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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Palladium-Catalyzed Enantioselective Desymmetrization of Silacyclobutanes: Construction of Silacycles Possessing a Tetraorganosilicon Stereocenter

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Supporting Information

ABSTRACT: A palladium-catalyzed desymmetrization of alkyne-tethered silacyclobutanes to give silacycles possessing a tetraorganosilicon stereocenter has been developed, and high chemo- and enantioselectivities have been achieved by the use of a newly synthesized chiral phosphoramidite ligand.

Asymmetric catalysis has been a topic of extensive research in synthetic organic chemistry for decades, primarily focusing on the construction of carbon stereocenters.[1] In contrast, the development of catalytic enantioselective methods to create chiral silicon stereocenters has been much less explored despite the wide utility of organosilicon compounds, and the typical synthetic methods for these compounds rely on the use of stoichiometric amounts of chiral reagents.[2] Unlike the formation of carbon stereocenters, because of the difficulty of employing addition reactions to silicon−carbon or silicon−heteroatom double bonds,[3] the available strategy is mostly restricted to substitution reactions. In fact, most of the existing catalytic asymmetric methods are based on hydrosilylation of ketones[4] or alcoholysis[5] using diorganosilanes ($R^1R^2SiH_2$, $R^1 \neq R^2$), substituting one of the enantiotopic hydrogen atoms by an alkoxy group. Other than these approaches, only two studies have been carried out under transition-metal catalysis as far as we are aware: rhodium-catalyzed double intramolecular hydrosilylation of olefins to prepare axially chiral spirosilanes[6] and iridium-catalyzed Si−H insertion with diazo compounds to prepare triorganosilanes.[7] As a new entry for catalytic asymmetric construction of chiral organosilanes with a stereogenic silicon atom, herein we describe the development of a palladium-catalyzed enantioselective desymmetrization of silacyclobutanes to give silacycles possessing a tetraorganosilicon stereocenter.

In 1975, Sakurai and Imai reported that 1,1-dimethylsilacyclobutane reacts with several alkynes in the presence of a palladium catalyst to give ring-expanded 1,1-dimethyl-1-sila-2-cyclohexenes.[8] Oshima and Utimoto revisited the same reactions in 1991 and found that 1-sila-2-cyclohexenes are obtained with concomitant formation of ring-opened allyl(vinyl)silane derivatives.[9] Since then, several transition-metal-catalyzed synthetic reactions using silacyclobutanes have been reported,[10,11] but none of the existing methods have been applied to asymmetric catalysis to date. In this context, we decided to explore the possibility of constructing tetraorganosilicon stereocenters by the use of alkyne-tethered silacyclobutanes for the intramolecular ring-expansion reaction under the catalysis of a chiral palladium complex.

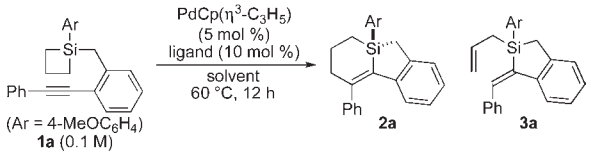
As a starting point, we prepared alkyne-tethered silacyclobutane **1a** and conducted a reaction in the presence of PdCp(η^3-C_3H_5) (5 mol %) and phosphoramidite ligand (*S*,*R*,*R*)-**L1**[12,13] (10 mol %) in THF at 60 °C.[14,15] Under these conditions, the reaction proceeded smoothly to give a 35/65 mixture of tricyclic compound **2a** and bicyclic compound **3a** in 97% combined yield, and the **2a** was obtained with 43% ee (Table 1, entry 1).[16] The use of the diastereomeric ligand (*S*,*S*,*S*)-**L2**[13] improved the enantioselectivity of **2a** to 76% ee with some increase in the formation of **2a** over **3a** (55/45; entry 2), and the 3,3′-dimethylated ligand (*S*,*S*,*S*)-**L3**[17] showed significantly higher selectivity toward **2a** (**2a**/**3a** = 87/13) with the same level of enantioselectivity (74% ee; entry 3). On the other hand, higher enantioselectivity of **2a** (84% ee) was observed by changing the 1,1′-binaphthyl backbone of (*S*,*S*,*S*)-**L2** to 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl [(*S*,*S*,*S*)-**L4**],[18] with **2a**/**3a** = 73/27 (entry 4). In the hope of merging the chemoselectivity with (*S*,*S*,*S*)-**L3** and the enantioselectivity with (*S*,*S*,*S*)-**L4**, we employed the newly synthesized ligand (*S*,*S*,*S*)-**L5** bearing methyl groups at the 3- and 3′-positions of the octahydrobinaphthyl moiety and found that this ligand did indeed improve both the product ratio and the enantioselectivity (**2a**/**3a** = 94/6, **2a** ee = 87%; entry 5). Further optimization revealed that the reaction in toluene instead of THF turned out to be slightly more favorable with respect to both chemo- and enantioselectivity (entry 6 vs entry 5), and the best result was obtained by conducting the reaction in toluene at 30 °C, which gave **2a** in high yield with high selectivity (**2a**/**3a** = 97/3, **2a** ee = 92%; entry 7).

