Asymmetric Catalysis

DOI: 10.1002/ange.201001883

Rhodium-Catalyzed Asymmetric Conjugate Addition of Organoboronic Acids to Nitroalkenes Using Chiral Bicyclo[3.3.0] Diene Ligands**

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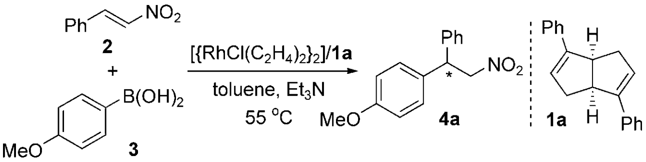
In recent years, the use of transition-metal-catalyzed reactions have been an important and general method in carbon–carbon and carbon–heteroatom bond-forming synthesis.[1] Among them, the rhodium-catalyzed asymmetric conjugate addition of organoboronic acids to electron-deficient olefins, pioneered by Miyaura, Hayashi, and co-workers,[2] has been established as one of the most powerful and convenient tools for the enantioselective synthesis of β-substituted functionalized compounds. In particular, excellent results were achieved in the addition to α,β-unsaturated carbonyl compounds.[3] However, despite the great synthetic importance of nitro compounds,[4] it is surprising that far fewer studies reported the efficient asymmetric addition of boronic acids to nitroalkenes, most likely because of the difficulty in controlling the reaction stereoselectivity.[5] In fact, high enantioselectivities were only achieved by the Hayashi group in the asymmetric addition of organoboronic acids to α-substituted 1-nitroalkenes using a rhodium/binap (binap = 2,2-bis(diphenylphosphanyl)-1,1 -binaphthyl) catalyst.[6] In other reports,[7] low levels of enantiomeric enrichment (< 50 % *ee*) were often observed with general 1-nitroalkene substrates that lack α substitutents. Therefore, the development of a capable catalyst system for efficient asymmetric boronic acid addition to nitroalkenes is highly desirable. Herein, we report our preliminary results on the rhodium-catalyzed asymmetric addition of organoboronic acids to nitroalkenes that lack α substitutents; high enantiocontrol is afforded using chiral bicyclo[3.3.0] diene ligands.

In 2007, we reported our discovery of a new family of C_2-symmetric chiral diene ligands bearing a simple bicyclo[3.3.0] backbone; these ligands were successfully applied in the rhodium-catalyzed enantioselective arylation of *N*-tosylarylimines and the 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds under mild conditions.[8] Inspired by these successes, we wondered whether these rhodium/diene complexes could also act as effective catalysts for the asymmetric addition of boronic acids to nitroalkenes. In spite of the recent significant advances, there has been no report on the use of chiral diene ligands[9] in this field.



Scheme 1. Initial attempts on using bicyclo[3.3.0] diene ligand.

Our initial investigation was carried out by examining the reaction of nitrostyrene **2** with *para*-anisylboronic acid (**3**) in the presence of chiral diene ligand **1a** (3 mol %) under the reaction conditions previously reported[8a] for the arylation of *N*-tosylarylimines with arylboronic acids (Scheme 1). However, the result was disappointing. The addition product **4a** was obtained in only 9 % yield, albeit with moderate enantioselectivity (40 %), and a large amount of starting material **2** was recovered. Considering the known catalytic cycle for the 1,4-addition of organoboron reagents to activated alkenes,[10] it is likely that the low yield can be attributed to poor catalyst regeneration from its rhodium nitronate intermediate in the hydrolysis step. Indeed, we were pleased to find that the reaction provided much better yield (70 %) and enantioselectivity (68 %) when performed in the presence of a stoichiometric amount of rhodium/**1a** catalyst. This result indicates the possibility of related asymmetric catalysis by new chiral rhodium/diene complex. A potential solution to the catalyst regeneration problem could be by tuning the reaction conditions.

To achieve an efficient catalytic process, the reaction conditions were carefully screened. One concern was that the in situ generation of the rhodium/diene catalyst would be facilitated by acidic conditions. After extensive studies, we found that the expected catalytic cycle took place when potassium acid fluoride (KHF_2) was employed in the reaction (Table 1). Further optimization of the conditions led to the

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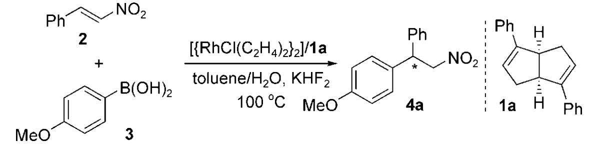
[**] We thank the National Natural Science Foundation of China, the Chinese Academy of Sciences, the Shanghai Municipal Committee of Science and Technology (09JC1417300, 08QH14027), and the Major State Basic Research Development Program (2010CB833302) for their generous financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001883.

