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Rh-Catalyzed Highly Enantioselective Hydroalkynylation Reaction of Norbornadiene Derivatives

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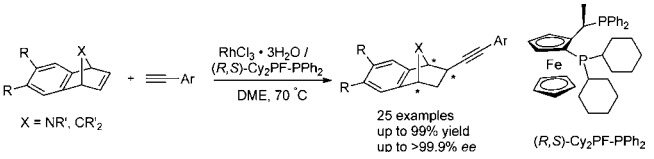
ABSTRACT



The complexes of various Rh precusors with ferrocenyl chiral ligand (*R*,*S*)-Cy_2PF-PPh_2 were found effective catalysts for the asymmetric hydroalkynylation reaction of norbornadiene derivatives. When $RhCl_3 \cdot 3H_2O$ was employed, good yields (up to 98%) and high enantioselectivities (up to >99.9% *ee*) could be obtained for the reactions of a broad scope of substrates.

The transition-metal-catalyzed asymmetric hydroalkynylation reaction of norbornadiene derivatives is emerging as a new paradigm for the direct addition of the *sp* hybridized C−H bond to the C=C double bond,[1] especially the nonpolar C=C double bond. In 2011, as the continuation of their first realization of racemic hydroalkynylation of norbornadienes,[2] Buono and his co-workers reported the asymmetric version of the same reaction by using a chiral palladium complex as catalyst.[3] In 2012, a chiral cobalt catalyst was developed by Hayashi's group, with which high enantioselectivities could be achieved for asymmetric addition of silylacetylenes to oxa/azabenzonorbornadienes.[4] At the same time, the complex of $[Ir(COD)Cl]_2$ and (*R*)-SYNPHOS was found as an effective catalyst for the asymmetric hydroalkynylation reaction of norbornadiene derivatives by our group.[5] However, low enantioselectivities and/or poor compatibilities suffered with these reported catalysts. Developing new and efficient chiral catalysts for this type of reaction is still desired.

Rhodium catalysts have played an important role in modern organic chemistry.[6] As one of the distinguished achievements, the rhodium-catalyzed asymmetric addition of terminal alkynes to various unsaturated prochiral compounds has attracted extensive study, and many successful chiral rhodium catalysts have been established.[7] However, to the best of our knowledge, the application of rhodium catalysts to the asymmetric addition of the *sp* hybridized C−H bond to the nonpolar C=C double bonds has not been reported up to now. Recently, a chiral rhodium catalyst, which was generated by the coordination of $[Rh(OAc)(C_2H_4)_2]_2$ with (*R*)-DTBM-segphos, was developed by Hayashi's group and found effective for the asymmetric alkynylative ring-opening reaction of azabenzonorbornadienes with (triisopropylsilyl)acetylene.[8]

(1) (a) Shirakura, M.; Suginome, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3827. (b) Nishimura, T.; Guo, X.-X; Hayashi, T. *Chem.—Asian J.* **2008**, *3*, 1505.

