NEW LEWIS ACID/LEWIS BASE BINDER

By

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Approved by:

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New Lewis Acid/Lewis Base Binder for Hydrogen Activation

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The synthesis of an amino-borane binder was examined in order to study the potential reactivity of the binder for hydrogen activation. In addition to hydrogen activation, the amino-borane binder is proposed to be a catalyst for nucleophilic attack of carbonyl compounds. The binder is composed of a Lewis acid, boron, and a Lewis base, nitrogen, which are locked by the quinoline structure of the binder to prevent the Lewis pair from forming an adduct. The synthesis of a chiral version of the amino-borane binder could lead to the enantioselective attack as well as enantioselective reduction of carbonyl compounds.

Introduction

An amino-borane Frustrated Lewis pair (FLP) binder is a promising candidate for hydrogen activation and nucleophilic attack of carbonyl compounds. Examining the reactivity of this binder should provide information toward the syntheses of several related binders, including chiral versions. The lack of transition metals and the proposed low cost of synthesizing the amino-borane FLP are desirable aspects of the binder.[1] The synthesis of a quinoline based amino-borane binder is outlined below.

In 2006, Welch *et al.* reported research on FLPs, which are Lewis acid/Lewis base compounds that are inhibited from forming adducts by sterically prohibiting the interaction.[2] Several bimolecular FLPs have been synthesized,[2] however the use of a unimolecular binder is expected to provide a more efficient method of catalysis. Scheme 1 describes the proposed mechanism of activation of hydrogen by heterolytic cleavage. This heterolytic cleavage depends on the activities of both the 2,2,6,6,-tetramethylpiperidine and the trisubstituted boron compound (**1**, Scheme 1).[3] Thus, the use of a unimolecular binder is expected to activate hydrogen with greater ease. A comparison of Schemes 1 and 2 suggests how the proposed amino-borane binder may present a more facile method of activation.

Stephan has reported the synthesis of a unimolecular trimesitylphosphine aryl boron binder (**2**, Scheme 3), which releases and regenerates molecular hydrogen upon heating to 100 °C.[2] Stephan proposes two mechanisms for this release (Scheme 3).[2] The activation of hydrogen into its proton and hydride counterparts provides a reactive species to reduce several functional groups. Sumerin *et al*. report the reduction of benzaldehyde using a stoichiometric amount of an activated piperidine derived borohydride/ammonium salt (**1**, Scheme 1).[3]

The mechanism of hydrogen activation is yet unknown however, it is most likely that a proton or hydride migration occurs before the proton/hydride reactive species is formed.[2] Thus, the proposed amino borane binder (**3**, Scheme 7) is designed such that its Lewis acid and Lewis base active sites could act on a single substrate concurrently, without the need for migrations. Having the Lewis acidic boron and Lewis basic nitrogen locked in place by the quinoline structure creates an active site for hydrogen to simultaneously be in optimal proximity to both components of the binder.

FLPs have also been shown to hydrogenate of several functional groups.[2, 4] Scheme 4 outlines how the activated binder could reduce carbonyl groups to their corresponding alcohols. The proposed binder is achiral, where X represents a hydrogen, but if a chiral group were attached at the X-position, reduction of the carbonyl may be enantioselective.

In addition to hydrogen activation and reduction of functional groups, it is proposed that the binder may allow for nucleophilic attack of carbonyl compounds (Scheme 5a). A chiral amino borane binder will favor one face of the carbonyl for nucleophilic attack, producing an enantiomeric excess of product. One possibility for creating a chiral binder would be to add a cyclopentane ring with a chiral group, R^1, which is locked into a position where it would interfere with the carbonyl if attacked from that face (**4**, Scheme 5b). Scheme 5b suggests that interaction between R^1 of the binder and R of the carbonyl will make the

formation of **6** less favorable than the formation of **5**.

Boron is an essential component of the binder because it adopts a tetrahedral geometry when bonded to four ligands, providing the optimal angle for substrates to interact with both the boron and the nitrogen. Additionally, the known tetrahedral geometry of boronate compounds eliminates the possibility of more than one substrate adding to the boron atom of the binder and interfering with its reactivity. The binder has fluorinated aryl substituents to increase the Lewis acidity of the boron atom.[5] The Lewis base nitrogen is desirable because of the ease of synthesis of nitrogen containing compounds.

The proposed synthesis of the binder is outlined in Scheme 6, where the 8-lithioquinoline would add to the boron compound to make the binder. However, due to anticipated difficulties and the toxicity of tin containing compounds,[6] this proposed synthesis was replaced with the projected synthesis outlined in Scheme 7.

