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Application of Rhodium Complexes of Chiral Diphenylphosphino-Functionalized N-Heterocyclic Carbenes as Catalysts in Enantioselective Conjugate Additions of Arylboronic Acids

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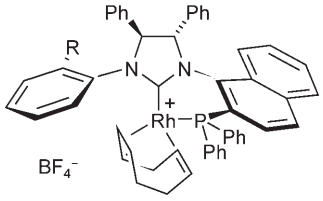
Abstract: The Rh complex **1a** of (*S*,*S*)-1-(2-diphenylphosphanylnaphthalen-1-yl)-3-(2-isopropylphenyl)-4,5-diphenylimidazolidin-2-ylidene was found to promote enantioselective conjugate additions of arylboronic acids to enones and α,β-unsaturated esters with up to 98% yield and >99% ee. Products of the latter reaction can be transformed into GABA antagonists.

Keywords: asymmetric catalysis; boronic acids; chiral N-heterocyclic carbenes; conjugate addition; rhodium

N-Heterocyclic carbenes (NHCs) have found useful applications as ligands of late transition metal catalysts or as organocatalysts over the last few years.[1] An emerging area of application of NHCs is asymmetric catalysis using chiral NHCs.[2] In a previous report, we have described a short and efficient route to the rhodium complex **1a** (Figure 1).[3] This complex is stable against air and moisture. It efficiently catalyzed asymmetric hydrogenations of substituted acrylic acid derivatives.[2] Herein, we report the application of **1a** as a new catalyst for asymmetric conjugate additions of arylboronic acids to electron-deficient alkenes.[4] This reaction was previously employed by us for the synthesis of GABA analogues using BINAP as a chiral ligand.[5]

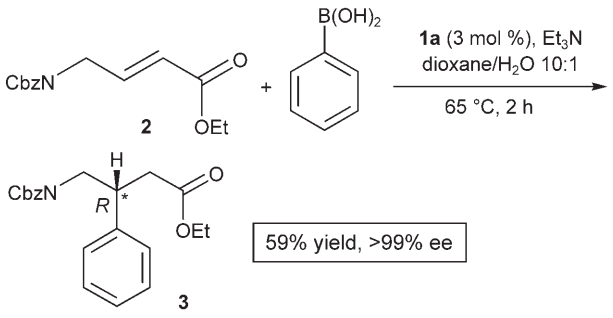
Complex **1a** was obtained as a 2:1 mixture of isomers.[3] We had assumed that these isomers are atropisomers with respect to the *i*-PrC_6H_4–N bond. In order to corroborate this hypothesis, we decided to synthesize the rhodium complex **1b** (Figure 1), which cannot give rise to atropisomers with respect to the C_6H_5–N bond. Complex **1b** was prepared *via* a route analogous to that reported for **1a**. As anticipated, ^{31}P NMR ($CDCl_3$) indicated for **1b** the presence of only one compound, characterized by a doublet at $\delta = 21.7$ ppm (d, $J_{Rh,P} = 163.9$ Hz).



1a: R = *i*-Pr
1b: R = H

Figure 1. Chiral rhodium(I) carbene complexes **1a** and **1b**.

In our previous synthesis of GABA analogues according to Scheme 1 we used a catalyst prepared from (*R*)- or (*S*)-BINAP and [Rh(acac)(C_2H_4)$_2$] (3 mol %); the addition reaction required a reaction time of 24–48 h at 100 °C.[5] Among a series of arylboronic acids the parent compound phenylboronic acid gave the lowest enantiomeric excess of only 86% in the addition to ester **2**. In view of the importance of 4-amino-3-aryl-butyric acids,[6] improvement was desirable. Naturally, we evaluated complex **1a** as catalyst, when it became available. For this purpose, the α,β-unsaturated ester **2** was reacted with phenylboronic acid (2.0 equivs.) using 3 mol % of **1a** as catalyst. Remarkably, the addition product (*R*)-**3** was obtained with >99% ee[7] within 2 h at a reaction temperature of 65 °C. This is an enormous improvement in comparison to our previous results. Even considered



Scheme 1. Use of complex **1a** as catalyst in the conjugate addition of phenylboronic acid to α,β-unsaturated ester **3**.

