

Cite this: *Chem. Sci.*, 2021, 12, 14224

All publication charges for this article have been paid for by the Royal Society of Chemistry

Silacyclization through palladium-catalyzed intermolecular silicon-based C(sp²)-C(sp³) cross-coupling†

Ying Qin, Lianghui Li, Jin-Yuan Liang, Kailong Li and Dongbing Zhao*

Silicon-based cross-coupling has been recognized as one of the most reliable alternatives for constructing carbon-carbon bonds. However, the employment of such reaction as an efficient ring expansion strategy for silacycle synthesis is comparatively little known. Herein, we develop the first intermolecular silacyclization strategy involving Pd-catalyzed silicon-based C(sp²)-C(sp³) cross-coupling. This method allows the modular assembly of a vast array of structurally novel and interesting sila-benzo[*b*]oxepines with good functional group tolerance. The key to success for this reaction is that silicon atoms have a stronger affinity for oxygen nucleophiles than carbon nucleophiles, and silacyclobutanes (SCBs) have inherent ring-strain-release Lewis acidity.

Received 30th July 2021
Accepted 7th October 2021

DOI: 10.1039/d1sc04180k

rsc.li/chemical-science

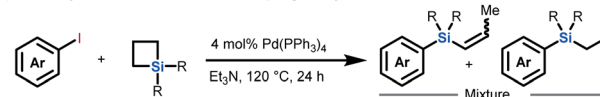
Introduction

Because of the high availability, low toxicity, and high-stability of organosilicon molecules, silicon-based cross-coupling reactions have been recognized as one of the most reliable alternatives for constructing carbon-carbon bonds.¹ Although rapid progress in silicon-based cross-coupling has been achieved, the employment of Hiyama-Denmark cross-coupling as an efficient ring expansion strategy for silacycle synthesis is comparatively rare. Recently, we described the first intramolecular strain-release silicon-based cross-coupling reaction, which constitutes an efficient ring expansion route for the synthesis of diversified silacycles.² However, the necessity of pre-synthesized starting substrates in this intramolecular method limits the full utilization of this elegant method. Further expanding this concept to intermolecular reactions would represent a significant and important step in organosilicon-based cross-coupling for silacycle synthesis.

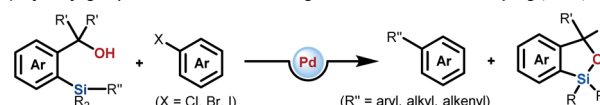
However, in this effort, we may face some challenges: (1) the use of alkylsilanes for construction of the Csp²-Csp³ bond in silicon-based coupling has the problem that the alkyl palladium intermediates formed by the transmetalation step normally tend to undergo β-hydride elimination; (2) a competitive reaction involving C-Si bond formation, in which the C-nucleophile attacks the silicon atom on SCBs, may occur during the reaction as the Pd-catalyzed cross-coupling of simple aryl iodides with

SCBs has been reported to deliver a mixture of allylsilanes (Scheme 1a).³ Inspired by the mode of activation of the Si-C bonds in silicon-based cross-coupling reaction presented by Hiyama (Scheme 1b)⁴ and Denmark,⁵ involving coordination of the oxygen atom to the silicon atom, and the ample body of

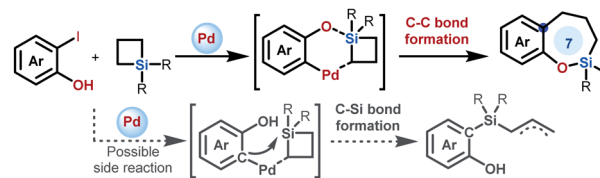
a) Pd-catalyzed silicon-based cross-coupling of aryl iodide with SCBs (Ref. 3)



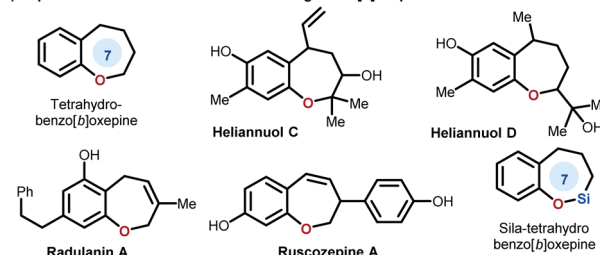
b) Hydroxyl group-assisted C-Si bond cleavage in silicon-based cross-coupling (Ref. 4)



c) Silacyclization via intermolecular silicon-based cross-coupling (This work)