Under the optimized conditions, several para- or meta-substituted aryl groups are tolerated on the silicon atom of **1**, giving the corresponding silacycles **2** with high selectivity (**2**/**3** = 96/4−98/2, 87−95% ee; Table 2, entries 1−4), but the aryl group with an ortho-substituent leads to somewhat lower chemo- and enantioselectivity (**2e**/**3e** = 86/14, 71% ee; entry 5). With regard to the substituent on the alkyne terminus, various aryl groups as well as an alkenyl group can be incorporated to give products **2** with similarly high efficiency (**2**/**3** = 91/9−98/2, 84−93% ee; entries 6−10).[19] In addition, the tether between the silicon and the alkyne can be altered as shown in entries 11−15, although the selectivities become lower with an alkyl tether (**2o**/**3o** = 69/31, 75% ee; entry 15). The absolute configuration of **2n** obtained in entry 14 was determined to be *R* by X-ray crystallographic

Received: September 13, 2011
Published: September 21, 2011

dx.doi.org/10.1021/ja208621x | *J. Am. Chem. Soc.* 2011, 133, 16440–16443

Table 1. Palladium-Catalyzed Desymmetrization of Silacyclobutane 1a: Optimization



entry	ligand	solvent	yield of 2a + 3a (%)[a]	ratio of 2a/3a [a]	ee of 2a (%)[b]
1	(*S*,*R*,*R*)-**L1**	THF	97	35/65	43
2	(*S*,*S*,*S*)-**L2**	THF	99	55/45	76
3	(*S*,*S*,*S*)-**L3**	THF	96	87/13	74
4	(*S*,*S*,*S*)-**L4**	THF	99	73/27	84
5	(*S*,*S*,*S*)-**L5**	THF	95	94/6	87
6	(*S*,*S*,*S*)-**L5**	toluene	91	95/5	88
7[c]	(*S*,*S*,*S*)-**L5**	toluene	96[d]	97/3	92

[a] Determined by ^{1}H NMR analysis. [b] Determined by chiral HPLC on a Chiralpak OT(+) column with 98:2 hexane/2-propanol after complete separation of **2a** from **3a**. [c] The reaction was conducted for 48 h at 30 °C. [d] Isolated yield.

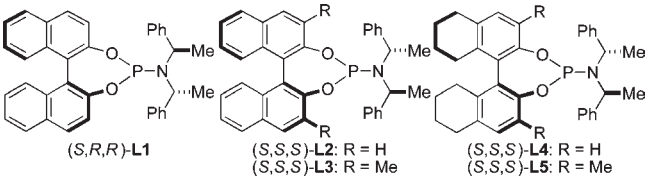
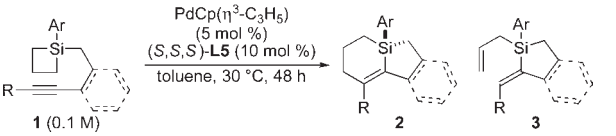


