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Highly enantioselective rhodium-catalyzed conjugate addition of arylboronic acids to enones at room temperature

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Abstract—The rhodium–phosphoramidite-catalyzed asymmetric conjugate addition of arylboronic acids to enones proceeds at room temperature using $[Rh(OH)(cod)]_2$ or $[RhCl(cod)]_2$/KOH as stable and readily available catalyst precursors.

1. Introduction

The formation of carbon–carbon bonds by asymmetric conjugate addition of organometallic reagents is one of the most fundamental reactions in organic chemistry.[1] Among the existing methods developed for this purpose, it is important to discern the nature of the organometallic species employed. The introduction of aliphatic groups to prochiral centers turned out to be very efficient using copper phosphoramidite-catalyzed conjugate addition of dialkylzinc reagents to enones.[2] In recent years, numerous chiral catalysts have been introduced for this asymmetric reaction.[3] On the other hand, the method of choice for the introduction of aryl or alkenyl moieties to unsaturated systems, is the rhodium-catalyzed conjugate addition of boronic acids, pioneered by Miyaura and Hayashi.[4] In course of time, the rhodium-catalyzed conjugate addition of arylboronic acids to unsaturated systems has proved to be very effective in terms of enantioselectivies and the broad scope of substrates used.[5] Rhodium-catalyzed conjugate additions of arylstannane,[6] arylsilicon,[7] aryltitanium,[8] and alkenylzirconium[9] reagents have also been reported. The majority of chiral ligands employed in this reaction are bidentate and most frequently, BINAP[10] is used although binol-based diphosphonites,[11] amidomonophosphines,[12] chiral bicyclodienes,[13] and chiral norbornadienes,[14] are also successful.[15]

Recently, we demonstrated that monodentate phosphoramidite ligands (e.g., ligand **L** in Scheme 1), which are modular and easily synthesized, give excellent enantioselectivities in the rhodium-catalyzed asymmetric conjugate addition of arylboronic acids to enones (Scheme 1).[16] The successful use of phosphoramidites in this reaction has been confirmed further by Miyaura and co-workers.[17]

The catalytic cycle proposed for the rhodium–BINAP-catalyzed reaction of phenylboronic acid with 2-cyclohexenone **1** is shown in Scheme 2.[18] Three key intermediates were observed by ^{31}P NMR spectroscopy:[18] phenyl–rhodium **A** (obtained by transmetalation of a phenyl group from phenylboronic acid to hydroxo–rhodium **C**), oxa-π-allylrhodium **B** (formed by insertion of the carbon–carbon bond of the enone into the phenyl–rhodium bond, followed by isomerization into the thermodynamically stable complex), and hydroxo–rhodium **C** (obtained after hydrolysis of oxa-π-allylrhodium **B** with water).

Furthermore, Hayashi et al.[18] have shown that each of the three steps shown in the catalytic cycle can take place at 25 °C, but that the catalytic reaction in the presence of a rhodium catalyst generated from $Rh(acac)(eth)_2$, does not proceed at 60 °C or below (it is worth noting that in the case of phosphoramidite-based catalyst full conversion can be obtained at 45 °C).[16b] It was reported that in case of a BINAP-based catalyst,

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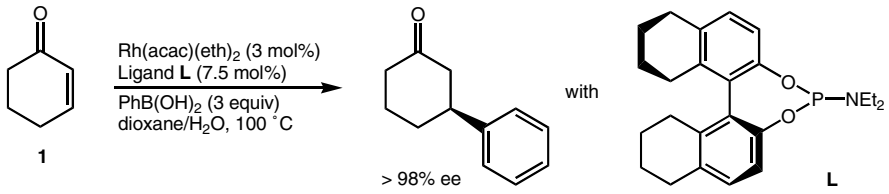
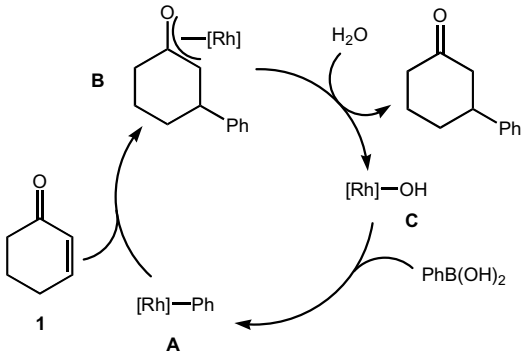


Scheme 1. Rhodium-catalyzed conjugate addition of phenylboronic acid to cyclohexenone **1** using $Rh(acac)(eth)_2$ as catalyst precursor.