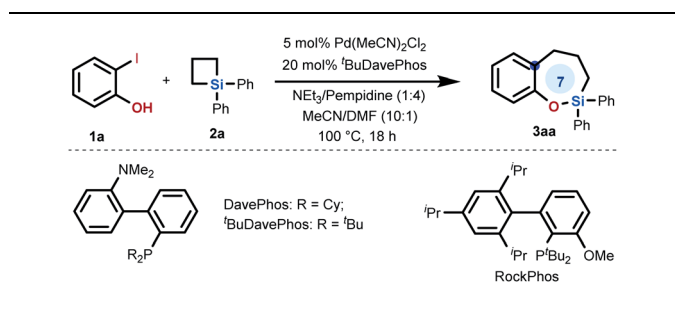
d) Representative bioactive molecules bearing benzo[*b*]oxepine units and sila-substitution



Scheme 1 Research background, inspiration, challenge and our study.

State Key Laboratory and Institute of Elemento-Organic Chemistry, Frontiers Science Center for New Organic Matter, College of Chemistry, Nankai University, Tianjin, 300071, China. E-mail: dongbing.chem@nankai.edu.cn

† Electronic supplementary information (ESI) available: CCDC 2083478. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc04180k

Table 1 Control experiments for the screening of reaction conditions^a

Entry	Deviation from standard condition	Yield ^b [%]
1	None	72
2	NEt ₃ instead of NEt ₃ /pempidine	54
3	Pempidine instead of NEt ₃ /pempidine	50
4	NEt ₃ /pempidine (1 : 1)	61
5	K ₂ CO ₃ as the base	Trace
6	Without base	Trace
7	MeCN as the solvent	41
8	DMF as the solvent	33
9	MeCN/DMF (1 : 1)	44
10	[Pd(allyl)Cl] ₂ instead of Pd(MeCN) ₂ Cl ₂	61
11	Pd ₂ (dba) ₃ instead of Pd(MeCN) ₂ Cl ₂	34
12	Without [Pd] catalyst	N. P.
13	DavePhos instead of tBuDavePhos	Trace
14	RockPhos instead of tBuDavePhos	41
15	Reaction at 100 °C for 36 h	71
16	2-Bromophenol instead of 1a	N. P.

^a Reactions were carried out by using [M] precatalyst (5 mol%), ligand (20 mol%), **1a** (0.2 mmol), and **2a** (0.22 mmol) in solvent for 18 h at 100 °C under an N₂ atmosphere. ^b Isolated yield after purification of the product **3aa** by column chromatography. N. P.: No desired products.

reactions utilizing SCBs as synthetic linchpins,⁶ we designed a new intermolecular cascade reaction between 2-halophenols and SCBs involving Si–O bond formation by an inter-reaction between the hydroxyl moiety of 2-halophenols and the silicon atom of SCBs, followed by Hiyama–Denmark C(sp²)–C(sp³) cross-coupling (Scheme 1c). If successful, the reaction is expected to provide facile access to sila-benzo[*b*]oxepines from readily available substrates. Notably, benzo[*b*]oxepine scaffolds are prevalent in various bioactive molecules (Scheme 1d).⁷ Incorporation of silicon into benzo[*b*]oxepines is of great significance because sila-congeners generally possess significantly altered physicochemical properties with a lack of element-associated toxicity,⁸ but remains a great synthetic challenge.⁹ Herein, we describe the implementation of the first intermolecular silicon-based C(sp²)–C(sp³) cross-coupling between 2-iodophenols and SCBs. This strategy is essentially the state of the art in terms of practicality and versatility for the synthesis of sila-benzo[*b*]oxepines and allows efficient late-stage modification of natural products.

