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Asymmetric Nitroallylation of Arylboronic Acids with Nitroallyl Acetates Catalyzed by Chiral Rhodium Complexes and Its Application in a Concise Total Synthesis of Optically Pure (+)-γ-Lycorane

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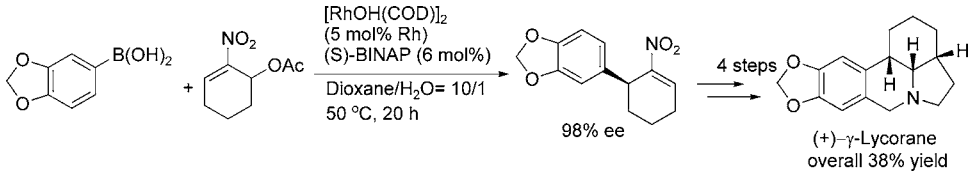
ABSTRACT

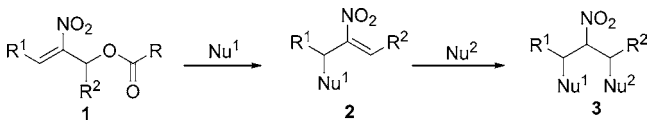


A new rhodium-catalyzed highly enantioselective nitroallylation of 2-nitrocyclohex-2-enol esters with arylboronic acids is described. A rhodium complex of [RhOH(COD)]$_2$ and optically pure BINAP is the optimal catalyst that provides good yields and high enantioselectivities ranging from 90 to 99% ee for various arylboronic acids at 50 °C. A concise total synthesis of optically pure (+)-γ-lycorane in overall 38% yield was achieved on the basis of this new method.

Nitroallyl acetates **1** were first introduced as multiple coupling reagents to react with two different nucleophilic components (Nu^1 and Nu^2) by Seebach and Knochel (Scheme 1).[1] The resulting nitroalkanes **3** can be transformed into a variety of useful compounds because the nitro group can be converted into various functionalities.[2] Although various types of nucleophiles have been evaluated with regard to their ability to couple with nitroallyl acetates **1** in good results,[1,3] this useful transformation has not yet been a catalytic asymmetric process. Thus, the development of the catalytic asymmetric reaction of nitroallyl acetates with nucleophiles is of great importance in organic synthesis.

Hayashi and co-workers reported that the 1,4-addition of 1-nitrocyclohexene (**4**)[4] with phenylboronic acid[5] in the presence of a rhodium complex of (*S*)-binap occurred via a rhodium nitronate intermediate **5** to afford 2-phenyl-1-nitrocyclohexane (**6**) in a high yield and excellent enantioselectivity (eq 1).

Scheme 1. Nitroallyl Acetates Potentially Coupled with Different Nucleophiles



(1) (a) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1981**, *22*, 3223. (b) Seebach, D.; Knochel, P. *Nouv. J. Chim.* **1981**, *5*, 75. (c) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261.

(2) Ono, N. *The nitro group in organic synthesis*; Wiley-VCH: New York, 2001.

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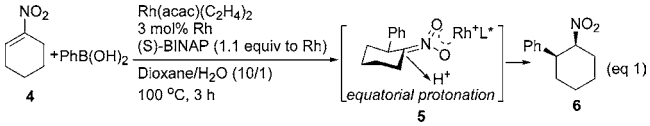
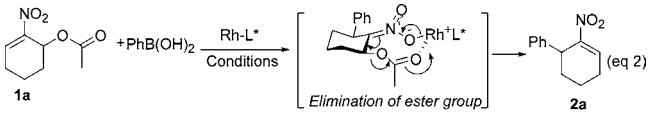


Despite the success in the rhodium-catalyzed 1,4-addition of nitrocylcohexene with arylboronic acids,[4] *so far it is not clear* if the reaction of a 2-nitrocyclohex-2-enol ester such as **1a** with an arylboronic acid in the presence of a chiral rhodium complex can undergo the 1,4-addition of phenylboronic acid and then β-elimination of an ester group via an assumed intermediate **7**[6] to regenerate the catalyst and liberate compound **2a** (eq 2). To address this question, we describe here the first asymmetric nitroallylation of arylboronic acids with nitroallyl acetate **1a** and its structural analogues in the presence of chiral rhodium complexes to generate chiral nitroalkenes **2** with high enantioselectivities. The utility of this method is also demonstrated in a concise asymmetric total synthesis of optically pure (+)-γ-lycorane.[7,8]