Table 2. Palladium-Catalyzed Desymmetrization of Silacyclobutanes 1: Scope



entry	structure of 2	yield of 2 + 3 (%)[a]	ratio of 2/3[b]	ee of 2 (%)[c]
1	**2a**: Ar = 4-MeOC$_6$H$_4$	96	97/3	92
2	**2b**: Ar = 4-ClC$_6$H$_4$	91	96/4	87
3	**2c**: Ar = 3,5-(MeO)$_2$C$_6$H$_3$	93	98/2	95
4	**2d**: Ar = 3-MeOC$_6$H$_4$	85	97/3	90
5	**2e**: Ar = 2-MeOC$_6$H$_4$	73[d]	86/14	71
6	**2f**: R = 4-MeC$_6$H$_4$	77[d]	95/5	92
7	**2g**: R = 4-CF$_3$C$_6$H$_4$	96	98/2	88
8	**2h**: R = 3-ClC$_6$H$_4$	97	98/2	93
9	**2i**: R = 2-naphthyl	94	98/2	92
10[e]	**2j**: R = 1-cyclohexenyl	84[f]	91/9	84
11	**2k**: X = 7-Cl	95	97/3	92
12	**2l**: X = 7-F	90	97/3	92
13	**2m**: X = 6-Me	93	97/3	93
14	**2n**: X = 6-F	92	96/4	91
15[e]	**2o**	90	69/31	75

[a] Isolated yields. [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC with hexane/2-propanol after complete separation of **2** from **3**. [d] Isolated yield of **2**. [e] The reaction was conducted at 40 °C. [f] Determined by ^{1}H NMR analysis after chromatographic purification on silica gel.

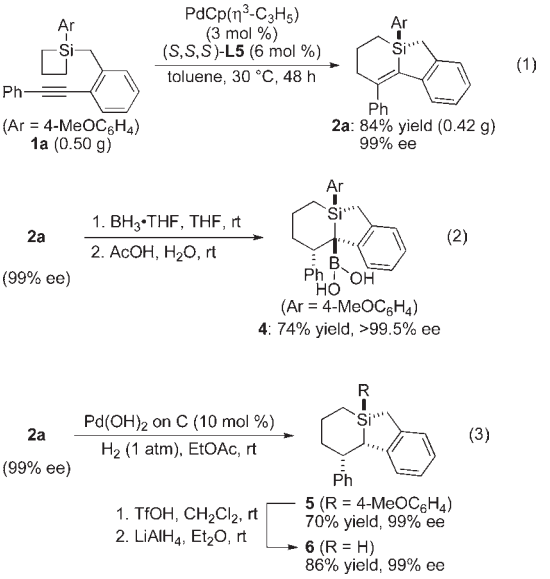
analysis with Cu Kα radiation after recrystallization from chlorobenzene/nonane (Figure 1).[20]

The present catalytic reactions can also be conducted on a preparative scale with a reduced catalyst loading. Thus, 0.50 g of **1a** was fully converted to **2a**/**3a** in the ratio of 97/3 (**2a** ee = 92%) in the presence of a 3 mol % loading of the palladium catalyst, and treatment of the crude mixture with activated carbon followed by trituration with hexane readily provided pure compound **2a** without chromatographic purification in 84% yield (0.42 g) with 99% ee (eq 1).[21] The highly enantioenriched **2a** thus obtained could undergo further functionalization while retaining the stereochemical integrity. For example, hydroboration of **2a** with $BH_3\cdot$THF took place in a regio- and diastereoselective fashion, and successive acidic aqueous workup provided the corresponding organoboronic acid **4** with contiguous two-carbon and one-silicon stereocenters in 74% yield (eq 2).[20−22] In addition, diastereoselective hydrogenation of **2a** smoothly proceeded as well in the presence of a catalytic amount of $Pd(OH)_2$ on carbon to give compound **5** in 70% yield, which was converted to triorganohydrosilane **6** in 86% yield by removal of the 4-methoxyphenyl group on the silicon in **5** via treatment with triflic acid followed by reduction with $LiAlH_4$ (eq 3).[2,7]

