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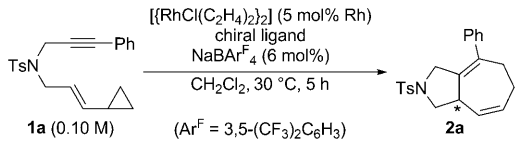
Rhodium-Catalyzed Asymmetric [5+2] Cycloaddition of Alkyne–Vinylcyclopropanes

Ryo Shintani,* Hiroki Nakatsu, Keishi Takatsu, and Tamio Hayashi*[a]

Transition-metal-catalyzed [5+2] cycloaddition of vinylcyclopropanes with carbon–carbon unsaturated bonds is an efficient way of constructing seven-membered carbocycles. Several transition metals such as rhodium,[1] ruthenium,[2] nickel,[3] and iron[4] can catalyze these reactions with alkynes as the reaction partner, and alkenes[1c,5] and allenes[6] can also be employed under rhodium catalysis.[7,8] Unfortunately, however, the development of asymmetric variants of this useful transformation has not met much success so far. In fact, to the best of our knowledge, only a recent report by Wender addressed this issue, achieving high enantioselectivity for several alkene-tethered vinylcyclopropanes using a cationic Rh/(*R*)-binap catalyst.[9] For cycloaddition of alkyne–vinylcyclopropanes, in contrast, there is no effective catalytic asymmetric method available to date.[10] Herein we describe the development of such an asymmetric catalysis by the use of a rhodium complex coordinated with chiral phosphoramidite ligand, achieving very high enantiomeric excesses (up to >99.5% *ee*).

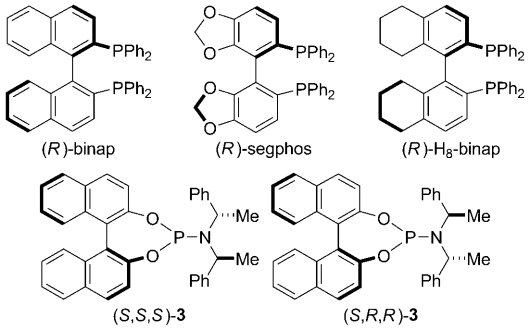
Initially, we employed alkyne–vinylcyclopropane **1a** as a model substrate and attempted a cycloaddition reaction in the presence of 5 mol% of a cationic Rh/(*R*)-binap[11] complex in dichloromethane at 30°C (Table 1, entry 1). Under these conditions, 37% yield of cycloadduct **2a** was obtained after 5 h with moderate *ee* value of 64%. The use of other axially chiral bisphosphine ligands such as (*R*)-segphos[12] and (*R*)-H_8-binap[13] resulted in lower yields and enantioselectivity under otherwise the same conditions (18–29% yield, 46–55% *ee*; entries 2 and 3). In contrast, chiral phosphoramidite ligand (*S*,*S*,*S*)-**3**[14] (1.5 equiv to Rh) induced somewhat better enantioselectivity (75% *ee*; entry 4) and its diastereomeric ligand (*S*,*R*,*R*)-**3**[14,15] dramatically improved both reactivity and stereoselectivity, giving product **2a** in 88% yield with as high as 99% *ee* (entry 5). The absolute configuration of **2a** thus obtained was determined to be (*R*) by X-ray crystallographic analysis as shown in Figure 1.[16]

Table 1. Ligand effect in the rhodium-catalyzed asymmetric [5+2] cycloaddition of **1a**.



Entry	Ligand (equiv to Rh)	Yield [%][a]	*ee* [%][b]
1	(*R*)-binap (1.1)	37	64 (*S*)
2	(*R*)-segphos (1.1)	29	46 (*S*)
3	(*R*)-H_8-binap (1.1)	18	55 (*S*)
4	(*S*,*S*,*S*)-**3** (1.5)	31	75 (*R*)
5	(*S*,*R*,*R*)-**3** (1.5)	88[c]	99 (*R*)

[a] Determined by ^{1}H NMR against an internal standard ($MeNO_2$). [b] Determined by chiral HPLC on a Chiralcel OD-H column with hexane/2-propanol 95:5. [c] Isolated yield.



