ORGANIC LETTERS

2008
Vol. 10, No. 4
589−592

Rhodium/Chiral Diene-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to Arylmethylene Cyanoacetates

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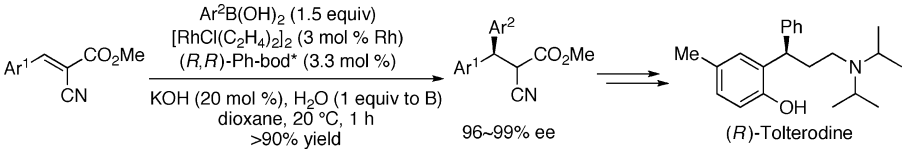
Received November 29, 2007

ABSTRACT



Asymmetric 1,4-addition of arylboronic acids to (*E*)-methyl 2-cyano-3-arylpropenoates proceeded in the presence of a rhodium catalyst (3 mol %) coordinated with a chiral diene ligand, (*R*,*R*)-Ph-bod*, to give high yields of the corresponding methyl 3,3-diaryl-2-cyanopropanoates with high enantioselectivity (up to 99% ee). This catalytic asymmetric transformation was applied to the asymmetric synthesis of (*R*)-tolterodine.

Rhodium-catalyzed asymmetric 1,4-addition of organoboron reagents has rapidly developed into a powerful tool for the stereoselective formation of carbon−carbon bonds.[1,2] Aryl and alkenyl groups have been successfully introduced into electron-deficient olefins with high enantioselectivity by this rhodium catalysis.[3] One of the most exciting advances in the transition-metal-catalyzed asymmetric reactions is discovery of chiral diene ligands,[4−7] which have been demonstrated to be highly effective especially in rhodium-catalyzed aryl transfer reactions. The chiral diene−rhodium complexes displayed catalytic activity and enantioselectivity higher than that of chiral phosphine complexes for the aryl transfer to *N*-sulfonylimines, α,β-unsaturated ketones, aldehydes, esters, and amides.[4−7]

The enantioselective construction of stereogenic carbon centers substituted with two aryl groups and one alkyl group is a subject of importance, because this structural motif is often found in pharmaceuticals (e.g., sertraline[8] and toltero-

(1) For the first example of the rhodium-catalyzed 1,4-addition, see: Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

(2) For reviews, see: (a) Miyaura, N. In *Organoboranes in Syntheses*; Ramachandran, P. V., Brown, H. C., Eds.; ACS Symposium Series 783; American Chemical Society: Washington, 2001; Chapter 7, pp 94−107. (b) Hayashi, T. *Synlett* **2001**, 879. (c) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284. (d) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (e) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (f) T. Hayashi *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13. (g) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279.

(3) For selected examples, see: (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara. M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

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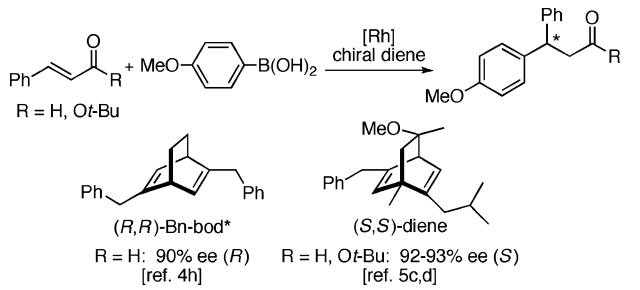
10.1021/ol702879u CCC: $40.75
Published on Web 01/25/2008

dine[9]) and natural products (e.g., podophyllotoxin[10]). Their asymmetric synthesis has been reported by the chiral diene/rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to β-aryl-substituted α,β-unsaturated aldehydes and esters,[4h,5c,d] which gave the corresponding β,β-diaryl-substituted products in 90−93% ee[11,12] (Scheme 1). Herein

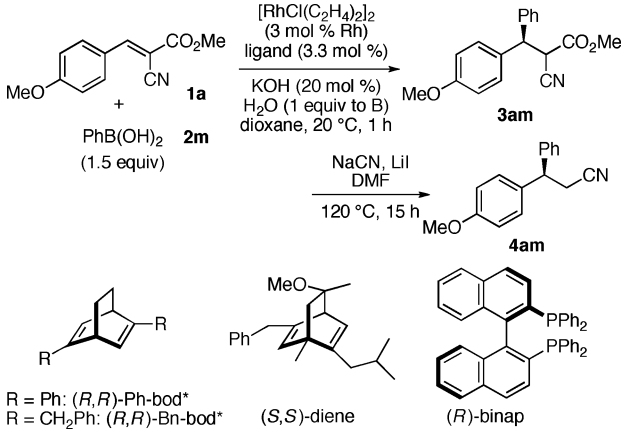
Scheme 1



we wish to report that arylmethylene cyanoacetates **1** are suitable substrates for the rhodium/chiral diene-catalyzed asymmetric 1,4-addition of arylboronic acids **2**, which gave the corresponding 3,3-diaryl-2-cyanopropanoates **3** in up to 99% ee. This methodology was used for the asymmetric synthesis of (*R*)-tolterodine, an important urological drug.[9]