Table 1: Exploration and optimization of the conjugate addition reaction.

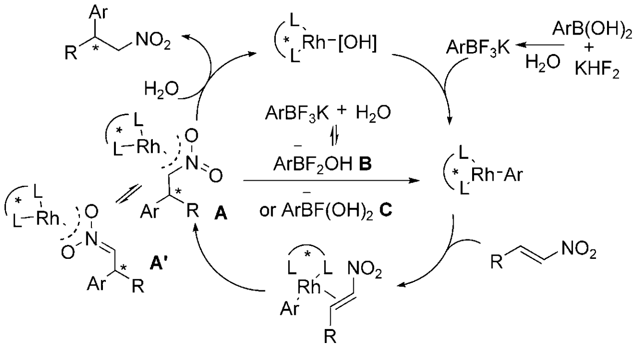


Entry[a]	**3** [equiv]	KHF_2 [equiv]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	1.1	5	14	76	68
2	1.5	5	14	97	68
3	1.5	3	1	98	70
4	1.5	2	1	96	70
5	1.5	1	1	92	70
6	1.5	0	19	60	68
7	1.5[d]	0	1	91	69

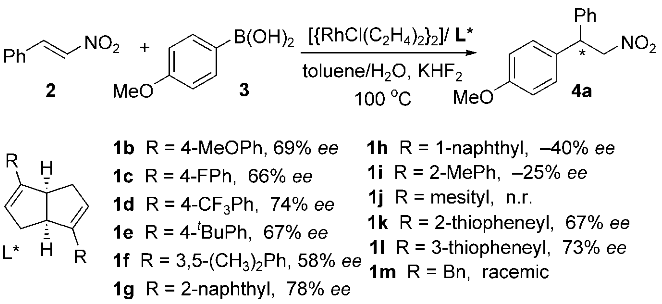
[a] The reaction was carried out on a 0.5 mmol scale with [{RhCl(C_2H_4)$_2$}$_2$] (0.0075 mmol), diene **1g** (0.0165 mmol, 1.1 equiv to Rh) in toluene/H_2O at 100 °C. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The corresponding trifluoroborate *p*-$MeOC_6H_4BF_3K$ was used.

formation of addition product in 98 % yield and 70 % *ee* when nitrostyrene **2** was treated with a small excess of *para*-anisylboronic acid (1.5 equiv) in the presence of 3 equivalents of KHF_2 in toluene/water (10:1) at 100 °C for 1 hour by the catalysis of rhodium/**1a** (3 mol %; Table 1, entry 3). Since KHF_2 in aqueous conditions can react with organoboronic acids to generate potassium organotrifluoroborates,[11,12] which are also capable of transmetalation with rhodium for addition reactions to unsaturated substrates, we speculated that the transformation was actually promoted by an organotrifluoroborate species formed in situ. To better understand the reaction, several control experiments were performed. It was found that the direct use of the corresponding potassium trifluoroborate (*p*-$MeOC_6H_4BF_3K$) in the presence of water did give comparable results (91 % yield, 69 % *ee*; Table 1, entry 7). In contrast, a significant decrease in the reaction rate was observed using boronic acid under identical conditions (Table 1, entry 6). The presence of excess KHF_2 also had a detrimental effect on the reaction rate (Table 1, entries 1 and 2). In line with most 1,4-addition processes, a small amount of water was essential for good conversion, and almost no reaction occurred under anhydrous conditions. Although the exact mechanism remains unclear, and the possibility of an equilibrium between the fluoroborate and the boronic acid is not ruled out, these results may suggest a pathway of fast transmetalation between the rhodium nitronate (**A**/**A′**) and the relevant organoborate intermediate (**B**/**C**) benefited by hydrolysis of potassium organotrifluoroborate (Scheme 2). It is worth noting that the fluoride ions may also play an important role in stabilizing the various catalytic intermediates.[13]

With the catalytic system developed, we then focused our efforts on the use of different chiral diene ligands to attain excellent enantioselectivity. A series of bicyclo[3.3.0] dienes with various R substituents were evaluated (Scheme 3). In most cases, the reaction proceeded smoothly under the catalysis of rhodium/**1**. The enantioselectivity could be increased to 78 % by using 2-naphthyl-substituted diene **1g** as the ligand. We also tested the use of an (*R*)-binap ligand under same conditions; however, only trace amounts of product was observed. As the catalytic asymmetric addition of organoboronic acids to α-unsubstituted nitroalkenes with high enantiocontrol remains unprecedented,[14] this result represents a rather promising achievement.