The scope of the present catalysis using ligand (*S*,*R*,*R*)-**3** is illustrated in Table 2. Not only aryl groups (**1a**–**c**) but also alkyl groups (**1d** and **1e**) are well tolerated as the substituent on the alkyne, leading to the corresponding cycloadducts **2** with uniformly high yield and excellent enantioselectivity (87–90% yield, ≥94% *ee*; entries 1–6), and the amount of ligand (*S*,*R*,*R*)-**3** can be reduced to 6 mol% (1.2 equiv to Rh) as shown in entry 2. High enantioselectivity is also achieved with substrate **1f** having a terminal alkyne, although

[a] Dr. R. Shintani, H. Nakatsu, 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

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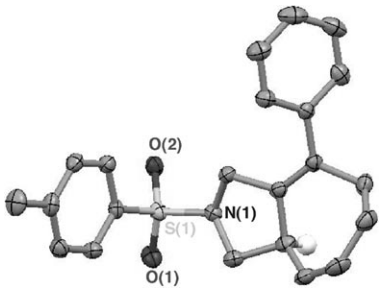
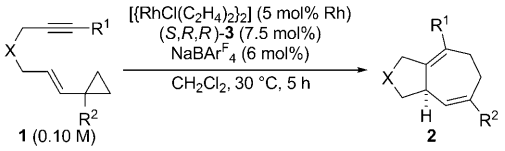
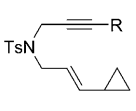
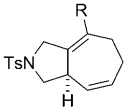
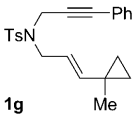
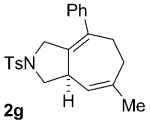
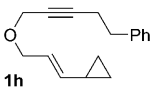
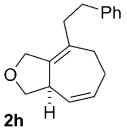
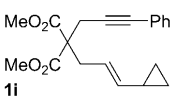
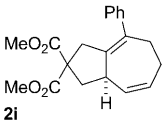


Figure 1. X-ray crystal structure of (*R*)-**2a**.

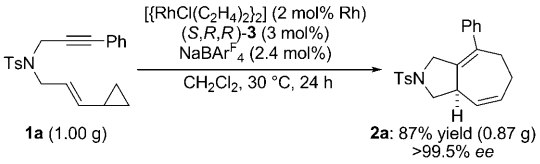
Table 2. Scope of the rhodium-catalyzed asymmetric [5+2] cycloaddition of alkyne–vinylcyclopropanes **1**.



Entry	Substrate	Product	Yield [%][a]	*ee* [%][b]
				
1	**1a** (R = Ph)	**2a**	88	99
2[c]	**1a** (R = Ph)	**2a**	89	99
3	**1b** (R = 4-$MeOC_6H_4$)	**2b**	89	98
4	**1c** (R = 4-ClC_6H_4)	**2c**	90	94
5	**1d** (R = Me)	**2d**	87	>99.5
6	**1e** (R = *i*Pr)	**2e**	87	99
7[d]	**1f** (R = H)	**2f**	53	92
8	 **1g**	 **2g**	87	99
9[e]	 **1h**	 **2h**	90	95
10	 **1i**	 **2i**	82	83

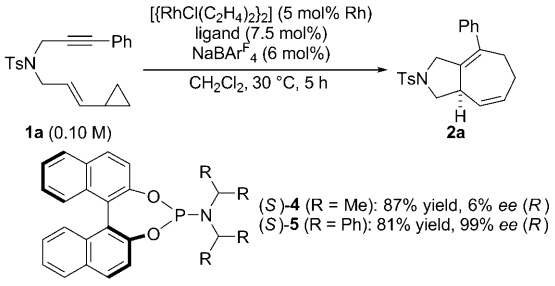
[a] Isolated yield. [b] Determined by chiral HPLC with hexane/2-propanol. [c] 6 mol% of (*S*,*R*,*R*)-**3** was used. [d] The reaction was conducted at 40 °C for 48 h at 0.01 M. [e] The reaction was conducted for 24 h at 0.01 M.

the yield becomes somewhat lower due to the decomposition of **1f** during the reaction (53% yield, 92% *ee*; entry 7). Other alkyne–vinylcyclopropanes, such as **1g** with methyl group on the cyclopropane, **1h** with an oxygen tether, and **1i** with a carbon tether, can be effectively employed as well under these reaction conditions (82–90% yield, 83–99% *ee*; entries 8–10). Furthermore, the reaction of **1a** can be conducted on a gram scale with a reduced catalyst loading (2 mol% Rh), and simple recrystallization of the crude material from CH_2Cl_2/hexane readily provides product **2a** without chromatographic purification in essentially enantiopure form [87% yield, >99.5% *ee*; Eq. (1)].