A rhodium complex coordinated with chiral diene ligand (*R*,*R*)-Ph-bod*,[4c,e] which is a C_2-symmetric bicyclic diene bearing two phenyl groups on the double bonds, was found to be highly catalytically active and enantioselective for the addition of phenylboronic acid (**2m**) to 4-methoxyphenylmethylene cyanoacetate (**1a**) (entry 1 in Table 1). Thus, the reaction was completed in 1 h at 20 °C in the presence of 3 mol % of the rhodium catalyst to give 99% yield of 3,3-diaryl-2-cyanopropanoate **3am**. Its enantiomeric purity was determined to be 99% (*R*) by HPLC analysis (Chiralcel OD-H) of 3,3-diarylpropanenitrile **4am**, which is readily obtained in a high yield by decarbomethoxylation of **3am**. Other rhodium/diene complexes, where the dienes are (*R*,*R*)-Bn-bod*[4c,e] and Carreira's (*S*,*S*)-diene,[5] were as catalytically active as the Rh/(*R*,*R*)-Ph-bod*, but the enantioselectivity was lower (entries 2 and 3). Rhodium/phosphine complexes were much less catalytically active. For example, (*R*)-binap[13] catalyst gave **3am** in 33% yield under otherwise the same reaction conditions (entry 4).

Table 1. Rhodium-Catalyzed Asymmetric 1,4-Addition of Phenylboronic Acid (**2m**) to Arylmethylene Cyanoacetate **1a**



entry	ligand	yield[a] (%)	ee[b] (%)
1	(*R*,*R*)-Ph-bod*	99	99 (*R*)
2	(*R*,*R*)-Bn-bod*	94	81 (*R*)
3	(*S*,*S*)-diene	96	71 (*S*)
4	(*R*)-binap	33[c]	46 (*S*)

[a] Isolated yield of a 1:1 mixture of diastereomers. [b] Determined after the deesterification giving **4am**. [c] 60% **1a** recovered.

As illustrated in Table 2, the present catalytic asymmetric 1,4-addition is applicable to a broad range of arylboronic acids and arylmethylene cyanoacetates. The 1,4-addition proceeded in high yield (>90%) with excellent enantioselectivity (96−99% ee) for all of the substrate combinations we examined. Arylmethylene cyanoacetates substituted with a methoxy group at the 4-, 3-, and 2-positions on the phenyl are all good substrates, giving the corresponding arylation products **3** with over 96% ee in the reaction with phenyl-, 4- or 3-methylphenyl-, and 4-bromophenyl boronic acids. The enantioselectivities are also very high for arylmethylene cyanoacetates where the aryl groups are 2-methylphenyl, 2-naphthyl, and 4-chlorophenyl.

The presence of both cyano and ester groups at the α-position of the reaction substrates is essential for the high reactivity and enantioselectivity in the present reaction, which is demonstrated by the results summarized in Table 3. Arylmethylene malononitrile **5a** and malonate **5b**, which are

(5) (a) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (b) Defieber, C.; Paquin, J.-F.; Serna, S.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 3873. (c) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (d) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. *Org. Lett.* **2005**, *7*, 3821. (e) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.: Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331.

(6) (a) Läng, F.; Breher, F.; Stein, D.; Grützmacher, H. *Organometallics* **2005**, *24*, 2997. (b) Grundl, M. A.; Kennedy-Smith, J. J.; Trauner, D. *Organometallics* **2005**, *24*, 2831. (c) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-C. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (d) Helbig, S.; Sauer, S.; Cramer, N.; Laschat, S.; Baro, A.; Frey, W. *Adv. Synth. Catal.* **2007**, *349*, 2331.

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(8) McRae, A. L.; Brady, K. T. *Expert Opin. Pharmacother.* **2001**, *2*, 883.

(9) (a) Hills, C. J.; Winter, S. A.; Balfour, J. A. *Drugs* **1998**, *55*, 813. (b) Wefer, J.; Truss, M. C.; Jonas, U. *World J. Urol.* **2001**, *19*, 312. (c) Rovner, E. S.; Wein, A. J. *Eur. Urol.* **2002**, *41*, 6.