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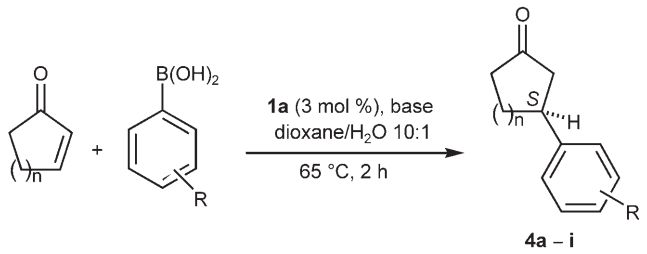

Scheme 2. Conjugate addition of arylboronic acids to cyclic enones.

in the more general context of additions of boronic acids to α,β-unsaturated esters it is remarkable; the best ee values so far obtained are in the range 90–96%, to the best of our knowledge,[4] with the exception of an addition to an unsaturated lactone wherein 98% ee was achieved.[4j]

The excellent result described above prompted us to study the catalytic activity of **1a** in reactions of cyclic enones with various arylboronic acids (Scheme 2). The reaction conditions were optimized by using 2-cyclohexenone and phenylboronic acid as benchmark substrates (Table 1).

2-Cyclohexenone was initially reacted at room temperature with an excess of phenylboronic acid (2.0 equivs.) in dioxane/H_2O (10:1) in the presence of Cs_2CO_3 (2.0 equivs.) as base. No reaction took place and the substrates were recovered. Better results were obtained by heating the reaction mixture at 65 °C for 2 h: 74% yield, 67% ee (entry 1). Improved yield and ee resulted upon using a homogeneous mixture with Et_3N as a base: 91% yield, 94% ee (entry 2). Noteworthy, no reaction occurred in the absence of a base. Decreasing the amount of the arylboronic acid to 1.5 equivs. afforded the addition product in a lower yield (53%), yet high ee of 93% (entry 3). Other bases, for example, diisopropylethylamine or diethylmethylamine, gave no further improvement with respect to yield and enantiomeric excess (entries 4 and 5); no product was observed in the presence of DBU, DABCO, piperidine or 3-methylpyrrolidine. Only traces (<10%) of product were formed under the optimal reaction conditions with a decreased catalyst loading of 1 mol %.

The procedure was then applied successfully to a variety of arylboronic acids, containing both electron-withdrawing or electron-donating substituents. Very high yields and >90% ee were generally obtained (entries 6–10). While the sterically hindered 2-tolylboronic acid also gave the expected addition product with 87% yield and 84% ee (entry 11), the conjugate addition of 2-naphthylboronic acid afforded only naphthalene, resulting from the hydrolysis of the arylboronic acid.

The reaction of 2-cyclopentenone with phenylboronic acid gave the expected product in 73% yield and 88% ee (entry 12); the reaction rate was lower than that with 2-cyclohexenone, and a large excess of phenylboronic acid (5.0 equivs.) has to be used in order to obtain full conversion of the enone. 2-Cycloheptenone afforded the expected product in 50% yield and 78% ee under standard conditions (entry 13). Increasing the amount of phenylboronic acid to 5.0 equivs. did not improve the yield but gave rise to a lower ee of 49%. A decrease of enantioselectivity with >2.0 equivs. of arylboronic acid was generally observed. Much lower yield and ee was obtained with **1b** as catalyst, presumably due to rapid degradation

Table 1. Enantioselective conjugate additions of arylboronic acids to cyclic enones according to Scheme 2 (reaction temperature: 65 °C, solvent: dioxane/H_2O, 10:1, reaction time: 2 h).