Scheme 2. Proposed mechanism for the rhodium–BINAP-catalyzed conjugate addition of phenylboronic acid to cyclohexenone **1**.[18]

a higher temperature is required, which is attributed to the high stability of the rhodium–acac species.[18] Moreover, experiments have shown that when Rh(acac)(binap) complex is used, the transmetalation step of the phenyl group from phenylboronic acid at 25 °C is very slow, while transmetalation occurs at 25 °C with $[Rh(OH)(binap)]_2$ complex.[18] Based on these insights, it was shown that the use of the hydroxo–rhodium complex $[Rh(OH)(binap)]_2$, which can be prepared from $[Rh(OH)(cod)]_2$, as a catalyst precursor, allowed the catalytic 1,4-addition reaction to proceed at 35 °C in 3 h with high yield and high enantioselectivity. In this context, Miyaura and co-workers have also reported that the asymmetric 1,4-addition of phenylboronic acids to enones can be performed at 25 °C in 6 h using BINAP-based rhodium catalyst in the presence of 1 equiv of Et_3N.[19]

To date, the major drawback of the reaction conditions are the use of a large excess of organoboronic acid reagents required because of competitive hydrolysis under the reaction conditions (high temperature), and the fairly high catalyst loading.

Therefore, in connection with our interest in the catalytic asymmetric conjugate addition using phosphoramidite ligands, we report the development of the rhodium–phosphoramidite-catalyzed conjugate addition of arylboronic acids to enones at room temperature using dimer rhodium(I) complex $[Rh(OH)(cod)]_2$ or $[RhCl(cod)]_2$/KOH as stable and readily available catalyst precursors. Under these conditions, only 1.5 equiv of arylboronic acid reagents is required and high enantioselectivities are achieved with 0.4 mol % catalyst.

2. Results and discussion

In the present study, the monodentate phosphoramidite **L** was applied. As reported previously, this ligand provides full conversion and excellent enantioselectivity when used in combination with $Rh(acac)(eth)_2$ in dioxane/water at 100 °C requiring 3 equiv of boronic acids.[16b]

Assuming that a hydroxo–rhodium species is the catalytically active species, we focused our attention on the known, air stable, hydroxo–rhodium(I) complex, $[Rh(OH)(cod)]_2$ (cod = cycloocta-1,5-diene), which can be synthesized easily from chloro–rhodium(I) complex, $[RhCl(cod)]_2$, by reaction with KOH.[20]

The preliminary results, summarized in Table 1, were obtained using 3 mol % of $[Rh(OH)(cod)]_2$ as the rhodium catalyst, 7.5 mol % of phosphoramidite ligand **L**, dioxane/H_2O = 10/1 as solvent, 1.5 equiv of phenylboronic acid and a reaction temperature of 25 °C.

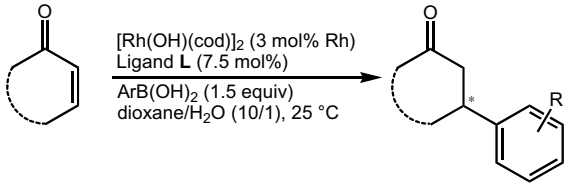
The conjugate addition of phenylboronic and 4-fluorophenylboronic acid to cyclohexenone **1** occurred in 5–6 h at 25 °C with full conversion, high yields, and very high enantioselectivities (Fig. 1, Table 1, entries 1 and 2). Despite longer reaction times, the enantioselectivities obtained with the other substrates were similar with those obtained previously with $Rh(acac)(eth)_2$ and ligand **L** at 100 °C (Fig. 1, Table 1, entries 3–5). These results open the possibility to perform rhodium–phosphoramidite-catalyzed asymmetric conjugate addition of arylboronic acids to enones at room temperature. The milder reaction conditions allow for a reduction in the amount of arylboronic acid reagents used.

As the reaction with cyclohexenone **1** proceeded rapidly, the reaction was optimized in order to further reduce the amount of rhodium used. The results are summarized in Table 2.

As expected, the reduction in the amount of rhodium catalyst slows down the reaction, but without significant effect on the selectivity. More importantly, the catalyst loading can be reduced to less than 1 mol % in the rhodium–phosphoramidite-catalyzed conjugate addition.

After having demonstrated the feasibility of performing rhodium–phosphoramidite-catalyzed conjugate addition of arylboronic acids to enones at room temperature with a catalyst loading as low as 1 mol %, we decided to improve the cost efficiency of our method. Therefore,

Table 1. Asymmetric conjugate addition of arylboronic acid to cyclic enones **1**–**4**[a]



Entry	Enone	R =	Time (h)	Conv[b] (%)	Yield[c] (%)	ee[d] (%)
1	**1**	H	5	100	86	99
2	**1**	4-F[e]	6	100	84	98
3	**2**	H	6	100	90	87
4	**3**	H	16	100	78	95
5	**4**	H	16	100	66	73

[a] Reactions performed in dioxane/H_2O = 10/1 at 25 °C, with 1.5 equiv of boronic acid on a 0.2 mmol scale and a loading of 3 mol % Rh. Ratio Rh/**L**: 1/2.5.
[b] Conversions were determined by ^1H NMR spectroscopy.
[c] Isolated yields.
[d] ee's were determined by chiral HPLC (DAICEL AD or DAICEL OD columns) or chiral GC (α-TA-column).
[e] 2 equiv of 4-fluorophenylboronic acid were used.