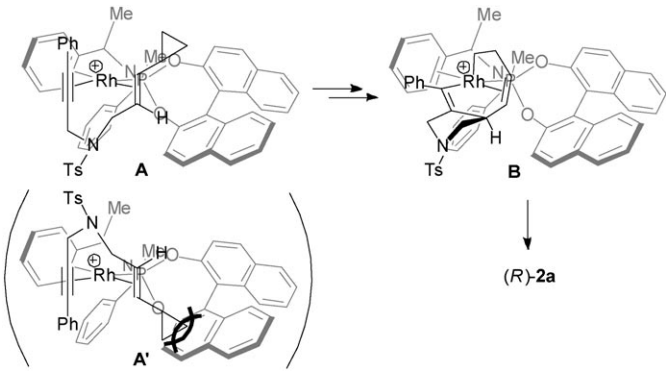
(1)

To gain some insight into the active catalyst species in the present transformation, we conducted some control experiments using **1a** as the substrate and made the following observations. 1) By using 2.2 equiv, rather than 1.5 equiv, of (*S*,*R*,*R*)-**3** to Rh, **1a** remained mostly unreacted, giving **2a** only in 4% yield. 2) Replacement of phenyl groups of (*S*,*R*,*R*)-**3** by methyl groups ((*S*)-**4**[14]) resulted in a dramatic decrease of enantioselectivity [6% *ee*; Eq. (2)], whereas replacement of methyl groups of (*S*,*R*,*R*)-**3** by phenyl groups ((*S*)-**5**) did not affect the enantioselectivity (99% *ee*). These results indicate that catalytically active species of the present asymmetric reaction is presumably a 1:1 complex of Rh/phosphoramidite, and that the presence of phenyl groups in the nitrogen substituent is necessary to induce significantly high enantioselectivity.



(2)

With regard to the structure of a Rh/(*S*,*R*,*R*)-**3** complex, Mezzetti recently disclosed that (*S*,*R*,*R*)-**3** can coordinate to a cationic rhodium(I) as a P–(η^2-arene) bidentate ligand using its phenyl moiety of the nitrogen substituent.[17] Because phosphoramidite ligands with pendant phenyl groups ((*S*,*S*,*S*)-**3**, (*S*,*R*,*R*)-**3**, and (*S*)-**5**) display much higher enantioselectivity than ligand (*S*)-**4** in the present catalysis, η^2 coordination of the phenyl group seems to play an important role for the stereocontrol of this process. On the basis of the X-ray crystal structure of [{Rh(nbd)((*R*,*S*,*S*)-**3**)}SbF_6] reported by Mezzetti,[17] along with the studies by Yu, Wender, and Houk on the reaction mechanism for [5+2] cycloadditions,[7,9] a proposed stereochemical pathway for the reaction of **1a** catalyzed by Rh/(*S*,*R*,*R*)-**3** is illustrated in Scheme 1. Thus, η^2 coordination of one of the phenyl groups in



Scheme 1. Proposed stereochemical pathway for asymmetric [5+2] cycloaddition of **1a** catalyzed by Rh/(*S*,*R*,*R*)-**3**.

(*S*,*R*,*R*)-**3** would organize the conformation of its rhodium complex in such a way that one of the naphthyl moieties of (*S*,*R*,*R*)-**3** effectively blocks the bottom right quadrant and the top right quadrant becomes wide open. This organized chiral environment around the rhodium would facilitate a face-selective coordination of **1a** in the form of **A**, rather than **A′**, to minimize the steric repulsion of the cyclopropyl moiety of **1a**. Oxidative cyclization of vinylcyclopropane from complex **A**, followed by insertion of alkyne, would lead to intermediate **B**, reductive elimination of which gives cycloadduct **2a** with *R* configuration.

In summary, we have developed a highly efficient asymmetric intramolecular [5+2] cycloaddition of alkyne–vinylcyclopropanes under rhodium catalysis. High enantioselectivities of up to >99.5% *ee* have been achieved by the use of a chiral phosphoramidite ligand. The reaction can be easily scaled up and the stereochemical model of the present catalysis has also been proposed.

Experimental Section

General procedure for Table 2: A solution of [{RhCl(C_2H_4)$_2$}$_2$] (1.9 mg, 9.8 μmol Rh) and (*S*,*R*,*R*)-**3** (7.9 mg, 15 μmol) in CH_2Cl_2 (1.0 mL) was stirred for 20 min at room temperature. Substrate **1** (0.20 mmol) was added to it with additional CH_2Cl_2 (0.5 mL), and then sodium tetrakis-(3,5-bis(trifluoromethyl)phenyl)borate (11 mg, 12 μmol) was added to it with additional CH_2Cl_2 (0.5 mL). The resulting solution was stirred for 5 h at 30 °C, and the reaction was quenched with water. After extraction with CH_2Cl_2, the organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel preparative TLC to afford cycloadduct **2**.

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Keywords: asymmetric catalysis · cycloaddition · phosphoramidite · rhodium

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