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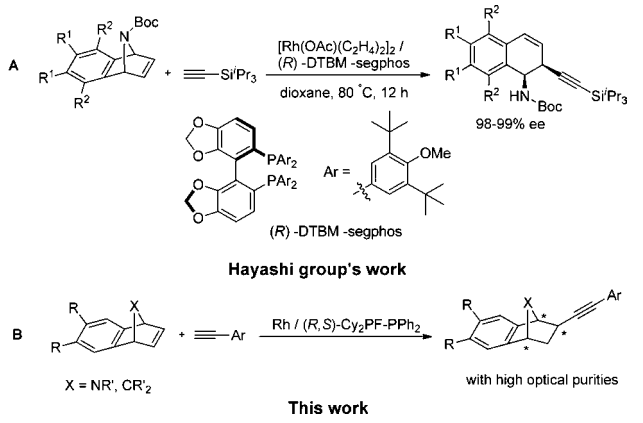
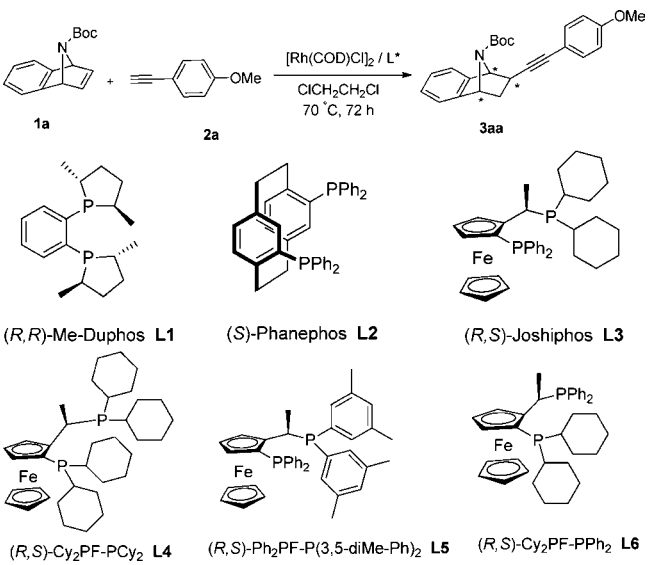


Figure 1. From asymmetric ring-opening reaction to asymmetric hydroalkynylation reaction between azabenzonorbornadienes and terminal alkynes.

It could be seen that the conversion of the reaction from the ring-opening one (reaction A in Figure 1) to the simple addition one (reaction B in Figure 1) was possible by tuning the activity of rhodium catalyst. As the result of our continuous exploration of catalytic reactions between norbornadiene derivatives and terminal alkynes,[5,9] this possibility was proved to be true, and here we report our rhodium-catalyzed asymmetric hydroalkynylation reaction of norbornadiene derivatives in high enantioselectivities.

The determination of the proper chiral ligand for the Rh catalyst was the emphasis of our initial experiments. Using Boc-protected azabenzonorbornadiene **1a**/*p*-methoxyphenylacetylene **2a** as benchmark substrates, and $[Rh(COD)Cl]_2$ as catalyst precursor, diphosphine ligands with different chiral backbones (except diaryl backbones) were screened (Table 1). **L1** ((*R*,*R*)-Me-Duphos) and **L2** ((*S*)-Phanephos) were found ineffective in this reaction, and no reaction took place at all. Encouraged by their remarkable exhibition in rhodium-catalyzed ring-opening reactions of oxa/azabenzonorbornadienes with various nuceophiles,[10] the Josiphos ligands (**L3** to **L6**), which have mixed chiralities, were then mainly focused on. To our delight, though all of its analogues, such as **L3** (Josiphos), **L4** and **L5**, could not form any active rhodium catalyst for the reactions of **1a** and **2a**, **L6** was found effective here. Promoted by the complex of $[Rh(COD)Cl]_2$ and **L6**, **1a** and **2a** reacted smoothly and generated the aimed hydroalkynylative product

Table 1. Screening of Chiral Ligands[a]



entry	chiral ligand	yield (%)[b]	*ee* (%)[c]
1	(*R*,*R*)-Me-Duphos **L1**	NR	/
2	(*S*)-Phanephos **L2**	NR	/
3	(*R*,*S*)-Josiphos **L3**	NR	/
4	(*R*,*S*)-Cy_2PF-PCy_2 **L4**	NR	/
5	(*R*,*S*)-Ph_2PF-P(3,5-diMe-Ph)$_2$ **L5**	NR	/
6	(*R*,*S*)-Cy_2PF-PPh_2 **L6**	63	95

[a] Reaction conditions: **2a** (0.4 mmol), **1a**:**2a**:$[Rh(COD)Cl]_2$:Ligand (1:2:0.025:0.065), in $ClCH_2CH_2Cl$ (2 mL) at 70 °C under Ar for indicated period of time. [b] Isolated yield by column chromatography. [c] *ee* % were determined by chiral HPLC using a Chiralcel OD-H column.

