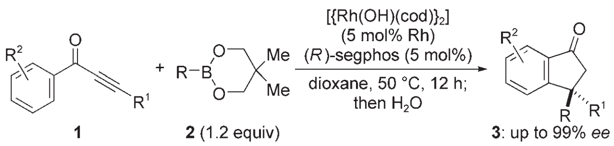
DOI: 10.1002/anie.200700226

Asymmetric Catalysis

Rhodium-Catalyzed Asymmetric Synthesis of 3,3-Disubstituted 1-Indanones**

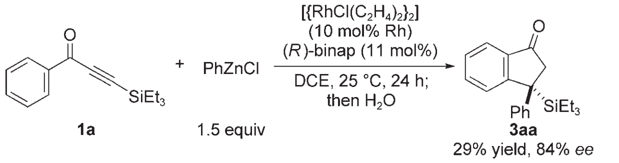
Ryo Shintani, Keishi Takatsu, and Tamio Hayashi**

The enantioselective construction of 1-indanones with a stereocenter at the 3-position is a subject of importance because of the high utility of indan structures in organic chemistry.[1] Several research groups have focused on the development of a catalytic asymmetric synthesis of these compounds, but most were successful only in the preparation of 3-monosubstituted 1-indanones.[2] In fact, to the best of our knowledge, only one recent report by Murakami and co-workers describes the catalytic asymmetric construction of 3,3-disubstituted 1-indanones.[3] Herein we describe the development of a highly enantioselective synthesis of 3,3-disubstituted 1-indanones by the addition of aryl boronates to aryl silylethynyl ketones under rhodium catalysis [Eq. (1)].



(1)

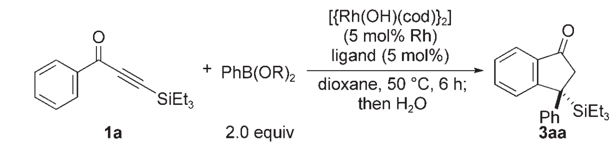
In 2005, we reported the Rh/dppf-catalyzed addition of aryl zinc chlorides to aryl alkynyl ketones to give 3,3-disubstituted 1-indanones (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene).[4] Our efforts to develop an effective asymmetric variant of this reaction were hampered by the fact that the indanones are only formed in high yield with the dppf ligand on rhodium. For example, in the reaction of 1-phenyl-3-triethylsilyl-2-propyn-1-one (**1a**) with phenylzinc chloride, we found that indanone **3aa** was formed with relatively high enantioselectivity (84% *ee*) when (*R*)-binap[5] was used as the ligand, but in very low yield (29%), with significant decomposition of the substrate **1a** [Eq. (2); DCE = 1,2-dichloroethane, cod = 1,5-cyclooctadiene].



(2)

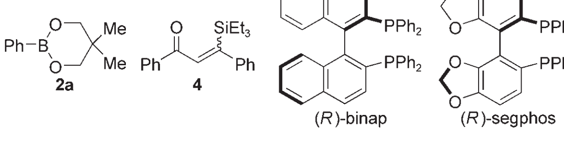
We therefore decided to reinvestigate the reaction conditions and alter them to favor formation of the indanone in high yield in the presence of an axially chiral bisphosphine ligand, such as (*R*)-binap. When phenylboronic acid (2.0 equiv) was employed as the nucleophile in the reaction of **1a** catalyzed by Rh/(*R*)-binap (5 mol%) at 50 °C, indanone **3aa** was produced in 29% yield with 80% *ee*; the major product was found to be the uncyclized hydrophenylation product **4**[6] (Table 1, entry 1). This outcome indicates that intermediate **A**, generated by phenylrhodation of the alkyne, can be protonated easily before it is engaged in the subsequent cyclization process (Scheme 1). To suppress the undesired formation of **4**, we used aprotic phenylboronic acid pinacol ester (PhBpin) as the nucleophile. As expected, enone **4** was not obtained under these conditions; however, unfortunately the reaction became very sluggish, with **3aa** isolated in only 20% yield after 10 h and 65% recovery of the starting alkyne **1a** (Table 1, entry 2). The slowness of this reaction is probably due to the bulkiness of the pinacol moiety, which may retard the transmetalation of the phenyl group and thus decrease catalytic turnover. On the basis of this hypothesis, we tested the less bulky boronic ester **2a** and found that the reaction proceeded smoothly to give **3aa** in 83% yield with 86% *ee* (Table 1, entry 3).[7] The use of (*R*)-segphos[8] as the ligand gave **3aa** in higher yield and with a higher *ee* value

