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Harnessing the β -Silicon Effect for Regioselective and Stereoselective Rhodium(II)-Catalyzed C-H Functionalization by Donor/Acceptor Carbenes Derived from 1-Sulfonyl-1,2,3-Triazoles

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Abstract

The regioselective and enantioselective intermolecular sp^3 C–H functionalization of silicon-substituted alkanes was accomplished using $Rh_2(S\text{-NTTL})_4$ with readily available 1-sulfonyl-1,2,3-triazoles as carbene precursors. These reactions generate a diverse array of stereodefined substituted silaalkanes.

Graphical abstract

Organosilicon compounds (Figure 1) represent an important area of chemical space for such diverse fields as agrochemistry¹, materials science², and pharmaceutical chemistry³, and hence, novel reactions that explore this rich and largely untapped chemical space are desirable. These compounds benefit from the unique atomic properties of silicon which include larger covalent radius, decreased electronegativity, and ability to engage hypervalent interactions with electron donors via availability of 3d orbitals. Moreover, the specific exploitation of silicon in medicinal chemistry has matured into the development of the “sila-substitution” strategy, which seeks to improve stability, reactivity, and lipophilicity of medicinal agents by generating silicon analogues of known drugs. Examples include silperisone (a muscle relaxant),⁴ the spirocyclic σ -receptor ligands,⁶ the silicon analogue of linezolid,⁶ and M2 proton channel probe of influenza A virus.⁷

Organosilicon compounds are often generated by appending the silicon functional group either by polar reactions (e.g., Grignard attack to Si–C1 bonds) or through organometallic transformations (e.g., addition of Si–H bonds using Pt, Rh, or Ir).⁸ While these strategies are important because they establish new carbon-silicon connectivities, an alternative approach

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Supporting Information

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resulting from the C-H functionalization of silicon-substituted alkanes could provide a diverse set of stereodefined functionalized organosilicon compounds from simple and readily available precursors. Selective functionalization of C-H bonds has rapidly evolved as a viable synthetic disconnection, and has transformed the way chemists strategize during chemical synthesis.⁹

One approach to C-H functionalization is the selective intermolecular insertion of rhodium-stabilized donor/acceptor carbenes, which are generated from either aryldiazoacetates or 1-sulfonyl-1,2,3-triazoles. These reactions often employ rhodium tetracarboxylate catalysts to accomplish regio- and stereoselective C-H functionalization reactions. In general, donor/acceptor metallocarbene intermediates insert into C-H bonds where a developing positive charge is most readily stabilized. As such, C-H bonds α to π systems (e.g., benzylic or allylic systems) or protected oxygen or protected nitrogen atoms readily undergo insertion.¹⁰ More recently, regioselective activation of aliphatic C-H bonds distal to stabilizing interactions has been achieved by deploying bulky catalysts.¹¹ All of these investigations have provided a map for C-H functionalization reactivity, and yet, C-H bonds in the β position of silicon have been understudied, even though the lability of these hydrogen atoms is enhanced by the so-called β -silicon effect.¹²

Prior efforts directed towards the intermolecular functionalization of organosilicon compounds by C-H insertion reactions with carbenes focused on establishing highly regioselective reactions (Scheme 1). Seyferth and coworkers first showed that phenyl(bromo-dichloromethyl)mercury-derived dichlorocarbene inserts regioselectively into the β position of a variety of tetraalkylsilanes (Scheme 1a).¹³ This work unveiled the delicate balance of sterics and electronics around the silicon which can favorably dispose carbene insertion into the β position of silicon. Migita and coworkers later showed that photolysis of acceptor/acceptor carbenes in the presence of tetraalkylsilanes could also achieve β C-H functionalization, although the regioselectivity was poor (Scheme 1b).¹⁴ Danilkina and Sidorenko first implemented a dirhodium tetracarboxylate catalyst for β functionalization of tetraorganosilanes with ethyl diazoacetate, but the yields were low (10–26%);¹⁵ most recently, Sakurai and coworkers reported that silacycloalkanes can undergo regioselective Rh-catalyzed insertion reactions with α -diazo esters in high yields if long addition times were used (Scheme 1c).¹⁶ Despite all of the studies described above, no effort was made to explore the combined regio- and stereoselective functionalization at the β position of organosilicon compounds.