3aa in 63% yield. The further chiral HPLC analysis showed that **3aa** had 95% *ee* optical purity.

Using **L6** as chiral ligand, the reaction conditions for this rhodium-catalyzed asymmetric hydroalkynylation reaction were then optimized (Table 2). It could be seen that both neutral and cationic Rh(I) compounds could serve as a suitable catalyst precursor here, and high enantioselectivities (about 95% *ee*) could be achieved in all cases, though different yields were resulted. It is quite surprising that Rh(III) compounds, which generally acted as sp^2 and sp^3 hybridized C−H bond activators,[11] were also effective in this hydroalkynylation reaction. A 62% yield and 95% *ee* were obtained when $[RhCp^*Cl_2]_2$ was used as a catalyst precursor. A slightly better result, 66% yield and 96% *ee*, was achieved by using the simpler and cheaper $RhCl_3 \cdot 3H_2O$. The solvent experiments showed that DME was the best one, and the other generally used solvents were all acceptable in this reaction except THF and DMF. Using DME as solvent, the yield was raised to 92%, and the high enantioselectivity (96% *ee*) was maintained. 70 °C was found to be the proper reaction temperature. When the reaction was carried out at

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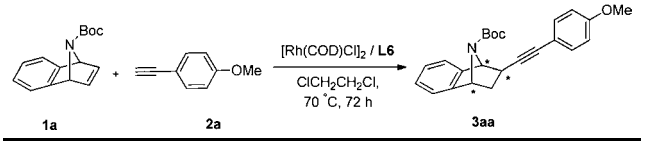
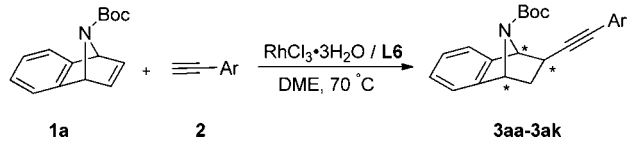
Table 2. Optimization of Reaction Conditions[a]



entry	Rh precursor	solvent	time (h)	yield (%)[b]	*ee* (%)[c]
1	$[Rh(COD)Cl]_2$	$ClCH_2CH_2Cl$	74	63	95
2	$Rh(acac)(CO)_2$	$ClCH_2CH_2Cl$	78	34	94
3	$[Rh(NBD)_2Cl]_2$	$ClCH_2CH_2Cl$	82	34	96
4	$Rh(COD)_2BF_4$	$ClCH_2CH_2Cl$	80	69	95
5	$[RhCp^*Cl_2]_2$	$ClCH_2CH_2Cl$	72	62	95
6	$RhCl_3 \cdot 3H_2O$	$ClCH_2CH_2Cl$	72	66	96
7	$RhCl_3 \cdot 3H_2O$	THF	72	NR	/
8	$RhCl_3 \cdot 3H_2O$	DMF	72	trace	/
9	$RhCl_3 \cdot 3H_2O$	toluene	46	34	95
10	$RhCl_3 \cdot 3H_2O$	DME	22	92	96
11	$RhCl_3 \cdot 3H_2O$	dioxane	72	69	94
12	$RhCl_3 \cdot 3H_2O$	*i*PrOH	72	73	92
13[d]	$RhCl_3 \cdot 3H_2O$	DME	72	NR	/
14[e]	$RhCl_3 \cdot 3H_2O$	DME	16	53	96

[a] Reaction conditions: **2a** (0.4 mmol), **2a**:**1a**:Rh:(*R*,*S*)-Cy_2PF-PPh_2 (2:1:0.05:0.065), in solvent (2 mL) at 70 °C under Ar for indicated period of time. [b] Isolated yield by column chromatography. [c] *ee* % were determined by chiral HPLC using a Chiralcel OD-H column. [d] The reaction was carried out at 50 °C. [e] The reaction was carried out at 90 °C.