Table 1: Optimization of the rhodium-catalyzed asymmetric synthesis of **3aa**.



Entry	PhB(OR)$_2$	Ligand	Yield [%]	*ee* [%]
1	PhB(OH)$_2$	(*R*)-binap	29[a]	80
2[b]	PhBpin	(*R*)-binap	20[c]	86
3	**2a**	(*R*)-binap	83	86
4	**2a**	(*R*)-segphos	87	99
5[d]	**2a**	(*R*)-segphos	89	98

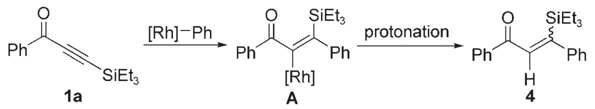
[a] The enone **4** was obtained in 69% yield. [b] Reaction time: 10 h. [c] Compound **1a** was recovered in 65% yield. [d] The reaction was conducted with 1.2 equiv of **2a** for 12 h.



[*] Dr. R. Shintani, K. Takatsu, Prof. Dr. T. Hayashi
Department of Chemistry, Graduate School of Science
Kyoto University, Sakyo, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-3988
E-mail: shintani@kuchem.kyoto-u.ac.jp
thayashi@kuchem.kyoto-u.ac.jp

[**] Financial support was provided in part by a Grant-in-Aid for Scientific Research and the Ministry of Education, Culture, Sports, Science, and Technology, Japan (21st Century COE, Kyoto University Alliance for Chemistry).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

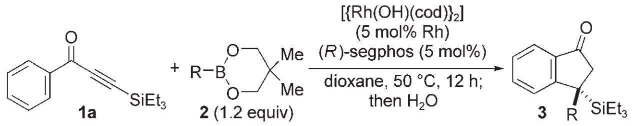


Scheme 1. A possible pathway for the formation of the undesired enone **4**.

(Table 1, entry 4; 87% yield, 99% *ee*). A similar result was obtained with (*R*)-segphos even with 1.2 equivalents of **2a** (Table 1, entry 5; 89% yield, 98% *ee*).

Under these conditions, a variety of aryl boronates can be used with substrate **1a** to give 3,3-disubstituted 1-indanones in high yield with excellent enantioselectivity (Table 2, entries 1–7). A methyl group can also be installed with moderate efficiency (Table 2, entry 8; 51% yield, 87% *ee*). With regard to the variability of the substrate, substituents on

Table 2: Scope of the rhodium-catalyzed asymmetric synthesis of 3,3-disubstituted 1-indanones with respect to the nucleophile.



Entry	R	Product	Yield [%]	*ee* [%]
1	Ph (**2a**)	**3aa**	89	98
2[a]	4-$MeOC_6H_4$ (**2b**)	**3ab**	71	98
3	4-MeC_6H_4 (**2c**)	**3ac**	83	99
4[b]	4-BrC_6H_4 (**2d**)	**3ad**	88	98
5	4-$CF_3C_6H_4$ (**2e**)	**3ae**	89	98
6	3-ClC_6H_4 (**2f**)	**3af**	91	96
7	2-naphthyl (**2g**)	**3ag**	91	98
8[c]	Me (**2h**)	**3ah**	51	87

