Synthesis of chiral boranes via asymmetric insertion of carbenes into B-H bonds catalyzed by the rhodium(I) diene complex

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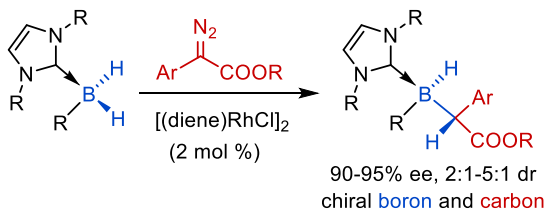
Supporting Information Placeholder

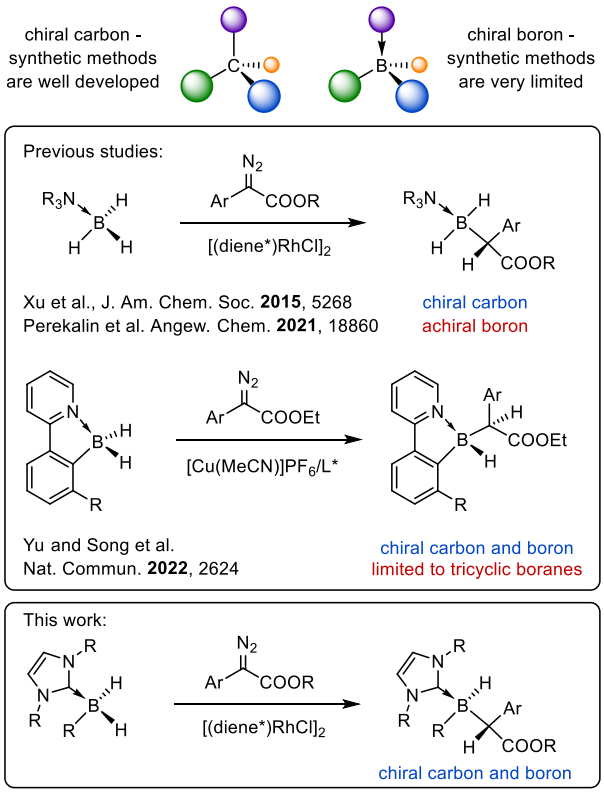


ABSTRACT: Asymmetric insertion of arydiazoacetates into B-H bonds of NHC-BH2R adducts gives rare compounds with chiral boron centers. The reaction is catalyzed by the rhodium(I) complex with the chiral diene ligand $^{t}Bu_2$-TFB, which can be conveniently synthesized by diastereoselective coordination of the racemic diene with (*S*–Salox)Rh(CO)$_2$. The target boranes were obtained typically in 75–90% yields with 90-95% ee and 2:1-5:1 dr.

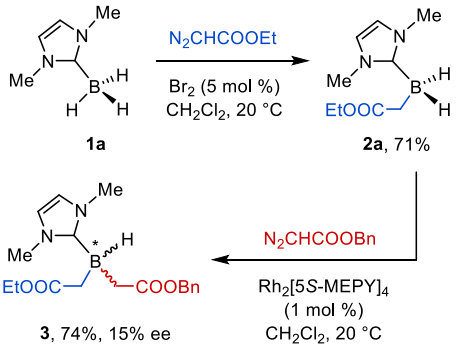
Compounds with chiral carbon atoms play a vital role in organic chemistry, and therefore numerous methods for their synthesis have been developed. On the contrary, compounds with chiral boron atoms have been only cursory studied, despite their potential utility arising from the diverse reactivity of organoboranes. Methods for the synthesis of such compounds are still very limited.[1–4] About a decade ago, Li and Curran reported the first example of rhodium-catalyzed insertion of diazo compounds into B-H bonds to form the racemic boranes with a general formula NHC-BHRR', a couple of which were separated into enantiomers using preparative chiral chromatography.[5] More recently, Yu and Song et al. demonstrated the first enantioselective variant of this transformation catalyzed by the copper complexes with a bis-oxazoline ligands (Scheme 1).[6] Although this method is very remarkable, it is suitable only for boron derivatives of 7-subsituted-2-phenylpyridines and similar heterocycles.

Recently, Xu et al.,[7] and other authors,[8] including our group,[9] have shown that iron, copper, ruthenium, and rhodium complexes can catalyze the insertion of diazo compounds into B-H bonds to give boranes with chiral α-carbon atoms. Herein, we report the application of this approach for the synthesis of compounds containing chiral boron atoms.

Scheme 1. Asymmetric insertion into B-H bonds.



