Asymmetric Catalysis

DOI: 10.1002/anie.200603533

Highly Enantioselective Hydrosilylation/Cyclization of 1,6-Enynes Catalyzed by Rhodium(I) Complexes of Spiro Diphosphines**

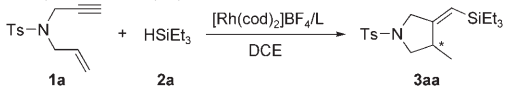
*Bao-Min Fan, Jian-Hua Xie, Shen Li, Li-Xin Wang, and Qi-Lin Zhou**

The transition-metal-catalyzed cyclization of 1,6-enynes has been extensively studied and has emerged as an efficient and atom-economic method for the construction of five-membered carbocyclic and heterocyclic frameworks.[1] These structures exist in many natural products and biologically active compounds, and the synthesis of nonracemic compounds containing these rings has given an impetus to chemists to design and develop highly efficient synthetic protocols. Prompted by the work of Trost,[2] asymmetric cyclizations of 1,6-enynes catalyzed by chiral palladium[3] and rhodium complexes[4] have been realized and excellent enantioselectivities (up to 99% *ee*) have been achieved in recent years. However, the silylcyclization of 1,6-enynes, which was first reported by Ojima et al. in 1992,[5] was less successful. This tandem hydrosilylation/cyclization reaction employs silane as a stoichiometric reductant and is a synthetically useful transformation that allows the formation of both a carbocycle and a carbon–silicon bond.[6] In 2003, Widenhoefer and co-workers reported the first, and so far the only, example of the asymmetric silylcyclization of 1,6-enynes by using a rhodium complex of 6,6′-bis(diphenylphosphino)-2,2′-dimethylbiphenyl (BIPHEMP) as a catalyst and obtained the silylalkylidene cyclopentanes in good enantioselectivities (77–92% *ee*).[7]

Recently we developed a new type of chiral phosphorus ligands containing a 1,1′-spirobiindane scaffold and demonstrated that they are highly enantioselective for rhodium- or ruthenium-catalyzed asymmetric hydrogenation[8] and other transition-metal-catalyzed asymmetric reactions.[9] Among the chiral spiro phosphorus ligands studied, *N*-dimethyl(1,1′-spirobiindane-7,7′-diyl)phosphoramidite (SIPHOS) and 7,7′-bis(diphenylphosphino)-1,1′-spirobiindane (SDP) were found to be efficient for the asymmetric rhodium-catalyzed Pauson–Khand reaction, converting 1,6-enynes into bicyclopentenone derivatives under a CO atmosphere in high yields with good enantioselectivities.[10] Encouraged by this result, we decided to investigate the asymmetric rhodium-catalyzed silylcyclization of 1,6-enynes by using chiral spiro phosphorus ligands in order to develop efficient methods for the synthesis of optically active functionalized carbocyclic and heterocyclic compounds. Herein, we wish to report an asymmetric silylcyclization of 1,6-enynes catalyzed by rhodium complexes of SDP with excellent enantioselectivities (up to 99.5% *ee*).

The asymmetric silylcyclization reaction of 1,6-enyne **1a** with 5 equivalents of $HSiEt_3$ (**2a**) was chosen to optimize the reaction conditions (Table 1). The reaction was carried out in 1,2-dichloroethane (DCE) at 70°C in the presence of a rhodium catalyst generated in situ from 5 mol% [Rh(cod)$_2$]BF$_4$ and 6 mol% (*R*)-SDP. Substrate **1a** was rapidly consumed within two hours and the silylcyclization product **3aa** was produced in 60% yield with 98% *ee* (Table 1, entry 1). In other solvents, such as 1,2-dimethoxyethane, THF, dioxane, and toluene, the reaction gave the desired product in very low yields. Varying the reaction temperature in the range from room temperature to 90°C had only a small effect on the enantioselectivity of the reaction, although the reaction at room temperature took 24 h and the yield was lowered to only 43% (Table 1, entry 2). The best result in terms of enantioselectivity was achieved at 70°C. The catalyst loading experiments demonstrated that the reaction could be performed with 1 mol% catalyst without obvious loss of enantioselectivity or yield (Table 1, entry 5).

