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Rhodium-Catalyzed Asymmetric Functionalization of Quinoxalinium Salts

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Abstract

We report a rhodium-catalyzed asymmetric addition of aryl and alkenyl boronic acids to quinoxalinium salts that generates dihydroquinoxalines with high enantioselectivity. Functionalization of the reaction products, dihydroquinoxaline, allows the preparation of tetrahydroquinoxalines with various substitution patterns.

Introduction

Chiral tetrahydroquinoxalines (THQs) are common structural motifs in bioactive compounds (Figure 1).[1] Despite their representation in important bioactive molecules, such as potent CETP and BET inhibitors, methods for their asymmetric synthesis are limited. Traditionally, synthetic access to chiral tetrahydroquinoxalines has been achieved through asymmetric hydrogenation of quinoxalines and various cyclization reactions (Scheme 1A).[2] While these methods can produce THQs, the scope of asymmetric reductions of quinoxalines is limited, and when there are two substituents present, often *syn*-disubstituted THQs are obtained.[3] Cyclization approaches to THQs require multistep syntheses to access starting materials, and often the desired stereogenic center is already present in one of the starting materials.

Inspired by asymmetric nucleophilic dearomatization of pyridines for the synthesis of piperidines, we envisioned an alternative approach to the asymmetric synthesis of substituted tetrahydroquinoxalines involving an enantioselective dearomatization of quinoxalinium salts to obtain dihydroquinoxalines (DHQs), which could then be converted into THQs (Scheme 1B).[4] This is an attractive approach, as it utilizes readily available starting materials and allows for the stereoselective and lates-stage introduction of substituents on THQs. Specifically, herein, we report a rhodium-catalyzed dearomatization of quinoxalinium salts for the synthesis of chiral dihydroquinoxalines. In addition, we demonstrate that the C3 = N4 imine bond of the DHQ reaction products can be functionalized through both reduction and addition reactions to produce substituted THQs with one and two stereocenters, respectively.

Results and Discussion

Our studies began using the reaction conditions we have developed for the dearomatization of pyridinium salts (Table 1).[4g,i,x] Thus, quinoxalinium salt **3** was reacted with $PhB(OH)_2$ in the presence of the $Rh(COD)_2BF_4$/(*S*)-Binap combination as the catalyst, Na_2CO_3 as the base, and a 10:1 dioxane/H2O mixture as the solvent system. Under these conditions, dihydroquinoxaline **4a** was obtained in 47% yield and 62% ee (Table 1, entry 1). Subsequent evaluation of Et_2O, PhMe, and DME as solvents resulted in significantly lower yields of **4a** (Table 1, entries 2−4, respectively). Diene ligands such as COD and **L2**−**L4** instead of Binap gave DHQ **4a** in low to moderate yield and in the case of **L**2−**L4** moderate ee (Table 1, entries 5− 8, respectively). Commercial bis-phosphine ligands (*R*)-Segphos (**L5**) and (*R*)-(*S*)-Josiphos (**L10**) were evaluated, and while both ligands gave low yields, Josiphos (**L10**) gave **4a** in 93% ee (Table 1, entries 9 and 10, respectively). (*R,R*)- QuinoxP* was identified as the best ligand for this transformation, affording **4a** in 73% yield and 93% ee (Table 1, entry 11). Finally, increasing the catalyst loading to 6 mol % and increasing the reaction temperature to 80 °C afforded DHQ **4a** in 80% yield and 94% ee (Table 1, entry 12). An increase or decrease in the dioxane:H_2O ratio diminished the yields of **4a** (entries 13−15). Without any catalyst, the desired dihydroquinoxaline **4a** was obtained in only 8% yield (Table 1, entry 16).