Experimental

Synthesis of 8-bromoquinoline

A solution of 2-bromoaniline (50.0 g, 0.290 mol), glycerol (42.4 mL, 0.580 mol), and nitrobenzene (29.7 mL, 0.290 mol) was added to a 1L round bottomed flask. To this stirring solution was added ferrous sulfate heptahydrate (5.00 g, 0.01 mol) and sulfuric acid (81 mL). The solution was heated to 100 °C for 5 hours. The reaction progress was checked by TLC using hexanes-ethyl acetate (20:80). The solution was neutralized with 12N NaOH and filtered with Celite. The resulting mixture was dark and no visible organic layer could be seen. Salt and silica gel were added to the mixture and allowed to sit overnight and separation of the organic and aqueous layers occurred. Extensive extractions were carried out with ether and the combined organic solution was dried with $MgSO_4$ and evaporated. The residue was distilled at 128 °C at 2 torr to obtain the 24.3 g (40%) product. ^{1}H NMR ($CDCl_3$): δ 9.05 (d, 1H, J = 2.5 Hz), 8.18 (d, 1H, J = 8.2 Hz), 8.07 (d, 1H, J = 7.4 Hz), 7.80 (d, 1H, J = 8.1 Hz), 7.47 (q, 1H, J = 4.1 Hz), 7.41 (t, 1H, J = 15.7 Hz).[17] ^{1}H NMR (CD_3OD): δ 8.84 (d, 1H, J = 5.7 Hz), 8.27 (d, 1H, 9.J = 6 Hz), 8.03 (d, 1H, J = 8.2 Hz), 7.83 (d, 1H, J = 8.2 Hz), 7.52 (q, 1H, J = 4.0 Hz), 7.40 (t, 1H, J = 16 Hz). ^{1}H NMR (C_6D_6): δ 8.70 (d, 1H, J = 4.1 Hz), 7.74 (d, 1H, J = 7.4 Hz), 7.35 (d, 1H, J = 8.2 Hz), 7.14 (d, 1H, J = 7.9 Hz), 6.76 (t, 1H, J = 16 Hz), 6.65 (q, 1H, J = 4.1 Hz).

Synthesis of 8-quinoline boronic acid

To a solution of 8-bromoquinoline (5.00 g, 0.0243 mol) and THF (8 mL) cooled to -78 °C purged under argon was added dropwise *n*-butyllithium (2.46 M, 11.7mL, 0.0291mol) over 5 minutes. The solution was stirred for an hour before trimethylborate (5.60 mL, 0.0494 mol) was added dropwise over 5 minutes. The solution was warmed to room temperature and stirred for 1 hour before 100 mL of 1M hydrochloric acid was added. This solution was extracted with ether 3 times and neutralized with saturated sodium bicarbonate. 3.85 g (92.6%) of product was obtained after filtration as a brown precipitate. ^{1}H NMR (CD_3OD): δ 9.19 (d, 1H, J = 5.2 Hz), 8.41 (d, 1H, J = 8.2 Hz), 8.01 (d, 1H, J = 6.8 Hz), 7.69 (d, 1H, J = 1.6 Hz), 7.60 (q, 1H, J = 3.0 Hz), 7.49 (t, 1H, J = 8.5 Hz). ^{11}B NMR (CD_3OD): δ 6.4.

Synthesis of 8-quinoline ethyl boronic ester

Several methods for the synthesis of 8-quinoline ethyl boronic ester were investigated, but the desired product was not successfully synthesized. Outlined below are a few of the modifications.

Version A

8-quinoline boronic acid (1.0 g, 5.77 mmol), benzene (20 mL, 0.224 mol) and butanol (4.07 mL, 44.5 mmol) were heated for 3 hours and water was allowed to collect in a Dean-Stark trap.

Version B

8-quinoline boronic acid (1.2 g, 6.92 mmol), ethanol (2.42 mL, 41.5 mmol) and benzene (4.92 mL, 55.3 mmol) were continously distilled at 80 °C for 6 days and solvent was added as needed to maintain volume. After 6 days, 60 mg of camphor sulfonic acid was added, but no product was obtained.

Version C (8-quinoline methyl boronic ester)

To a cooled solution (-78 °C of 8-bromoquinoline (1.00 g, 4.81 mmol) in THF (5 mL) was added sec-BuLi (6.07 mL, 0.86 M in cyclohexane) dropwise over 5 minutes. The solution was stirred for 5 minutes after which trimethyl borate (292 µL, 5.25 mmol) was added dropwise over 5 minutes.