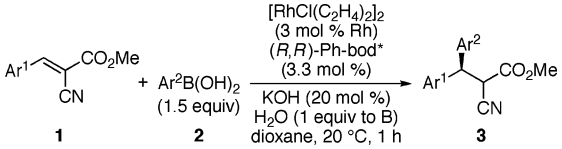
(10) Gordaliza, M.; García, P. A.; Miguel del Corral, J. M.; Castro, M. A.; Gómez-Zurita, M. A. *Toxicon* **2004**, *44*, 441.

(11) Higher enantioselectivity (99% ee) has been reported in the reaction of ArZnCl/$ClSiMe_3$ with 3-arylpropenals calyzed by a rhodium-binap complex: Tokunaga, N.; Hayashi, T. *Tetrahedron: Asymmetry* **2006**, *17*, 607.

(12) The catalytic asymmetric synthesis of β,β-diaryl-substituted carbonyl compounds has been also reported by use of chiral phosphine-palladium catalysts: (a) Nishikata, T.; Yamamoto, Y.; Gridnev, I. D.; Miyaura, N. *Organometallics* **2005**, *24*, 5025. (b) Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Tetrahedron Lett.* **2007**, *48*, 4007.

(13) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

Table 2. Asymmetric 1,4-Addition of Arylboronic Acids **2** to Arylmethylene Cyanoacetates **1** Catalyzed by Rh/(*R*,*R*)-Ph-bod*



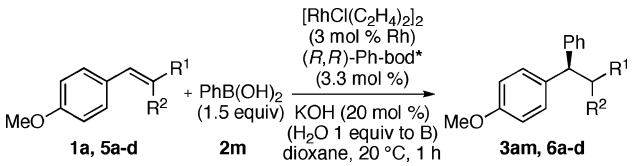
entry	Ar^1	Ar^2	yield[a] (%)	ee[b] (%)
1	4-$MeOC_6H_4$ (**1a**)	Ph (**2m**)	99 (**3am**)	99 (*R*)
2	3-$MeOC_6H_4$ (**1b**)	Ph (**2m**)	99 (**3bm**)	98 (*R*)
3	2-$MeOC_6H_4$ (**1c**)	Ph (**2m**)	94 (**3cm**)	99 (*R*)
4	2-MeC_6H_4 (**1d**)	Ph (**2m**)	92 (**3dm**)	96 (*R*)
5	2-naphthyl (**1e**)	Ph (**2m**)	91 (**3em**)	98 (*R*)
6	4-$MeOC_6H_4$ (**1a**)	4-MeC_6H_4 (**2n**)	96 (**3an**)	97 (*R*)
7[c]	4-$MeOC_6H_4$ (**1a**)	3-MeC_6H_4 (**2o**)	95 (**3ao**)	96 (*S*)
8	4-$MeOC_6H_4$ (**1a**)	4-BrC_6H_4 (**2p**)	92 (**3ap**)	98 (*S*)
9	Ph (**1f**)	4-MeC_6H_4 (**2n**)	95 (**3fn**)	97 (*S*)
10	Ph (**1f**)	4-BrC_6H_4 (**2p**)	96 (**3fp**)	98 (*S*)
11	4-ClC_6H_4 (**1g**)	4-BrC_6H_4 (**2p**)	90 (**3gp**)	96 (*S*)

[a] Isolated yield of a 1:1 mixture of diastereomers. [b] Determined after the deesterification giving **4**. [c] The reaction was carried out at 30 °C.

substituted with two nitriles and esters, respectively, in place of the one-each combination, are much less reactive than the cyanoacetate **1a**, giving the corresponding phenylation products in only about 10% yield (entries 2 and 3). The 1,4-addition of phenylboronic acid took place readily for the olefinic substrates **5c** and **5d** bearing either a single cyano or ester functionality (entries 4 and 5), but the enantioselectivity was much lower than that observed for the cyanoacetate **1a**. Thus, the combination of a cyano and an ester group realizes both high yield and high enantioselectivity.

The present asymmetric arylation catalyzed by a (*R*,*R*)-Ph-bod*/rhodium complex was applied to the synthesis of (*R*)-tolterodine (**7**).[14] Scheme 2 illustrates the reaction scheme