With the optimized reaction conditions in hand, we explored the scope of boronic acids that can be used in this reaction (Scheme 2). Electron-neutral and electron-rich aryl boronic acids afforded the corresponding dihydroquinoxalines in good to moderate yields and excellent %ee (Scheme 2, **4a**−**4e**, **4m**, and **4n**, respectively). Electron-deficient boronic acid gave the corresponding DHQ **4k** in diminished yields compared to those of electron-neutral and electron-rich aryl boronic acids, albeit with excellent %ee. When halogen-functionalized aryl boronic acids were used, DHQs were obtained in moderate to good yields depending on the nature and ring position of the halogens (Scheme 2, DHQs **4h**−**4j**, **4t**, and **4u**). Thus, boronic acids with *m*-chlorophenyl, *p*-fluorophenyl, and *p*-chlorophenyl substituents gave DHQs **4h**−**4j**, respectively, in good yields and excellent ee values, while *o*-fluorophenyl- and *m*-bromophenyl substituted DHQs (**4t** and 4**u**, respectively) were obtained in modest yields.

In general, meta and para substituents were better tolerated than ortho substituents (e.g., **4e**−**4h** vs **4d** and **4t**). It is worth noting that sterically hindered boronic acids with ortho substituents still gave moderate yields of the corresponding DHQs with excellent %ee (Scheme 2, **4d** and **4t**). N-Boc-pyrrole-2-boronic acid gave DHQ **4v** in 74% yield but with only 2% ee.

The reaction tolerates a wide range of functional groups, including ether, ester, alkene, amide, primary alcohol, and heterocycle functionalities (Scheme 2, **4f**, **4k**−**4m**, and **4o**−**4q**). We found that in addition to aryl boronic acids, alkenyl boronic acids could also be employed in this methodology. Cyclic alkene boronic acid gave the corresponding DHQ **4r** in 69% yield and 94% ee. A linear alkene containing DHQ, **4s**, was obtained in 48% yield and 78% ee. The latter result is particularly exciting as it opens the door for the synthesis of enantioenriched alkyl-functionalized tetrahydroquinoxalines after reduction of the C = C and C = N bonds (see Scheme 4, compound **7c**). A preparative scale reaction (1 mmol)

gave **4a** in 76% isolated yield and 98% ee. Finally, under the standard reaction conditions, PhBpin as the nucleophile instead of $PhB(OH)_2$ gave **4a** in a lower yield but higher ee (for details, see the Supporting Information).

Next, we investigated the dearomatization of quinoxaline derivatives to produce chiral DHQs (Scheme 3). 6,7- Disubstituted quinoxalinium salts gave the corresponding DHQs in moderate yield and excellent ee (Scheme 3, **6a**−**6c**). DHQs substituted at position C5 also underwent dearomatization to give the corresponding dearomatization products in moderate yields and 96% ee (Scheme 3, **6d** and **6e**). It is worth noting that for the synthesis of **6e** we used N-benzyl quinoxalinium salt as attempts to methylate the corresponding quinoxaline resulted in a mixture of quinoxalinium salts arising from methylation of N1 or N4. Next, the effect of quinoxalinium counterions was explored. Triflate and phosphorus hexafluoride counterions (Scheme 3, **6f**) were well tolerated under our reaction conditions and gave DHQ **6f** in moderate yield and 92% ee. A bromide counteranion gave DHQ **6f** in only a trace amount. An attempt to form dihydroquinoxaline **6g** containing a fully substituted stereocenter by dearomatization of the corresponding quinoxalinium salt resulted in the elimination product of the starting quinoxalinium salt (for details, see the Supporting Information).

In addition, under the optimized reaction conditions, pyrazinium salts did not produce any of the corresponding functionalized dihydropyrazine product. Finally, we found that treatment of **3** with an additional portion of MeOTf did not provide the desired second alkylation at N4 for a potential double dearomatization.

To demonstrate the utility of DHQs, we explored their further functionalization to prepare tetrahydroquinoxalines (Scheme 4). Reduction of the C = N bond using $NaCNBH_3$ provided the corresponding tetrahydroquinoxaline compounds **7a** and **7b** in good yields without significant erosion of the ee. Catalytic hydrogenation of **4s** afforded enantioenriched tetrahydroquinoline **7c** that contains an alkyl substituent at the stereogenic center. Reduction of **4a** under the same catalytic hydrogenation conditions gave the reduced tetrahydroquinoxaline compound in yields lower than that of NaCNBH3 with erosion of the ee (for details, see page S43 of the Supporting Information). Catalytic hydrogenation of **4s** afforded tetrahydroquinoxaline **7c** that contains an alkyl substituent at the stereogenic center. Reaction of **4a** under Streker-type reaction conditions afforded **8** in 51% yield. Aryl lithium, alkyl Grignard, and aryl Grignard reagents reacted with **4a** and gave tetrahydroquinoxalines **9a**−**9c**, respectively, with >20:1 dr and good yields. Furthermore, **4a** was amenable to reductive amination conditions to give N,N-dialkylated THQ **10**.