Table 1: Optimization of the reaction conditions for the rhodium-catalyzed asymmetric silylcyclization of **1a** with silane **2a**.[a]



1a **2a** **3aa**

Entry	Ligand	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	(*R*)-SDP	70	2.0	60	98
2	(*R*)-SDP	RT	24.0	43	94
3	(*R*)-SDP	50	3.5	62	96
4	(*R*)-SDP	90	0.5	59	96
5[d]	(*R*)-SDP	70	2.0	58	96
6	(*R*)-Tol-SDP	70	0.5	56	87
7	(*R*)-An-SDP	70	0.5	53	96
8	(*R*)-Xyl-SDP	70	2.0	56	89
9	(*S*)-BINAP	70	3.0	50	88
10	(*R*)-SYNPHOS	70	1.0	34	83
11	(*R*,*R*)-Me-DuPHOS	70	3.0	–	–
12	(*R*,*S*)-JOSIPHOS	70	3.0	18	38

[a] Reaction conditions: **2a**/**1a**/[Rh(cod)$_2$]BF$_4$/L = 5:1:0.05:0.06. [b] Yield determined by column chromatography. [c] Determined by chiral HPLC analysis of the desilylated compound. [d] 1 mol% catalyst. Ts = toluene-4-sulfonyl, cod = 1,5-cyclooctadiene, L = ligand.

The effect of substituents on the SDP ligand was also studied systematically. Introduction of 4-methyl (Tol-SDP)

[*] Dr. B.-M. Fan, Prof. J.-H. Xie, S. Li, Prof. L.-X. Wang, Prof. Q.-L. Zhou
State Key Laboratory and Institute of Elemento-organic Chemistry
Nankai University
Tianjin 300071 (P.R. China)
Fax: (+86) 22-2350-6177
E-mail: qlzhou@nankai.edu.cn

[**] We thank the National Natural Science Foundation of China and the Ministry of Education of China for financial support. Throughout this Communication hydrosilylation/cyclization will be written in the short form silylcyclization.

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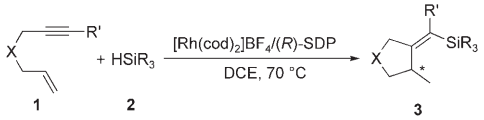
and 4-methoxy (An-SDP) groups onto the *P*-phenyl rings of SDP significantly increased the reaction rate, thus allowing a shortening of the reaction time to 0.5 h (Table 1, entries 6 and 7). However, the enantioselectivities of the reactions were reduced to 87% and 89% *ee*, respectively, with Tol-SDP and Xyl-SDP as ligands (Table 1, entries 6 and 8, respectively).

Some commercially available chelating diphosphine ligands were also tested in this reaction. The ligands 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) and (5,6),-(5′,6′)-bis(ethylenedioxy)-2,2′-bis(diphenylphosphino)-1,1′-biphenyl (SYNPHOS) gave lower enantioselectivities than the SDP ligands, and the ligand 1-[2-(diphenylphosphino)-ferrocenyl]ethyldicyclohexylphosphine (JOSIPHOS) gave both low enantioselectivity and a poor yield (18%, 38% *ee*). The ligand 1,2-bis(2,5-dimethylphospholano)benzene (Me-DuPHOS) was found to be completely inert in the reaction, providing none of the desired silylcyclization product. These results apparently indicate that the rigid spiro backbone of the SDP ligands is the key factor for achieving high enantioselectivity in the silylcyclization of 1,6-enynes.

