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Enantioselective Synthesis of 2-Aryl-4-piperidones via Rhodium/Phosphoramidite-Catalyzed Conjugate Addition of Arylboroxines

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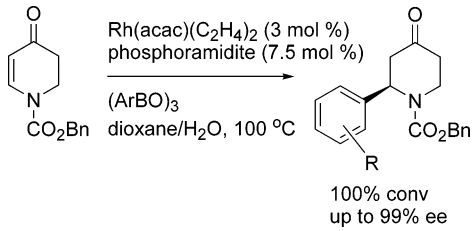
ABSTRACT



The highly enantioselective synthesis of 2-aryl-4-piperidones by rhodium/phosphoramidite-catalyzed conjugate addition of arylboroxines to 2,3-dihydro-4-pyridones is described. Both enantiomers of a variety of products with sterically and electronically different R substituents were obtained in high isolated yield and with excellent enantioselectivity up to 99%.

The piperidine ring system is a frequently encountered heterocyclic unit in natural compounds and drug candidates.[1] Piperidine alkaloids exhibit a range of biological activities and as such represent important synthetic targets. Piperidones serve an important role as intermediates *en route* to substituted piperidines[2] and can be found as a part of more complex biologically active compounds.[3] Therefore, the development of short, enantioselective routes to substituted piperidones is a major goal.[4] An attractive catalytic route toward enantiopure piperidones is based on the enantioselective conjugate addition to readily accessible *N*-protected 2,3-dihydro-4-pyridones,[5] which are frequently used in alkaloid synthesis.[6] Until recently,[7−9] however, no suitable procedures had been developed.

Monodentate phosphoramidite ligands comprise a cheap and easily tunable class of ligands that has already proven to be successful in a variety of reactions, including rhodium-catalyzed asymmetric hydrogenations,[10] rhodium-catalyzed conjugate additions of trifluoroborates[11] and boronic acids,[12] and copper-catalyzed asymmetric conjugate additions of

(1) For a general review on piperidines, see: Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine: Structure, Preparation and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991.

(2) For some recent examples of the use of 4-piperidones in the synthesis of biologically active 4-piperidines, see: (a) Tawara, J. N.; Lorenz, P.; Stermitz, F. R. *J. Nat. Prod.* **1999**, *62*, 321−323. (b) Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679−3681. (c) Brooks, C. A.; Comins, D. L. *Tetrahedron Lett.* **2000**, *41*, 3551−3553.

(3) For an example, see: Mukhtar, T. A.; Wright, G. D. *Chem. Rev.* **2005**, *105*, 529−542.

(4) (a) For a review of the recent developments in asymmetric routes to substituted piperidines, see: Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633−640. (b) For a review on the recent advances in the synthesis of piperidines and piperidones, see: Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989.

(5) For the preparation of *N*-protected 2,3-dihydropyridones, see: (a) Kozikowski, A. P.; Park, P.-U. *J. Org. Chem.* **1990**, *55*, 4668−4682. (b) Comins, D. L.; Chung, G.; Foley, M. A. *Heterocycles* **1994**, *37*, 1121−1140.

(6) For a review on the asymmetric preparation and synthetic utility of 2,3-dihydro-4-pyridones, see: Comins, D. L. *J. Heterocycl. Chem.* **1999**, *36*, 1491−1500.

(7) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240−6241.

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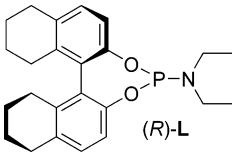

Figure 1. Phosphoramidite **L**, a highly efficient ligand in the rhodium-catalyzed conjugate addition of boronic acids.

diorganozinc reagents.[13] Recently, we have reported the synthesis of 2-alkyl-4-piperidones with high enantiomeric excess using the copper/phosphoramidite-catalyzed conjugate addition of dialkylzinc reagents to *N*-protected 2,3-dihydro-4-pyridones.[8] It was noted that this type of substrate is less reactive toward 1,4-addition than cyclic enones, *e.g.*, 2-cyclohexenone.