Herein, we report the first enantioselective C-H functionalization of sila-substituted alkanes using donor/acceptor carbenes derived from 1-sulfonyl-1,2,3-triazoles (Scheme 1d). The implementation of 1-sulfonyl-1,2,3-triazoles as carbenoid precursors is attractive because they are easily handled and they provide unique opportunities for incorporating aldehyde or amine functionalities; however, 1,2,3-triazoles have found limited use in C-H functionalization reactions, even though these carbenoid precursors have been effectively utilized for a plethora of other reactions.¹⁷ To date, only two reports delineate effective intermolecular C-H functionalization reactions with these carbenoid precursors.¹⁸ Fokin and coworkers showcased the first enantioselective C-H functionalization reaction of simple unsubstituted alkanes with 1,2,3-triazoles.¹⁹ Later, our group demonstrated that 1,2,3-

triazoles could be utilized in the enantioselective C-H functionalization of activated allylic and benzylic C-H bonds.²⁰ Other efforts towards exploring the intermolecular reactivity of 1,2,3-*N*-sulfonyl triazoles with heteroatom containing compounds, such as tetrahydrofuran or oxetane generated products derived from ylide intermediates, which may be the reason why intermolecular C-H functionalization reactions with these carbene precursors has been slow to develop.²¹

Our study began by investigation of commercially available silacyclobutane **1**.²² Optimization reactions were conducted by reacting **1** with 4-phenyl-l-(methanesulfonyl)-1,2,3-triazole in the presence of a variety of dirhodium tetracarboxylate catalysts in chloroform, a solvent that has been shown to be particularly effective for the triazole reactions (Figure 1). The reaction was regioselective with exclusive functionalization at the β position to silicon. Four of the standard chiral dirhodium catalysts were examined (entries 1–4), and the highest levels of yield and enantioselectivity were obtained with $\text{Rh}_2(\text{S-NTTL})_4$.

With an optimal catalyst in hand, the substrate scope was evaluated by reacting a variety of different substituted triazoles with 2–4 equivalents of silacyclobutanes (Figure 2). A variety of substitution patterns on the phenyl ring of the triazole were well tolerated, including electron-rich and electron-poor triazoles, as well as triazoles bearing ortho, meta, and para substitution.²³ The mesyl group could be replaced by a tosyl group although the enantiopurity was diminished (92% ee for Ms and 64% ee for Ts). When substrates bearing *p*-Cl-Ph groups rather than methyl groups on the silicon were evaluated, the enantioselectivity dropped slightly to 80–90% ee, but the reaction yield was improved (84–95% yield) as shown for **12**–**14**. The absolute configuration of **11** was determined to be *S* by X-ray crystallography, and the other products are tentatively assigned as *S* by analogy.

Having demonstrated that high levels of enantioselectivity can be obtained by C-H functionalization of silacyclobutanes, larger silacycles, such as **17** were considered as plausible targets for C-H functionalization (eq 1). Larger silacycles introduce higher orders of complexity because multiple stereoisomers can be generated by desymmetrization arising from the silicon heterocycle.

When **17** was tested, the functionalization product **19** was generated in 89% combined yield with a 3:1 d. r. and 88% ee and 86% ee for the major and minor diastereomer, respectively.

The initial success with silacycles prompted inquiries into the reactivity of aliphatic silaalkanes as illustrated in Figure 3. This study commenced with the investigation of commercially available tetraethylsilane. Tetraethylsilane represents a unique opportunity for C-H functionalization as the targeted C-H bond is primary which has been historically less

accessible because the buildup of positive charge at a primary carbon is less stabilized. As shown for **26**, successful C-H functionalization was achieved in 65% yield and 90% ee, representing the first example of primary C-H functionalization with 1-sulfonyl-1,2,3-triazoles. Unfortunately, the synthesis of **21** and **22** suffered from lower yields even though the enantioselectivity was high. The lower yield of **21** likely derives from the *p*-fluoro triazole which serves as a poorer source of the requisite carbene intermediate while the lower yield of **22** is probably due to a less effective β -silicon effect influenced by the *t*BuO-substituent.²⁴ In contrast, propyl groups on the silane served as excellent substrates for achieving site-selective C-H functionalization at the β position of silicon. Products **23** and **24** were generated in good yields (69%–76%) and diastereoselectivity (4:1–5:1 dr) and great enantioselectivity (90–97% ee).

