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Rhodium-catalyzed enantioselective 1,4-additions of arylboronic acids to substituted enones

Laura Mediavilla Urbaneja and Norbert Krause*

Dortmund University, Organic Chemistry II, D-44221 Dortmund, Germany

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Dedicated to Professor Jack Halpern on the occasion of his 80th birthday

Abstract—The rhodium-catalyzed enantioselective 1,4-addition of arylboronic acids to the bifunctional Michael acceptors **1**–**3** in the presence of phosphoramidites **L2**–**L4** occurs regioselectively at the endocyclic C–C double bond and in up to 95% ee. The presence of KOH is required to increase the reactivity so that less boronic acid and lower reaction temperatures can be used. The corresponding addition to chiral enone **4** takes place with epimerization of the product to the thermodynamically more stable trans-isomer, which was obtained with up to 98% ee.

1. Introduction

The catalytic enantioselective Michael addition is one of the most powerful and frequently used methods for the construction of a new stereogenic center in a substrate of limited complexity.[1] Whereas many catalyst types (often containing copper) have been described for the highly stereoselective transfer of an alkyl group to a Michael acceptor,[1] the method of choice for introducing aryl- or alkenyl groups with high yields and excellent enantioselectivities is the rhodium-catalyzed asymmetric conjugate addition of organoboronic acids developed by Hayashi and Miyaura.[2] These reactions are usually carried out by heating the substrate with an excess of the nucleophile and catalytic amounts of Rh(acac)-$(C_2H_4)_2$ and (*R*)- or (*S*)-BINAP to 100 °C for several hours. Recent improvements comprise the use of chiral phosphoramidites[3] or dienes[4] as the ligand, as well as the introduction of an inorganic base (usually KOH),[5] which strongly accelerates the addition, so that milder reaction conditions can be used.

Whereas various types of Michael acceptors, such as cyclic or acyclic enones, α,β-unsaturated esters, amides, phosphonates, and even nitroolefins, have successfully been employed in this transformation, the use of chiral or bifunctional substrates, posing additional issues of regio- and stereoselectivity, has so far not been reported. In a previous study concerning copper-catalyzed enantioselective 1,4-additions to 6-substituted cyclohex-2-enones,[6] we showed that product epimerization can be a useful tool for stereocontrol. We herein report that bifunctional Michael acceptors **1**–**3**,[7] as well as 6-methylcyclohex-2-enone **4**, can be employed in highly regio- and enantioselective rhodium-catalyzed Michael additions, using the chiral ligands **L1**–**L4** (Fig. 1).

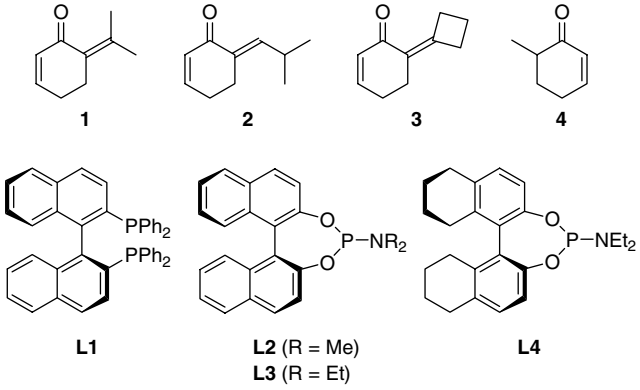

Figure 1.

* Corresponding author. Tel.: +49 231 755 3882; fax: +49 231 755 3884; e-mail: norbert.krause@uni-dortmund.de

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2. Results and discussion

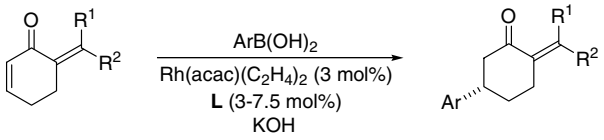
The bifunctional Michael acceptors **1**–**3**[7] can undergo sequential 1,4-additions of two nucleophiles to the endocyclic and exocyclic acceptor system. In order to determine the regio- and stereoselectivity of the first addition, we initially treated dienone **1** under Hayashi's standard conditions [5 equiv $PhB(OH)_2$, 3 mol % $Rh(acac)(C_2H_4)_2$, 3.6 mol % (*S*)-BINAP (**L1**), 1,4-dioxane/water, 100 °C], which afforded a complete conversion of cyclohex-2-enone after 5 h reaction time.[8] It turned out that **1** is considerably less reactive, giving only 6% yield of the addition product after 72 h under these conditions (Table 1, entry 1). As expected, the reactivity was increased in the presence of 1 equiv of KOH, providing the adduct with good chemical yield (87%) and enantiomeric excess (89%; entry 2). In all cases examined here, exclusive addition at the endocyclic double bond took place.

