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Organoborane Reagents in the *C*-Alkylation of Aromatic Aldimines

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Dedicated to Prof. Miguel Yus Astiz on the occasion of his 60th birthday

Keywords: Boranes / Imines / Alkylation / Amines / Multicomponent reactions

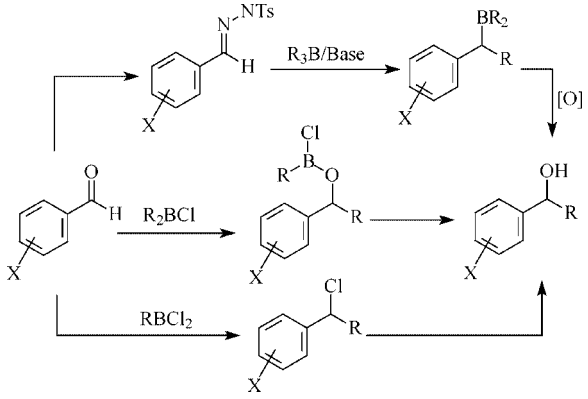
The reaction of an aldimine with dicyclohexylboron chloride in the presence of hydrogen peroxide gives *N*-[cyclohexyl(aryl)methyl]arylamines **2** in good yields via oxidized imine–borane complexes. The amines can also be obtained by a three-component reaction involving an arenecarbaldehyde, an arylamine and a dialkylchloroborane reagent.

Introduction

Organoboranes are among the most versatile intermediates currently available to organic chemists.[1] The electron deficiency caused by the vacant p orbital on the boron atom and the metallic properties of boron derivatives endow these reagents with enhanced flexibility. The Grignard-like reactivity of organoborane compounds toward carbonyl or imine derivatives is still being explored.[2]

1,2-Addition of alkyl groups to the C=N bond constitutes a key method for the preparation of a variety of amines. Most synthetically efficient reactions are based either on the use of organometallic reagents[3] or on radical additions.[4] The addition of organometallic reagents is severely limited by the poor electrophilicity of the azomethine carbon and the tendency of the substrates to undergo azaenolization with acidic α protons. The former problem could be avoided by activating the C=N bond either by *N*-substitution with an electron-withdrawing group or by *N*-coordination to a Lewis acid. The use of less-basic organometallic reagents such as organocopper or organocerium derivatives constitutes an effective approach that prevents enolization in aliphatic aldimines. The imine derivatives can also act as radical acceptors and several synthetically useful intra- and intermolecular carbon–carbon bond-forming reactions have been reported.[4]

The C=N bond typically reacts with organoborane derivatives such as alkenyl, aryl or allyl boronates.[5] However, no direct addition in a Grignard-like fashion of a trialkylborane reagent to imines has to date been observed except for allylboranes.[6] Although borane reagents are typically unreactive toward carbonyl compounds, in recent years Kabalka and coworkers[2] developed a number of novel reactions involving these derivatives as nucleophilic alkyl donors. Generally, an activated carbonyl derivative or halo- or dihaloalkylborane is required to obtain the corresponding alkylated alcohols in good yields. Examples include the Grignard-like alkylation of arenecarbaldehydes or their arylsulfonylhydrazone derivatives with organoboron reagents (Scheme 1).



Scheme 1. Known reactivity of R_3B, R_2BCl and $RBCl_2$ with benzaldehyde derivatives.

To the best of our knowledge, however, these borane derivatives remain unreactive with imines. This encouraged us to investigate the reaction of aldimines with trialkylborane and dicyclohexylchloroborane.

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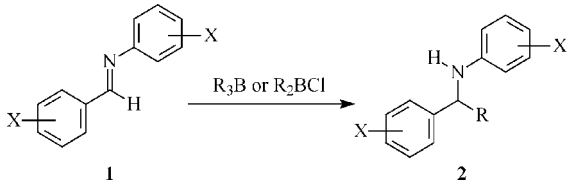
Results and Discussion

We hereby report our initial results for this novel reaction (Scheme 2). We chose *N*-(4-methoxyphenyl)aldimine **1a**, derived from anisaldehyde, as the model compound. We first examined its reactivity toward various trialkylboranes and found that no reaction occurred. Only the imine–borane complexes were detected (by NMR spectroscopy) upon the addition of R_3B (R = Et or *n*Bu, 1.2 equiv.) to the imine solution (dichloromethane, *n*-hexane) in a nonaqueous medium. No change was detected if oxygen or a base was added to the reaction mixture.

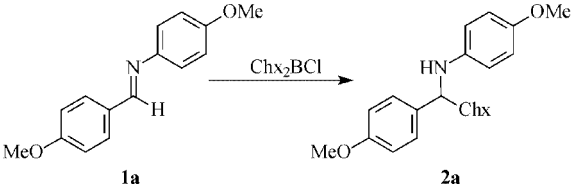


1 2

Scheme 2. General alkylation scheme for aldimines.