A series of silane reagents **2** were compared in the silylcyclization reaction of 1,6-enyne **1a** under the optimized reaction conditions. The results summarized in Table 2 show

Table 2: Asymmetric silylcyclization of 1,6-enynes **1** with silanes **2** catalyzed by the rhodium(I) complex of SDP.[a]

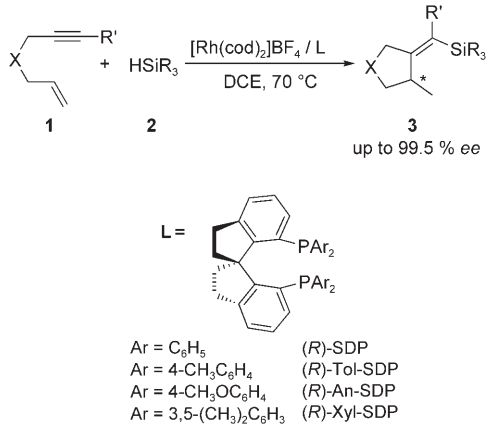


Entry	**1**	X[b]	R′	**2**	Silane	**3**	Yield [%]	*ee* [%][c]
1	**1a**	TsN	H	**2a**	$HSiEt_3$	**3aa**	60	98
2	**1a**	TsN	H	**2b**	$HSiMeEt_2$	**3ab**	75	98
3	**1a**	TsN	H	**2c**	$HSinPr_3$	**3ac**	41	99
4	**1a**	TsN	H	**2d**	$HSiiPr_3$	**3ad**	trace	–
5	**1a**	TsN	H	**2e**	$HSiMe_2Ph$	**3ae**	72	93
6	**1a**	TsN	H	**2f**	$HSiMePh_2$	**3af**	70	89
7	**1a**	TsN	H	**2g**	$HSi(OMe)_3$	**3ag**	67	96
8	**1a**	TsN	H	**2h**	$HSi(OEt)_3$	**3ah**	75	98
9	**1b**	$PhSO_2N$	H	**2a**	$HSiEt_3$	**3ba**	59	92
10	**1c**	NsN	H	**2a**	$HSiEt_3$	**3ca**[d]	67	95
11	**1d**	MsN	H	**2a**	$HSiEt_3$	**3da**	56	92
12	**1e**	TsN	Me	**2h**	$HSi(OEt)_3$	**3eh**	93	92
13	**1f**	$(EtO_2C)_2C$	H	**2h**	$HSi(OEt)_3$	**3fh**	67	96
14	**1g**	$(EtO_2C)_2C$	Me	**2a**	$HSiEt_3$	**3ga**	48	95
15	**1h**	$(MeO_2C)_2C$	H	**2a**	$HSiEt_3$	**3ha**	72	94
16	**1i**	$(MeO_2C)_2C$	Me	**2a**	$HSiEt_3$	**3ia**	50	95
17	**1j**	$(NC)_2C$	H	**2a**	$HSiEt_3$	**3ja**	50	99.5

[a] Reaction conditions: see Table 1, entry 1. [b] Ns: nitrobenzene-4-sulfonyl, Ms: methanesulfonyl. [c] Determined by chiral GC or HPLC (see Supporting Infomation). [d] (*S*)-**3ca**, determined by X-ray crystallography (see Supporting Information).

that both trialkylsilanes ($HSiR_3$) and trialkoxysilanes ($HSi(OR)_3$) can serve as the silane reagents, although the silanes with phenyl groups give slightly lower enantioselectivities (Table 2, entries 5 and 6). The yield of silylcyclization product decreases dramatically when silanes containing bulky alkyl groups are used. For example, in the reaction with $HSiiPr_3$ (**2d**) only a trace amount of silylcyclization product was obtained (Table 2, entry 4). The use of 5 equivalents of silane is necessary to limit side reactions such as the dimerization of 1,6-enynes.

A variety of 1,6-enynes (**1**) can be silylcyclized by the catalyst Rh/(*R*)-SDP to form the silylalkylidene cyclopentane and pyrrolidine derivatives **3** in excellent enantioselectivities (Scheme 1). The N-linked 1,6-enynes **1a–e**, which have

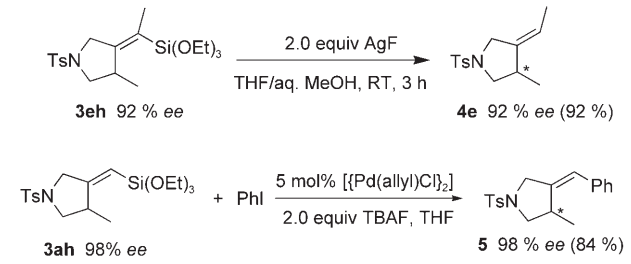


Scheme 1. The asymmetric rhodium-catalyzed silylcyclization of 1,6-enynes. For R, R′, and X, see Table 2.