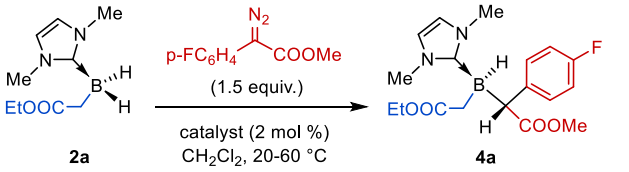
Scheme 2. Sequential insertion of two different diazoacetates into B–H bonds generates a chiral boron center.



We selected the borane adduct with dimethyl-imidazol-2-ylidene $ImNMe_2$-BH_3 (**1a**, Scheme 2) as the starting compound for this study due to its high nucleophilicity and the strong carbene–boron bond, which can prevent potential racemization. In accordance with the reported procedure,[10] the reaction of **1a** with ethyl diazoacetate in the presence of catalytic amounts of Br_2 gave the expected prochiral borane $ImNMe_2$-BH_2CH_2COOEt (**2a**, 71%). Subsequent insertion of benzyl diazoacetate provided compound **3** with a stereogenic boron center. However, despite the extensive screening of chiral copper and rhodium catalysts (see SI), we were able to obtain **3** with a maximum enantioselectivity of only 15% ee using complex Rh_2[5*S*-MEPY]$_4$.[11] Therefore, we switched to the insertion of p-fluoro-phenyldiazoacetate into the prochiral borane **2a** which gives the product **4a** with the simultaneous formation of chiral boron and carbon centers (Table 1). Thanks to electronic and steric stabilization of the aryl group this diazo compound reacted more slowly and selectively. Hence, after screening of various catalysts, we were able to obtain the target borane **4a** in a good yield of 80% with a 5:1 diastereomeric ratio and excellent enantiomeric purity of 93% ee (entry 6). A control reaction with the achiral catalyst $Rh_2(OAc)_4$ gave the racemic product **4a** with 97% yield and 1:1 dr (entry 7).[5]

The most selective catalyst for this reaction was found to be the rhodium(I) complex **5** with the bulky chiral tetrafluorobenzobarrelene ligand *R,R*-^{t}Bu_2TFB (Scheme 3). It was synthesized by a new convenient procedure in three steps from $RhCl_3$. First, rhodium was coordinated with the auxiliary chiral ligand *S*-Salox[12] to give the carbonyl complex (*S*-Salox)Rh(CO)$_2$. Subsequent replacement of CO with an excess of the racemic diene ligand ^{t}Bu_2TFB proceeded with high selectivity and gave the intermediate complex (*R,R*-^{t}Bu_2TFB)Rh(*S*-Salox) (**7**) as the most stable diastereomer.[9] Finally, removal of the auxiliary *S*-Salox by HCl gave the enantiomerically pure catalyst **5** in 65% overall yield and >99% ee.

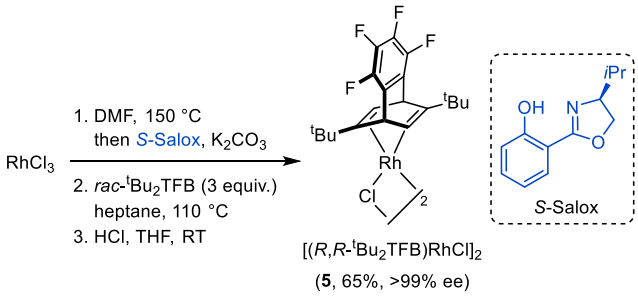
Table 1. Optimization of the catalyst for the asymmetric insertion into B-H bonds.



entry	catalyst	yield (%)[a]	ee (%)[b]
1	Rh_2(*S*-PTPA)$_4$	18	33
2	Rh_2[*S*-TPPTTL]$_4$	22	40
3	Rh_2(*S*-NTTL)$_4$	33	62
4	Rh_2[*S*-PTTL]$_4$	28	75
5[c]	[(*R,R*-^{i}Pr_2TFB)RhCl]$_2$	82	87
6[c]	[(*R,R*-^{t}Bu_2TFB)RhCl]$_2$	80	93
7	$Rh_2(OAc)_2$	97	-

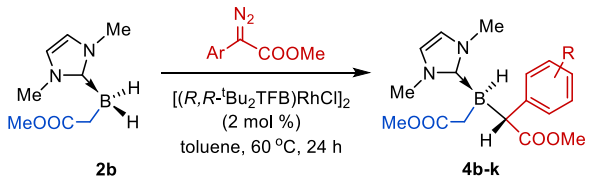
[a] NMR yields for the mixtures of diastereomers are given. [b] Measured for the major diastereomer by chiral HPLC. [c] Reaction was conducted at 60 °C in toluene.