Conclusions

In summary, we have developed the first asymmetric Rh-catalyzed dearomatization of quinoxalinium salts for the synthesis of chiral dihydroquinoxalines. The reaction tolerates the addition of electron-rich, electron-neutral, and electron-poor aryl and alkenyl boronic acids with varying functional groups, including amides, free alcohols, and heterocycles. Subsequent functionalization of DHQ derivatives enables the enantioselective synthesis of tetrahydroquinolines containing one or two stereogenic centers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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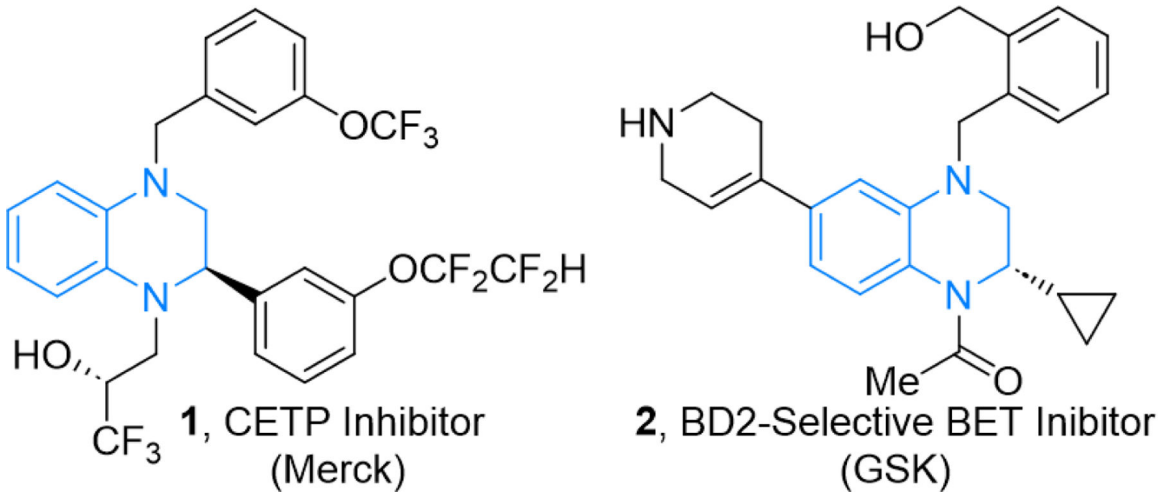
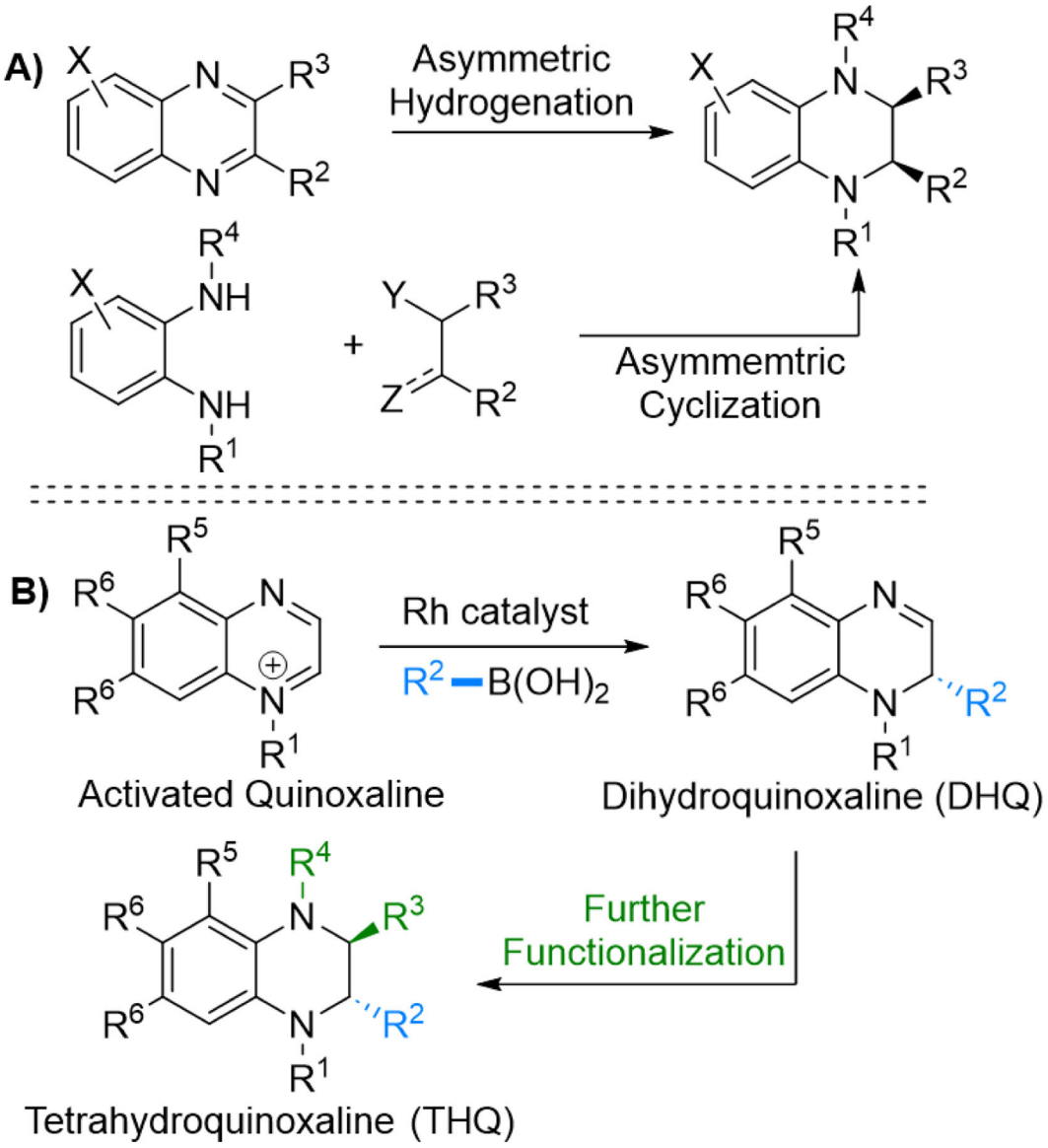
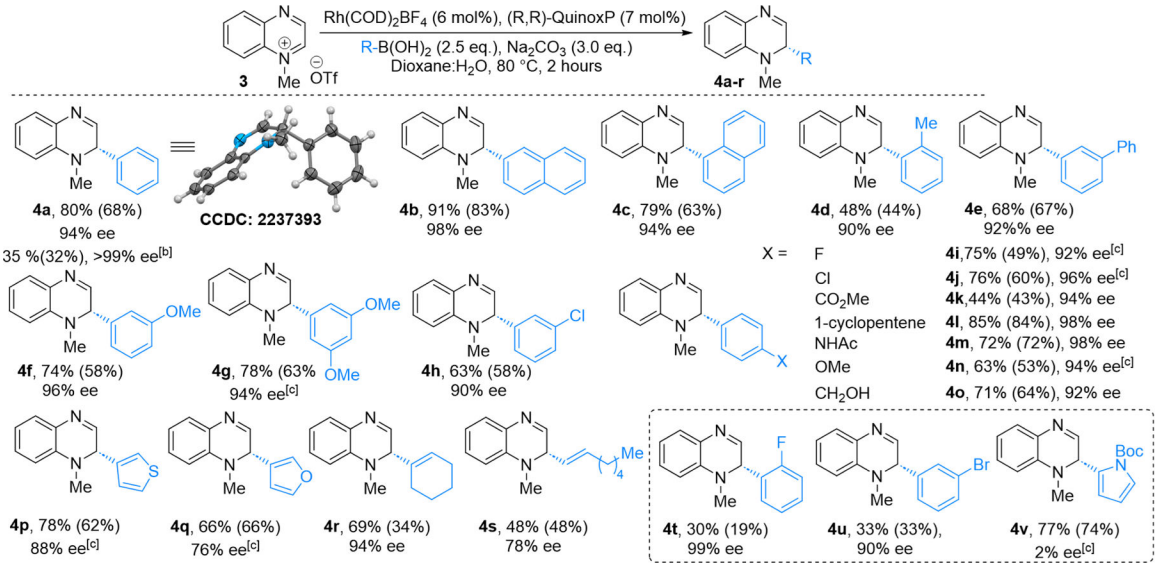