Results and discussion

Condition optimization

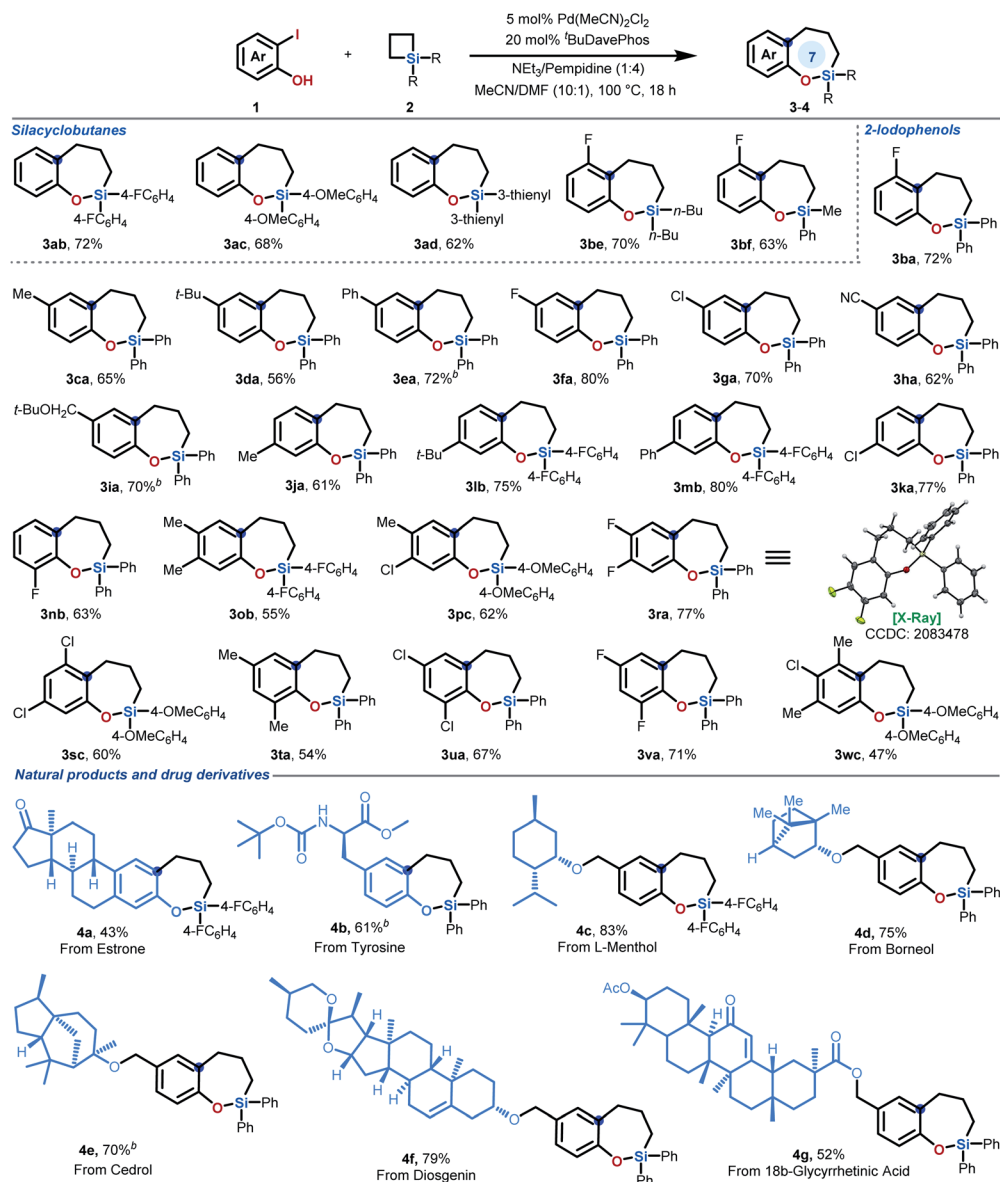
We first conducted an intermolecular strain-release silicon-based ring expansion between 2-iodophenol **1a** and

