl group were observed. [Only reductive chlorination occurred, leading to the formation of benzyl chloride if reaction times were prolonged.] In a separate experiment, oxygen was introduced to the reaction mixture and the NMR spectra revealed that the chloroalkylation product, 1-phenylpentyl chloride, gradually formed. In addition, the addition of a radical scavenger, galvinoxyl did not inhibit the alkylation reaction. It is likely that this reaction proceeds via oxidation of the organoborane to form a peroxide intermediate which then undergoes alkyl transfer through an intramolecular six-membered ring transition state **3** to give the borinate ester **4**. The product would then form after migration of the chlorine (Scheme 3). In a separate experiment, the reaction was carried out at −20°C, and no alkylation occurred, but *n*-butyl peroxide was isolated upon hydrolysis of the reaction mixture. This experiment supports the presence of peroxide intermediate in the reaction. In order to confirm the presence of intermediate **4**, 1-phenylpentyloxyboron dichloride was prepared by the reaction of lithium 1-phenylpentyloxide with BCl_3 which gradually led to the formation of benzyl chloride **5** at room temperature.

Table 2. Synthesis of arylalkyl chlorides via reaction of aryl aldehydes with $RBCl_2$

Entry	X	R	Time (h)	Product	Yield (%)[a]
1	H (1a)	*n*-Butyl	2	(5a)	62
2	4-F (1b)	*n*-Butyl	1	(5b)	85
3	4-Cl (1c)	*n*-Butyl	1	(5c)	75
4	2-Cl (1d)	*n*-Butyl	3	(5d)	50
5	3-Cl (1e)	*n*-Butyl	2	(5e)	51
6	4-Br (1f)	*n*-Butyl	1	(5f)	63
7	3-Br (1g)	*n*-Butyl	2	(5g)	45
8	4-Me (1h)	*n*-Butyl	2	(5h)	55
9	1,4-$(CHO)_2$ (1i)	*n*-Butyl	2	(5i)	73
10	H (1j)	Cyclohexyl	2	(5j)	81
11	4-Cl (1k)	Cyclohexyl	1	(5k)	79
12	2-Cl (1l)	Cyclohexyl	3	(5l)	20
13	4-Br (1m)	Cyclohexyl	1	(5m)	86
14	3-Br (1n)	Cyclohexyl	2	(5n)	16
15	4-F (1o)	Cyclohexyl	1	(5o)	92
16	1,4-$(CHO)_2$ (1p)	Cyclohexyl	1	(5p)	67
17	H (1q)	*sec*-Butyl	2	(5q)	65
18	4-Cl (1r)	*sec*-Butyl	1	(5r)	67
19	4-F (1s)	*sec*-Butyl	1	(5s)	74
20	2-Me (1t)	*sec*-Butyl	2	(5t)	25

[a] Isolated yields based on starting aldehydes.

A series of aryl aldehydes were subjected to the reaction sequence. Essentially all aldehydes were successfully converted to the corresponding chlorides (Table 2).

3. Conclusion

A new alkylation reaction has been developed which 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. Dialkylboron chlorides react with aryl aldehydes to produce the corresponding alkylarylmethanols in excellent yields whereas alkylboron dichlorides afford the corresponding chlorides in good yields.

4. Experimental

4.1. General

All glassware was dried in an oven at 120°C and flushed with dry argon prior to use. Hexane was distilled from CaH_2. *n*-Butylboron dichloride (1 M in hexane) and dicyclohexylboron chloride were purchased from Aldrich Chemical Company. Cyclohexylboron dichloride and *sec*-butylboron dichloride were prepared by hydroboration of the corresponding alkenes with $HBCl_2(SMe_2)$ followed by addition of BCl_3.[30] Dicyclopentylboron chloride, di(*exo*-norbornyl)-boron chloride, di(*n*-hexyl)boron chloride and di(*sec*-butyl)-boron chloride were prepared according to literature procedures.[31] All aldehydes were dried and distilled prior to use. Products were purified by flash chromatography using silica gel (60 Å 230–400 mesh) with hexane as eluent for arylalkyl chlorides and methylene chloride for arylalkyl methanols. Melting points are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. ^{1}H NMR spectra were recorded in $CDCl_3$ at 250 MHz. ^{13}C NMR spectra were recorded at 62.9 MHz in $CDCl_3$. Chemical shifts are listed relative to $SiMe_4$ for ^{1}H NMR and to $CDCl_3$ for ^{13}C NMR. In cases where more than one diastereoisomer formed, the NMR shifts of all isomers are reported. High-resolution mass spectra were obtained using ZAB-EQ instrument.