Proposed catalytic cycles for the reaction of **1a** in the presence of Pd/(*S*,*S*,*S*)-**L5** are illustrated in Scheme 1. Thus, oxidative addition of a carbon−silicon bond of silacyclobutane **1a** to palladium(0) gives 1-pallada-2-silacyclopentane **A**.[9,23] This then undergoes intramolecular insertion of the alkyne to give 1-pallada-4-sila-2-cycloheptene **B**, reductive elimination of which leads to the formation of compound **2a** along with regeneration of palladium(0). In contrast, β-hydrogen elimination from intermediate **B** gives alkenylpalladium hydride species **C**, and successive reductive elimination results in the formation of compound **3a**. Because a carbon−carbon bond-forming reductive elimination is known to become more facile with sterically demanding

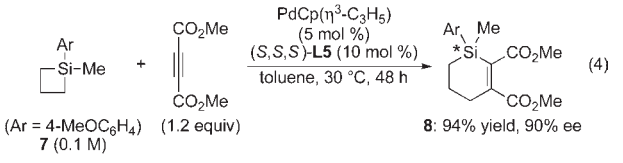
dx.doi.org/10.1021/ja208621x |*J. Am. Chem. Soc.* 2011, 133, 16440–16443

Figure 1. X-ray crystal structure of (*R*)-**2n** (Flack parameter = 0.012; H atoms have been omitted for clarity).



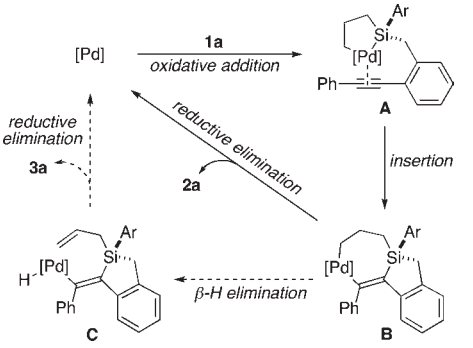
ligands on palladium,[24] the observed trend of chemoselectivity between compounds **2a** and **3a** in Table 1 can be explained by the bulkiness of the phosphoramidite ligands, with the highest selectivity toward **2a** being achieved with ligand (*S*,*S*,*S*)-**L5**.

We have also begun to explore an intermolecular variant of the present asymmetric catalysis,[8,9] and in our preliminary experiment, the reaction of 1-(4-methoxyphenyl)-1-methylsilacyclobutane (**7**) with dimethyl acetylenedicarboxylate proceeded smoothly under the same conditions as in Table 2 in the presence of Pd/(*S*,*S*,*S*)-**L5** to give 1-sila-2-cyclohexene derivative **8** with a silicon stereogenic center exclusively in 94% yield with 90% ee (eq 4).



In summary, we have developed a palladium-catalyzed asymmetric ring expansion of alkyne-tethered silacyclobutanes to obtain silacycles possessing tetraorganosilicon stereocenters, and high chemo- and enantioselectivities have been achieved by the use of a newly synthesized chiral phosphoramidite ligand. We have also demonstrated that the present catalysis is similarly effective for the intermolecular process. Future studies will be directed toward further expansion of the reaction scope and mechanistic investigations to understand the origin of the stereoselectivity.

Scheme 1. Proposed Catalytic Cycles for the Palladium-Catalyzed Desymmetrization of Silacyclobutane 1a ([Pd] = Pd/(*S*,*S*,*S*)-L5, Ar = 4-MeOC$_6$H$_4$)



■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterization data, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

Support was provided in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (the Global COE Program "Integrated Materials Science" at Kyoto University).

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(19) The use of a substrate having an alkyl group on the alkyne terminus resulted in the predominant formation of ring-opened product **3**.

(20) CCDC-824899 and CCDC-842098 contain 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. Also see the Supporting Information for details.

(21) The ee value was upgraded as a result of the purification by trituration.

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