silacyclobutane **2a** to try to directly access sila-tetrahydrobenzo[*b*]oxepine **3aa** under the reported conditions for intramolecular strain-release organosilicon-based ring expansion.² Unfortunately, the reaction did not proceed at all. Then, a range of reaction parameters (*e. g.*, solvents, bases, palladium sources, and ligands) were evaluated (Table S1 in the ESI[†]), and the reaction occurred smoothly to yield sila-tetrahydrobenzo[*b*]oxepine **3aa** in 72% isolated yield under the optimized conditions, which were identified to be 5 mol% Pd(MeCN)₂Cl₂, 20 mol% tBuDavePhos, NEt₃/1,2,2,6,6-pentamethylpiperidine (2.0 equiv.; 1 : 4) and a mixture of acetonitrile and DMF (10 : 1) as the solvent at 100 °C for 18 h (Table 1, entry 1). An array of control experiments were subsequently performed to investigate the function of each component (Table 1). The mixture of triethylamine and pempidine in a ratio of 1 : 4 as the base is essential to ensure the yield of **3aa**. Employment of single-component Et₃N as the base led to lower yield with incomplete consumption of **2a** and **1a** (entry 2). On the other hand, pempidine improved the reactivity in the conversion of **2a** and **1a** but along with more serious unknown side reactions, leading to a lower yield of **3aa** (entry 3). Modification of the Et₃N/pempidine ratio to 1 : 1 also afforded inferior results (entry 4). The use of K₂CO₃ as the base or the absence of a base resulted in termination of this reaction (entries 5 and 6). The reaction also suffered low yields if the MeCN–DMF binary solvent was switched to a single solvent or the MeCN/DMF ratio was modified to 1 : 1 (entries 7–9). Addition of a small amount of DMF would facilitate opening of the strained four-membered SCB **2a** *via* transient coordination with the silicon atom.¹⁰ However, the use of DMF as the solvent would lead to the consumption of the product **3aa** during the reaction. Replacement of Pd(MeCN)₂Cl₂ with [Pd(allyl)Cl]₂ or Pd₂(dba)₃ resulted in a decrease in the yield (entries 10 and 11). The [Pd] catalyst was shown to be essential to initiate this reaction (entry 12). The effect of ligands was also investigated by replacement of tBuDavePhos by DavePhos or RockPhos (entries 13 and 14). Prolonging the reaction time was shown to be ineffective for improving the yield (entry 15). 2-Bromophenol was incapable of cross-coupling with SCB **2a** under the optimized conditions (entry 16).

Substrate scope

Then, the scope of the ring expansion reaction between 2-iodophenols **1** and SCBs **2** was explored. As shown in Table 2, a series of silacyclobutanes with different aryl and alkyl substituents on silicon could be employed as substrates, affording the corresponding sila-tetrahydrobenzo[*b*]oxepines efficiently (**3aa–ad** & **3be**). Additional experiments revealed that the current protocol for sila-tetrahydrobenzo[*b*]oxepine synthesis was efficient, as a wide array of 2-iodophenols could react well with silacyclobutane **2a**. For monosubstituted 2-iodophenols, the starting materials bearing different functional groups in the *para*-, *meta*-, and *ortho*-positions with different electronic characters all proceeded well in the reaction (**3ba–nb**). In addition to monosubstituted 2-iodophenols, 2-iodophenols bearing two or three substituents at different positions



Table 2 Substrate scope for the intermolecular cross-coupling of 2-iodophenols **1** and silacyclobutanes **2** to access 7-membered silacycles^a