different protecting groups on the nitrogen atom, were silylcyclized in moderate to good yields with 92–98% *ee*, thus showing that sulfonyl groups are suitable protecting groups for N-linked 1,6-enyne substrates, with the tosyl group being the best choice (Table 2, entries 8–12). To extend the scope of substrates in this silylcyclization reaction, carbon-linked 1,6-enynes (**1f–j**) were also studied. They all reacted smoothly to produce the corresponding silylcyclization compounds in reasonable yields and excellent enantioselectivities (Table 2, entries 13–17). The highest enantioselectivity (99.5% *ee*) was achieved in the silylcyclization of 4,4-bis-(cyano)hept-1-en-6-yne (**1j**) with $HSiEt_3$ (Table 2, entry 17). However, when 1,6-enyne substrates having a phenyl group attached to the alkyne or alkene terminus were silylcyclized, only trace amounts of the desired products were obtained.

The silyl groups in the silylcyclization products can be easily converted into other functional groups by reported methods,[11] which increases the impact of this asymmetric silylcyclization reaction of 1,6-enynes on the synthesis of optically active compounds containing a cyclopentane or pyrrolidine structure. As shown in Scheme 2, the silylalkylidene pyrrolidine derivative **3eh** can be desilylated by treatment with 2 equivalents of AgF in aqueous MeOH/THF at room temperature for three hours to afford compound **4e** in 92% yield.[11c] Pd-catalyzed, the silylcyclization product **3ah** can react with iodobenzene to form phenylated compound **5** in 84% yield.[11b] The optical purities of the silylalkylidene pyrrolidines were completely retained in these two reactions.

To explain the stereoselectivity of the spiro catalyst in the silylcyclization, a transition-state (TS) model is proposed in



Scheme 2. Examples for the conversion of the silyl groups of the silylcyclization products. TBAF = tetrabutylammonium fluoride.

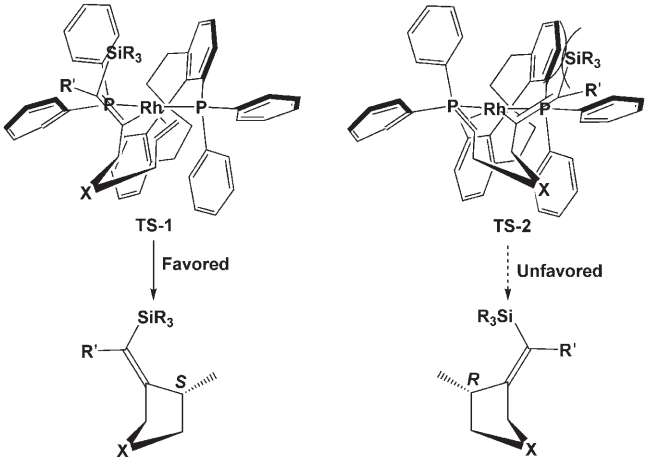


Figure 1. Proposed model for the stereoselectivity in the silylcyclization reactions.

Figure 1. In TS-1 the bulky silyl group is located in a relatively open area; this orientation favors the formation of the *S* product, which is consistent with the absolute configuration of (*S*)-**3ca** determined by X-ray analysis.

In conclusion, we have developed an efficient catalyst, namely the rhodium complex of spiro diphosphine SDP, for the asymmetric silylcyclization of 1,6-enynes. This highly enantioselective reaction provides a facile access to optically active silylalkylidene cyclopentane and pyrrolidine derivatives, along with other functionalized carbocyclic and heterocyclic compounds after subsequent appropriate transformations.

Received: August 30, 2006
Revised: October 18, 2006
Published online: January 4, 2007

Keywords: asymmetric catalysis · enynes · hydrosilylation/cyclization · P ligands · rhodium

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