We first reacted acetic acid 2-nitrocyclohex-2-enyl ester (**1a**) with phenylboronic acid, catalyzed by a rhodium complex of $[Rh(acac)(C_2H_4)]_2$ with (R)-BINAP under the standard conditions used for rhodium-catalyzed 1,4-addition of arylboronic acids to nitroalkenes.[4] We were delighted to observe that the reaction gave the desired product **2a**, the structure of which was confirmed by X-ray diffraction (Figure 1),[9] with high enantioselectivity of 94% ee (entry 1). The absolute configuration of the stereogenic center was determined to be *R* by correlation with a known compound (see the Supporting Information). However, the product was only isolated in 30% yield because the starting substrate **1a** decomposed at 100 °C. Thus, optimization of the reaction conditions is required (Table 1). The use of pivalic acid 2-nitro-cyclohex-2-enyl ester **1b** to replace **1a** as a substrate did not suppress the decomposition, and a low yield was

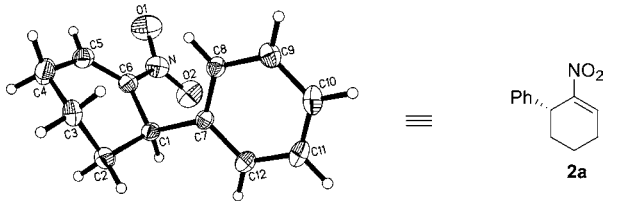
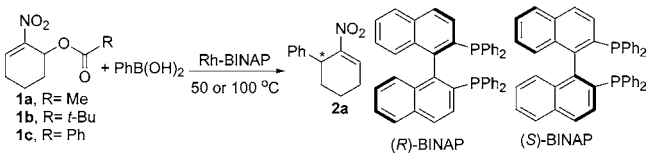


Figure 1. X-ray structure of **2a**.

Table 1. Rhodium-Catalyzed Asymmetric Nitroallylation of 2-Nitrocyclohex-2-enol Esters **1** with Phenylboronic Acid[a]



entry	metal	1	T (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	$Rh(acac)(C_2H_4)_2$	**1a**	100	5	30	94
2	$Rh(acac)(C_2H_4)_2$	**1b**	100	5	30	95
3	$Rh(acac)(C_2H_4)_2$	**1c**	100	5	48	93
4	$[RhCl(COD)]_2$	**1a**	100	5	20	94
5	$Rh(acac)(C_2H_4)_2$	**1a**	50	20	41	94
6	$[Rh(OH)(COD)]_2$	**1a**	50	20	55	97
7	$[Rh(OH)(COD)]_2$	**1a**	50	20	56	97[d]

[a] The reaction of arylboronic acid was performed in the presence of 5 mol % of rhodium complex and 6 mol % of (*R*)-BINAP in a solvent mixture of dioxane/H_2O = 10/1. [b] Isolated yield. [c] The ee values were determined by GC. [d] The ligand is (*S*)-BIANP.

(3) (a) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625. (b) Denmark, S. E.; Kramps, L. A.; Montgomery, J. I. *Angew. Chem., Int. Ed.* **2002**, *41*, 4122. (c) Denmark, S. E.; Montgomery, J. I. *Angew. Chem., Int. Ed.* **2005**, *44*, 3732.

(4) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

(5) For asymmetric 1,4-addition of arylboronic acids with electron-deficient olefins, see a recent review: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(6) A β-oxygen elimination was proposed as a key step for the asymmetric ring-opening reaction of oxanorbornene derivatives with arylboronic acids catalyzed by chiral rodium complexes, see the leading references: (a) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311. (b) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. (c) Marakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390.