The solution was stirred for 30 min and then stirred at room temperature for 1.5 hours. The solution was filtered and evaporated. Kugelrohr distillation of the residue at 200 °C and 2 torr afforded quinoline. ^{1}H NMR (C_6D_6): δ 8.76 (d, 1H, J = 2.6 Hz), 8.29 (d, 1H, J = 8.5 Hz), 7.57 (d, 1H, J = 8.4 Hz), 7.37 (d, 1H, J = 5.3 Hz), 7.34 (t, 1H, J = 14.0 Hz), 7.15 (d, 1H, J = 7.1 Hz), 6.78 (q, 1H, J = 4.1 Hz). ^{13}C NMR (CD_3OD): δ 144.6, 143.2, 134.8, 129.3, 127.9, 121.5

Results

Several synthetic pathways toward synthesizing 8-bromoquinoline (**7**, Scheme 7) were explored. Synthesis A involves a reaction of 8-aminoquinoline with copper (II) bromide and *tert*-butyl nitrite in acetonitrile to afford 8-bromoquinoline via a modified Sandmeyer reaction.[7] This synthesis was reported by Wada and co-workers to work with 70% yield.[7] Synthesis B involves the reaction of 8-aminoquinoline with sodium nitrate, HBr, and copper (I) bromide in water via a Sandmeyer synthesis.[8] Synthesis C involves the reaction of 2-bromoaniline with glycerol to produce the 8-bromoquinoline via a modified Skraup synthesis.[9] In this synthesis, acrolein is first formed from glycerol before it reacts with the 2-bromoaniline to form the fused ring product. In the present work, Synthesis C was pursued and afforded the desired product in 40% yield.

The original quinoline synthesis outlined by Zdenko Hans Skraup in *Berichte* 1880 was violent and difficult to control.[10] Thus, Cohn and Gustavon discovered that the addition of ferrous sulfate to the reaction mixture slowed the reaction to a manageable rate, making it feasible to work on larger scales.[11] Nitrobenzene was added in addition to the ferrous sulfate to act as the solvent, as well as an oxidizing reagent. Clarke and Davis report that the glycerol should contain less than 0.5% water to obtain good yields.[10] Lastly, the order of addition of reagents is an important step. Rodriguez *et al*. report the addition of ferrous sulfate heptahydrate and sulfuric acid to a mixture of aniline, glycerol and nitrobenzene.[9] However, Clarke and Davis suggest that the ferrous sulfate be added first, and then the glycerol, aniline, nitrobenzene, and lastly, sulfuric acid.[10] In the present work, the 2-bromoaniline was added first with the glycerol and nitrobenzene. The ferrous sulfate and sulfuric acid were then added. Due to the low yield, the mode of addition reported by Clarke and Davis should be considered for future experiments.[10] The water content of the glycerol should also be examined to optimize yield.

The synthesis of 8-quinoline boronic acid (**8**, Scheme 7) was described by Letsinger and Dandegaonker in 1959.[12] Two modifications were made in this synthesis to afford the desired product in good yield. Letsinger and Dandegaonker report stirring a solution of *n*-butyllithium and 8-bromoquinoline for 30 minutes however, Suggs and Pearson report that letting the organolithium compound stir for longer than 5 minutes decreases yield when they reacted the organolithium compound with methyl iodide.[13] The yield after 5 minutes was 87% while the yield after 60 minutes was 73%. Additionally, the use of *sec*-butyllithium instead of *n*-butyllithium was predicted to produce a greater yield.[13] Suggs and Pearson report that after 5 minutes of stirring, the 8-lithioquinoline species was produced in 87% yield when *sec*-butyllithium was used, while 15 minutes of stirring with *n*-butyllithium produced a 58% yield. They also report that using 2 equivalents of *sec*-butyllithium decreased the yield to 56% although using 2 equivalents of *n*-butyllithium increased the corresponding yield to 66%. In the synthesis toward the amino-borane binder, 1.1 equivalents of *n*-butyllithium was used and the solution was allowed to stir for 5 minutes before the addition of trimethyl borate to give the boronic acid in 93% crude yield.