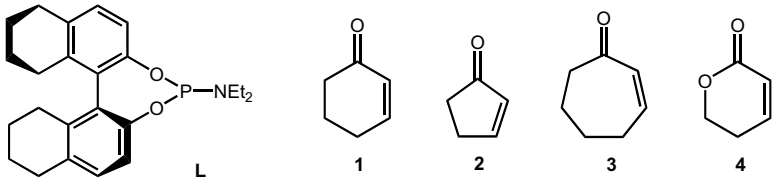
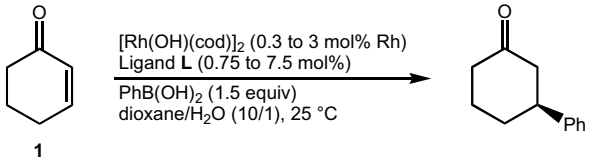


Figure 1. Structure of the ligand and substrates used in the rhodium-catalyzed conjugate addition.

Table 2. Reduction in the amount of rhodium catalyst in the asymmetric conjugate addition of phenylboronic acid to cyclohexenone **1**[a]



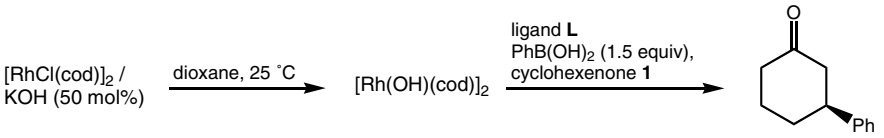
Entry	[Rh(OH)(cod)]$_2$ (mol % Rh)	Time (h)	Conv[b] (%)	Yield[c] (%)	ee[d] (%)
1	3	5	100	86	99
2	1.5	20	100	81	97
3	1	22	100	84	99
4	0.3	23	91	nd	96

nd = not determined.
[a] Reactions performed in dioxane/H_2O = 10/1 at 25 °C, with 1.5 equiv of phenylboronic acid on a 0.2 mmol scale and the loading (mol % Rh) as shown in the table above. Ratio Rh/**L**: 1/2.5.
[b] Conversions were determined by ^1H NMR spectroscopy.
[c] Isolated yields.
[d] ee's were determined by chiral HPLC on a DAICEL AD column.

the in situ formation of the active hydroxo–rhodium(I) species, [Rh(OH)(cod)]$_2$, from the cheaper chloro–rhodium(I) species, [RhCl(cod)]$_2$, in the same reaction vessel, was studied. The results presented in Table 3 show that this approach was successful. Reduction in the loading of the catalyst to as low as 0.4 mol % still provided excellent yield without deterioration of the enantioselectivity of the reaction (Table 3, entry 3).

To the best of our knowledge, this is the first time that the rhodium–phosphoramidite-catalyzed conjugate addition of phenylboronic acid has been conducted with less than 1 mol % of rhodium and [RhCl(cod)]$_2$/KOH as catalyst precursors at room temperature with excellent (97%) enantioselectivity. This is a considerable improvement of this C–C bond formation in terms of cost efficiency.

Table 3. Asymmetric conjugate addition of phenylboronic acid to cyclohexenone **1** using in situ formation of the hydroxo–rhodium catalyst[a]



Entry	$[RhCl(cod)]_2$ (mol % Rh)	Time (h)	Conv[b] (%)	Yield[c] (%)	ee[d] (%)
1	3	4	100	73	99
2	1.5	19	100	81	98
3	0.4	22	100	90	97

[a] See Ref. 21.
[b] Conversions were determined by ^1H NMR spectroscopy.
[c] Isolated yields.
[d] ee's were determined by chiral HPLC on a DAICEL AD column.

3. Conclusions

We have developed a system, which allows the rhodium–phosphoramidite-catalyzed conjugate addition of arylboronic acid to enones to be carried out at room temperature by combining a cheap easy accessible monodentate phosphoramidite ligand and $[Rh(OH)(cod)]_2$ or $[RhCl(cod)]_2$/KOH catalyst precursors. Furthermore, we were able to reduce the loading of catalyst to 0.4 mol % without reducing the enantioselectivity, using a more stable and cost effective rhodium precursor.

Acknowledgments

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21. General procedure: to a stirred solution of $[RhCl(cod)]_2$ (0.5 mg, 1.0 μmol) in dioxane (1 mL) in a Schlenk tube, under a nitrogen atmosphere, was added a solution of KOH (0.25 mL, 1.0 M, 0.25 mmol). After 30 min at 25 °C, ligand **L** (2.0 mg, 5.1 μmol) was added, followed after 5 min by the addition of phenylboronic acid (92.7 mg, 0.76 mmol) and cyclohexenone (48.7 mg, 0.51 mmol). After being stirred at 25 °C for 22 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with diethyl ether. The organic phase was dried on sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate, 90/10) to afford the 1,4-adduct (80.0 mg, 90%) as a slightly yellow oil. Enantioseparation was achieved on chiral HPLC, DAICEL AD column, heptane/*i*-PrOH, 99/1, rt 11.6, 13.6.