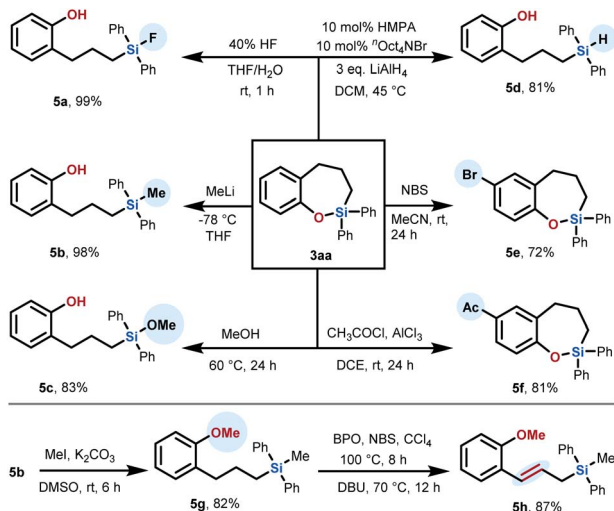
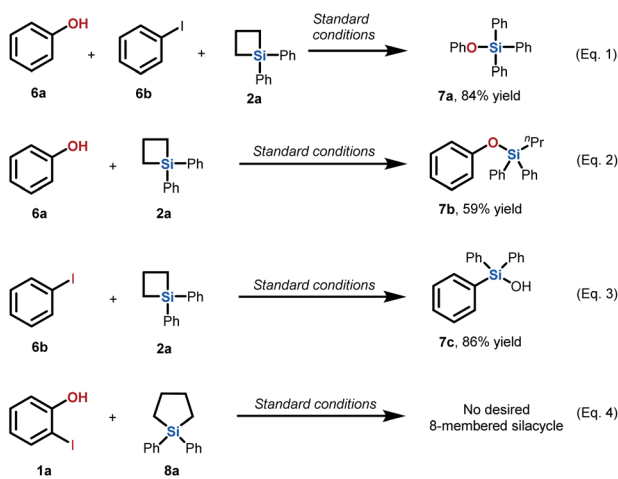
^a Reaction conditions: Pd(CH₃CN)₂Cl₂ (5 mol%), ^tBuDavePhos (20 mol%), NEt₃ (0.08 mmol), pempidine (0.32 mmol), CH₃CN/DMF (1 mL; 10/1), 100 °C, 18 h. Values represent isolated yields. ^b The reaction was performed in the presence of 2-iodophenol **1** (0.22 mmol), silacyclobutane **2** (0.2 mmol), Pd(MeCN)₂Cl₂ (2.6 mg, 5 mol%) and ^tBuDavePhos (13.6 mg, 20 mol%) in DMF (91 μL) and MeCN (0.91 mL) at 100 °C under N₂ for 8 h. Then additional Pd(MeCN)₂Cl₂ (2.6 mg, 5 mol%) was added to the reaction and heated for another 10 h. For more experimental details, see ESI.

on the aromatic ring are also suitable substrates for this transformation, affording cyclic products **3nb–wc** in moderate to good yields. Notably, given the importance of fluorinated aryl systems in drug discovery,^{9,11} we tried many 2-iodophenols bearing one or two fluoro groups at different positions of the phenol coupling partners for this ring expansion reaction. Fortunately, all of these substrates can react smoothly with moderate to high yields under the optimized conditions (**3ba**, **3fa**, **3nb**, **3ra**, **3va** & **3wc**). It is worthwhile to mention that the chloro group on the substrates remained intact (**3ga**, **3ka**, **3pc**, **3sc** & **3ua**), offering opportunities for downstream

transformations. The structure of our products was clearly confirmed by X-ray structural analysis of single-crystal **3ra**,¹² which was generated by recrystallization from a toluene/hexane solution.

The broad substrate scope encouraged the evaluation of this newly developed ring expansion method with natural products for potential application in the area of fragment-based drug discovery. The terpene derivative 4-iodoestrone successfully underwent ring expansion to deliver product **4a** (43% yield), enabling access to 7-membered silacycles in the parent hormone. Similarly, starting from commercially available 3-



Scheme 2 Synthetic applications of sila-benzosuberane **3aa**.

Scheme 3 Control experiments.

iodotyrosine, a seven-membered silacycle moiety can be efficiently introduced to give product **4b** in 61% yield. In addition to natural product derivatives, this reaction can also be applied to natural product-tethered 2-iodophenols. 2-Iodophenols with ether-linked *l*-menthol, borneol, cedrol, diosgenin, and ester-linked 18 β -glycyrrhetic acid smoothly participated in this ring expansion reaction, furnishing the desired products **4c–g** in moderate to good yields.