The use of the monodentate phosphoramidites **L2**–**L4** under basic conditions[3] made it possible to carry out the reaction at lower temperature with full conversion and improved stereoselectivity. Whereas (*S*)-Monophos **L2** displayed an inferior enantioselectivity of 75% ee (entry 3), ligands **L3** and **L4** catalyzed the formation of the addition product of phenylboronic acid to dienone **1** with high ee (up to 95%) and excellent chemical yield (up to 98%; entries 4–7). Remarkably, the best results were obtained with only 1.5 equiv of $PhB(OH)_2$ at 70 °C (entries 6 and 7); at this temperature, the main side reaction, the hydrolysis of the arylboronic acid, is negligible. Likewise, the reaction of dienone **1** with 4-(trifluoromethyloxy)phenylboronic acid, catalyzed by $Rh(acac)(C_2H_4)_2$ and phosphoramidite **L3** in the presence of KOH, afforded the 1,4-addition product with 90% ee and 67% yield (entry 8).

Substrate **2**, which contains a trisubstituted exocyclic double bond also reacted at the endocyclic acceptor system exclusively. In the presence of **L3**, the addition products of $PhB(OH)_2$ and 4-$CF_3OC_6H_4B(OH)_2$ were obtained with 92% and 90% ee, respectively (entries 9 and 10). Similarly, dienone **4** bearing a cyclobutylidene group afforded the adduct of phenylboronic acid with excellent yield and high enantioselectivity (entry 11). Thus, rhodium-catalyzed 1,4-addition to the bifunctional Michael acceptors **1**–**3** opens up a general and highly stereoselective access to endocyclic addition products, which may be further elaborated to novel chiral auxiliaries.[9]

In contrast to dienones **1**–**3**, the 6-methyl-substituted cyclohex-2-enone **4** is chiral. Enantioselective 1,4-additions to Michael acceptors of this type can take place either under reagent control (with or without product epimerization to the thermodynamically more stable diastereomer), or as a kinetic resolution of the racemic enone.[6] As before, we first treated substrate **4** with phenylboronic acid under Hayashi's standard conditions to observe a slow reaction (33% conversion after 14 h at 100 °C; Table 2, entry 1). Once again, phosphoramidites **L2**–**L4** provided an increased reactivity. In the absence of KOH, epimerization to the more stable (*S*,*S*)-trans-isomer was slow, meaning that considerable amounts of the (2*R*,5*S*)-cis-isomer were present in the product mixture, with enantioselectivities ranging from 68% to 86% ee (entries 2 and 3). Similar to the rhodium-catalyzed addition reactions of dienones **1**–**3**, the addition of KOH to the reaction mixture made it possible to use a smaller excess of boronic acid and to lower the reaction temperature; furthermore, the base-promoted epimerization prevails under these reaction conditions, so that the trans-isomer is the major product (entries 4–6). Again, ligands **L3** and **L4** gave slightly higher enantioselectivities than **L2**; the best result of 98% ee was obtained with phosphoramidite **L4** bearing a partly reduced binaphthyl system (entry 6). Unfortunately, the corresponding addition reactions to

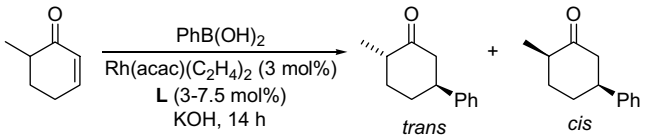
Table 1. Rhodium-catalyzed 1,4-addition of arylboronic acids to dienones **1**–**3**