A lithium-halogen exchange of the 8-bromoquinoline produces the organolithium compound, which then attacks the trimethyl borate to form the boronate ion. This species is then hydrolyzed to the acid. Letsinger and Dandegaonker perform an azeotropic distillation with butanol, benzene, and the boronic acid to produce the corresponding butyl boronic ester in good yield.[12] However, synthesis of the 8-quinoline butylboronate (**8**, Scheme 7) proved difficult and the product was never isolated. Analysis by NMR shows peaks corresponding mainly to the boronic acid starting material. Several adjustments were made in order to synthesize the product, including heating for several days, using different solvents, and adding catalytic amounts of camphor sulfonic acid, and still no product was made. Preliminary NMR

analysis shows the presence of very small secondary peaks that could correspond to the product and thus, the resulting reaction mixtures were heated for several days in an attempt to drive the reaction to completion. Additionally, Brindley and co-workers report producing an ethyl boronate by performing an azeotropic distillation of ethanol and benzene.[14] Use of this method still did not afford the product. Camphor sulfonic acid was added to aid in the protonation of the hydroxyl groups on boron to release water and produce the ester. Despite these modifications, the synthesis that Letsinger and Dandegaonker report could not be reproduced. The product may be prone to hydrolysis and may reform the starting material when exposed to water. Due to solubility issues, deuterated methanol was initially used as the solvent for NMR. The product thus may have hydrolyzed when dissolved in the highly hygroscopic methanol. Deuterated benzene was then used as the solvent but the product may have extreme sensitivity toward hydrolysis and even exposure to air may have produced the acid.

In an attempt to bypass the difficult synthesis of the boronic ester from the boronic acid, Albrecht and co-workers report the synthesis of boronate esters from aromatic derivatives without hydrolysis to the boronic acid (Synthesis F).[15] Analysis by TLC shows the presence of 8-bromoquinoline, quinoline, and a new "product" spot. However, after Kugelrohr distillation, the isolated product was found to be quinoline by NMR spectroscopy.

Discussion

The current attempts at utilizing molecular hydrogen for possible use in fuel cells are hindered by the inability to liquefy hydrogen. High pressure cylinders used for storing hydrogen gas are large, dangerous, and impractical for use as an energy source. The synthesis of a rechargeable hydrogen storage binder would significantly change the way hydrogen is activated for use. The U.S. Department of Energy (DOE) has outlined specifications for hydrogen storage compounds including a gravimetric capacity of at least 6 wt.%. The proposed binder would not meet this specification however, once the fundamentals of reactivity are explored, the synthesis of a more practical binder can be investigated.

This synthesis of the proposed binder was not completed, although advances were made in determining the possible pathways of synthesis. Modifications of several known reactions were investigated to produce optimal yields. In future experiments, the synthesis of 8-quinoline boronic ester should be attempted using different trialkyl borates.

References:

1. Dalko, P.I., Moisan, L. (2001) *Angew. Chem. Int. Ed.* **40**, 3726-3748
2. Welch, G. C., San Juan, R. R., Masuda, J. D., Stephan, D. W. (2006) *Science*, **314**, 1124-1126
3. Sumerin, V., Schulz, F., Nieger, M., Leskel, M., Repo, T., Rieger, B. (2008) *Angew. Chem. Int. Ed.* **47**, 6001-6003
4. Stephan, D. W. (2008) *Org.Biomol. Chem.* **6**, 1535-1539
5. Ishihara, K., Yamamoto, H. (1999) *Eur. J. Org. Chem*. 527-538
6. Parks, D. J., Piers, W. E., Yap, G. P. A. (1998) *Organometallics* **17**, 5492-5503
7. Wada, K., Mizutani, T., Kitagawa S. (2003) *J. Org. Chem.* **68**, 5123-5131
8. Butler, J. L., Gordan, M. (1975) *J. Heterocyclic. Chem.* **12**, 1015-1020
9. Rodriguez, J. G., De los Rios, C., Lafuente, A. (2005) *Tetrahedron*. **61**, 9042-9051
10. Clarke, H. T., Davis, A. W. (1941) *Org. Synth.* **1**, 478
11. Cohn, B.E., Gustavson, R.G. (1928) *J. Am. Chem. Soc.* **50**, 2709-2711
12. Letsinger, R. L., Dandegaonker, S. H. (1959) *J. Am. Chem. Soc.* **81**, 498-501
13. Suggs, J.W., Pearson, G.D.N. (1980) *J. Org. Chem.* **45**, 1514-1515
14. Brindley, P. B., Gerrard, W., Lapper, M.F. (1955) *J. Chem. Soc. 2956*
15. Albrecht, K., Kaiser, B., Boese, R., Adams, J., Kaufmann, D.E. (2000) *J. Chem. Soc., Perkin Trans.* **2**, 2153-2157
16. Tochilkin, A. I., Kovel'man, I. R., Prokof'ev, E. P., Gracheva, I. N., Levinskii, M. V. (1988) *Chem. Heterocycl. Compd.* **24** (8), 1084-1090

Schemes

Syntheses

Synthesis A. This synthesis utilized a modified Sandmeyer reaction to afford the 8-bromoquinoline.[7]

Synthesis B. This synthesis used conditions for the original Sandmeyer reaction.[8]