Dialkylchloroborane reagents are more electron-deficient and coordinate more efficiently to the imine nitrogen than do trialkylboranes. This led us to examine reactions involving dicyclohexylboron chloride (Chx_2BCl) under different conditions. Generally, the imine–borane complex precipitates from nonpolar or ethereal solvents. However, its high solubility in dichloromethane makes this solvent a good choice as the reaction medium. As can be seen from Table 1, no reaction product was obtained in the absence of a base, whether at room temperature or under reflux, and using various solvents (Table 1, Entries 1, 2). By contrast, the cyclohexylated amine was formed in the presence of triethylamine under reflux conditions (Table 1, Entry 5) or in the presence of sodium hydroxide at room temperature (Table 1, Entry 7), although the amine yield was quite modest (5–25%). Interestingly, we found that the cyclohexylamine could be formed in good yields (80–85%) when hydrogen peroxide was added as coreagent (Table 1, Entry 8).

Table 1. Reaction of aldimine **1a** with dicyclohexylboron chloride.



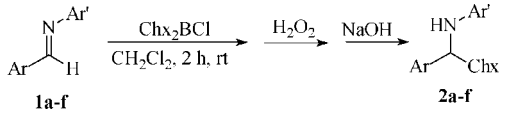
1a 2a

Entry	Solvent	*T* [°C]	Additive	Yield [%][a]
1	dichloromethane, THF or toluene	room temp.	–	<5[b]
2	dichloromethane, THF or toluene	reflux	–	<5[b]
3	dichloromethane or THF	room temp.	triethylamine	<5[b]
4	THF	reflux	triethylamine	<5[b]
5	dichloromethane	reflux	triethylamine	20–25
6	dichloromethane	room temp.	NaOH (1 M)	<5[b]
7	dichloromethane	room temp.	NaOH (10 M)	5–10
8	dichloromethane	room temp.	H_2O_2	80–85

[a] Determined by ^{1}H NMR spectroscopy; the detection limits for the products in the crude NMR spectra were estimated to be 5%. [b] Although the yield is quoted as <5%, compound **2a** was not detected by NMR spectroscopy.

After optimization, we directly used the best reaction conditions with aromatic *N*-arylimines **1a**–**f** having different substitution patterns in the aromatic rings (Table 2). Essentially, all aldimines were successfully converted into the corresponding amine derivatives **2a**–**f**.

Table 2. Synthesis of Amines **2a**–**f**.



1a-f 2a-f

Entry	Amine	Ar	Ar′	Yield [%][a]
1	**2a**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	60
2	**2b**	4-$MeOC_6H_4$	3-$MeOC_6H_4$	68
3	**2c**	4-$MeOC_6H_4$	2-$MeOC_6H_4$	65
4	**2d**	3-$MeOC_6H_4$	4-$MeOC_6H_4$	70
5	**2e**	2-$MeOC_6H_4$	4-$MeOC_6H_4$	65
6	**2f**	2,3-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	66[b]

[a] Isolated yields after silica gel chromatography. [b] Isolated along with *N*-[1-cyclohexyl-1-(2-hydroxy-3-methoxyphenyl)methyl]-*p*-anisidine when an excess of dicyclohexylboron chloride was used (1.5:1).

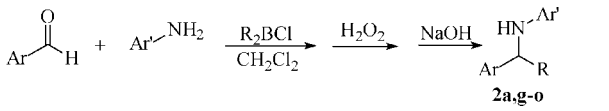
As can be seen from Table 2, the yield of cyclohexylated product was independent of the methoxy substituent on the aromatic rings. Imine **1f** yielded a significant amount of a demethylated product {*N*-[1-cyclohexyl-1-(2-hydroxy-3-methoxyphenyl)methyl]-*p*-anisidine} when an excess of dicyclohexylboron chloride was used. However, the product was not observed when a 1:1 mol ratio of reactants was used.

Next, we examined the one-step reaction of anisaldehyde and 4-methoxyaniline with an excess of dicyclohexylboron chloride. Under these conditions, the chloroborane reagent acts both as a Lewis acid catalyst for the imine formation and as a chain donor to the C=N bond. As can be seen from Table 3, the corresponding amine derivative, **2a** (Table 3, Entry 1), was obtained in a yield similar to that for the preformed imine **1a** (Table 2, Entry 1).

The electronic nature of the substituents on the benzene rings of the aldehyde and amine had no effect on the reaction efficiency. With Chx_2BCl, ^{1}H NMR spectroscopic analysis of the crude reaction mixture revealed the almost exclusive presence of amine derivatives (70–80% yields). The differences in yields between compounds **2a**–**l** (Table 3, Entries 1–7) were due to the purification procedure used.