In conclusion, the regio- and stereoselective C-H functionalization reaction of silicon-substituted alkanes was accomplished. These reactions show high stereoselectivity at the β position of both silacycloalkanes and aliphatic sila-alkanes. We hope our studies herein will inspire others toward the C-H functionalization of organosilanes as a mode for accessing new chemical space.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- (1). Cash GG. Pestic. Sci. 1997; 49:29.(e)Moberg, WK., ; Basarab, GS., ; Cuomo, J., ; Liang, PH., Biologically Active Organosilicon Compounds: Fungicidal Silylmethyltriazoles.; In Synthesis and Chemistry of Agrochemicals. ; ACS Symposium Series 355; American Chemical Society: Washington, DC, 1987. ; pp p. 288–301..
- (2). (a)Jones, RG., ; Ando, W., ; Chojnowski, J., Silicon-Containing Polymers. , Springer: Berlin, 2000. .(b) Kumagai T, Itsuno S. Macromolecules. 2002; 35:5323.(c) Bai D, Han S, Lu Z-H, Wang S. Can. J. Chem. 2008; 86:230.(d) Su TA, Widawsky JR, Li H, Klausen RS, Leighton JL, Steigerwald ML, Venkataraman L, Nuckolls C. J. Am. Chem. Soc. 2013; 135:18331. [PubMed: 24261548]
- (3). (a) Tacke R, Zilch H. Endeavor. 1986; 10:191.(b)Tacke, R., ; Linoh, H., . Bioorganosilicon Chemistry.; In Organic Silicon Compounds. ; John Wiley & Sons, Ltd: New York, 1989. ; Vol. Vol. 2. , p. 1143.(c) Showell GA, Mills JS. Drug Discovery Today. 2003; 8:551. [PubMed: 12821303] (d) Mills JS, Showell GA. Expert Opin. Invest. Drugs. 2004; 13:1149.(e) Franz AK, Wilson SO. J. Med Chem. 2013; 56:388. [PubMed: 23061607] (f) Franz AK. Curr. Opin. Drug Discovery Dev. 2007; 10:654.(g) Fujii S, Hashimoto Y. Future Med. Chem. 2017; 9:485. [PubMed: 28362125] (h) Ramesh, R., Reddy, DS., J. Med. Chem. 2017. DOI: 10.1021/acs.jmedchem.7b00718.
- (4). Farkas S. CNS Drug Reviews. 2006; 12:218. [PubMed: 17227288]
- (5). Tacke R, Handmann VI, Bertermann R, Burschka C, Penka M, Seyfried C. Organometallics. 2003; 22:916.