Moreover, we also demonstrated the synthetic usefulness of the sila-tetrahydrobenzo[*b*]oxepine skeletons obtained by our developed transformation as versatile synthetic intermediates *via* diverse downstream transformations (Scheme 2). Treatment of **3aa** with 40% HF in THF/H₂O resulted in Si–O bond cleavage to deliver the compound **5a** in 99% yield at room temperature for 1 h. We proved that the Si–O bond of product **3aa** can also be preferentially cleaved by treatment with organolithium reagent or methanol through a nucleophilic ring-opening reaction, permitting access to phenolic silane **5b** (98% yield) or **5c** (83%

yield). Additionally, product **3aa** can be reduced by LiAlH₄ in the presence of 10 mol% HMPA and ¹⁸Oct₄NBr to afford noncyclic phenolic hydrosilane **5d** (81% yield), which can further participate in hydrosilylation reactions as the synthetic intermediate to increase the complexity of molecules. In addition to ring-opening of the Si–O bond, the aromatic moiety on **3aa** can be decorated with a bromo substituent, resulting in 7-bromo-sila-tetrahydrobenzo[*b*]oxepine **5e** (72% yield), which could be readily modified through diverse cross-coupling reactions. For example, Stille coupling of **5e** with tributyl(phenyl)stannane proceeds smoothly to afford the product **3ea** in 65% yield. Friedel–Crafts acylation of the product **3aa** by employment of CH₃COCl/AlCl₃ also proceeded smoothly to give 7-acetyl-sila-tetrahydro-benzo[*b*]oxepine **5f** in 81% yield. Furthermore, we wondered whether the alkyl chain of our products could also be further functionalized. Taking **5b** as a substrate, we first protected the hydroxyl group by treatment with methyl iodide and K₂CO₃ in DMSO to produce product **5g** in 82% yield. Compound **5g** could further smoothly undergo tandem oxidation/elimination to yield allylic silane **5h** in 87% yield.

We then conducted several control experiments to support our proposal on the mechanism of this palladium-catalyzed intermolecular ring expansion reaction (Scheme 3). First, we found that no ring expansion occurred when phenol **6a**, iodobenzene **6b**, and SCB **2a** were used as substrates under standard conditions (eqn (1)). This finding indicates that assembly of the iodo group and hydroxy group at adjacent positions of the aromatic ring is necessary to initiate this intermolecular cyclization. The ring opening reaction of SCB **2a** occurred in the presence of phenol **6a** to deliver product **7b** in 59% yield (eqn (2)). This result indicates that phenol as the substrate is capable of attacking the silicon atom on SCB **2a** under standard conditions. The reaction of iodobenzene **6b** with SCB **2a** produced triphenyl silanol **7c** by C–Si bond formation (eqn (3)), which is in accordance with results reported in the literature. This proved that the hydroxy group on the aryl iodide played a pivotal role in inhibiting problematic C–Si bond formation and facilitating transmetalation to form C–C bonds in our newly developed reaction. In addition, we subjected 2-iodophenol **1a** and 5-membered silacycle **8a** to the standard conditions. No desired 8-membered silacycle was observed (eqn (4)). This result indicates that the high ring strain of SCBs is essential in this intermolecular Pd-catalyzed ring expansion reaction.

Conclusions

In summary, we have described the first silacyclization strategy involving intermolecular silicon-based cross-coupling reaction enabled by a Pd-catalytic system, which offers a straightforward but strategically distinct approach for preparing sila-benzo[*b*]oxepines. Moreover, the formed sila-benzo[*b*]oxepines were shown to be versatile synthetic intermediates for the synthesis of an array of important building blocks. The key to success for this reaction is that silicon atoms have a stronger affinity for oxygen nucleophiles than carbon nucleophiles, and SCBs have inherent ring-strain-release Lewis acidity.



Data availability

Data for all compounds in this manuscript are available in the ESI,† which includes experimental details, characterization and copies of ^1H and ^{13}C NMR spectra. Crystallographic data for compound **3ra** has been deposited at the CCDC under CCDC 2083478.

Author contributions

Y. Q., L. L., J.-Y. L. and K. L. performed the experiments. D. Z. conceived the concept, directed the project and wrote the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (22071114, 22022103, and 21871146), the National Key Research and Development Program of China (2019YFA0210500), the “Frontiers Science Center for New Organic Matter”, Nankai University (Grant Number 63181206), the Natural Science Foundation of Tianjin (18JCYBJC20400), and the Fundamental Research Funds for the Central Universities and Nankai University.