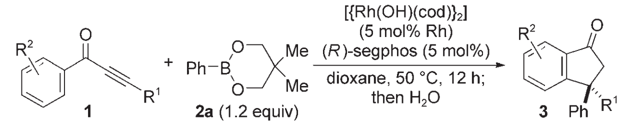
[a] The reaction was conducted with 8 mol% of the catalyst and 1.5 equiv of **2b** for 24 h. [b] The reaction was conducted with 8 mol% of the catalyst. [c] The reaction was conducted with 8 mol% of the catalyst and 3 equiv of **2h** for 24 h.

the benzene ring can be varied both sterically and electronically with maintenance of the high yield and *ee* value of the product (Table 3, entries 1–5). Other silyl groups or a germyl group can also be used as a substituent on the alkyne (Table 3, entries 6–8).[9]

Indanone **3jg**, which was obtained from the reaction of 1-(3-chlorophenyl)-3-triethylsilyl-2-propyn-1-one (**1j**) with the 2-naphthylboronate **2g** [Eq. (3)], furnished single crystals suitable for X-ray analysis. Its absolute configuration was determined to be *R* (Figure 1).[10]

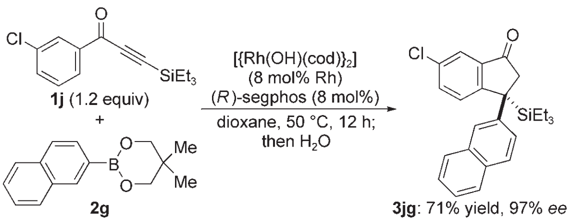
By analogy with the rhodium-catalyzed formation of 3,3-disubstituted 1-indanones by using aryl zinc chlorides,[4] a proposed reaction pathway to indanone **3aa** under the present conditions is illustrated in Scheme 2. Thus, insertion of the alkyne of **1a** into the phenyl–rhodium bond generates the alkenyl rhodium species **A**, which undergoes a 1,4-rhodium migration to produce the aryl rhodium intermediate **B**.[6,11] Intramolecular 1,4-addition of **B** leads to the oxa-π-allyl rhodium species **C**, and transmetalation of the phenyl group from boron to rhodium releases the product as the

Table 3: Scope of the rhodium-catalyzed asymmetric synthesis of 3,3-disubstituted 1-indanones with respect to the substrate **1**.



Entry	Substrate	Product	Yield [%]	*ee* [%]
1	**1b**: $R^1 = SiEt_3$, $R^2 = 2$-Me	**3ba**	86	94
2	**1c**: $R^1 = SiEt_3$, $R^2 = 3$-Me	**3ca**	84[a]	98
3	**1d**: $R^1 = SiEt_3$, $R^2 = 4$-Me	**3da**	83	98
4	**1e**: $R^1 = SiEt_3$, $R^2 = 4$-MeO	**3ea**	82	98
5[b]	**1f**: $R^1 = SiEt_3$, $R^2 = 4$-F	**3fa**	79	99
6	**1g**: $R^1 = SiMe_2Et$, $R^2 = H$	**3ga**	90	94
7[c]	**1h**: $R^1 = SiMe_2tBu$, $R^2 = H$	**3ha**	75	98
8[b]	**1i**: $R^1 = GeEt_3$, $R^2 = H$	**3ia**	88	97

[a] The cyclization occurred exclusively at the less hindered site on the aromatic ring. [b] The reaction was conducted with 8 mol% of the catalyst. [c] The reaction was conducted with 8 mol% of the catalyst and 1.5 equiv of **2a** for 24 h.