Table 3. Rhodium-Catalyzed Asymmetric Hydroalkynylation of Azabenzonorbornadiene **1a** with Various Arylacetylenes[a]

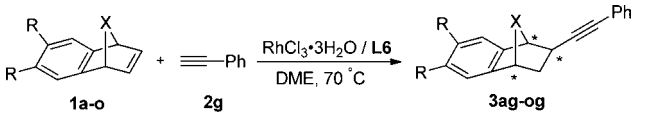


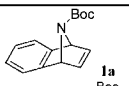
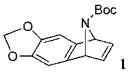
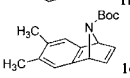
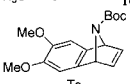
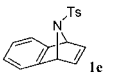
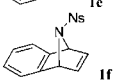
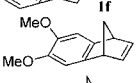
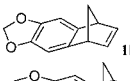
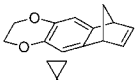
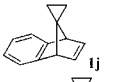
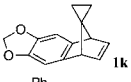
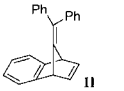
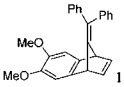
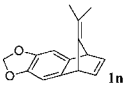
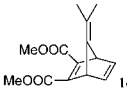
entry	Ar	products	time (h)	yield (%)[b]	*ee* (%)[c]
1	4-MeO-C_6H_4 **2a**	**3aa**	22	92	96
2	2-MeO-C_6H_4 **2b**	**3ab**	43	91	97
3	3-MeO-C_6H_4 **2c**	**3ac**	32	90	97
4	3,5-diMeO-C_6H_3 **2d**	**3ad**	30	98	97
5	4-Me-C_6H_4 **2e**	**3ae**	51	85	96
6	4-Me_2N-C_6H_4 **2f**	**3af**	55	74	95
7	Ph **2g**	**3ag**	20	98	99
8	4-F-C_6H_4 **2h**	**3ah**	48	95	98
9	4-CF_3O-C_6H_4 **2i**	**3ai**	45	90	99
10	4-Br-C_6H_4 **2j**	**3aj**	60	82	99
11	4-CH_2OH-C_6H_4 **2k**	**3ak**	70	93	98

[a] Reaction conditions: **2** (0.4 mmol), **2**:**1a**:Rh:(*R*,*S*)-Cy_2PF-PPh_2 (2:1:0.05:0.065), in DME (2 mL) at 70 °C under Ar. [b] Isolated yield by column chromatography. [c] *ee* % were determined by chiral HPLC using Chiralcel OD-H or AD-H column.

50 °C, no reaction took place after 72 h of heating and stirring. Raising the temperature to 90 °C could accelerate the reaction speed obviously, and the reaction could be completed in 16 h with the enantioselectivity unaffected. However, the yield of the target product decreased greatly to 53%. Thus, the optimal reaction conditions were determined to be using $RhCl_3 \cdot 3H_2O$ as catalyst precursor, **L6** as chiral ligand, DME as solvent, and 70 °C as reaction temperature.

Table 4. Rhodium-Catalyzed Asymmetric Hydroalkynylation of Different Norbornadiene Derivatives[a]



entry	norbornadiene derivatives	products	time (h)	yield (%)[b]	*ee* (%)[c]
1	 **1a**	**3ag**	20	98	99
2	 **1b**	**3bg**	23	95	97
3	 **1c**	**3cg**	25	94	95
4	 **1d**	**3dg**	26	99	96
5	 **1e**	**3eg**	42	62	95
6	 **1f**	**3fg**	46	40	94
7	 **1g**	**3gg**	44	80	98
8	 **1h**	**3hg**	34	92	94
9	 **1i**	**3ig**	54	81	97
10	 **1j**	**3jg**	46	62	>99.9
11	 **1k**	**3kg**	80	72	98
12	 **1l**	**3lg**	22	70	>99.9
13	 **1m**	**3mg**	42	92	97
14	 **1n**	**3ng**	30	85	98
15	 **1o**	**3og**	28	60	>99.9