Scheme 3. Synthesis of the diene rhodium catalyst via diastereoselective coordination.



With the optimized catalyst in hand, we moved on to explore the scope of the asymmetric insertion reaction (Table 2). It was found that aryldiazoacetates with halogen, acetyl, methyl, and phenyl substituents in para-positions cleanly reacted with the prochiral borane **2b** and gave the target products **4b-h** in high yields (87-94%) with decent diastereoselecitvity (3:1-5:1) and excellent enantioselectivity of both diastereomers (86-96% ee). Somewhat lower yields of ca. 40% were observed for p-methoxy- (**4i**) and m-difluoro-substituted derivatives (**4j**). The latter reacted slowly, but with remarkable selectivity, giving only one diastereomer. On the other hand, the reaction did not proceed in the case para-nitro-phenyldiazoacetate, which was probably not nucleophilic enough to form the metal-carbene intermediate from the catalyst **5**. The o-fluoro and o-methoxy aryldiazoacetates were also inactive, apparently for steric reasons. Such limitations have not been observed for the reactions with less hindered diene rhodium catalysts.[7,9]

Table 2. Scope of aryldiazoacetates suitable for the asymmetric insertion reaction.



product	R	yield (%)	dr	ee (major)	ee (minor)
4b	H	84[a]	3:1	89	89
4c	4-F	89	5:1	88	94
4d	4-Cl	77	3:1	93	93
4e	4-Br	81	5:1	93	86
4f	4-Ac	75	3:1	88	-[b]
4g	4-Me	88	3:1	94	95
4h	4-Ph	87	5:2	94	92
4i	4-OMe	41	4:1	96	93
4j	3,5-F_2	44	>10:1	92	-

[a] on 2 mmol scale, [b] diastereomers were not separated.

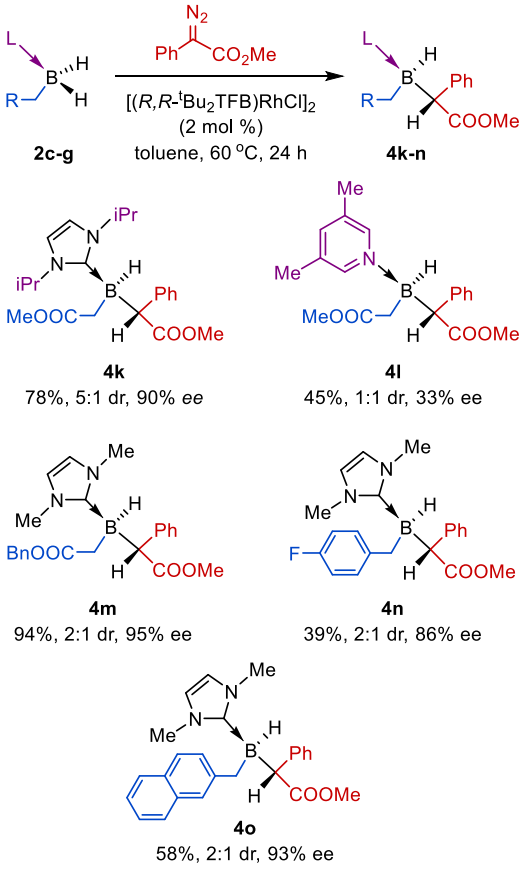
Rhodium-catalyzed asymmetric insertion can also be carried out with some other prochiral boranes **2c-g** (Scheme 4). For example, borane adduct with di-isopropyl-heterocyclic carbene ImNiPr$_2$-BH$_2$-CH$_2$COOMe cleanly reacted with methyl phenyldiazoacetate to give target product **4k**, while more hindered adduct with *ortho*-diisopropylphenyl-carbene was completely inactive. Dimethylpyridine-borane is less nucleophilic[13] than carbene-borane **2b**, therefore it reacted notably slower and gave the corresponding product **4l** in only 45% yield and with 33% ee. Interestingly, the product **4l** was obtained as a 1:1 mixture of diastereomers, apparently because of the slow racemization of the boron center via dissociation of pyridine (see SI).

