Palladium-Catalyzed Desymmetrization of Silacyclobutanes with Alkynes: Enantioselective Synthesis of Silicon-Stereogenic 1-Sila-2-cyclohexenes and Mechanistic Considerations

Ryo Shintani,*^{,†} Kohei Moriya,[†] and Tamio Hayashi^{*,†,‡}

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan, and Institute of Materials Research and Engineering, A*STAR, 3 Research Link, Singapore 117602

shintani@kuchem.kyoto-u.ac.jp; tamioh@imre.a-star.edu.sg

Received May 1, 2012



A palladium-catalyzed enantioselective desymmetrization of silacyclobutanes with alkynes has been developed to give silicon-stereogenic 1-sila-2-cyclohexenes with high enantioselectivity. The products thus obtained undergo further derivatizations with complete stereoselectivity, and a new catalytic cycle involving alkyne coordination (oxidative cyclization)—transmetalation (σ -bond metathesis)—reductive elimination has also been proposed.

Although asymmetric catalysis has been extensively investigated for decades, construction of chiral silicon stereocenters has been significantly less explored¹ in comparison to the rich chemistry available for the construction of carbon stereocenters.² Catalytic enantioselective synthesis of silicon-stereogenic organosilanes could provide efficient access to a new and potentially useful class of optically active compounds in light of the wide utility of organosilicon compounds in various fields of organic chemistry, but most of the existing methods are based on the use of a stoichiometric amount of chiral reagents.³ Other than rhodium-catalyzed enantioselective desymmetrization of prochiral diorganodihydrosilanes through hydrosilylation of ketones⁴ or alcoholysis,⁵ only a few reports have been made under transition metal catalysis to date:

ORGANIC LETTERS

2012 Vol. 14, No. 11 2902–2905

[†]Kyoto University.

[‡] Institute of Materials Research and Engineering.

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rhodium-catalyzed double intramolecular hydrosilylation of olefins to prepare axially chiral spirosilanes,⁶ iridiumcatalyzed Si–H insertion with diazo compounds to prepare triorganosilanes,⁷ palladium-catalyzed desymmetrization of alkyne-tethered silacyclobutanes to give tetraorganosilacycles,⁸ and palladium-catalyzed intramolecular C–H bond arylation of prochiral 2-(diarylsilyl) aryl triflates to produce silicon-stereogenic dibenzosiloles.⁹ As a continuation of our research program toward expansion of the catalytic asymmetric methods for creating chiral silicon stereocenters, here we describe a palladium-catalyzed intermolecular desymmetrization of silacyclobutanes with electron-deficient alkynes to give silicon-stereogenic 1-sila-2-cyclohexenes with high enantioselectivity.

As we recently reported,⁸ alkyne-tethered silacyclobutanes undergo enantioselective desymmetrization at 30 °C in the presence of a palladium catalyst coordinated with chiral phosphoramidite ligand (S,S,S)-L1 to give silacycles possessing a tetraorganosilicon stereocenter in high yield and ee (eq 1). When we applied these conditions to an intermolecular reaction of 1-(4-methoxyphenyl)-1-methylsilacyclobutane $(1a)^{10}$ with dimethyl acetylenedicarboxylate (2a), a nonasymmetric variant of which was first reported by Sakurai and Imai in 1975,¹¹⁻¹³ the corresponding silicon-stereogenic 1-sila-2-cyclohexene 3aa was obtained in 94% vield with 90% ee as shown in Table 1, entry 1.⁸ In comparison, ligand (S,S,S)-L2¹⁴ with the 1,1'-binaphthyl backbone instead of 5,5',6,6',7,7',8, 8'-octahydro-1,1'-binaphthyl was also similarly effective, giving 3aa in high yield but with a somewhat lower ee (86% ee; entry 2). On the other hand, the use of (S,S,S)- $L3^{15}$ having no methyl groups at the 3.3'-positions or (S,R,R)-L4, a diastereometric ligand to (S,S,S)-L1, gave 3aa with significantly lower enantioselectivity along with substantial formation of ring-opened byproduct 4aa (entries 3 and 4).¹²

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 Table 1. Palladium-Catalyzed Desymmetrization of Silacyclobutane 1a with Alkyne 2a: Ligand Effect



entry	ligand	ratio of 3aa/4aa ^a	yield of 3aa (%) ^b	ee of 3aa (%) ^c
1	(S,S,S)-L1	99/1	94	90
2	(S,S,S)-L2	98/2	87	86
3	(S,S,S)-L3	88/12	75	23
4	(S,R,R)-L4	95/5	87	67

^{*a*} Determined by ¹H NMR. ^{*b*} Isolated yield. ^{*c*} Determined by chiral HPLC on a Chiralpak AS-H column with hexane/2-propanol = 100/1.