(3)

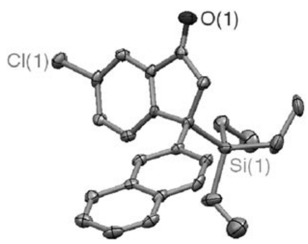
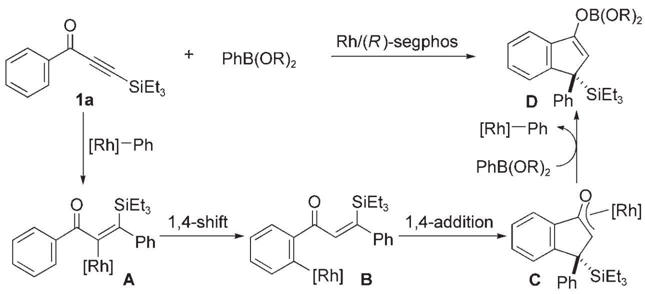


Figure 1. X-ray structure of **3jg** with thermal ellipsoids drawn at the 50% probability level (Flack parameter = 0.01(3); hydrogen atoms are omitted for clarity).



Scheme 2. Proposed catalytic cycle of the rhodium-catalyzed addition of the phenylboronate **2a** to the aryl alkynyl ketone **1a**.

boron enolate **D** along with a phenyl rhodium species for the next cycle. The formation of the boron enolate **D** was confirmed by ^{1}H NMR spectroscopy before the reaction was quenched with water (^{1}H NMR ($CDCl_3$): $\delta = 6.38$ (s, 1H at the 2-position of the indanone enolate), 3.74 (s, 4H on the two methylene carbon atoms of the boronate), and 1.02 ppm (s, 6H of the two methyl groups of the boronate)).

The stereodetermining step of the catalytic cycle is that from **B** to **C** (Scheme 2), and the observed stereochemical outcome can be rationalized as shown in Figure 2. Thus, the alkene binds to rhodium from its 2*Re* face to avoid steric repulsion between the Ar group at the 3-position and the phenyl group on the phosphorus atom of (*R*)-segphos. This facial selectivity leads to the formation of *R* indanones.

The highly enantioenriched indanone **3aa** can be manipulated further with high stereoselectivity. For example, the reduction of the carbonyl group followed by dehydration led to the synthetically useful allyl silane **4** (Scheme 3). The reduction of **3aa** with HAl*i*Bu_2 gave indanol **5** with *cis* selectivity (d.r. 93:7). The protection of **5** with $MeOCH_2Cl$ followed by separation of the diastereomers provided compound **6** as a single diastereomer with 98% *ee*, the triethylsilyl group of which could be removed diastereoselectively by treatment with TBAF to give compound **7** as the *cis* isomer (d.r. 91:9).

In summary, we have developed a highly enantioselective synthesis of 3,3-disubstituted 1-indanones through the addition of aryl boronates to aryl alkynyl ketones under rhodium catalysis. This new method allows rapid access to enantioenriched indanones that are difficult to obtain by other methods. Future studies will focus on the improvement of the catalyst system to overcome the current limitation in terms of applicable substrates and nucleophiles.

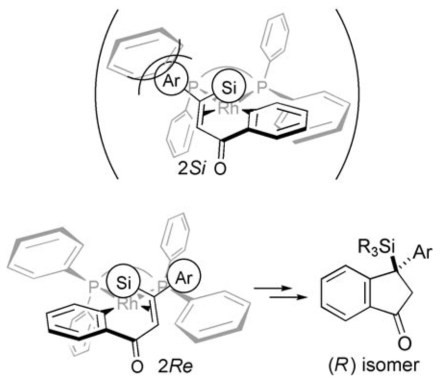
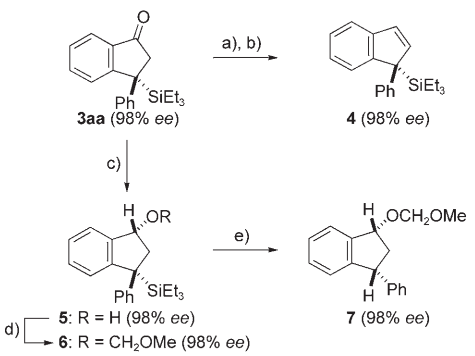


Figure 2. Proposed stereochemical pathway for the Rh/(*R*)-segphos-catalyzed asymmetric synthesis of 3,3-disubstituted 1-indanones.