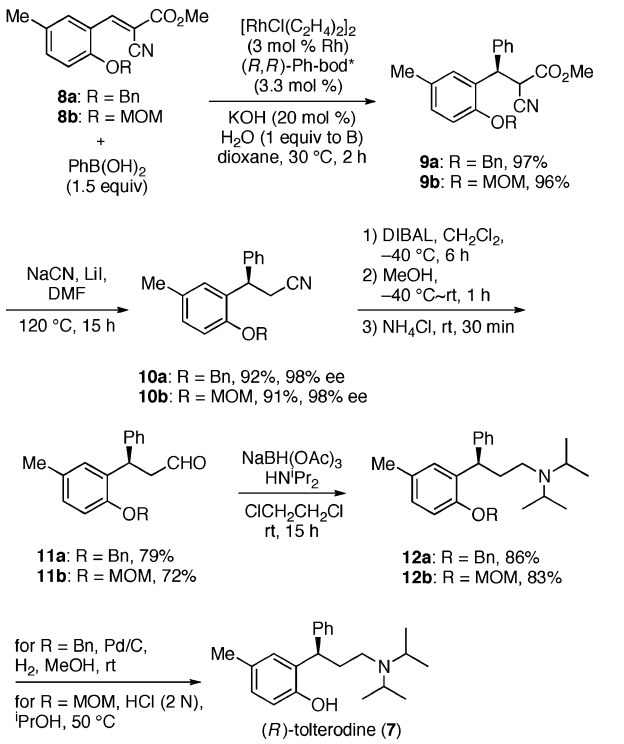
Table 3. Effects of Electron-Withdrawing Substituents on the Rhodium-Catalyzed Asymmetric Addition



entry	substrate	R^1	R^2	product	yield[a] (%)	ee[b] (%)
1	**1a**	CO_2Me	CN	**3am**	99	99[c] (*R*)
2	**5a**	CN	CN	**6a**	9[d]	n.d.
3	**5b**	CO_2Me	CO_2Me	**6b**	11[d]	n.d.
4	**5c**	CN	H	**6c**	74	52 (*R*)
5	**5d**	CO_2Me	H	**6d**	99	57 (*R*)

[a] Isolated yield. [b] Determined by HPLC on a Chiralcel OD-H column with hexane/2-propanol (4:1). [c] Determined after the deesterification giving **4am** (**6c**). [d] Determined by ^1H NMR.

Scheme 2



that involves, as a key step, the asymmetric addition of phenylboronic acid to a methylene cyanoacetate bearing a protected 2-hydroxy-5-methylphenyl group. The phenolic hydroxyl group was protected by either benzyl (Bn) or methoxymethyl (MOM). Both of the two substrates **8a** and **8b** were readily accessible in few steps and in high yields starting from inexpensive 4-methylphenol.[15]

The rhodium-catalyzed asymmetric 1,4-addition of phenylboronic acid proceeded smoothly at 30 °C with high enantioselectivity for both **8a** and **8b** using the chiral diene ligand, (*R*,*R*)-Ph-bod*, to give the corresponding phenylation products **9a** and **9b** in 97% and 96% yields, respectively. Removal of the carbomethoxy group by treatment with NaCN and LiI in DMF gave high yields of nitriles **10a** and **10b**, both of which are 98% enantiomerically pure. The remaining synthesis was completed in a three-step sequence. The cyano group in nitriles **10** was successfully reduced to the corresponding aldehydes **11**, and subsequent reductive amination with diisopropylamine and sodium triacetoxyborohydride[16] gave high yields of the protected tolterodine precursors **12**. Deprotection, applying hydrogenolysis for **12a** (Bn) or acidic hydrolysis for **12b** (MOM), resulted in smooth formation of (*R*)-tolterodine (**7**) in a quantitative yield. The *R* configuration was confirmed by comparison of the optical rotations, $[\alpha]^{20}_D$ +24 (*c* 0.33, MeOH) for **7** from the Bn route

(14) Rhodium-catalyzed asymmetric 1,4-addition to a coumarin derivative has been applied to the asymmetric synthesis of (*R*)-tolterodine: Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285.

(15) For details on the synthesis of **8a** and **8b**, see Supporting Information.

(16) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

and $[\alpha]^{20}_D$ +22 (*c* 0.32, MeOH) for **7** from the MOM route, with that reported for (*S*)-tolterodine {$[\alpha]^{20}_D$ −23.0 (*c* 1.5, MeOH)}.[17] Thus, using our new methodology as a key step, (*R*)-tolterodine was synthesized through a five-step sequence from cyanoacetate **8a** in an overall yield of 61%.

In summary, catalytic asymmetric construction of diarylmethine stereogenic centers was realized by the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to arylmethylene cyanoacetates. The reaction proceeded with high enantioselectivity (96−99% ee) in high yields (>90%) by use of 3 mol % of a chiral diene−rhodium catalyst.

Acknowledgment. Support of this work by the Japanese Society for the Promotion of Science (JSPS fellowship for S.S.) is gratefully acknowledged.

Supporting Information Available: Detailed description of representative experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Piccolo, O.; Ulgheri, F.; Marchetti, M. WO Patent 2005005356, 2005.