C−H Activation

Palladium-Catalyzed Silacyclization of (Hetero)Arenes with a Tetrasilane Reagent through Twofold C−H Activation
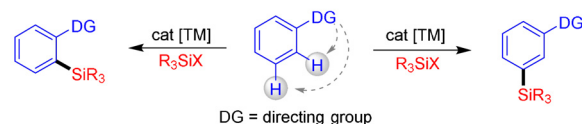
Dingyi Wang, Mingjie Li, Xiangyang Chen, Minyan Wang,* Yong Liang, Yue Zhao, Kendall N. Houk, and Zhuangzhi Shi*

Dedicated to the 100th anniversary of the College of Chemistry, Nankai University

Abstract: *The use of an operationally convenient and stable silicon reagent (octamethyl-1,4-dioxacyclohexasilane, ODCS) for the selective silacyclization of (hetero)arenes via twofold C−H activation is reported. This method is compatible with N-containing heteroarenes such as indoles and carbazoles of varying complexity. The ODCS reagent can also be utilized for silacyclization of other types of substrates, including tertiary phosphines and aryl halides. A series of mechanistic experiments and density functional theory (DFT) calculations were used to investigate the preferred pathway for this twofold C−H activation process.*

In the fields of complex molecule synthesis, advanced materials, and biomedical applications, (hetero)arenes containing C−Si bonds are of considerable interest.[1] Many methods are available to construct C−Si bonds,[2] among which C−H silylation is particularly attractive.[3] Significant progress has been made since the first appearance of seminal reports on aromatic C−H silylation in 1982,[4] and a variety of directing groups[5] have recently been identified that lead to excellent *ortho*[6] and remote *meta*[7] selectivity with common hydrosilanes or disilanes (Figure 1a). Octamethyl-1,4-dioxa-cyclohexasilane (ODCS) has been employed for ring-opening polymerization.[8] However, this compound has never been used as a silicon reagent to build C−Si bonds. Here, the application of the ODCS reagent to C−H silylation is reported for the first time (Figure 1b). A significant observation on the reactivity of this reagent is that two C−H bonds in (hetero)arenes can be silylated to form benzoxadisilole compounds[9] in the presence of a palladium catalyst, whereas conventional silicon reagents cannot deliver the related products directly. Notably, ODCS reagent is easily prepared

[*] D. Wang, M. Li, Prof. Dr. M. Wang, Prof. Dr. Y. Liang, Dr. Y. Zhao, Prof. Dr. Z. Shi
State Key Laboratory of Coordination Chemistry, Chemistry and Biomedicine Innovation Center (ChemBIC), School of Chemistry and Chemical Engineering, Nanjing University
Nanjing 210093 (China)
E-mail: wangmy@nju.edu.cn
shiz@nju.edu.cn

Dr. X. Chen, Prof. Dr. K. N. Houk
Department of Chemistry and Biochemistry, University of California
Los Angeles, CA 90095 (USA)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
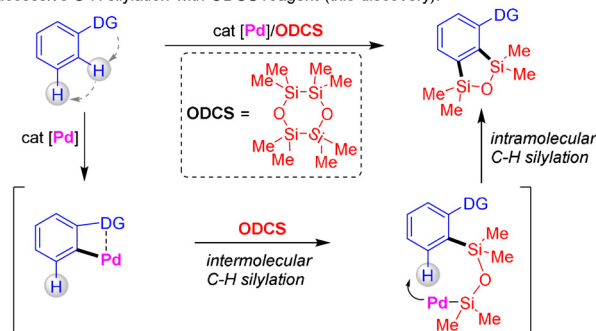https://doi.org/10.1002/anie.202015117.

Figure 1. Pd-catalyzed silacyclization using ODCS reagent through twofold C−H activation.

from the commercially available and inexpensive disilane **I** on the gram scale as an air-stable and colorless solid (Scheme 1).

The indole moiety is an intriguing structural motif,[10] and the C−H silylation of indoles has been explored over the years.[11] It is typically extremely challenging to circumvent the inherent C3/C2 selectivity of indoles to access the benzene core.[12] Our group recently found that P^{III}-directing groups[13] can enable the preferential regioselective C−H functionalization of indoles at the C7 position.[14] However, the simultaneous functionalization of two C−H bonds at the benzene core of indoles remains a largely elusive and unmet goal for chemical synthesis. We tested the applicability of the ODCS reagent to C−H silylation by investigating the reactions of a model substrate, N-P^{t}Bu$_2$ (^{t}Bu = *tert*-butyl) indole **1a** (Table 1). A series of experiments showed that the silacyclization product **2a** was obtained in an 86% GC yield using Pd(OAc)$_2$ as a catalyst and DMBQ as the oxidant in a toluene solvent at 120°C (entry 1). The structure of **2a** with two C−Si

Scheme 1. Large-scale synthesis of ODCS reagent.