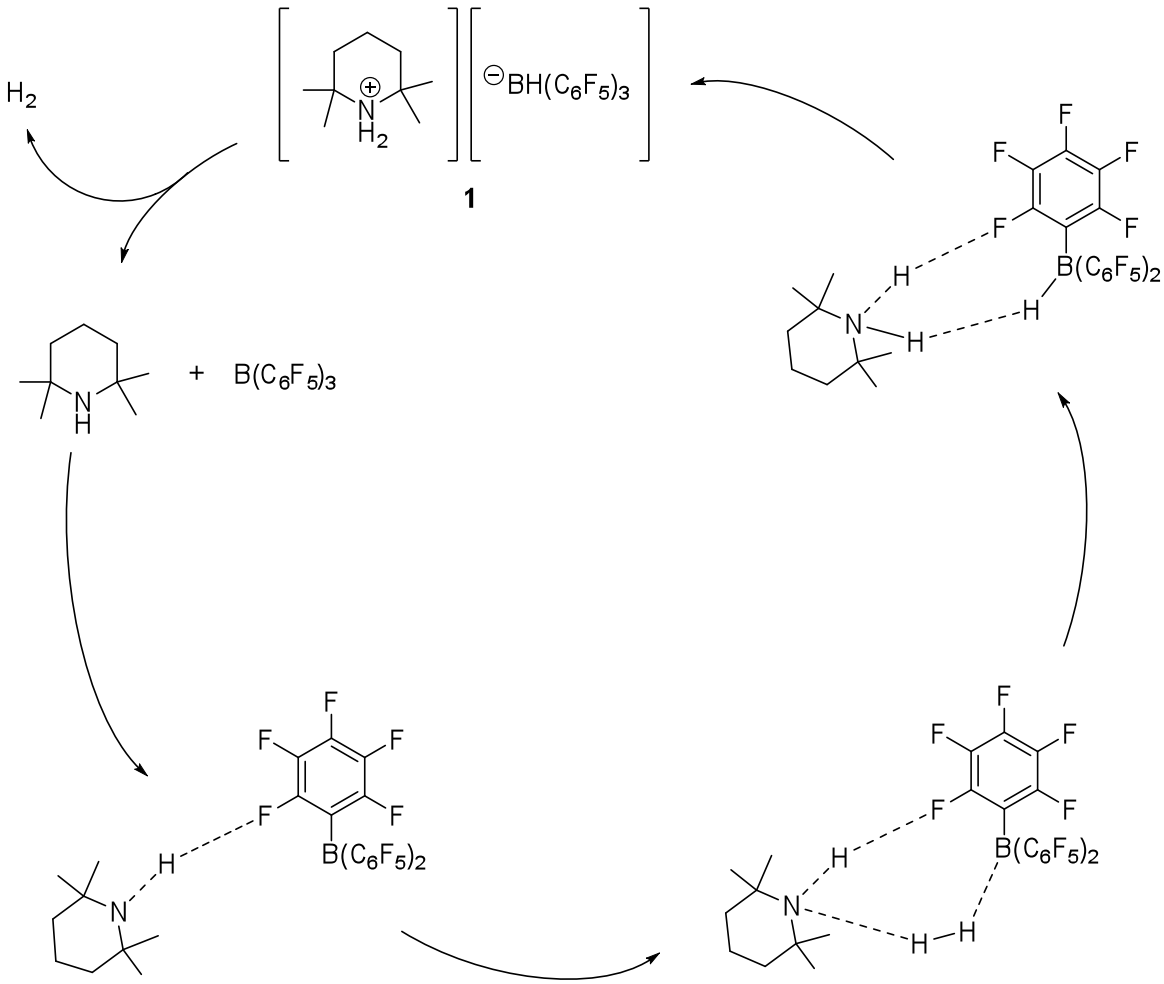
Synthesis C. This synthesis utilized a modified Skraup synthesis and was pursued for the synthesis of the amino-borane binder. [9]

Synthesis D. The 8-quinoline boronic acid was synthesized by forming 8-lithioquinoline and reacting it with trimethylborate and then hydrolyzing to the acid.[12]

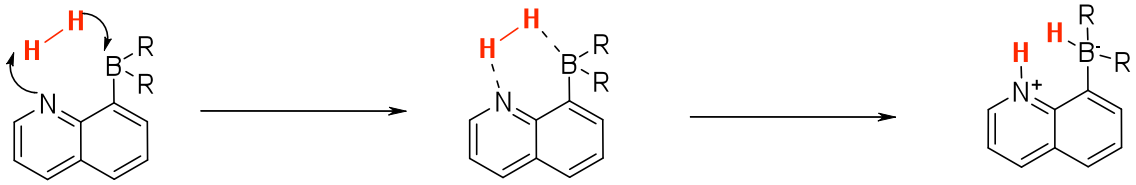
Synthesis E. The synthesis of 8-quinoline ethylboronate was attempted using an azeotropic distillation with ethanol and benzene.[12]

