Rhodium-Catalyzed Asymmetric Conjugate Addition of Organoboronic Acids to Nitroalkenes

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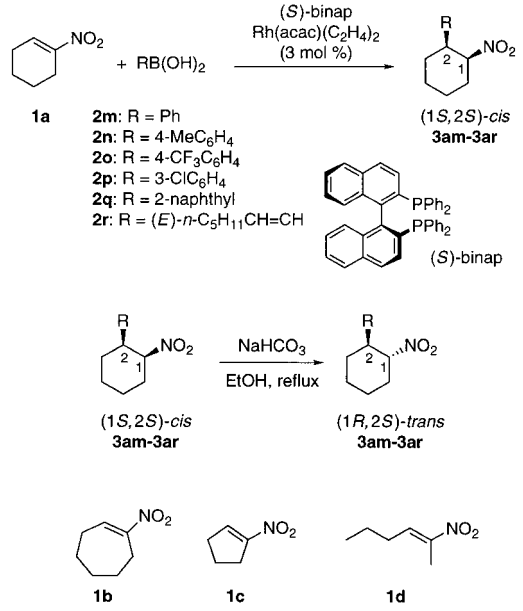
The conjugate addition of organometallic reagents to electron deficient olefins is an important method for the construction of new carbon−carbon bonds[1] and its enantioselective version using asymmetric catalysis has recently been an active field of research.[2] Although some successful results have been achieved on the asymmetric addition to α,β-unsaturated carbonyl compounds, there have been very few reports on the asymmetric addition to 1-nitroalkenes,[3−5] despite the wide applicability of nitro compounds to organic transformations.[6] In our previous studies on rhodium-catalyzed asymmetric 1,4-addition of organoboron reagents to electron-deficient olefins including α,β-unsaturated ketones, esters, and phosphonates,[7] the substrates we have employed are limited to those lacking the α-substituents due to their low reactivity toward the asymmetric addition, and as a result, no information on the relative stereochemistry at α and β positions has been obtained. Here we wish to report that 1-nitroalkenes containing α-substituents are good substrates for the rhodium-catalyzed asymmetric 1,4-addition and the reaction of 1-nitrocyclohexene proceeds with high diastereoselectivity giving thermodynamically less stable *cis* isomer preferentially (Scheme 1).

We chose 1-nitrocyclohexene (**1a**), which is a commercially available 1-nitroalkene, as a substrate for the asymmetric addition of phenylboronic acid (**2m**) and examined several reaction conditions for high chemical yield and high stereoselectivity. It was found that the asymmetric phenylation takes place with high enantioselectivity under the reaction conditions used for the reaction of α,β-unsaturated ketones.[7a] Thus, a mixture of **1a**, **2m** (5 equiv to **1a**), and 3 mol % of the rhodium catalyst Rh(acac)-$(C_2H_4)_2$/(*S*)-binap (1/1.1) in dioxane/H_2O (10/1) was heated at 100 °C for 3 h. Aqueous workup followed by silica gel chromatography gave 79% yield of 2-phenyl-1-nitrocyclohexane (**3am**). It turned out that the main phenylation product **3am** is a

Scheme 1



cis isomer (*cis*/*trans* = 87/13) and both of the *cis* and *trans* isomers are 98.3% enantiomerically pure (HPLC analysis with a chiral stationary phase column) (entry 2 in Table 1). Treatment of the *cis*-rich mixture with sodium bicarbonate in refluxing ethanol caused *cis*−*trans* equilibration giving thermodynamically more stable *trans* isomer (*trans*/*cis* = 97/3).[8] The enantiomeric purity was kept 98.3% ee after the equilibration, indicating that the *cis* and *trans* isomers have the same absolute configuration at 2 position and the opposite configuration at 1 position. Their absolute configurations were assigned to be (1*S*,2*S*) for *cis* isomer and (1*R*,2*S*) for *trans* isomer by correlation with known compounds (vide infra). It should be noted that the rhodium-catalyzed asymmetric phenylation produced thermodynamically less stable *cis* isomer of high enantiomeric purity and it can be isomerized, if one wishes, into *trans* isomer without loss of its enantiomeric purity. The isomers were readily separated pure by preparative TLC on silica gel or by a preparative GPC. The preferential formation of *cis*-**3am** in the catalytic phenylation may indicate the protonation of a rhodium nitronate intermediate[9] in the catalytic cycle (Scheme 2).

The chemical yield, *cis*-selectivity, and enantioselectivity in forming (1*S*,2*S*)-**3am** were dependent to some extent on the amount of the boronic acid **2m**, the reaction temperature, and the solvent used. The yield was higher (89%) with 10 equiv of **2m** (entry 1). The highest *cis*-selectivity (89/11) and the highest enantioselectivity (99.3% ee) was observed in the reactions carried out at 80 °C (entry 3) and in DMA/H_2O (entry 6), respectively.