Notes and references

- For some reviews on silicon-based cross-coupling reactions, see: (a) S. E. Denmark and R. F. Sweis, *Chem. Pharm. Bull.*, 2002, **50**, 1531; (b) S. E. Denmark and C. S. Regens, *Acc. Chem. Res.*, 2008, **41**, 1486; (c) Y. Nakao and T. Hiyama, *Chem. Soc. Rev.*, 2011, **40**, 4893; (d) W.-T. T. Chang, R. C. Smith, C. S. Regens, A. D. Bailey, N. S. Werner and S. E. Denmark, *Org. React.*, 2011, **75**, 213; (e) H. F. Sore, W. R. J. D. Galloway and D. R. Spring, *Chem. Soc. Rev.*, 2012, **41**, 1845; (f) S. E. Denmark and A. Ambrosi, *Org. Process Res. Dev.*, 2015, **19**, 982; (g) F. Foubelo, C. Nájera and M. Yus, *Chem. Rec.*, 2016, **16**, 2521; (h) T. Komiyama, Y. Minami and T. Hiyama, *ACS Catal.*, 2017, **7**, 631; (i) T. Komiyama, Y. Minami and T. Hiyama, *Synlett*, 2017, **28**, 1873; (j) S. Bähr, W. Xue and M. Oestreich, *ACS Catal.*, 2019, **9**, 16; (k) Y. Minami and T. Hiyama, *Chem.-Eur. J.*, 2019, **25**, 391; (l) T. Hiyama, Y. Minami, and A. Mori on Transition-Metal-Catalyzed Cross-Coupling of Organosilicon Compounds in Organosilicon Chemistry, *Novel Approaches and Reactions*, ed. T. Hiyama and M. Oestreich, Wiley-VCH, Weinheim, 2019, pp. 271–332.
- Y. Qin, J.-L. Han, C.-W. Ju and D. Zhao, *Angew. Chem., Int. Ed.*, 2020, **59**, 8481.
- Y. Tanaka, A. Nishigaki, Y. Kimura and M. Yamashita, *Appl. Organomet. Chem.*, 2001, **15**, 667.
- (a) Y. Nakao, H. Imanaka, A. K. Sahoo, A. Yada and T. Hiyama, *J. Am. Chem. Soc.*, 2005, **127**, 6952; (b) Y. Nakao, M. Takeda, T. Matsumoto and T. Hiyama, *Angew. Chem., Int. Ed.*, 2010, **49**, 4447; (c) A. Tsubouchi, D. Muramatsu and T. Takeda, *Angew. Chem., Int. Ed.*, 2013, **52**, 12719.
- Prof. Denmark’s group has proved that alkoxide nucleophiles are capable of promoting silicon-based cross-coupling *via* coordination with the silicon atom in an intermolecular manner. For some references, see: (a) S. E. Denmark and R. F. Sweis, *J. Am. Chem. Soc.*, 2001, **123**, 6439; (b) S. E. Denmark, J. D. Baird and C. S. Regens, *J. Org. Chem.*, 2008, **73**, 1440; (c) S. E. Denmark and J. M. Kallemeyn, *J. Org. Chem.*, 2005, **70**, 2839.
- For reviews on SCBs, see: (a) L. J. Li, Y. B. Zhang, L. Gao and Z. L. Song, *Tetrahedron Lett.*, 2015, **56**, 1466; (b) Q. C. Mu, J. Chen, C. G. Xia and L. W. Xu, *Coord. Chem. Rev.*, 2018, **374**, 93. For some recent progress, see: (c) K. Hirano, H. Yorimitsu and K. Oshima, *J. Am. Chem. Soc.*, 2007, **129**, 6094; (d) R. Shintani, K. Moriya and T. Hayashi, *J. Am. Chem. Soc.*, 2011, **133**, 16440; (e) N. Ishida, W. Ikemoto and M. Murakami, *J. Am. Chem. Soc.*, 2014, **136**, 5912; (f) Q. W. Zhang, K. An, L. C. Liu, S. X. Guo, C. R. Jiang, H. F. Guo and W. He, *Angew. Chem., Int. Ed.*, 2016, **55**, 6319; (g) S. Okumura, F. Sun, N. Ishida and M. Murakami, *J. Am. Chem. Soc.*, 2017, **139**, 12414; (h) Q.