4.2. General procedure for synthesis of arylalkylmethanols

4-Chlorobenzaldehyde (3.0 mmol, 0.42 g) was dissolved in hexane (10 ml) contained in a dry, argon-flushed, septum sealed, 50 ml round-bottomed flask and the mixture cooled to 0°C in an ice bath. Dicyclohexylboron chloride (3.0 mmol, 3.0 ml of a 1.0 M hexane solution) was added via a syringe to yield a yellow solution. Oxygen gas was introduced over the reaction solution by means of an oxygen filled balloon attached to a 18 gauge needle. The reaction solution gradually turned colorless. After being stirred at room temperature for 1 h, the reaction solution was hydrolized. The organic layer was separated, dried over anhydrous $MgSO_4$, the solvent removed and the product isolated by column chromatography to yield 0.66 g (98% yield) of the desired product, (4-chlorophenyl)cyclohexylmethanol.

4.3. General procedure for synthesis of arylalkyl chlorides

Benzaldehyde (4.2 mmol, 0.44 g) was dissolved in hexane (10 ml) contained in a dry, argon-flushed, septum sealed, 50 ml round-bottomed flask. *n*-Butylboron dichloride (4.2 mmol, 4.2 ml of a 1.0 M hexane solution) was added via a syringe and the solution allowed to stir at room temperature. Oxygen gas was introduced to the reaction solution via a syringe needle attached to a oxygen filled balloon. The reaction solution gradually turned cloudy. After 1 h, the reaction mixture was filtered. The filtrate was then hydrolyzed with water. The organic layer was separated, dried over anhydrous $MgSO_4$, and the product isolated by column chromatography to afford 0.49 g (62%)of the desired product, 1-(1-chloropentyl)benzene.

Compounds 1-(1-chloropentyl)-4-methylbenzene (5h) and 1-(1-chloro-2-methylbutyl)-4-methylbenzene (5t) decompose on silica-gel column. Therefore, they were purified by vacuum distillation.

4.3.1. (1-Chloropentyl)benzene (5a). Colorless liquid.[32] ^{1}H NMR: δ 7.38–7.21 (m, 5H), 4.83 (t, 1H, J=7.4 Hz), 2.16–1.97 (m, 2H), 1.51–1.24 (m, 4H), 0.88 (t, 3H, J=6.6 Hz). ^{13}C NMR: δ 142.0, 128.6, 128.1, 126.9, 63.8, 39.7, 29.2, 22.1, 13.9.

4.3.2. 1-(1-Chloropentyl)-4-fluorobenzene (5b). Colorless liquid. ^{1}H NMR: δ 7.36–7.30 (m, 2H), 7.04–6.97 (m, 2H), 4.81 (t, 1H, J=7.45 Hz), 2.14–1.97 (m, 2H), 1.46–1.22 (m, 4H), 0.88 (t, 3H, J=6.6 Hz). ^{13}C NMR: δ 164.3, 160.4, 137.9, 137.9, 128.7, 128.6, 115.6, 115.2, 62.9, 39.8, 29.1, 22.1, 13.8. Anal. Calcd for $C_{11}H_{14}ClF$: C, 65.84; H, 7.03. Found: C, 65.90; H, 6.99.

4.3.3. 1-(1-Chloropentyl)-4-chlorobenzene (5c). Colorless liquid. ^{1}H NMR: δ 7.31 (dd, 4H, J=3.3 Hz), 4.80 (t, 1H, J=7.2 Hz), 2.12–1.97 (m, 2H), 1.44–1.22 (m, 4H), 0.89 (t, 3H, J=6.7 Hz). ^{13}C NMR: δ 140.5, 133.9, 128.7, 128.3, 62.8, 39.7, 29.1, 22.1, 13.9. HRMS: Calcd for $C_{11}H_{14}Cl_2$ $[M]^+$, 216.0473. Found: *m/z*, 216.0479. Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.85; H, 6.50. Found: C, 60.96; H, 6.48.