Under similar reaction conditions, 1-nitrocyclohexene (**1a**) underwent asymmetric addition of some other arylboronic acids (**2n**−**2q**) in good yields with high enantioselectivity (entries 9−12). The corresponding *cis*-2-aryl-1-nitrocyclohexanes (**3an**−**3aq**) were produced with over 85% *cis*-selectivity and with the enantioselectivity ranging between 97.6 and 99.0% ee. The enantioselectivity in the addition of alkenylboronic acid (**2r**) was low compared with that of arylboronic acids, but it was improved by use of DMA/H_2O as a solvent (entries 13 and 14). The

(1) For a review on 1,4-addition reactions: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(2) For a pertinent review on asymmetric conjugate addition of organometallic reagents: Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1.

(3) Very recently, high enantioselectivity has been reported by Ji and Barnes on the addition of 1,3-dicarbonyl compounds to nitroalkenes: Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215.

(4) For examples of noncatalytic asymmetric 1,4-addition to nitroalkenes, see: (a) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271. (b) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305.

(5) For examples of catalytic asymmetric 1,4-addition to nitroalkenes, see (a) Brunner, H.; Kimel, B. *Monatsh. Chem.* **1996**, *127*, 1063. (b) Sewald, N.; Wendisch, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1341.

(6) For reviews: (a) Askani, R.; Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B, M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, Chapter 1.4. (b) Tamura, R.; Kamimura, A.; Ono, N. *Synthesis* **1991**, 423. (c) Fuji, K.; Node, M. *Synlett* **1991**, 603.

(7) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479. (c) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (d) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957. (e) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591.

(8) The equilibration of **3am** from *cis* to *trans* has been reported: Bordwell, F. G.; Yee, K. C. *J. Am. Chem. Soc.* **1970**, *92*, 5933.

(9) The preference for the formation of the less stable *cis* isomer has been reported on protonation of 2-substituted cyclohexane nitronate ions: Bordwell, F. G.; Yee, K. C. *J. Am. Chem. Soc.* **1970**, *92*, 5939.

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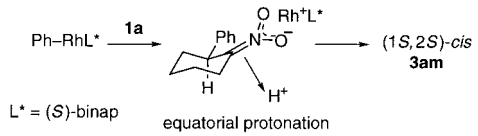
Table 1. Asymmetric Conjugate Addition of Boronic Acids **2** to Nitroalkenes **1** Catalyzed by (*S*)-BINAP-Rhodium(I)[a]

entry	nitroalkene **1**	$RB(OH)_2$ **2** (equiv to **1**)	solvent (10/1)	yield[b] (%) of **3**	*cis/trans*[c]	% ee[d]	after equiv *cis/trans*[c]
1	**1a**	**2m** (10)	dioxane/H_2O	89 (**3am**)	87/13	98.5	3/97
2	**1a**	**2m** (5)	dioxane/H_2O	79 (**3am**)	87/13	98.3	
3	**1a**	**2m** (5)	dioxane/H_2O[e]	54 (**3am**)	89/11	98.7	
4	**1a**	**2m** (5)	dioxane/H_2O[f]	<5 (**3am**)	—	—	
5	**1a**	**2m** (5)	DMF/H_2O	73 (**3am**)	81/19	99.0	
6	**1a**	**2m** (5)	DMA/H_2O	42 (**3am**)	83/17	99.3	
7	**1a**	**2m** (5)	1-propanol/H_2O	83 (**3am**)	84/16	93.7	
8	**1a**	**2m** (5)	toluene/H_2O	18 (**3am**)	81/19	91.8	
9	**1a**	**2n** (10)	dioxane/H_2O	89 (**3an**)	88/12	97.6	3/97
10	**1a**	**2o** (5)	dioxane/H_2O	88 (**3ao**)	85/15	99.0	3/97
11	**1a**	**2p** (5)	dioxane/H_2O	89 (**3ap**)	85/15	99.0	4/96
12	**1a**	**2q** (10)	dioxane/H_2O	84 (**3aq**)	85/15	98.0	2/98
13	**1a**	**2r** (5)	dioxane/H_2O	71 (**3ar**)	77/23	60.7	
14	**1a**	**2r** (10)	DMA/H_2O	90 (**3ar**)	75/25	82.9	10/90
15	**1b**	**2m** (10)	dioxane/H_2O	45 (**3bm**)	26/74	78.7	
16	**1b**	**2m** (5)	DMF/H_2O	73 (**3bm**)	17/83	90.6	8/92
17	**1c**	**2m** (5)	dioxane/H_2O	81 (**3cm**)	44/56	37.6	
18	**1c**	**2m** (10)	DMA/H_2O	93 (**3cm**)	40/60	73.0	13/87
19	**1d**	**2m** (10)	dioxane/H_2O	33 (**3dm**)	39/61[g]	96.8	36/64[g]

[a] The reaction was carried out with nitroalkene **1** (0.40 or 0.20 mmol), boronic acid **2** (2.0 mmol) in a given solvent (1.1 mL) at 100 °C for 3 h in the presence of 3 mol % of the catalyst generated from $Rh(acac)(C_2H_4)_2$ and (*S*)-BINAP (1/1.1) unless otherwise noted. [b] Isolated yield by silica gel chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC analysis with chiral stationary phase columns (Daicel Chiralcel OJ, OD-H, or Chiralpak AD) except for **3ar** whose % ee was determined by GLC analysis with CP-Cyclodex β236M. [e] At 80 °C. [f] At 60 °C. [g] Ratio of diastereomeric isomers.