We subsequently found that a slightly improved result can be achieved by using 5.5 mol % of (S,S,S)-L1 at 10 °C for this intermolecular reaction of 1a with 2a (95% yield, 92% ee; Table 2, entry 1).¹⁶ Under these conditions, several other electron-deficient alkynes can also be employed in the reaction with silacyclobutane 1a to give the corresponding 1-sila-2-cyclohexenes 3 with good to high enantioselectivity (77–91% ee; entries 2–5).¹⁷ It is worth noting that the use of unsymmetrical alkynes such as 2d and 2e gives products 3 as single regioisomers (entries 4 and 5).¹⁸ With regard to the substituent on the silicon atom of the silacyclobutane, various 1-alkyl-1-(hetero) arylsilacyclobutanes are well tolerated for the reaction with alkyne 2a, giving 1-sila-2-cyclohexenes 3 with uniformly high yield and enantioselectivity (89–97% yield,

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⁽¹⁰⁾ **1a** can be readily prepared from commercially available 1,1dichlorosilacyclobutane by successive treatment with 4-methoxyphenylmagnesium bromide and methylmagnesium iodide. See Supporting Information for details.

⁽¹¹⁾ Sakurai, H.; Imai, T. Chem. Lett. 1975, 8, 891.

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⁽¹⁶⁾ The reaction at 0 °C results in a slightly lower yield (89% yield) with the same enantioselectivity (92% ee).

⁽¹⁷⁾ Less electron-deficient alkynes such as phenylacetylene and diphenylacetylene are not suitable substrates under the current reaction conditions.

⁽¹⁸⁾ For these reactions, the lower yield is mostly due to the incomplete conversion of 1a.

90–94% ee; entries 6–13). A 1,1-dialkylsilacyclobutane such as **1j** also effectively undergoes the desymmetrization with alkyne **2a** to give product **3ja** with reasonably high enantioselectivity (84% ee; entry 14). The absolute configuration of **3ac** obtained in entry 3 was determined to be *S* by X-ray crystallographic analysis with Cu K α radiation after recrystallization from pentane.¹⁹

 Table 2. Palladium-Catalyzed Enantioselective Desymmetrization of Silacyclobutanes 1 with Electron-Deficient Alkynes 2



^aIsolated yield. ^bDetermined by chiral HPLC with hexane/2-propanol.

Enantioenriched 1-sila-2-cyclohexene **3aa** obtained in the present catalysis can undergo further derivatizations, retaining the stereochemical integrity. For example, olefin hydrogenation takes place stereoselectively,²⁰ giving silacyclohexane **5** in 79% yield as a single diastereomer with contiguous two carbon and one silicon stereocenters (Scheme 1).^{19,21} In addition, chemoselective reduction of the less hindered carbonyl moiety of compound **5** can be achieved by the use of 2.0 equiv of $HAl(i-Bu)_2$ to give bicyclic lactone **6** in 69% yield,^{19,21} whereas the reduction of **5** with excess LiAlH₄ provides 1,4-diol **7** in 87% yield.





Scheme 2. Proposed Catalytic Cycles for the Palladium-Catalyzed Enantioselective Desymmetrization of Silacyclobutane 1a with Alkyne 2a (Ar = 4-MeOC₆H₄)



On the basis of a catalytic cycle proposed by Oshima and Utimoto for the nonasymmetric variant of this process under the catalysis of a Pd/PPh₃ complex,¹² the reaction of **1a** with **2a** in the presence of Pd/(*S*,*S*,*S*)-L1 could also proceed through the same cycle as shown in Scheme 2, cycle A. Thus, oxidative addition of a carbon–silicon bond of silacyclobutane **1a** to palladium(0) gives 1-pallada-2-silacyclopentane **I**. This then undergoes insertion of alkyne **2a** to give 1-pallada-4-sila-2-cycloheptene **II**, the reductive elimination of which leads to the formation of product **3aa** along with regeneration of palladium(0). Alternatively, coordination of **2a** to palladium(0) (formation of **III**) could

⁽¹⁹⁾ CCDC-873846, CCDC-873847, CCDC-873848, and CCDC-873849 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. See also the Supporting Information for details.