4.3.4. 1-(1-Chloropentyl)-2-chlorobenzene (5d). Colorless liquid. ^{1}H NMR: δ 7.61–7.16 (m, 4H), 5.41 (t, 1H, J=6.9 Hz), 2.09–1.99 (m, 2H), 1.54–1.30 (m, 4H), 0.90 (t, 3H, J=6.8 Hz). ^{13}C NMR: δ 139.3, 132.5, 129.4, 129.0, 128.4, 127.3, 59.1, 38.9, 28.9, 22.1, 13.9. HRMS: Calcd for $C_{11}H_{14}Cl_2$ $[M]^+$, 216.0473. Found: *m/z*, 216.0466. Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.85; H, 6.50. Found: C, 60.86; H, 6.53.

4.3.5. 1-(1-Chloropentyl)-4-chlorobenzene (5e). Colorless liquid. ^{1}H NMR: δ 7.37 (s, 1H), 7.27–7.26 (m, 3H), 4.78 (t, 1H, J=6.8 Hz), 2.12–1.98 (m, 2H), 1.48–1.26 (m, 4H), 0.89 (t, 3H, J=6.9 Hz). ^{13}C NMR: δ 144.0, 134.4, 129.9, 128.3, 127.2, 125.2, 62.8, 39.7, 29.1, 22.1, 13.9. HRMS: Calcd for $C_{11}H_{14}Cl_2$ $[M]^+$, 216.0473. Found: *m/z*, 216.0462. Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.85; H, 6.50. Found: C, 60.72; H, 6.45.

4.3.6. 1-(1-Chloropentyl)-4-bromobenzene (5f). Colorless liquid. ^{1}H NMR: δ 7.47 (d, 2H, J=8.4 Hz), 7.24 (d, 2H, J=8.4 Hz), 4.78 (t, 1H, J=7.5 Hz), 2.10–1.96 (m, 2H), 1.52–1.21 (m, 4H), 0.88 (t, 3H, J=6.7 Hz). ^{13}C NMR: δ 141.0, 131.7, 128.6, 122.0, 62.9, 39.6, 29.1, 22.1, 13.8. HRMS: Calcd for $C_{11}H_{14}BrCl$ $[M]^+$, 261.9945. Found: *m/z*, 261.9940.

4.3.7. 1-(1-Chloropentyl)-3-bromobenzene (5g). Colorless liquid. ^{1}H NMR: δ 7.53 (s, 1H), 7.44–7.17 (m, 3H), 4.77 (t, 1H, J=7.1 Hz), 2.16–1.94 (m, 2H), 1.54–1.24 (m, 4H), 0.89 (t, 3H, J=6.6 Hz). ^{13}C NMR: δ 144.2, 131.2, 130.1, 130.0, 125.6, 122.5, 62.7, 39.6, 29.1, 22.1, 13.8. HRMS: Calcd for $C_{11}H_{14}BrCl$ $[M]^+$, 261.9945. Found: *m/z*, 261.9952.

4.3.8. 1-(1-Chloropentyl)-4-methylbenzene (5h). Colorless liquid. ^{1}H NMR: δ 7.26 (d, 2H, J=8.1 Hz), 7.14 (d, 2H, J=8.0 Hz), 4.82 (t, 1H, J=7.1 Hz), 2.33 (s, 3H), 2.14–1.99 (m, 2H), 1.45–1.28 (m, 4H), 0.88 (t, 3H, J=6.8 Hz). ^{13}C NMR: δ 139.1, 138.0, 129.2, 126.8, 63.9, 39.7, 29.3, 22.1, 21.1, 13.9. HRMS: Calcd for $C_{12}H_{17}Cl$ $[M]^+$, 190.102. Found: *m/z*, 190.102.

4.3.9. 1,4-Di-(1-chloropentyl)benzene (5i). Colorless liquid. ^{1}H NMR: δ 7.35 (s, 4H), 4.84 (t, 2H, J=6.7 Hz), 2.33 (s, 3H), 2.14–1.99 (m, 4H), 1.50–1.26 (m, 8H), 0.89 (t, 6H, J=6.7 Hz). ^{13}C NMR: δ 142.0, 127.2, 63.4, 39.9, 29.2, 22.1, 13.9. HRMS: Calcd for $C_{16}H_{24}Cl_2$ $[M]^+$, 286.1255. Found: *m/z*, 286.1257.

4.3.10. 1-(Chloro-cyclohexyl-methyl)benzene (5j). Colorless liquid.[33] ^{1}H NMR: δ 7.33–7.22 (m, 5H), 4.60 (d, 1H, J=8.4 Hz), 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, 26.1, 25.9, 25.9.