Prochiral boranes with benzyl and naphthyl substituents ImNMe$_2$-BH$_2$–CH$_2$R were notably less stable than **2b**, but nevertheless they can converted into the corresponding product **4n**,**o**, albeit in lower yields (40-60%) and diastereoselectivity (2:1). The vinyl borane ImNMe$_2$-BH$_2$-CMe=CHPh, the cyano borane ImNMe$_2$-BH$_2$-CN, and the phosphine borane Bu$_3$P-BH$_2$-CH$_2$COOMe did not react with phenyldiazoacetate in the presence of the catalyst **5**.

All the obtained boranes **4**, except **4n**,**o**, were air- and moisture-stable. The diastereomers of **4**, except for **4f**, **4l**, and **4o** were successfully separated by column or thin-plate chromatography. The absolute configuration of both stereocenters was proposed based on the X-ray diffraction study of the minor diastereomer of the product **4e** (Figure 1). The observed configuration of the carbon center matched with the one previously reported for the asymmetric insertion into amino-borane adducts.[9]

We proposed a possible mechanism of the asymmetric insertion reaction based on the previous theoretical and experimental studies (Scheme 5).[5,7,9] First, the monomeric form of the rhodium complex **5** reacts with phenyl-diazoacetate to give the intermediate carbene complex **A**.

Scheme 4. Scope of prochiral boranes suitable for the asymmetric insertion reaction.



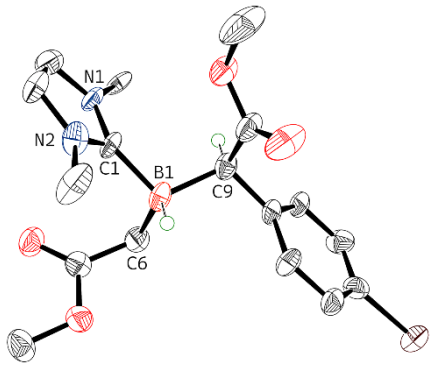
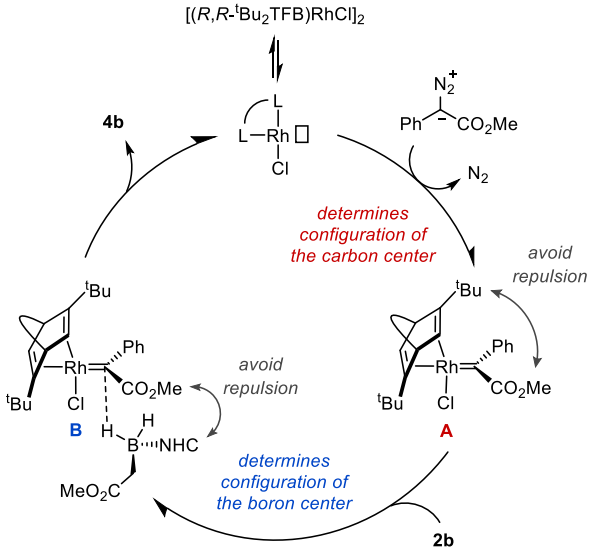


Figure 1. X-ray structure of the minor diastereomer of the chiral borane **4e**. Hydrogen atoms, except those connected to the chiral centers, are omitted for clarity.

Since the carbene atom in **A** is electrophilic, the donor phenyl ring assumes coplanar conformation with Rh=C bond, while COOMe group stay perpendicular. Therefore, the more stable carbene intermediate has less bulky phenyl group adjacent to the ^{t}Bu substituent of diene ligand.[9] This orientation determines the future chiral configuration of the carbon atom. Next, the electrophilic carbene interacts with the nucleophilic B–H bond of the borane **2b** via transition state **B**. In order to avoid steric repulsion between COOMe and NHC groups, the borane approaches with less bulky substituent CH_2R positioned under the carboxylic group. This step determines the chiral configuration of the boron atom and the structure of the major diastereomer. Brief DFT modelling at B97-3c level supported this hypothesis (see SI).

In summary, we developed a new method for the synthesis of rare chiral compounds with stereogenic boron atoms via the asymmetric insertion of diazo compounds into prochiral alkylborane adducts with NHC (**2**). The target products **4** were obtained typically in 75-90% yields with 2:1-5:1 dr and 90-95% ee. The most selective catalyst for this reaction was the rhodium diene complex $[(R,R\text{-}^t\text{Bu}_2\text{TFB})\text{RhCl}_2]_2$ (**5**), which was be prepared by a new convenient method by diastereoselective coordination of the racemic diene ligand.

Scheme 5. The proposed mechanism of asymmetric insertion reaction.



ASSOCIATED CONTENT

Supporting Information

Experimental details, copies of NMR spectra, X-ray crystallographic data, details of DFT calculations (PDF).

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