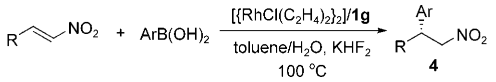
Scheme 2. Proposed reaction mechanism.



Scheme 3. Evaluation of catalytic activities of chiral diene ligands. n.r. = no reaction.

To explore the scope of this rhodium/diene catalyzed process, a variety of boronic acids with diverse steric and electronic properties were tested with aliphatic and aromatic nitroalkenes (Table 2). Under the optimized conditions, we were pleased to find that the addition reactions universally gave the expected products in very high yields and moderate to good *ee* values. Excellent enantioselectivities (95–97 %) were observed in the cases using sterically more hindered arylboronic acids, such as 1-naphthylboronic acid and 2-tolylboronic acid (Table 2, entries 8, 10, 12, and 14). The electron-withdrawing group on the phenyl ring of the boronic acids was helpful for obtaining high enantioselectivity (Table 2, entries 2–4). In contrast, the electronic properties of the substituent on the phenyl ring of the substrates did not seem to affect the reaction stereoselectivity significantly (Table 2, entries 8 and 11–13). More interestingly, when aliphatic 2-nitrovinylcyclohexane was subjected to the conjugate addition with 4-anisylboronic acid, the same level of enantioselectivity was observed (Table 2, entry 16). The use of linear nitroolefin 1-nitrohexene as the substrate resulted in appreciably lower enantioselectivity compared to 2-nitrovinylcyclohexane; however, a dramatic increase in the selectivity was obtained when sterically encumbered 2-tolylboronic acid was employed (Table 2, entries 17 and 18). It is worth noting that these results are among the best in the asymmetric addition of organoboronic acids to nitroalkenes

Table 2: Asymmetric conjugate addition to nitroalkenes catalyzed by [Rh]/**1g**.

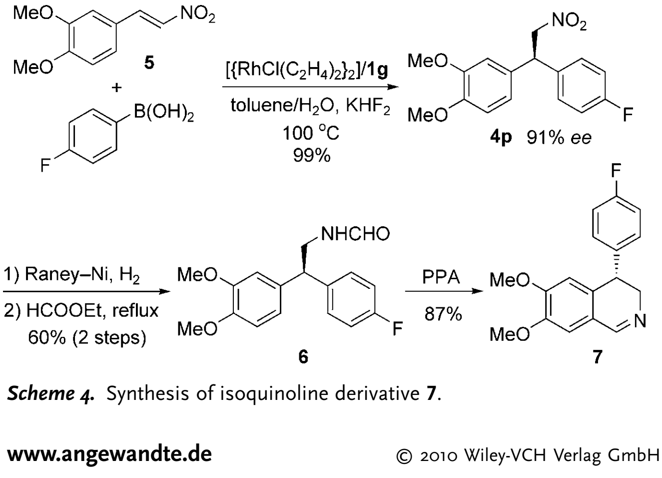


Entry[a]	R	Ar	4	Yield [%][b]	*ee* [%][c]
1	Ph	4-MeOC$_6$H$_4$	**4a**	96	78 (*R*)
2	Ph	4-FC$_6$H$_4$	**4b**	96	89 (*R*)
3	Ph	4-ClC$_6$H$_4$	**4c**	92	92 (*R*)
4	Ph	4-BrC$_6$H$_4$	**4d**	91	92 (*R*)
5	Ph	4-MeC$_6$H$_4$	**4e**	95	81 (*R*)
6	Ph	4-*t*BuC$_6$H$_4$	**4f**	92	81 (*R*)
7	Ph	3-ClC$_6$H$_4$	**4g**	99	92 (*R*)
8	Ph	2-MeC$_6$H$_4$	**4h**	85	97 (*R*)
9	Ph	2-Np	**4i**	99	84 (*R*)
10	Ph	1-Np	**4j**	92	95 (*R*)
11	4-MeOC$_6$H$_4$	Ph	**4a′**	99	89 (*S*)
12	4-MeOC$_6$H$_4$	2-MeC$_6$H$_4$	**4k**	85	97 (*R*)
13	4-ClC$_6$H$_4$	Ph	**4c′**	95	82 (*S*)
14	4-ClC$_6$H$_4$	2-MeC$_6$H$_4$	**4l**	97	97 (*R*)
15	1-Np	Ph	**4j′**	99	85 (*S*)
16	C$_6$H$_{11}$	4-MeOC$_6$H$_4$	**4m**	90	84 (*R*)
17	*n*Bu	4-MeOC$_6$H$_4$	**4n**	81	61 (*R*)
18	*n*Bu	2-MeC$_6$H$_4$	**4o**	95	86 (*R*)