Although highly enantioselective 1,4-addition of diphenylzinc, using the same catalyst, has been reported for 2-cyclohexenone,[14] the lack of readily available diarylzinc reagents severely limits this method. A more convenient method for the introduction of aryl and alkenyl moieties is the asymmetric rhodium-catalyzed conjugate addition of boronic acids pioneered by Hayashi and Miyaura.[15] Excellent levels of enantioselectivity have been achieved for a broad range of enones using BINAP.[15] Also phosphonites[16] and amidophosphines[17] were successfully applied as chiral ligands. It was shown by our group that phosphoramidites (*i.e.*, **L**, Figure 1) are exceptionally efficient ligands for this reaction in terms of reaction rate, chemoselectivity, and enantioselectivity.[12]

(9) For related 1,4-additions to 2-piperidones, see: Pineschi, M.; Del Moro, F.; Gini, F.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1244−1245.

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(11) (a) Duursma, A.; Boiteau, J.-G.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2004**, *69*, 8045−8052. (b) Duursma, A.; Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2004**, *2*, 1682−1684.

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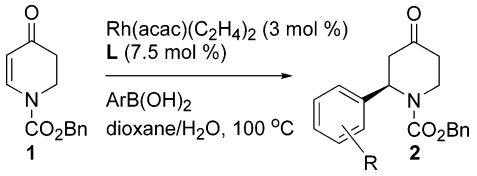
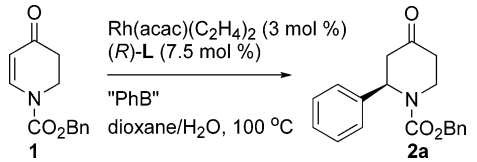
Scheme 1



We envisioned that introduction of aryl groups to **1** (Scheme 1), using the rhodium/phosphoramidite-catalyzed conjugate addition of arylboronic acids, could provide a pathway to 2-substituted 4-piperidones that is complementary to our work with dialkylzinc reagents. During our studies, Hayashi *et al.* reported the enantioselective addition of arylzinc chlorides to 2,3-dihydro-4-pyridones.[7] In that study, it was noted also that this type of substrate is less reactive toward 1,4-addition compared to other enones. The rhodium/BINAP-catalyzed conjugate addition of phenylboronic acid failed to proceed to full conversion, although the enantioselectivity was excellent.

Initial screening of our catalyst system on substrate **1** was performed under standard conditions in a mixture of dioxane/water (10/1) at 100 °C with a catalyst generated from 3 mol % $Rh(acac)(C_2H_4)_2$ and 7.5 mol % **L**. As in the report of Hayashi, with 3 equiv of phenylboronic acid, the reaction did not go to completion according to ^{1}H NMR (entry 1, Table 1). The enantioselectivity was, however, excellent

Table 1. Optimization of the Reaction Conditions for the Rhodium-Catalyzed Conjugate Addition to **1**



entry	"PhB" (equiv)	conditions[a]	conversion %[b]	ee (%)[c]
1	$PhB(OH)_2$ (3.0)	A	80	96
2	$(PhBO)_3$ (1.0)	B	60	99
3	$(PhBO)_3$ (3.0)	B	75	99
4	$(PhBO)_3$ (1.0)	C	84	99
5	$(PhBO)_3$ (2.0)	C	92	99
6	$(PhBO)_3$ (3.0)	C	100	99

[a] All reactions were performed on a 0.2 mmol scale with 3 mol % $Rh(acac)(C_2H_4)_2$ and 7.5 mol % (*R*)-**L** at 100 °C for 2 h. Conditions A: 0.55 mL of dioxane/H_2O (10/1). Conditions B: 0.5 mL of dioxane, 1 equiv of H_2O with respect to boron. Conditions C: 0.5 mL of dioxane, slow addition of water by syringe pump, 100 °C, 1 h. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC.