-W. Zhang, K. An, L.-C. Liu, Q. Zhang, H. Guo and W. He, *Angew. Chem., Int. Ed.*, 2017, **56**, 1125; (i) W. T. Zhao, F. Gao and D. Zhao, *Angew. Chem., Int. Ed.*, 2018, **57**, 6329; (j) H. Chen, Y. Chen, X. Tang, S. Liu, R. Wang, T. Hu, L. Gao and Z. Song, *Angew. Chem., Int. Ed.*, 2019, **58**, 4695; (k) X.-B. Wang, Z.-J. Zheng, J.-L. Xie, X.-W. Gu, Q.-C. Mu, G.-W. Yin, F. Ye, Z. Xu and L.-W. Xu, *Angew. Chem., Int. Ed.*, 2020, **59**, 790; (l) L. Zhang, K. An, Y. Wang, Y.-D. Wu, X. Zhang, Z.-X. Yu and W. He, *J. Am. Chem. Soc.*, 2021, **143**, 3571; (m) M.-H. Zhu, X.-W. Zhang, M. Usman, H. Cong and W.-B. Liu, *ACS Catal.*, 2021, **11**, 5703.
- (a) F. A. Macias, J. M. G. Molinillo, R. M. Varela, A. Torres and F. R. Fronczek, *J. Org. Chem.*, 1994, **59**, 8261; (b) J. B. P. A. Wijnberg, A. van Veldhuizen, H. J. Swarts, J. C. Frankland and J. A. Field, *Tetrahedron Lett.*, 1999, **40**, 5767; (c) M. Shiraishi, Y. Aramaki, M. Seto, H. Imoto, Y. Nishikawa, N. Kanzaki, M. Okamoto, H. S. Awada, O. N. Ishimura, M. B. Aba and M. Fujino, *J. Med. Chem.*, 2000, **43**, 2049; (d) D. G. Lloyd, R. B. Hughes, D. M. Zisterer, D. C. Williams, C. Fattorusso, B. Catalanotti, G. Campiani and M. J. Meegan, *J. Med. Chem.*, 2004, **47**, 5612; (e) V. K. Tandon, K. A. Singh, A. K. Awasthi, J. M. Khanna, B. Lal and N. Anand, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2867; (f) S. Kim, Y.-W. Chin, B.-N. Su, S. Riswan, L. B. S. Kardono, J. J. Afriastini, H. Chai, N. R. Farnsworth, G. A. Cordell, S. M. Swanson and A. D. Kinghorn, *J. Nat. Prod.*, 2006, **69**, 1769; (g) P. K. Singh and O. Silakari, *ChemMedChem*, 2018, **13**, 1071.
- (a) W. Bains and R. Tacke, *Curr. Opin. Drug Discovery Dev.*, 2003, **6**, 526; (b) G. A. Showell and J. S. Mills, *Drug Discovery Today*, 2003, **8**, 551; (c) P. Englebienne, A. V. Hoonacker and C. V. Herst, *Drug Des. Rev.*, 2005, **2**, 467; (d) A. K. Franz and S. O. Wilson, *J. Med. Chem.*, 2013, **56**, 388; (e) R. Ramesh and D. S. Reddy, *J. Med. Chem.*,



- 2018, **61**, 3779; (f) S. J. Barraza and S. E. Denmark, *J. Am. Chem. Soc.*, 2018, **140**, 6668.
- 9 (a) G. Bertrand, P. Mazerolles and J. Ancelle, *Tetrahedron*, 1981, **37**, 2459; (b) C. P. Lenges and M. Brookhart, *J. Am. Chem. Soc.*, 1997, **119**, 3165; (c) M. Parasram, V. O. Iaroshenko and V. Gevorgyan, *J. Am. Chem. Soc.*, 2014, **136**, 17926.
- 10 N. Ishida, S. Okumura, T. Kawasaki and M. Murakami, *Angew. Chem., Int. Ed.*, 2018, **57**, 11399.
- 11 (a) P. Jeschke, *Chem BioChem.*, 2004, **5**, 570; (b) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (c) J. Wang, M. Sánchez-Roselló, J. L. Aceño, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432; (d) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832.
- 12 CCDC 2083478 (3ra) contains the supplementary crystallographic data.