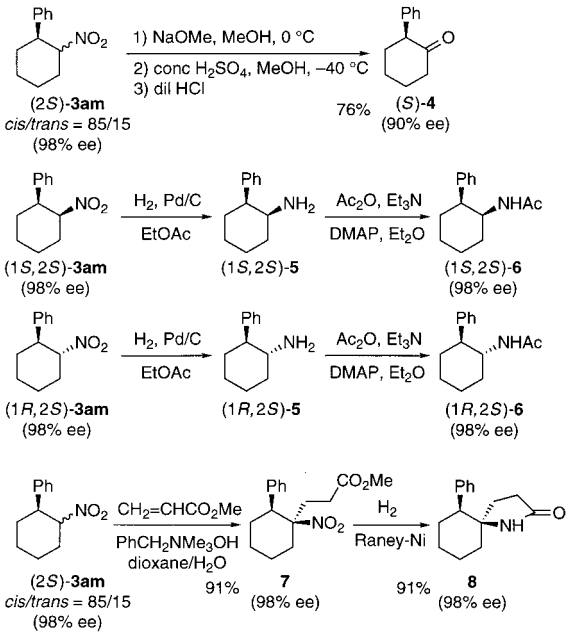
Scheme 2



asymmetric addition of phenylboronic acid was also successful for other cyclic nitroalkenes, 1-nitrocycloheptene (**1b**) and 1-nitrocyclopentene (**1c**), and for a linear nitroalkene **1d**, which gave the corresponding phenylation products with high enantioselectivity, though the diastereoselectivity is not so high (entries 16, 18, and 19).[10]

The optically active nitroalkanes obtained by the present rhodium-catalyzed asymmetric addition are useful chiral building blocks which can be readily converted into a wide variety of optically active compounds by taking advantage of the versatile reactivity of nitro compounds (Scheme 3). Thus, for example, exposure of **3am** (98% ee) to the Nef reaction conditions gave (*S*)-2-phenylcyclohexanone (**4**)[11] of 90% ee.[12] The reaction was accompanied by a slight loss of enantiomeric purity probably due to the presence of an acidic hydrogen at the stereogenic carbon center which is bonded to carbonyl and phenyl groups. Reduction of the nitro group in *cis*-**3am** (>99% *cis*) and *trans*-**3am** (>99% *trans*) by hydrogenation catalyzed by palladium on charcoal gave the corresponding optically active 2-phenyl-1-aminocyclohexanes,[13] *cis*-**5** and *trans*-**5**, respectively, without *cis/trans* isomerization or loss of their enantiomeric purity. Their % ee's (98% ee) were confirmed by an HPLC analysis of the acetamides **6**. Nitro compounds containing acidic hydrogen(s) are known to be

Scheme 3



good nucleophiles applicable to further carbon−carbon bond forming reactions. As an example, Michael addition of (2*S*)-**3am**, which is a mixture of *cis* and *trans* isomers in an 85/15 ratio, to methyl acrylate[14] followed by reduction of the nitro group in **7** gave spiro amide **8**[15] as a single isomer in a high yield.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for the substrates and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The asymmetric addition to the nitroalkenes which lack the α-substituent is also possible, though the yield or enantioselectivity is not so high as that for the cyclic nitroalkenes. For examples, the reaction (100 °C, 3 h in dioxane/H_2O (10/1)) of phenylboronic acid (**2a**) with (*E*)-1-nitro-3-methylbutene and (*E*)-1-nitro-3,3-dimethylbutene gave the corresponding phenylation products in 88% yield; 63% ee and 5% yield; 99.5% ee, respectively.

(11) $[\alpha]^{20}_D$ −97 (*c* 0.78, benzene). The reported value for (*S*)-2-phenylcyclohexanone is $[\alpha]^{24}_D$ −114 (*c* 0.60, benzene): Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Chem. Soc. (C)* **1971**, 3371.

(12) The enantiomeric purity was determined by HPLC analysis with Chiralcel OD-H (hexane/2-propanol = 9/1).

(13) *cis*-**5**: $[\alpha]^{20}_D$ +63 (*c* 0.42, MeOH). *trans*-**5**: $[\alpha]^{20}_D$ −36 (*c* 0.84, MeOH). The specific rotations of (1*S*, 2*S*)-**5** and (1*R*,2*S*)-**5** have been reported to be $[\alpha]^{27}_D$ +59 (*c* 0.26, MeOH) and $[\alpha]^{27}_D$ −45 (*c* 0.074, MeOH), respectively: Verbit, L.; Price, H. C. *J. Am. Chem. Soc.* **1972**, *94*, 5143.

(14) Moffett, R. B. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 652.

(15) The enantiomeric purities of **7** and **8** were determined to be 98% ee by HPLC analysis with chiral stationary phase columns (Chiralcel OJ for **7** and Chiralcel OD-H for **8** (hexane/2-propanol = 4/1)).