⁽²⁰⁾ The origin of this stereoselectivity is presumably derived from the half-chair conformation of **3aa** with the 4-methoxyphenyl group at the pseudoequatorial position.

⁽²¹⁾ The relative and absolute configurations were determined by X-ray crystallographic analysis.

⁽²²⁾ De Meijere, A.; Reiser, O. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: Hoboken, NJ, 2002; p 1647.

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⁽²⁴⁾ There are no reports on the evidence for oxidative addition of silacyclobutanes to Pd/PPh₃ complexes as far as we are aware. Silacyclobutanes are known to undergo oxidative addition to a Pd-(Me₂PCH₂CH₂PMe₂) complex, but a reaction of the oxidative adduct with alkyne **2a** does not provide a 1-sila-2-cyclohexene: Tanaka, Y.; Yamashita, H.; Shimada, S.; Tanaka, M. *Organometallics* **1997**, *16*, 3246.

precede cleavage of the carbon-silicon bond of **1a** as shown in cycle B. Because the palladium(0)-alkyne complex could also be considered as a 1-pallada-2-cyclopropene,²² subsequent transmetalation (or σ -bond metathesis) of **1a** can provide the same intermediate **II**, which eventually gives product **3aa** and palladium(0) by reductive elimination.

To gain some insight into the catalytic cycle, we conducted several experiments using PPh₃ as the ligand for palladium. As shown in eq 2, Pd(PPh₃)₄ is known to react with alkyne 2a at room temperature to give $Pd(PPh_3)_2$ (2a),²³ and both Pd(PPh₃)₄ and Pd(PPh₃)₂(2a) were found to be similarly effective as catalysts for the reaction of silacyclobutane 1a with alkyne 2a in toluene at 60 °C to give a mixture of 1-sila-2-cyclohexene 3aa and ring-opened byproduct 4aa in the ratio of ca. 85/15 (eq 3). A reaction of $Pd(PPh_3)_4$ with 1a (2.0 equiv to Pd) was monitored by ¹H NMR in toluene- d_8 at 60 °C, but both reactants remained unchanged for over 6 h with no formation of the oxidative adduct (1-pallada-2-silacyclopentane).²⁴ In contrast, a reaction of Pd(PPh₃)₂(2a) with 1a (2.0 equiv to Pd) in toluene at 60 °C for 6 h produced 3aa in 74% yield. This reaction was also monitored by ¹H NMR in toluene- d_8 at 60 °C, and it was confirmed that essentially all of the unreacted 2a stayed on palladium in the form of $Pd(PPh_3)_2(2a)$ during the course of the reaction with no evidence for the formation of 1-pallada-2-silacyclopentane (I in Scheme 2). These data cannot completely rule out the possibility of the oxidative addition-insertion pathway (cycle A in Scheme 2), but they are presumably more consistent with the alkyne coordination (oxidative cyclization)-transmetalation (σ -bond metathesis) pathway (cycle B). In addition, we were also able to obtain an X-ray crystal structure of Pd- $(PPh_3)_2(2a)$,^{25,26} and this indeed shows the character of 1-pallada-2-cyclopropene as illustrated in the Supporting Information (C–C of alkyne 2a = 1.270(4) Å; significantly longer than a typical C–C triple bond),¹⁹ indicating the feasibility of catalytic cycle B. Although we have not met much success in the mechanistic studies using (*S*,*S*,*S*)-L1 as the ligand for palladium so far, we tentatively believe that the same catalytic cycle is operative with this ligand system as well.



In summary, we have developed a palladium-catalyzed enantioselective desymmetrization of silacyclobutanes with alkynes to give silicon-stereogenic 1-sila-2cyclohexenes with high enantioselectivity. The products thus obtained can undergo further derivatizations with complete stereoselectivity. We have also carried out some mechanistic studies and proposed a new catalytic cycle that consists of alkyne coordination (oxidative cyclization), transmetalation (σ -bond metathesis), and reductive elimination.

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

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

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The authors declare no competing financial interest.