Entry	n	R	Base	Conditions[a]	Product	Yield [%][b, c]	ee [%][d]
1	2	H	Cs_2CO_3	A	**4a**	74	67
2	2	H	Et_3N	A	**4a**	91	94
3	2	H	Et_3N	B	**4a**	53	93
4	2	H	*i*-Pr_2EtN	A	**4a**	91	93
5	2	H	Et_2NMe	A	**4a**	91	94
6	2	3-Cl	Et_3N	A	**4b**	79	94
7	2	4-Cl	Et_3N	A	**4c**	98	94
8	2	4-F	Et_3N	A	**4d**	93	94
9	2	4-CF_3	Et_3N	A	**4e**	73	95
10	2	4-OMe	Et_3N	A	**4f**	96	95
11	2	2-Me	Et_3N	A	**4g**	87	84
12	1	H	Et_3N	C	**4h**	73	88
13	3	H	Et_3N	A	**4i**	50	78

[a] Conditions A: 1.0 equiv. of enone, 2.0 equivs. of boronic acid, 2.0 equivs. of base. Conditions B: 1.0 equiv. of enone, 1.5 equivs. of boronic acid, 2.0 equivs. of base. Conditions C: 1.0 equiv. of enone, 5.0 equivs. of boronic acid, 2.0 equivs. of base.

[b] Isolated yield after flash chromatography on silica gel.

[c] ^1H and ^{13}C NMR spectra are in accordance with literature reports.[4i]

[d] Determined by chiral HPLC using separation conditions described in the literature.[4i]

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of this compound under the reaction conditions. Similar results were obtained upon replacing the BF_4^- counter anion by PF_6^- in **1b**.

Considering that our catalyst is a fairly new one and that this type of C,P-catalysts has been relatively little explored, ee values of up to 95% are respectable. However, it must be pointed out that for the addition of arylboronic acids to cyclic enones better results (>99% ee) have been already reported.[2i,4a–d]

Recently, Hayashi et al. described the use of organozinc reagents in the rhodium-catalyzed conjugate addition to enones.[8] However, when phenylzinc chloride was reacted with 2-cyclohexenone, using **1a** as a catalyst, the addition product was generated in <30% yield and <80% ee.

In summary, we have shown that the NHC complex **1a** induces high yields and enantioselectivities in rhodium-catalyzed enantioselective conjugate additions of arylboronic acids to enones and α,β-unsaturated esters. Combined with our previous results for hydrogenation reactions, this demonstrates considerable potential of this new class of catalysts. The synthesis of other chiral NHCs and their application in asymmetric catalysis are currently in progress.

Experimental Section

General

Catalysts **1a** and **1b** were prepared according to the procedure described in our previous report.[3] ^1H and ^{13}C NMR spectra of the products **3** and **4a–i** were in accordance with literature reports.[4i,5a]

General Procedure for the Enantioselective Conjugate Addition of Arylboronic Acids to Enones and α,β-Unsaturated Esters

Enones: Under an atmosphere of argon, a Schlenk tube was charged with a solution of freshly prepared **1a** (4.00 mg, 3.87 μmol, 0.03 equivs.) in dioxane (1 mL). Et_3N (50.0 μL, 258 μmol, 2.0 equivs.), arylboronic acid (258 μmol, 2.0 equivs.), enone (129 μmol, 1.0 equiv.) and water (0.1 mL) were successively added at room temperature. The mixture was heated at 65 °C for 2 h. Then, ethyl acetate (10–15 mL) was added and the mixture was extracted with water (10–15 mL). The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was subjected to flash chromatography on silica gel (column: 15 × 0.5 cm, eluent: petroleum ether/ethyl acetate, 9:1). The eluent was analyzed by TLC, the fractions containing the product were concentrated under vacuum and the residue kept under high vacuum until constant weight was reached.

α,β-Unsaturated esters: The same reaction conditions as described above were used. Work-up and characterization of the product are described in full detail in ref.[5a]

Acknowledgements

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