4.3.11. 1-Chloro-4-(chloro-cyclohexyl-methyl)benzene (5k). Colorless liquid.[34] ^{1}H NMR: δ 7.30 (d, 2H, J=8.7 Hz), 7.25 (d, 2H, J=8.7 Hz), 4.57 (d, 1H, J=8.3 Hz), 2.18–0.85 (m, 11H). ^{13}C NMR: δ 139.4, 133.6, 128.9, 128.5, 68.8, 45.6, 30.3, 30.1, 26.0, 25.8.

4.3.12. 1-Chloro-2-(chloro-cyclohexyl-methyl)benzene (5l). Colorless liquid. ^{1}H NMR: δ 7.58–7.15 (m, 4H), 5.24 (d, 1H, J=8.1 Hz), 2.16–0.84 (m, 11H). ^{13}C NMR: δ

138.6, 132.7, 129.5, 129.3, 128.8, 127.0, 64.6, 45.0, 30.1, 29.5, 26.1, 26.0, 25.8. HRMS: Calcd for $C_{13}H_{16}Cl_2$ $[M]^+$, 242.0629. Found: *m/z*, 242.0641. Anal. Calcd for $C_{13}H_{16}Cl_2$: C, 64.21; H, 6.63. Found: C, 64.30; H, 6.70.

4.3.13. 1-Bromo-4-(chloro-cyclohexyl-methyl)benzene (5m). Colorless liquid. ^{1}H NMR: δ 7.43 (d, 2H, J=8.4 Hz), 7.17 (d, 2H, J=8.4 Hz), 5.54 (d, 1H, J=8.2 Hz), 2.15–0.83 (m, 11H). ^{13}C NMR: δ 139.8, 131.4, 129.1, 121.7, 68.7, 45.5, 30.2, 30.0, 26.0, 25.8, 25.7. HRMS: Calcd for $C_{13}H_{16}BrCl$ $[M]^+$, 288.0102. Found: *m/z*, 288.0114.

4.3.14. 1-Bromo-3-(chloro-cyclohexyl-methyl)benzene (5n). Colorless liquid. ^{1}H NMR: δ 7.48 (s, 1H), 7.43–7.17 (m, 3H), 4.54 (d, 1H, J=8.2 Hz), 2.17–0.88 (m, 11H). ^{13}C NMR: δ 143.2, 131.0, 130.6, 129.9, 126.2, 122.3, 68.6, 45.6, 30.4, 30.0, 26.0, 25.8. HRMS: Calcd for $C_{13}H_{16}BrCl$ $[M]^+$, 288.0102. Found: *m/z*, 288.0096.

4.3.15. 1-(Chloro-cyclohexyl-methyl)-4-fluorobenzene (5o). Colorless liquid. ^{1}H NMR: δ 7.32–7.24 (m, 2H), 7.06–6.96 (m, 2H), 4.58 (d, 1H, J=8.4 Hz), 2.20–0.84 (m, 11H). ^{13}C NMR: δ 164.2, 160.3, 136.8, 129.3, 129.1, 115.4, 115.0, 68.9, 45.8, 30.2, 26.1, 25.9. Anal. Calcd for $C_{13}H_{16}ClF$: C, 68.87; H, 7.11. Found: C, 68.66; H, 7.14.

4.3.16. 1,4-Di-(chloro-cyclohexyl-methyl)benzene (5p). White solid. Mp 94–86°C. ^{1}H NMR: δ 7.28 (s,4H), 4.60 (d, 2H, J=8.2 Hz), 2.19–0.83 (m, 22H). ^{13}C NMR: δ 140.5, 127.4, 69.3, 45.6, 30.4, 30.1, 26.0, 25.9, 25.9. HRMS: Calcd for $C_{20}H_{28}Cl_2$ $[M]^+$, 338.1568. Found: *m/z*, 338.1561.

4.3.17. (1-Chloro-2-methylbutyl)benzene (5q). Colorless liquid. ^{1}H NMR: δ 7.37–7.23 (m, 5H), 4.81 (d, 0.55H, J=6.7 Hz), 4.70 (d, 0.45H, J=8.0 Hz), 2.06–0.80 (m, 9H). ^{13}C NMR: δ 141.1, 140.8, 128.3, 127.9, 127.7, 127.6, 127.4, 69.3, 69.1, 42.9, 42.6, 26.8, 26.0, 16.1, 15.3, 11.4, 10.8. Anal. Calcd for $C_{11}H_{15}Cl$: C, 72.32; H, 8.28. Found: C, 72.11; H, 8.15.