Synthesis F. The synthesis of 8-quinoline methylboronate was attempted by forming the 8-lithioquinoline and reacting it with trimethylborate.[13]

Scheme 1



Scheme 2



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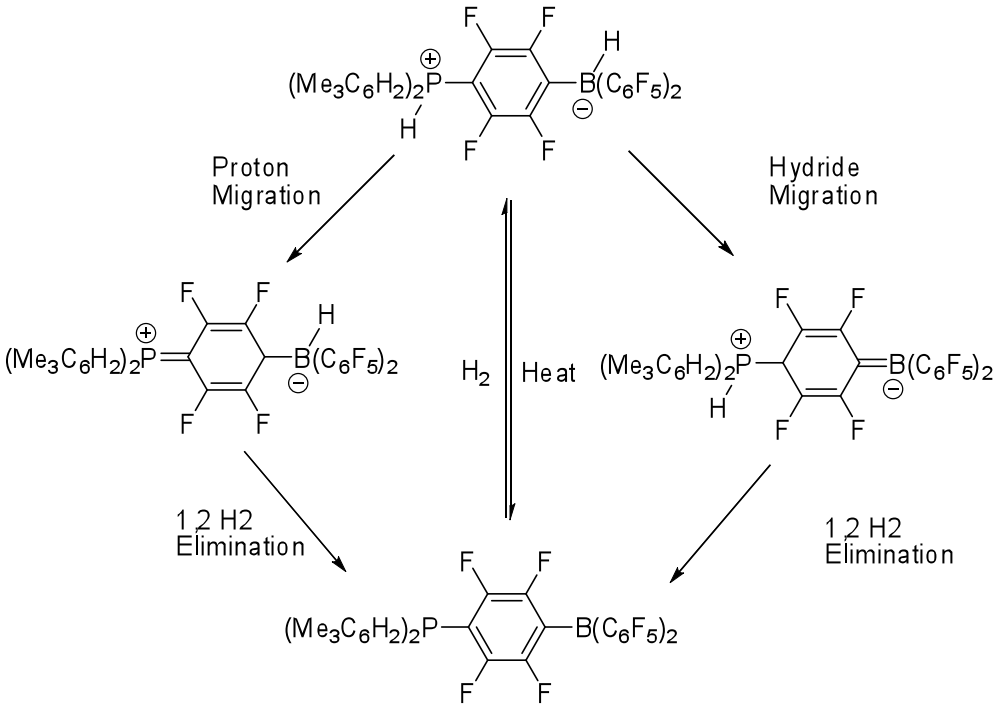
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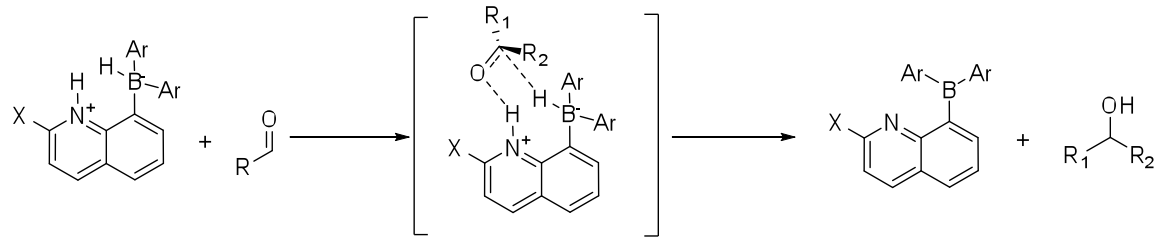
Hydride Migration
H2 Heat
1,2 H2 Elimination
1,2 H2 Elimination