[a] Reaction conditions: **2g** (0.4 mmol), **2g**:**1**:Rh:(*R*,*S*)-Cy_2PF-PPh_2 (2:1:0.05:0.065), in DME (2 mL) at 70 °C under Ar. [b] Isolated yield by column chromatography. [c] *ee* % were determined by chiral HPLC using Chiralcel OD-H or AD-H column.

To evaluate the effectiveness of this chiral Rh(III) catalyst, a series of substituted arylacetylenes were examined under the optimized reaction conditions (Table 3). It seemed that this Rh(III) catalyst was not sensitive to the positional properties of the substituents on the phenyl ring in arylacetylenes, since the monosubstituted arylacetylenes

with a methoxy group on different positions, as well as 3,5-dimethoxyphenylacetylene, resulted in hydroalkynylative products in quite similar yields and almost the same enantioselectivities (97% *ee*). The electronic property of the substituents had little effect on the reactions' enantioselectivities. All of the arylacetylenes, with electron-donating, electron-withdrawing or neutral substituents, could react with **1a** smoothly to generate the corresponding additive products in high enantioselectivities (95% to 99% *ee*). The free −OH group was also well tolerated in this Rh(III)-catalyzed reaction, and 4-hydroxymethylphenylacetylene **2k** proved to be a favorable hydroalkynylative reagent, with which high yield and high enantioselectivity could be obtained.

Using **2g** as the acetylene moiety, a variety of norbornadiene derivatives were also employed as substrates in this reaction to investigate the compatibility of this Rh(III) catalyst further (Table 4). Beside **1a**, the Boc-protected azabenzonorbornadienes with different substituents on the phenyl ring could all react with **2g** smoothly to generate the target hydroalkynylative products in high yields and high *ee*s. Though low reactivities and low yields resulted, Ts- and Ns- were proved suitable protective groups for the nitrogen atom in azabenzonorbornadienes, and high enantioselectivities could be maintained for the reactions of the corresponding substrates. With no heteroatoms on the bridge chain, benzonorbornadienes, especially those having bulky substituents on the carbon-bridged chain, were also found to be good substrates for this reaction. In all cases, high to excellent enantioselectivities could be observed by this Rh(III) catalyst. The phenyl ring in benzonorbornadienes was not an essential element for the realization of high enantioselectivities, since >99.9% *ee* had been achieved for the hydroalkynylaiton reaction of norbornadiene **1o**. However, oxabenzonorbornadienes proved unsuitable substrates here, since complex results without or with trace hydroalkynylative products were obtained.

In summary, we have successfully demonstrated that simple addition reactions of terminal alkynes to azabenzonorbornadienes could take place by choosing rhodium complexes with special chiral ligands as catalysts, thereby avoiding alkynylative ring-opening reaction. It was found that the complex of simple $RhCl_3 \cdot 3H_2O$ and chiral ferrocenyl ligand L6 catalyzed the asymmetric hydroalkynylation reaction of azabenzonorbornadienes and arylacetylenes efficiently. High yields and high to excellent enantioselectivities could be achieved. Good compatibility has also been observed for this chiral Rh(III) catalyst. Br, F, OH, and Me_2N groups are all well tolerated. Benzonorbornadienes, which had no heteroatoms on the bridge chain, were also found to be good substrates for this catalytic reaction. The further application of the chiral hydroalkynylation products in the synthesis of bioactive molecules, as well as the expansion of new catalytic reactions for this Rh(III) catalyst, are still in process.

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Supporting Information Available. Experimental details and characterization data including ^1H NMR, ^{13}C NMR, HRMS and HPLC conditions. This material is avilable free of charge via the Internet at http://pubs.acs.org.

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