Entry	Dienone	Ligand[a]	$ArB(OH)_2$ (equiv)	KOH (equiv)	*T* (°C)/*t* (h)	Yield (%)[b]	ee (%)[c,d]
1	**1**	**L1**	$PhB(OH)_2$ (5.0)	0	100/72	6	n.d.
2	**1**	**L1**	$PhB(OH)_2$ (5.0)	1.0	100/72	87	89
3	**1**	**L2**	$PhB(OH)_2$ (3.0)	1.0	100/14	90	75
4	**1**	**L3**	$PhB(OH)_2$ (3.0)	1.0	100/14	95	86
5	**1**	**L3**	$PhB(OH)_2$ (3.0)	1.0	70/14	98	88
6	**1**	**L3**	$PhB(OH)_2$ (1.5)	1.0	70/14	98	93
7	**1**	**L4**	$PhB(OH)_2$ (1.5)	1.0	70/12	93	95
8	**1**	**L3**	4-$CF_3OC_6H_4B(OH)_2$ (1.5)	1.0	70/14	67	90
9	**2**	**L3**	$PhB(OH)_2$ (1.5)	1.0	70/14	93	92
10	**2**	**L3**	4-$CF_3OC_6H_4B(OH)_2$ (1.5)	1.0	70/14	53	90
11	**3**	**L3**	$PhB(OH)_2$ (1.5)	1.0	70/16	98	94

[a] 3 mol % (**L1**), 7.5 mol % (**L2**–**L4**).
[b] Isolated yield after column chromatography.
[c] Determined by HPLC.
[d] Absolute configuration is assumed to be (*S*) for all products in accordance to the corresponding addition reactions to cyclohex-2-enone.[2,3]

Table 2. Rhodium-catalyzed 1,4-addition of phenylboronic acid to enone **4**



Entry	Ligand[a]	$PhB(OH)_2$ (equiv)	KOH (equiv)	T (°C)	Yield (%)[b]	trans (% ee):cis (% ee)[c,d]
1	**L1**	5.0	0	100	33 (conv.)	n.d.
2	**L2**	3.0	0	100	n.d.	56 (82):44 (86)
3	**L3**	3.0	0	100	91	67 (83):33 (68)
4	**L3**	3.0	1.0	70	90	85 (93):15 (93)
5	**L3**	1.5	1.0	70	n.d.	90 (93):7 (93)
6	**L4**	1.5	1.0	70	92	85 (98):15 (>99)

[a] 3 mol % (**L1**), 6–7.5 mol % (**L2**–**L4**).
[b] Isolated yield after column chromatography.
[c] Determined by GC (LIPODEX G).
[d] The absolute configuration was assumed to be (5*S*) in accordance to the corresponding addition reactions to cyclohex-2-enone.[2,3]

6-*tert*-butylcyclohex-2-enone proceeded so slowly that useful levels of conversion could not be reached under any conditions examined.

3. Conclusion

The rhodium-catalyzed enantioselective conjugate addition of arylboronic acids to the bifunctional Michael acceptors **1**–**3** occurs regioselectively at the endocyclic C–C double bond. The reactivity was very low when (*S*)-BINAP **L1** was used as the chiral ligand, but can be strongly increased by employing basic reaction conditions and monodentate phosphoramidites **L2**–**L4**. Under these conditions, the 1,4-addition products were obtained with high yields and enantioselectivities.

Similar trends were observed in Michael addition to the chiral enone **4**. Here, the presence of KOH not only improves the reactivity, but also causes an epimerization of the product to the thermodynamically more stable trans-isomer, which was obtained with up to 98% ee. In conclusion, our study shows for the first time that the rhodium-catalyzed enantioselective 1,4-addition can be successfully applied to various substituted cycloenones.

Acknowledgements

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9. Typical procedure: In a Schlenk tube flushed with argon, $Rh(acac)(C_2H_4)_2$ (3.1 mg, 12 μmol, 3 mol %), phosphoramidite **L4** (11.9 mg, 0.03 mmol, 7.5 mol %) and $PhB(OH)_2$ (73.0 mg, 0.6 mmol) were dissolved in 1.2 ml of 1,4-dioxane. Water (0.2 ml) and 40 μl of aq KOH (0.4 mmol, 10 M) were successively added. The resulting mixture was stirred for 1 h at room temperature. Then dienone **1** (54.5 mg, 0.4 mmol) in 1,4-dioxane (0.2 ml) was added. The solution was heated to 70 °C for 12 h, then cooled to room temperature, quenched with 5 ml of a saturated aqueous $NaHCO_3$ solution and washed with diethyl ether (3 × 5 ml). The combined organic layers were dried with anhydrous Na_2SO_4 and the solvent was evaporated. Purification by flash chromatography on silica gel (pentane/diethyl ether/triethylamine = 15:1:0.02) afforded 79.5 mg (93%) of (*S*)-5-phenyl-2-(propan-2-ylidene)cyclohexanone as a colorless oil with 95% ee (determined by HPLC: CHIRALPAK AD, heptane/isopropanol = 9:1). $[\alpha]_D^{20} = -22.8$ (*c* 1.06, $CHCl_3$).