(7) For total syntheses of racemic γ-lycorane, see: (a) Ueda, N.; Tokuyama, T.; Sakan, T. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2012. (b) Irie, H.; Nishitani, Y.; Sugita, M.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1970**, 1313. (c) Tanaka, H.; Nagai, Y.; Irie, H.; Uyeo, S.; Kuno, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 874. (d) Genem, B. *Tetrahedron Lett.* **1971**, *12*, 4105. (e) Hara, H.; Hoshino, O.; Umezawa, B. *Tetrahedron Lett.* **1972**, *13*, 5031. (f) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sato, S.; Numao, N. *J. Org. Chem.* **1977**, *42*, 4272. (g) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1978**, *100*, 3598. (h) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1979**, *44*, 1074. (i) Higashiyama, H.; Honda, T.; Otomasu, H.; Kametani T. *Planta Med.* **1983**, *48*, 268. (j) Sugiyama, N.; Narimiya, M.; Iida, H.; Kibuchi, T. *J. Heterocycl. Chem.* **1988**, *25*, 1455. (k) Bäckvall, J. E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem.* **1991**, *56*, 2988. (l) Pearson W. H.; Sckeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 6783. (m) Grotjahn, D. B.; Vollhardt, P. C. *Synthesis* **1993**, 579. (n) Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671. (o) Angle, S. R.; Boyce, J. P. *Tetrahedron Lett.* **1995**, *36*, 6185. (p) Ikeda, M.; Ohtani, S.; Sato, T.; Ishibashi, H. *Synthesis* **1998**, 1803. (q) Huang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125. (r) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716. (s) Tamura, O.; Matsukida, H.; Toyao, A.; Takeda, Y.; Ishibashi, H. *J. Org. Chem.* **2002**, *67*, 5537. (t) Shao, Z.; Chen, J.; Huang, R.; Wang, C.; Li, L.; Zhang, H. *Synlett* **2003**, 2228. (u) Yasuhara, T.; Osafune, E.; Nishimura, K.; Yamashita, M.; Yamada, K.-i.; Muraoka, O.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 3043. (v) Gao, S.; Tu, Y. Q.; Song, Z.; Wang, A.; Fan, X.; Jiang, Y. *J. Org. Chem.* **2005**, *70*, 6523.

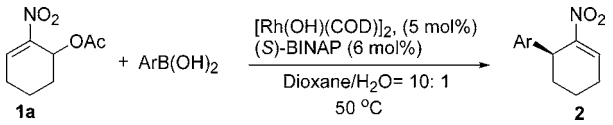
(8) For total syntheses of optically active (+)-γ-lycorane, see: (a) Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016. (b) Cossy, J.; Tresnard, L.; Pard, D. G. *Eur. J. Org. Chem.* **1999**, 1925. (c) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. *J. Org. Chem.* **2000**, *65*, 4241.

(9) Crystal data of **2a**: $C_{12}H_{13}NO_2$, MW= 203.23, orthorhombic, space group $P2_12_12_1$, a = 6.1206(5) Å, b = 12.592(1) Å, c = 14.007(1) Å, α = 90°, β = 90°, γ = 90°, U = 1079.57(12) Å^3, T = 290(2) K, Z = 4, D_c = 1.250 mg/m^3, μ = 0.085 mm^{-1}, λ = 0.71073 Å, F(000) 432, crystal size: 0.56 × 0.50 × 0.42 mm^3, 1483 reflections collected, 1380 [R(int) = 0.0122]; refinement method: full-matrix least-squares on F^2; goodness-of-fit on F^2 = 0.961, final R indices [$I > 2\sigma(I)$] R1 = 0.0327, wR2 = 0.0652.

still observed, with a maintained enantioselectivity (entry 2). Although a higher yield was observed for **1c**, the enantioselectivity decreased slightly (entry 3). The yield could be slightly improved to 41% by performing the reaction at 50 °C (entry 5). Screening of the transition-metal source revealed that $[Rh(OH)(COD)]_2$[10] is a better precatalyst (entries 1−6). Thus, further improvement in the yield and the enantioselectivity was achieved by using a rhodium complex generated in situ from $[Rh(OH)(COD)]_2$ and (*R*)- or (*S*)-BINAP, which catalyzed the reaction in good yield with 97% ee at 50 °C, and the decomposition of **1a** was minimized (entries 6 and 7). Despite the moderate yield observed for the reaction, considering that the transformation proceeds in a two-step reaction sequence (eq 2), the rhodium complex of $[Rh(OH)(COD)]_2$ and BINAP can be considered an optimal catalyst system.

To determine if the optimal catalyst generated from $[Rh(OH)(COD)]_2$ and (*S*)-BINAP maintains a generally high enantioselectivity for aryl boronic acids, the nitroallylation of a range of aryl boronic acids bearing either electron-donating or -withdrawing substituents with **1a** was examined. As shown in Table 2, the reactions gave desired products in

Table 2. Nitroallylation of Acetic Acid 2-Nitrocyclohex-2-enol Ester **1a** with Arylboronic Acids[a]