(96% ee). We then decided to generate phenylboronic acid *in situ* from phenylboroxine ($(PhBO)_3$)[18] and water (one

(18) Arylboroxines are obtained by dehydration of arylboronic acids by azeotropic removal of water from their xylene solution or heating at 300 °C *in vacuo*. For a review, see: Lappert, M. F. *Chem. Rev.* **1956**, *56*, 959−1064.

equivalent with respect to boron), providing mild reaction conditions (entries 2−5).[19] The use of this reagent did not improve the conversion but did improve the enantioselectivity to an excellent ee of 99%. Upon slow addition of water, thereby preventing premature hydrolysis of the boroxine, the reaction could be driven to 84% conversion using 1 equiv of boroxine (entry 4) and to full conversion with retention of 99% ee using 3 equiv of the reagent (entry 6).

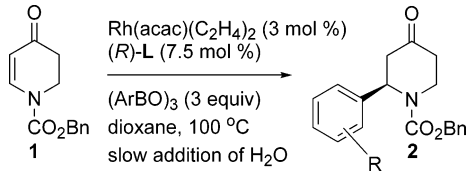
To show the applicability of this reaction for synthesis on a laboratory scale, it was performed on a 0.5 g (2.2 mmol) scale. After flash chromatography, the product was isolated in 86% yield with 99% ee.

With these optimized conditions in hand, the scope of the asymmetric conjugate addition of arylboroxines to **1** was investigated. High ee values could be obtained with a variety of sterically and electronically diverse arylboroxines (entries 1−8, Table 2). *meta*- and *para*-tolyl groups can be introduced with high enantioselectivity and high yield (entries 3 and 4). A dramatic drop in enantioselectivity was observed for the more sterically demanding *ortho*-tolyl group (entry 2), illustrating a possible limitation of the catalytic method. Products with one or two electron-donating substituents on the aryl were obtained in high yield with high enantioselectivity (entries 5 and 6). However, electron-withdrawing groups such as choride or fluoride slow the reaction, leading to incomplete conversions (entries 7 and 8). Despite this observation, the enantioselectivity is largely independent of the electronic properties of the substituents, and all *para*- or *meta*-substituted products are obtained with excellent ee values between 94 and 98%.

In summary, we have shown that conjugate addition of arylboroxines with a rhodium/phosphoramidite catalyst can be used to prepare 2-aryl-4-piperidones in high isolated yield (82−92%) and with excellent enantioselectivity (up to 99%). We are currently directing our efforts toward enhancing the scope and applications of this method in the synthesis of more complex heterocycles.

(19) Use of arylboroxines was previously reported to have a beneficial effect on both conversion and enantioselectivity in the conjugate addition to highly deactivated 1-alkenylphosphonates; see: Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591−11592.

Table 2. Scope of Arylboroxines in the Rhodium-Catalyzed Asymmetric 1,4-Addition to **1**[a]



entry	Ar	product	yield (%)[b]	ee (%)[c]
1	Ph	**2a**	86[d]	99
2	*o*-MeC_6H_4	**2b**	82[d]	24
3	*m*-MeC_6H_4	**2c**	92[d]	98
4	*p*- MeC_6H_4	**2d**	86[d]	95
5	*p*-$MeOC_6H_4$	**2e**	85[d]	96
6	*m*,*p*-$(MeO)_2C_6H_3$	**2f**	86[d]	98
7	*p*-FC_6H_4	**2g**	71	94
8	*p*-ClC_6H_4	**2h**	55	96

[a] All reactions were performed in duplicate with both enantiomers of the ligand on a 0.2 mmol scale with 3 mol % Rh(acac)$(C_2H_4)_2$ and 7.5 mol % **L** at 100 °C for 2 h. (*R*)-**L** gave the (*R*)-enantiomer of the product in all cases; see Supporting Information. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Thin-layer chromatography shows a spot to spot conversion in 2 h.

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Supporting Information Available: Experimental details and chromatographic and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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