The reaction was found to require a longer time for completion when a borane derivative containing primary alkyl groups was used (Table 3, Entries 8–10). The desired products, **2m**–**o**, were obtained in low yields and accompanied by unidentified byproducts. To avoid a decrease in the yield in the purification step, we acetylated the clean crude product of amine **2a** to obtain the corresponding acetyl derivative in 80% yield.

Table 3. Three-component reactions: Synthesis of amines **2a**, **g**–**o**.



2a,g-o

Entry	Amine	R	Ar	Ar′	Yield [%][a]
1	**2a**	Chx	4-$MeOC_6H_4$	4-$MeOC_6H_4$	66
2	**2g**	Chx	4-FC_6H_4	4-$MeOC_6H_4$	78
3	**2h**	Chx	4-ClC_6H_4	4-$MeOC_6H_4$	38
4	**2i**	Chx	4-MeC_6H_4	4-$MeOC_6H_4$	50
5	**2j**	Chx	4-$MeOC_6H_4$	4-MeC_6H_4	62
6	**2k**	Chx	4-MeC_6H_4	4-MeC_6H_4	65
7	**2l**	Chx	C_6H_5	C_6H_5	57
8	**2m**	Hex	4-$MeOC_6H_4$	4-$MeOC_6H_4$	26
9	**2n**	Hex	4-FC_6H_4	4-$MeOC_6H_4$	34
10	**2o**	Hex	4-MeC_6H_4	4-$MeOC_6H_4$	32

[a] Isolated yields after silica gel chromatography.

Although no detailed mechanistic study was undertaken, we focused on the imine reaction with Chx_2BCl; the rate of the reaction was found to decrease in the presence of an oxygen stream. Furthermore, the addition of radical scavengers, such as cumene, failed to inhibit the alkylation reaction. These results suggest that a radical reaction mechanism is less likely. In an attempt to elucidate the alkylating intermediate, we added the corresponding imine to a solution of dicyclohexyl borate. Under these conditions, no alkylated product was observed. In a separate experiment, we reversed the order of the addition and we found that the sequential addition of hydrogen peroxide and dicyclohexylboron chloride to the imine solution resulted in the expected cyclohexylated derivatives. This alkylation reaction developed smoothly with other oxidants such as Oxone, UHP or MCPBA. In contrast, the direct treatment of the nitrone derivative from **1a** with dicyclohexylboron chloride provided no alkylated derivatives. Although the radical pathway could not be completely disregarded, an alternative pathway proceeding via an imine-borate intermediate could be considered. A similar mechanism was proposed for the boronic acid multicomponent reaction of amines and aldehydes.[5b]

Conclusions

We developed a one-pot alkylative amination reaction for benzaldehyde derivatives that involves up to three components with dialkylchloroborane as the alkylating agent. Further studies to elucidate the mechanism of this reaction and to expand its synthetic utility are currently being explored by our group.

Experimental Section

Reaction of Imines with Dicyclohexylboron Chloride. General Procedure: The imine (1 mmol) was dissolved in dichloromethane (10 mL) contained in a dry, nitrogen-flushed, 25-mL round-bottomed flask. Dicyclohexylboron chloride (1 M in hexane, 1 mmol) was added by syringe, and the solution was allowed to stir for 2 h at room temp. A solution of hydrogen peroxide (0.2 mL, 30%) was then added, and the mixture was stirred for 30 min. Later, a solution of sodium hydroxide (1 M, 1 mL) was added and stirred for 30 min. The crude reaction was washed with water (2 × 10 mL) and the organic phase dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The ^1H NMR spectrum of the crude product exhibited the almost exclusive presence of amine derivatives (yields 80–85%). Purification by column chromatography (ethyl acetate/hexane, 1:9) afforded the amines in 60–70% yield.

One-Pot Reaction of Aldehyde, Amine and Dialkylboron Chloride: The corresponding alkene (7.6 mmol) was added to a solution of monochloroborane–methyl sulfide complex (1 M) in dichloromethane (3 mL) at 0 °C. The mixture was warmed to room temp. and stirred for 3 h. A solution of aldehyde (1 mmol) and amine (1 mmol) in dichloromethane was then added, and the mixture was stirred at room temp. for 2 h. A solution of hydrogen peroxide (0.2 mL, 30%) was added, and the mixture was stirred for 30 min. Later, a solution of sodium hydroxide (1 M, 1 mL) was added and stirred for 30 min. The crude reaction was washed with water (2 × 10 mL), and the organic phase was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The ^1H NMR spectrum of the crude product exhibited the almost exclusive presence of amine derivatives (yields 70–80%). Purification by column chromatography (ethyl acetate/hexane, 1:9) afforded the amines in 78–32% yield.

Supporting Information (see footnote on the first page of this article): Full experimental procedures and spectroscopic and analytical data.

Acknowledgments

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