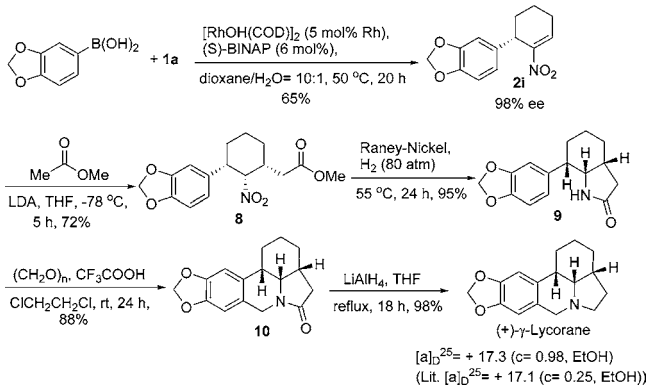
entry	product	Ar	yield[b] (%)	ee[c] (%)
1	**2a**	Ph	56	97
2	**2b**	4-MeC_6H_4	63	95
3	**2c**	4-$MeOC_6H_4$	58	96
4	**2d**	4-ClC_6H_4	64	99
5	**2e**	4-FC_6H_4	61	98
6	**2f**	4-^{t}Bu-C_6H_4	67	90
7	**2g**	4-$CF_3C_6H_4$	52	94
8	**2h**	3-$MeOC_6H_4$	58	96

[a] All reactions were carried out on a 0.3 mmol scale (see the Supporting Information). [b] Isolated yields. [c] Determined by HPLC or GC.

good yields and excellent enantioselectivities ranging from 90 to 99% ees. The electron nature of the substituent in arylboronic acids does not considerably affect the reaction. However, the enantioselectivity is to some degree dependent on the steric bulkiness of the arylboronic acids. For example, an enantioselectivity of only 90% ee was observed for 4-*tert*-butylphenylboronic acid, which is much lower than those of its structural analogues.

γ-Lycorane is a deoxygenated skeleton of Amarylliaceae alkaloids.[11] All of the ring junctures of γ-lycorane are *cis*.[12] Total syntheses of racemic γ-lycorane have been reported by several groups.[7] A number of efforts[8] have also been reported toward asymmetric syntheses of optically active (+)-γ-lycorane with only one example regarding the asymmetric catalytic construction of stereogenic centers with 46% ee,[8a] a concisely asymmetric catalytic total synthesis of optically pure (+)-γ-lycorane is therefore of great importance. Our newly developed nitroallylation of acetic acid 2-nitrocyclohex-2-enyl ester (**1a**) can be used for the concise asymmetric total synthesis of (+)-γ-lycorane (Scheme 2). The nitroallylation of **1a** with

Scheme 2. Highly Enantioselective Total Synthesis of (+)-γ-Lycorane



3,4-methylenedioxyphenylboronic acid in the presence of 5 mol % of rhodium complex of $[Rh(OH)(COD)]_2$ and (*S*)-BINAP gave the product **2i** in 65% yield and with 98% ee. The treatment of **2i** with methyl acetate and lithium diisopropylamine (LDA) at −78 °C furnished compound **8** with a high diastereomeric ratio of 7:1 in favor of the *cis,cis*-diastereomer. The *cis,cis*-**8** was subjected to a hydrogenation catalyzed by Raney nickel under 80 atm of hydrogen at 55 °C, which directly formed lactam **9** in 95% yield. A modified Pictet−Spengler ring closure[13] of **9** with paraformaldehyde and trifluoroacetic acid afforded **10** in 88% yield. Reduction of **10** with lithium aluminum hydride gave (+)-γ-lycorane in 98% yield with an optical rotation that is consistent with that of the natural product.[12] The overall yield of this concise total synthesis of optically pure (+)-γ-lycorane from **1a** is 38%. Logically, (−)-γ-lycorane can be synthesized by this strategy starting with the nitroallylation of **1a** with 3,4-methylenedioxyphenylboronic acid in the presence of the rhodium complex of $[Rh(OH)(COD)]_2$ and (*R*)-BINAP.

In conclusion, we have developed the first enantioselectiverhodium-catalyzed nitroallylation of nitroallyl acetates with arylboronic acids. This study demonstrates

(10) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984.

(11) (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, p 323.

(12) Kotera, K. *Tetrahedron* **1961**, *12*, 248.

(13) Fan, C.-A.; Tu, Y.-Q.; Song, Z.-L.; Zhang, E.; Shi, L.; Wang, M.; Wang, B.; Zhang, S.-Y. *Org. Lett.* **2004**, *6*, 4691.

that the rhodium complex of $[RhOH(COD)]_2$ and optically pure BINAP is an optimal catalyst, which provides igh enantioselectivities ranging from 90 to 99% ees for various arylboronic acids. A concise total synthesis of optically pure (+)-γ-lycorane in overall 38% yield was accomplished on the basis of this new method. Application of this method to the asymmetric synthesis of other alkaloids is under development.

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Supporting Information Available: Experimental details and selected HPLC and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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