[a] The reaction was carried out on a 0.5 mmol scale with 1.5 equiv of arylboronic acid, [{RhCl(C$_2$H$_4$)$_2$}$_2$] (0.0075 mmol), diene **1g** (0.0165 mmol, 1.1 equiv to Rh), and 3 equiv of KHF$_2$ in toluene/H$_2$O at 100 °C for 4–7 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. Np = napthyl.

that lack α substitutents. Gratifyingly, the stereochemistry of the newly formed stereogenic center of product **4d** (Table 2, entry 4) was determined to be *R* by X-ray crystallography.[15] Assuming an analogous reaction mechanism, the absolute configuration of the products obtained was assigned as indicated in the table.

To further demonstrate the synthetic utility of this methodology, the transformation of nitroalkene **5** into pharmaceutically interesting isoquinoline derivative **7** was also carried out (Scheme 4). The enantioselective addition of 4-furophenylboronic acid to **5** in the presence of a rhodium/**1g** catalyst afforded product **4p** in 99% yield with 91% *ee*. Raney nickel reduction followed by formamide formation provided the intermediate **6**, which underwent Bischler–Napieralski cyclization to form optically active (*S*)-4-(4-fluorophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**7**) in good yield in three steps.



Scheme 4. Synthesis of isoquinoline derivative **7**.

In summary, we have developed a rhodium-diene catalyzed asymmetric conjugate addition of organoboronic acids to challenging α-unsubstituted nitroalkene substrates, for which chiral bicyclo[3.3.0] dienes were identified as superior ligands. Under optimal conditions, the reaction proceeds with high enantioselectivity to give a broad range of synthetically useful chiral β,β-disubstituted nitroalkanes. The simple use of boronic acids in combination with potassium acid fluoride as reactive organoboron reagents is a promising alternative to organotrifluoroborates in transition-metal-catalyzed reactions. Further investigation on the reaction mechanism as well as extensions of this new reaction system are underway in our laboratories.

Experimental Section

General procedure for the asymmetric conjugate addition reaction (Table 2): Under a nitrogen atmosphere, a mixture of [{RhCl(C$_2$H$_4$)$_2$}$_2$] (2.9 mg, 0.007 mmol), diene ligand **1g** (6.0 mg, 0.023 mmol), and arylboronic acid (0.75 mmol) in toluene (1 mL) was stirred at 60 °C for 30 min. Then nitroalkene (0.5 mmol) in toluene (1 mL) and aqueous KHF$_2$ (3.0 M, 0.5 mL) were added successively. After being heated to reflux at 100 °C for 4–7 h, the reaction was cooled to room temperature and water (20 mL) was added. The mixture was extracted with ethyl acetate and the combined organic phases were washed with brine and dried over anhydrous Na$_2$SO$_4$. After being concentrated under reduced pressure, the residue was purified by column chromatography on silica gel to afford the desired product **4**.

Received: March 30, 2010
Revised: April 22, 2010
Published online: July 7, 2010

Keywords: asymmetric catalysis · diene ligands · conjugate addition · nitroalkenes · rhodium

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[13] The use of KF as additive in the boronic acid addition reaction was also examined; the reaction did not give any products, even at 55 °C, thus suggesting that the fluoride ion itself is not helpful for a smooth reaction process.

[14] In the work by Hayashi and co-workers (Ref. [6]), it was mentioned that the asymmetric addition of phenylboronic acid to (*E*)-1-nitro-3,3-dimethylbutene catalyzed by Rh/binap could give the corresponding product with 99 % *ee*; however, the yield was not ideal in only 5 %. In our hands, when aromatic substrate (*E*)-1-chloro-4-(2-nitrovinyl)benzene was subjected to addition with phenylboronic acid under their conditions, a low yield (16 %) as well as enantioselectivity (8 % *ee*) was observed.

[15] See the Supporting Information for details. CCDC 770554 (**4d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.