Scheme 3. Conversion of indanone **3aa** into several indan derivatives: a) $LiAlH_4$, THF, RT; b) cat. TsOH, C_6H_6, reflux, 96% (over 2 steps); c) HAl*i*Bu_2, THF, −78°C, 97% (d.r. 93:7); d) $MeOCH_2Cl$, *i*Pr_2NEt, CH_2Cl_2, RT; then separation of diastereomers, major: 90%; e) TBAF, THF, 0°C, 98% (d.r. 91:9). TBAF = tetrabutylammonium fluoride.

Experimental Section

General procedure (Tables 2 and 3): A solution of [{Rh(OH)(cod)}$_2$] (2.3 mg, 10 μmol Rh) and (*R*)-segphos (6.2 mg, 10 μmol) in 1,4-dioxane (0.5 mL) was stirred for 5 min at room temperature. The aryl boronate **2** (0.24 mmol) and **1** (0.20 mmol) were then added successively with additional 1,4-dioxane (0.5 mL), and the resulting mixture was stirred for 12 h at 50°C. The reaction was quenched with water (60 μL), and the mixture was filtered through a pad of silica gel with Et_2O. Removal of the solvent under vacuum was followed by chromatography of the residue on silica gel with Et_2O/hexane to afford **3**.

Received: January 17, 2007
Published online: April 3, 2007

Keywords: alkynes · asymmetric catalysis · boron · indanones · rhodium

[1] For examples, see: a) C. Hedberg, P. G. Andersson, *Adv. Synth. Catal.* **2005**, *347*, 662; b) W. M. Clark, A. M. Tickner-Eldridge, G. K. Huang, L. N. Pridgen, M. A. Olsen, R. J. Mills, I. Lantos, N. H. Baine, *J. Am. Chem. Soc.* **1998**, *120*, 4550; c) R. T. Lum, M. G. Nelson, A. Joly, A. G. Horsma, G. Lee, S. M. Meyer, M. M. Wick, S. R. Schow, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 209.

[2] For examples, see: a) J. Yun, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 767; b) Y. Caro, M. Torrado, C. F. Masaguer, E. Raviña, *Tetrahedron: Asymmetry* **2003**, *14*, 3689; c) N. Kumagai, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2001**, *3*, 4251; d) F. O. Arp, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 10482; e) K. Kundu, J. V. McCullagh, A. T. Morehead, Jr., *J. Am. Chem. Soc.* **2005**, *127*, 16042; f) R. Shintani, K. Yashio, T. Nakamura, K. Okamoto, T. Shimada, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 2772.

[3] T. Matsuda, M. Shigeno, M. Makino, M. Murakami, *Org. Lett.* **2006**, *8*, 3379.

[4] R. Shintani, T. Hayashi, *Org. Lett.* **2005**, *7*, 2071.

[5] H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, R. Noyori, *J. Org. Chem.* **1986**, *51*, 629.

[6] T. Hayashi, K. Inoue, N. Taniguchi, M. Ogasawara, *J. Am. Chem. Soc.* **2001**, *123*, 9918.

[7] For examples of the effect of phenylboronate substituents on reactivity, see: a) F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 5936; b) K. Ukai, M. Aoki, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2006**, *128*, 8706.

[8] T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi, *Adv. Synth. Catal.* **2001**, *343*, 264.

[9] To date we have not been successful in employing alkynes with carbon-based substituents as the substrate.

[10] CCDC-631569 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] a) K. Oguma, M. Miura, T. Satoh, M. Nomura, *J. Am. Chem. Soc.* **2000**, *122*, 10464; b) T. Miura, T. Sasaki, H. Nakazawa, M. Murakami, *J. Am. Chem. Soc.* **2005**, *127*, 1390; c) R. Shintani, K. Okamoto, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 2872; d) H. Yamabe, A. Mizuno, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2005**, *127*, 3248.