Figure 1.
Examples of bioactive compounds with tetrahydroquinoxaline cores containing stereogenic centers.



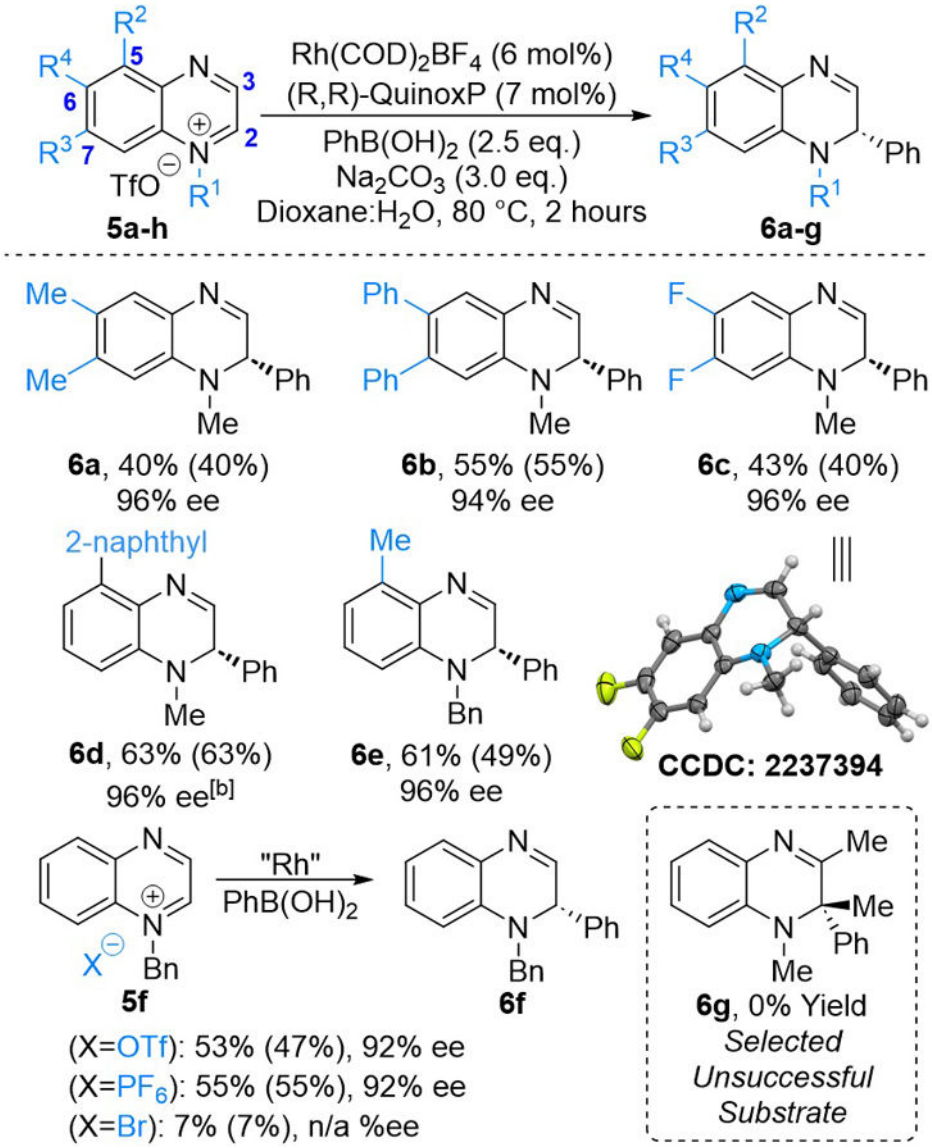
Scheme 1.