4.3.18. 1-Chloro-4-(1-chloro-2-methylbutyl)benzene (5r). Colorless liquid. ^{1}H NMR: δ 7.31 (d, 2H, J=8.8 Hz), 7.26 (d, 2H, J=8.7 Hz), 4.78 (d, 0.45H, J=6.6 Hz), 4.66 (d, 0.55H, J=7.9 Hz), 2.01–0.79 (m, 9H). ^{13}C NMR: δ 39.7, 139.4, 133.6, 133.5, 129.0, 128.8, 128.5, 68.3, 68.1, 42.9, 42.6, 26.8, 25.9, 16.0, 15.2, 11.4, 10.8. Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.85; H, 6.50. Found: C, 60.90; H, 6.52.

4.3.19. 1-(1-Chloro-2-methylbutyl)-4-fluorobenzene (5s). Colorless liquid. ^{1}H NMR: δ 7.35–7.28 (m, 2H), 7.05–6.99 (m, 2H), 4.79 (d, 0.40H, J=6.8 Hz), 4.68 (d, 0.60H, J=8.0 Hz), 2.06–0.79 (m, 9H). ^{13}C NMR: δ 164.2, 160.0, 136.7, 129.3, 129.2, 115.4, 115.0, 68.5, 68.2, 43.1, 42.7, 26.8, 26.0, 16.1, 15.3, 11.4, 10.8. Anal. Calcd for $C_{11}H_{14}ClF$: C, 65.84; H, 7.03. Found: C, 65.64; H, 67.11.

4.3.20. 1-(1-Chloro-2-methylbutyl)-4-methylbenzene (5t). Colorless liquid. ^{1}H NMR: δ 7.51–7.10 (m, 4H), 5.07 (d, 0.40H, J=7.0 Hz), 4.93 (d, 0.60H, J=8.9 Hz), 2.36 (s, 3H), 2.12–0.78 (m, 9H). ^{13}C NMR: δ 139.5, 135.0, 130.4, 127.6, 127.6, 126.4, 126.2, 65.4, 65.1, 41.7, 41.5, 27.0, 26.0, 19.4, 19.3, 16.3, 15.5, 11.5, 10.7. HRMS: Calcd for $C_{12}H_{17}Cl$ $[M]^+$, 190.102. Found: *m/z*, 190.101.

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References

1. (a) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall: New York, 1954. (b) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18. (c) Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989 pp 553–567. (d) Sweeny, J. B. *Comprehensive Organic Functional Group Transformations*; Katrizky, A. R., Meth-Cohn, O., Rees, C. W., Ley, S. V., Eds.; Pergamon: Cambridge, 1995; Vol. 2, p. 37.
2. Wakefield, B. J. *Organolithium Method*; Academic Press: New York, 1988.
3. (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* **1974**, *12*, 103.
4. Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1.
5. (a) Kauffmann, T.; Hamsen, A.; Beirich, C. *Angew. Chem. Int.* **1982**, *21*, 144. (b) Kauffmann, T.; Abel, T.; Schreer, M.; Wingbermuhle, D. *Tetrahedron* **1987**, *43*, 2021. (c) Kauffmann, T.; Hopp, G.; Laarmann, B. *Tetrahedron Lett.* **1990**, *31*, 511.
6. Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem. Int.* **1982**, *21*, 135.
7. Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723.
8. Fukuzawa, S.; Tsuchimoto, T.; Tanai, T. *Chem. Lett.* **1994**, 1981.
9. Kataoka, Y.; Makihira, I.; Utsunomiya, M.; Tani, K. *J. Org. Chem.* **1997**, *62*, 8540.
10. (a) Nigishi, E. *Organometallics in Organic Synthesis*, Vol. 1; Wiley-Interscience: New York, 1980 p 304. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
11. Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806.
12. Brown, H. C.; Randad, R. A.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.
13. Jacob, P.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 579.
14. Batey, R. A.; Mackay, D. B.; Santhakumar, V. *J. Am. Chem. Soc.* **1999**, *121*, 5075.
15. Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765.
16. (a) Mikhailov, B. M.; Kiselev, V. G.; Bubnov, Y. N. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1965**, 865. (b) Mikhailov, B. M.; Bubnov, Y. N.; Kiselev, V. G. *J. Gen. Chem. USSR* **1966**, *36*, 65.
17. (a) Kabalka, G. W.; Maddox, J. T.; Bogas, E.; Kelly, S. W. *J. Org. Chem.* **1997**, *62*, 3688. (b) Okada, K.; Hosoda, Y.; Oda, M. *Tetrahedron Lett.* **1986**, 6213.
18. Mikhailov, B. M.; Baryshnikova, T. K.; Shashkov, A. S. *J. Organomet. Chem.* **1981**, *219*, 301.
19. (a) Brown, H. C.; Kramer, G. W.; Ley, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975 p 11. (b) Eleveld, M. B.; Hogevven, H. *Tetrahedron Lett.* **1984**, *25*, 5187. (c) Mukaiyama, T.; Soai,