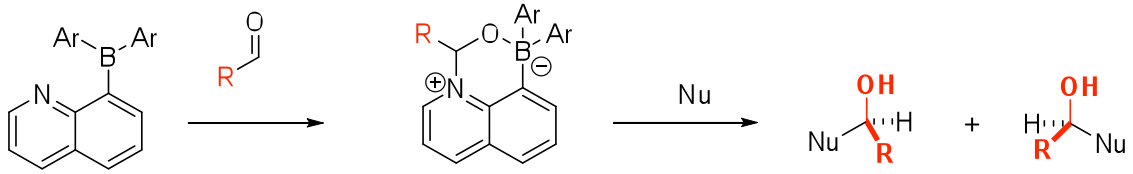
2

Scheme 4



Scheme 5

a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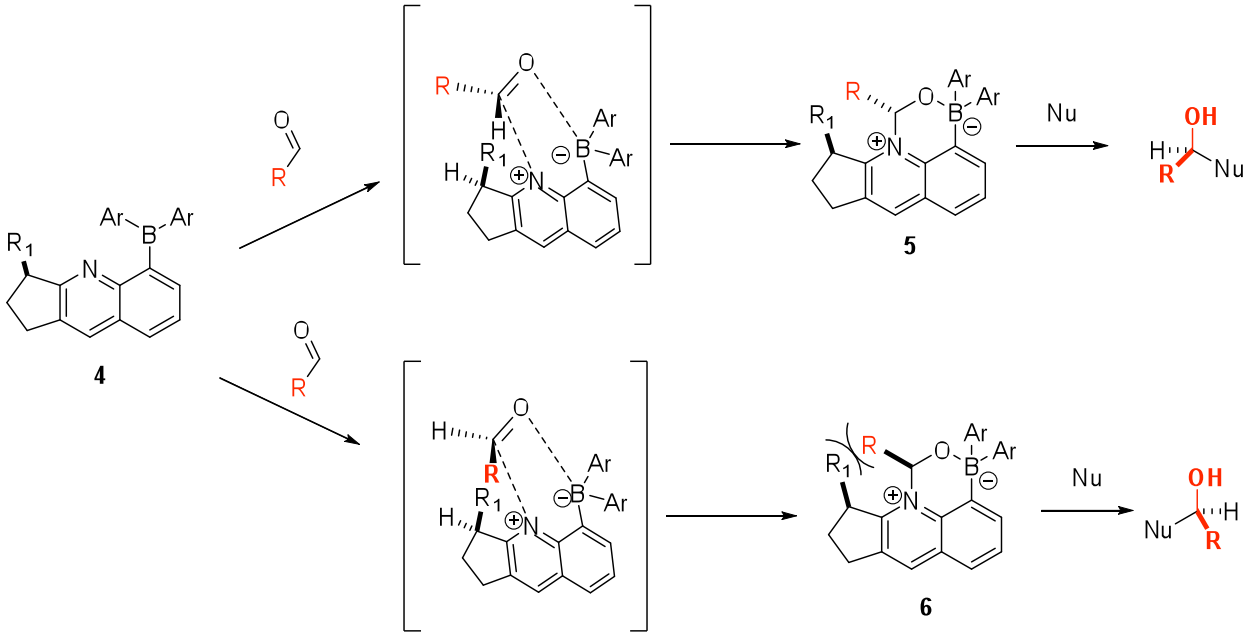
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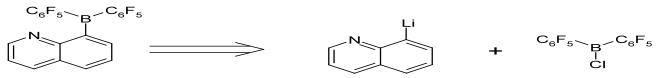
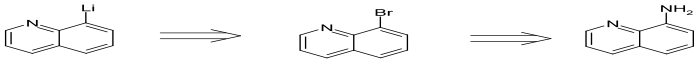
Scheme 6



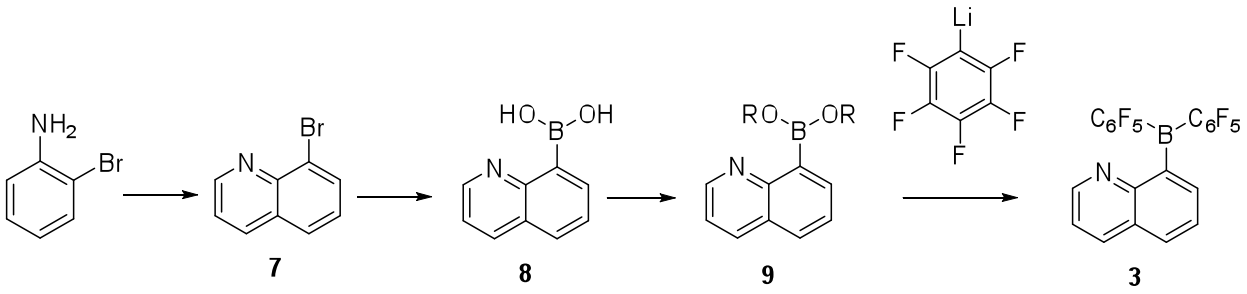
Building Block 1 Building Block 2

Synthesis of Building Block 1.



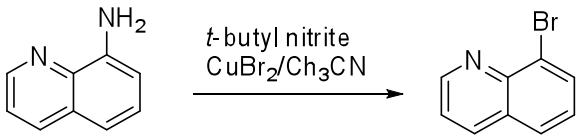
Synthesis of Building Block 2.