(A) Common Approaches to the Asymmetric Synthesis of Tetrahydroquinoxalines and (B) Our Approach to the Synthesis of Dihydro- and Tetrahydroquinoxalines

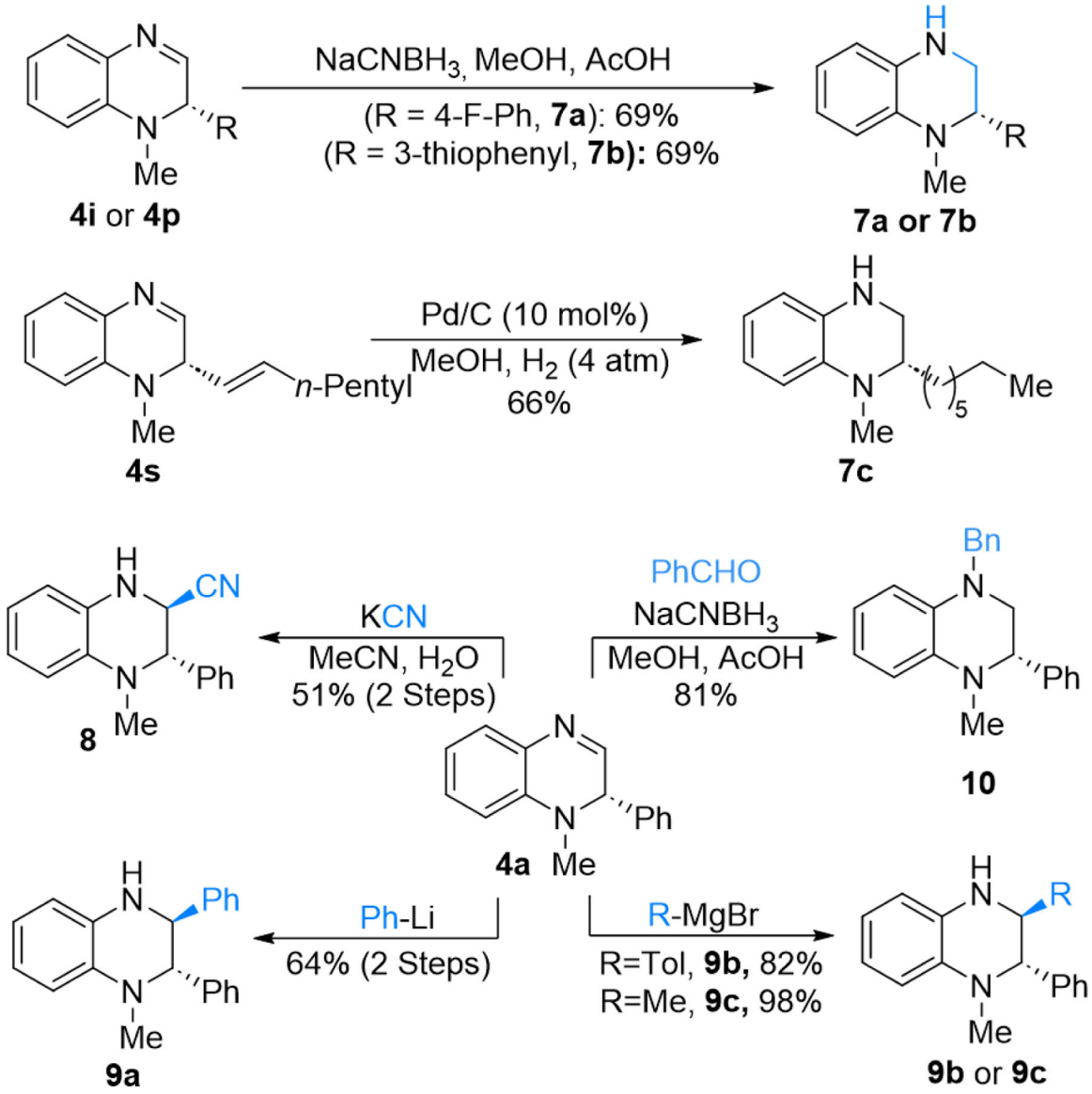


Scheme 2.