K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455. (d) Mazalerrat, J. P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585. (e) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823. (f) Joshi, N. N.; Srebnik, M.; Brown, H. C. *Tetrahedron Lett.* **1989**, *30*, 5551.

20. Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Rev.* **1992**, *25*, 16.
21. (a) Beardsley, D. A.; Fisher, G. B.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *Tetrahedron Lett.* **1994**, *35*, 1511. (b) Barret, A. G. M.; Seefeld, M. A. *J. Chem. Soc., Chem. Commun.* **1994**, 1053.
22. (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Topics in Stereochemistry*, Vol. 2; Wiley: New York, 1982 p 1. (c) Kim, B. M.; Williams, S. F.; Masamune, S. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2 p 239.
23. (a) Kabalka, G. W.; Wu, Z.; Trotman, S. E.; Gao, X. *Org. Lett.* **2000**, *2*, 255. (b) Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron* **2001**, *57*, 1663.
24. (a) Brown, H. C.; Midland, M. M.; Kabalka, G. W. *Tetrahedron* **1986**, *42*, 5523. (b) Brown, H. C.; Midland, M. M. *Tetrahedron* **1987**, *43*, 4059.
25. (a) Devin, P.; Fensterbank, L.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 4473. (b) Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465.
26. (a) Suzuki, A.; Matsumoto, H.; Itoh, M.; Brown, H. C.; Rogic, M. M.; Rathke, M. W. *J. Am. Chem. Soc.* **1967**, *89*, 5708. (b) Ollivier, C.; Renaud, P. *Chem. Eur. J.* **1999**, *5*, 1468. (c) Brown, H. C.; Rogic, M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1967**, *89*, 5709. (d) Brown, H. C.; Kabalka, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 714. (e) Kabalka, G. W. *Intra-Sci. Chem. Rep.* **1973**, *7*, 57. (f) Brown, H. C.; Basavaiah, D. *J. Org. Chem.* **1982**, *47*, 754. (g) Beraud, V.; Gnanou, Y.; Walton, J. C.; Maillard, B. *Tetrahedron Lett.* **2000**, *41*, 1195.
27. Miyaura, N.; Itoh, M.; Suzuki, A.; Brown, H. C.; Midland, M. M.; Jacob, I. I. I. P. *J. Am. Chem. Soc.* **1972**, *94*, 6549.
28. Kabalka, G. W.; Wu, Z.; Ju, Y. *Tetrahedron Lett.* **2000**, *41*, 5161.
29. (a) Kabalka, G. W.; Wu, Z. *Tetrahedron Lett.* **2000**, *41*, 579. (b) Lansinger, J. M.; Ronald, R. C. *Synth. Commun.* **1979**, *9*, 341.
30. Brown, H. C.; Ravindran, N.; Kulkarni, U. *J. Org. Chem.* **1980**, *45*, 384.
31. Brown, H. C.; Ravindran, N.; Kulkarni, U. *J. Org. Chem.* **1979**, *44*, 2417.
32. Levene, M. *J. Biol. Chem.* **1926**, *70*, 377.
33. Coleman, J. P.; Shah-Malak, F. I.; Utley, J. H. P. *J. Chem. Soc.* **1970**, 666.
34. Hamlin, K. E.; Weston, A. W.; Fischer, F. E.; Michaels, J. R. J. *J. Am. Chem. Soc.* **1949**, *71*, 2731.