Scheme 7

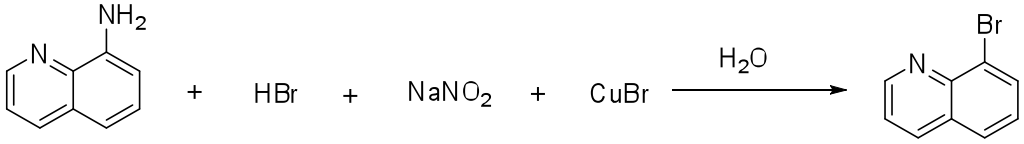


7 **8** **9** **3**

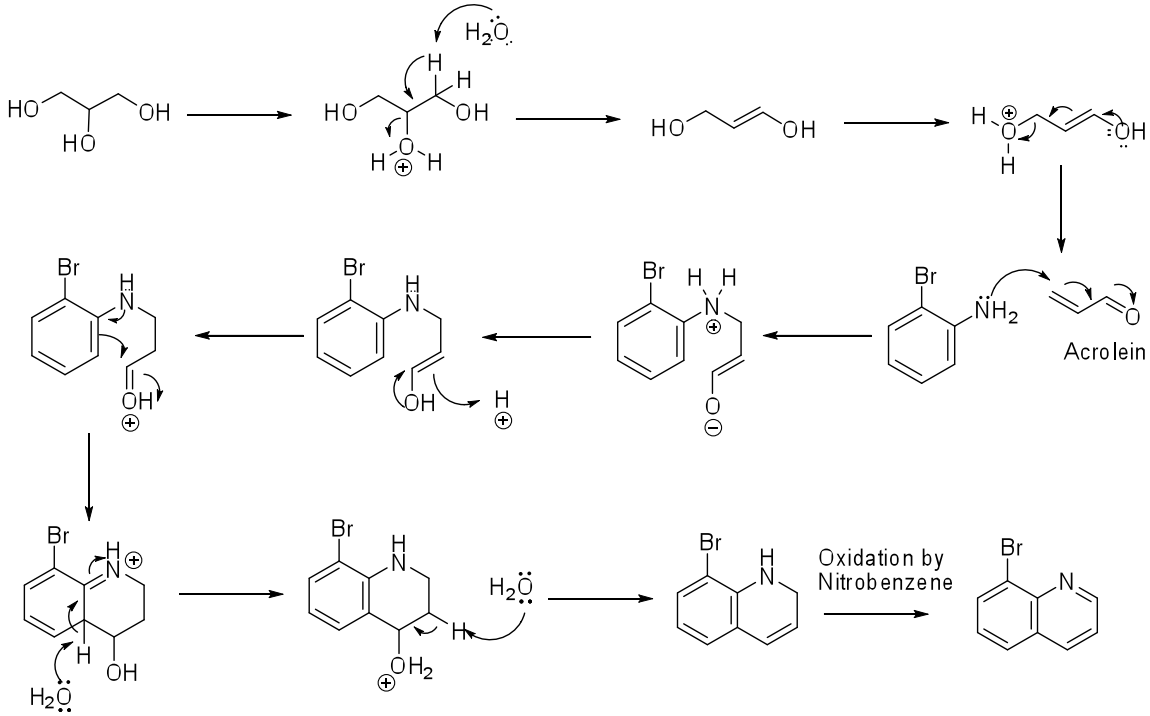
Synthesis A



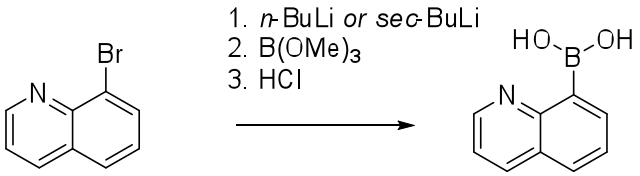
Synthesis B



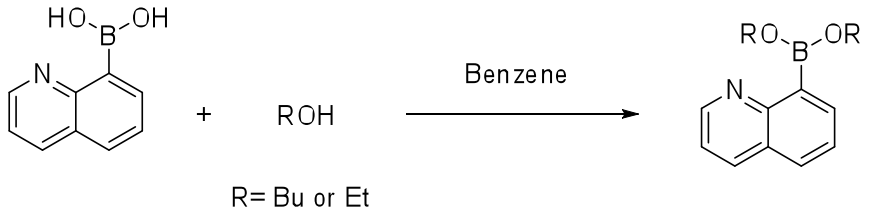
Synthesis C



Synthesis D



Synthesis E



Synthesis F