Scope of the Boronic Acids for Dearomatization of Quinoxalinium Salt 3a.



Scheme 3.
Scope of Substituted Quinoxalinium Saltsa

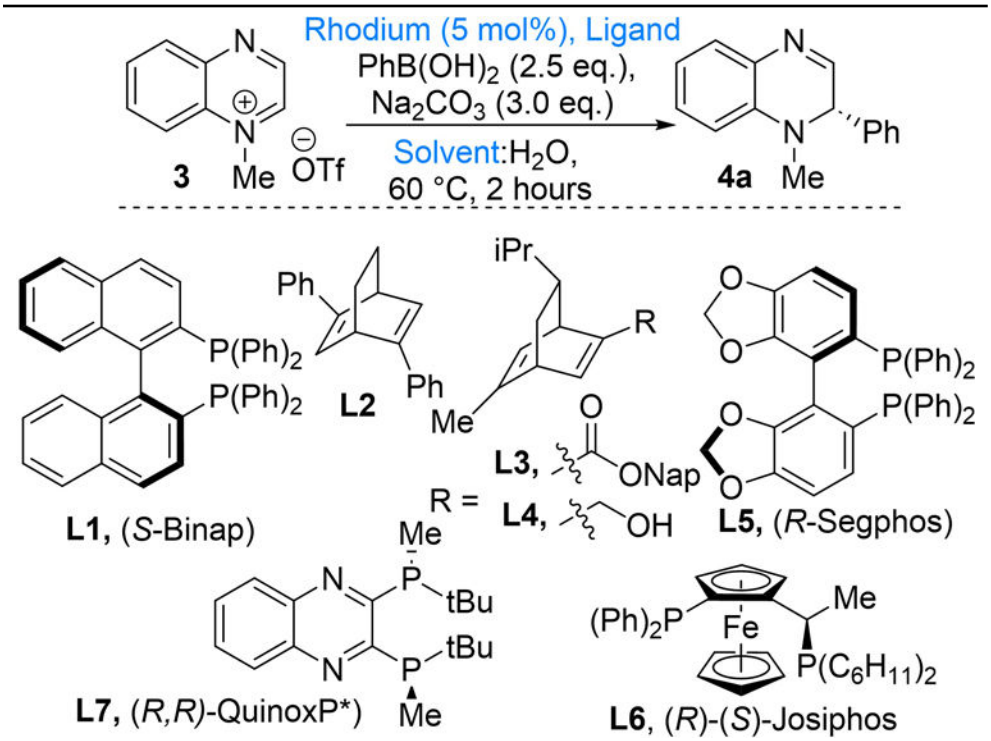


Scheme 4.

Synthesis of Tetrahydroquinoxaline Derivatives from Dihyroquinoxalines.

Table 1.

Optimization of the Reaction Conditionsa



entry	solvent/water	ligand (mol %)	yield (%)[b] (% ee[c])
1	dioxane (10:1)	**L1** (5)	47 (62)
2	Et_2O (10:1)	**L1** (5)	12 (50)
3	PhMe (10:1)	**L1** (5)	9 (4)
4	DME (10:1)	**L1** (5)	18 (62)
5	dioxane (10:1)	none	5 (ND)
6[d]	dioxane (10:1)	**L2** (10)	17 (70)
7[d]	dioxane (10:1)	**L3** (20)	39 (64)
8[d]	dioxane (10:1)	**L4** (20)	57 (82)
9	dioxane (10:1)	**L5** (5)	27 (76)
10	dioxane (10:1)	**L6** (5)	20 (93)
11	dioxane (10:1)	**L7** (5)	73 (93)
12[e]	dioxane (10:1)	**L7** (7)	80 (94)
13	dioxane (5:1)	**L7** (5)	68 (ND)
14	dioxane (20:1)	**L7** (5)	51 (ND)
15	dioxane[f]	**L7** (5)	53 (74)
16[g]	dioxane (10:1	none	8 (ND)