- (6). Seetharamsingh B, Ramesh R, Dange SS, Khaimar PV, Singhal S, Upadhyay D, Veeraraghavan S, Viswanadha S, Vakkalanka S, Reddy DS. ACS Medicinal Chemistry Letters. 2015; 6:1105. [PubMed: 26617962]
- (7). Wang J, Ma C, Wu Y, Lamb RA, Pinto LH, DeGrado WF. J. Am. Chem. Soc. 2011; 133:13844. [PubMed: 21819109]
- (8). (a) Cheng C, Hartwig JF. Chem. Rev. 2015; 115:8946. [PubMed: 25714857] (b) Komiyama T, Minami Y, Hiyama T. ACS Catal. 2017; 7:631.
- (9). (a) Gutekunst WR, Baran PS. Chem. Soc. Rev. 2011; 40:1976. [PubMed: 21298176] (b) Newhouse T, Baran PS. Angew. Chem. Int. Ed. 2011; 50:3362. (c) Yamaguchi J, Yamaguchi AD, Itami K. Angew. Chem. Int. Ed. 2012; 51:8960.
- (10). Davies HML, Morton D. Chem. Soc. Rev. 2011; 40:1857. For a review, see. [PubMed: 21359404]
- (11). Liao K, Negretti S, Musaev DG, Bacsá J, Davies HML. Nature. 2016; 533:230. [PubMed: 27172046]
- (12). (a) Lambert JB, Zhao Y, Emblidge RW, Salvador LA, Liu X, So J-H, Chelius EC. Acc. Chem. Res. 1999; 32:183. (b) Lambert JB. Tetrahedron. 1990; 46:2677.
- (13). Seyferth D, Washburne SS, Attridge CJ, Yamamoto KJ. Am. Chem. Soc. 1970; 92:4405. (b) Seyferth D, Damrauer R, Andrews SB, Washburne SS. J. Am. Chem. Soc. 1971; 93:3709. (c) Seyferth D, Shih H-M, Dubac J, Mazerolles P, Serres B. J. Organometal. Chem. 1973; 50:39.
- (14). Ando W, Konishi K, Migita TJ. Organometal. Chem. 1974; 67:C7.
- (15). Danilkina LP, Sidorenko GV. J. Gen. Chem. USSR (Engl. Transl.). 1979; 49:2460.
- (16). Hatanaka Y, Watanabe M, Onozawa S, Tanaka M, Sakurai HJ. Org. Chem. 1998; 63:422. Hosomi A, Mikami M. Bull. Chem. Soc. Jpn. 1983; 56:2784. For another example of the β -silicon effect related to carbenes, see:
- (17). (a) Davies HML, Alford JS. Chem. Soc. Rev. 2014; 43:5151. For reviews on triazole-based reactions, see. [PubMed: 24802192] (b) Chattopadhyay B, Gevorgyan V. Angew. Chem. Int. Ed. 2012; 51:862. (c) Anbarasan P, Yadagiri D, Rajasekar S. Synthesis. 2014; 46:3004. (d) Jiang Y, Sun R, Tang X-Y, Shi M. Chem. Eur. J. 2016; 22:17910. [PubMed: 27406408]
- (18). (a) Lindsay VNG, Viart HMF, Sarpong R. J. Am. Chem. Soc. 2015; 137:8368. For intramolecular C-H functionalization reactions with triazoles, see. [PubMed: 26096731] (b) Shen M-H, Pan Y-P, Jia Z-H, Ren X-T, Zhang P, Xu H-D. Org. Biomol. Chem. 2015; 13:4851. [PubMed: 25826185] (c) Ma X, Wu F, Yi X, Wang H, Chen W. Chem. Commun. 2015; 51:6862. (d) Li L, Xia X-H, Wang Y, Bora PP, Kang Q. Adv. Synth. Catal. 2015; 357:2089. (e) Senoo M, Fumkawa A, Hata T, Urabe H. Chem. Eur. J. 2016; 22:890. [PubMed: 26549045] (f) Shen H, Fu J, Yuan H, Gong J, Yang Z. J. Org. Chem. 2016; 81:10180. [PubMed: 27171797]
- (19). Chuprakov S, Malik JA, Zibinsky M, Fokin VV. J. Am. Chem. Soc. 2011; 133:103582.
- (20). Kubiak II RW, Mighion JD, Wilkerson-Hill SM, Alford JS, Yoshidomi T, Davies HML. Org. Lett. 2016; 18:3118. [PubMed: 27333162]
- (21). (a) Homeff T, Chuprakov S, Chernyak N, Gevorgyan V, Fokin VV. J. Am. Chem. Soc. 2008; 130:14972. [PubMed: 18855475] (b) Medina F, Besnard C, Lacour J. Org. Lett. 2014; 16:3232. [PubMed: 24885761] (c) Guarnieri-Ibáñez A, Medina F, Besnard C, Kidd SL, Spring DR, Lacour J. Chem. Sci. 2017; 8:5713. [PubMed: 28989611]
- (22). Hirano K, Yorimitsu H, Oshima K. 1,1 Dimethylsilacyclobutane. e-EROS Encyclopedia of Reagents for Organic Synthesis. Commercially available from Gelest or Sigma Aldrich. 2001
- (23). Attempted extension of the reaction to alkyl *N*-sulfonyltriazoles failed to give any C-H functionalization product.
- (24). Shimizu N, Watanabe S-I, Hayakawa F, Yasuhara S, Tsuno Y, Inazu T. Bull. Chem. Soc. Jpn. 1994; 67:500.

Figure 1. Catalyst Optimization for Intermolecular C-H Functionalization of Silacycloalkanes^a

Figure 2. Selective C-H Functionalization of Silacyclobutanes^a

Figure 3. Selective C-H Functionalization of Acyclic Organosilanes

Previous Work**(a) Regioselective C-H Functionalization Organosilanes with Dichlorocarbenes** **(b) C-H Functionalization of Organosilanes with Acceptor/Acceptor Carbenes** **(c) Regioselective Rh-catalyzed C-H Functionalization of Organosilanes** **This work****(d) Asymmetric Rh-catalyzed C-H Functionalization of Organosilanes** **Scheme 1. C-H Functionalization Reactions of Tetraalkylsilanes**