7066 **Wiley Online Library**

© 2020 Wiley-VCH GmbH

Angew. Chem. Int. Ed. **2021**, *60*, 7066–7071

Table 1: Reaction development.[a]

CCDC 2041900

Entry	Variation from "standard conditions"	Yield of **2a** [%][b]
1	none	86 (77)[c]
2	Use of Ag$_2$CO$_3$ instead of DMBQ	5
3	Use of CuCl$_2$ instead of DMBQ	19
4	Use of BQ instead of DMBQ	28
5	Use of Pd(TFA)$_2$ instead of Pd(OAc)$_2$	47
6	At 100°C	76
7	Without DMBQ	14
8	Without Pd(OAc)$_2$	0

[a] Reaction conditions: **1a** (0.20 mmol), ODCS (0.5 mmol), catalyst (10 mol%), oxidant (0.5 mmol) in toluene (0.5 mL), 48 h, 120°C, under Ar; [b] GC yield; [c] isolated yield; 2,5-dimethyl-1,4-benzoquinone (DMBQ), 1,4-benzoquinone (BQ).

bonds at the indole C6 and C7 positions was unambiguously confirmed by X-ray crystallographic analysis. The use of DMBQ in the system appeared to be crucial for suppressing oxidation of the N-P^{t}Bu$_2$ motif and maintaining the catalytic cycle,[15] whereas other conventional oxidants, such as Ag$_2$CO$_3$, CuCl$_2$, and BQ, reacted to produce lower yields (entries 2–4). Reactions with palladium catalysts lacking OAc produced considerably lower yields than those catalyzed by Pd(OAc)$_2$ (entry 5). Good reactivity (in terms of the reaction outcome) was maintained upon lowering the reaction temperature to 100°C (entry 6). Finally, control experiments showed poor conversion without the use of the DMBQ oxidant (entry 7), and silylation did not proceed in the absence of the palladium catalyst (entry 8).

We next evaluated the scope and generality of this method under optimized reaction conditions (Table 2). Indoles bearing electron-neutral and electron-donating substituents, such as methyl (**1b–1d**), phenyl (**1e**), thioether (**1f**), ether (**1g**) and alkenyl (**1g**) groups at C3-C5 positions, were well tolerated, affording the corresponding silacycles **2b–2g** in 41–75% yields. These reactions proceed without any interference from halides, such as the F (**2i** and **2j**) and Cl (**2k**) units. Indoles containing electron-withdrawing groups, such as ester (**1l**) and acetyl (**1m**), were also suitable for P^{III}-directed silacyclization with ODCS, providing products **2l** and **2m** in 74% and 55% yields, respectively. The reaction of indole **1n** with a methyl group at the C2 position did not inhibit the process, but the smaller N-PCy$_2$ (Cy = cyclohexyl) directing group exhibited higher reactivity than the N-P^{t}Bu$_2$ motif, affording the desired product **2n** in a 63% yield. The 2,3-disubstituted indole skeletons **1o–1q** also underwent cyclization to form **2o**, **2p**, and **2q** in 46–71% yields. In addition to indoles, the silacyclization of carbazoles **1r–1s** occurred with excellent site selectivity for *ortho* and *meta* positions to the N-PCy$_2$ group. The regioselectivity of the silylation of unsymmetrical carbazoles with methyl (**1t**), methoxy (**1u**) and Cl (**1v**) groups at the less hindered benzene core led to a high level of steric control by substituents *ortho* to the reacting C–H bond. In addition, several highly π-extended heterocyclic skeletons,

Table 2: Substrate scope of silacyclization.[a]

[a] Reaction conditions: **1** (0.20 mmol), ODCS (0.5 mmol), Pd(OAc)$_2$ (10 mol%), DMBQ (0.5 mmol) in toluene (0.5 mL), 48 h, 120°C, under Ar; isolated yield; [b] at 140°C.

including 5H-benzo[b]carbazole **1w**, 7H-dibenzo[c,g]-carbazole **1x** and 5,11-dihydroindeno[1,2-b]carbazole **1y**, were also examined, and the silacyclization products (**2w–2y**) were obtained in 46–64% yields.

Further investigations were conducted to demonstrate the practicability of the ODCS reagent (Scheme 2). First, the ODCS reagent could also be used for the late-stage C−H modification of complex molecules (Scheme 2a). When complex indole molecules **3a** and **3b** were subjected to the developed system, high levels of selectivity were observed for C−H silylation in products **4a** and **4b**, despite multiple potentially reactive positions. Second, silacyclization with the ODCS reagent could be used for rapidly modification of
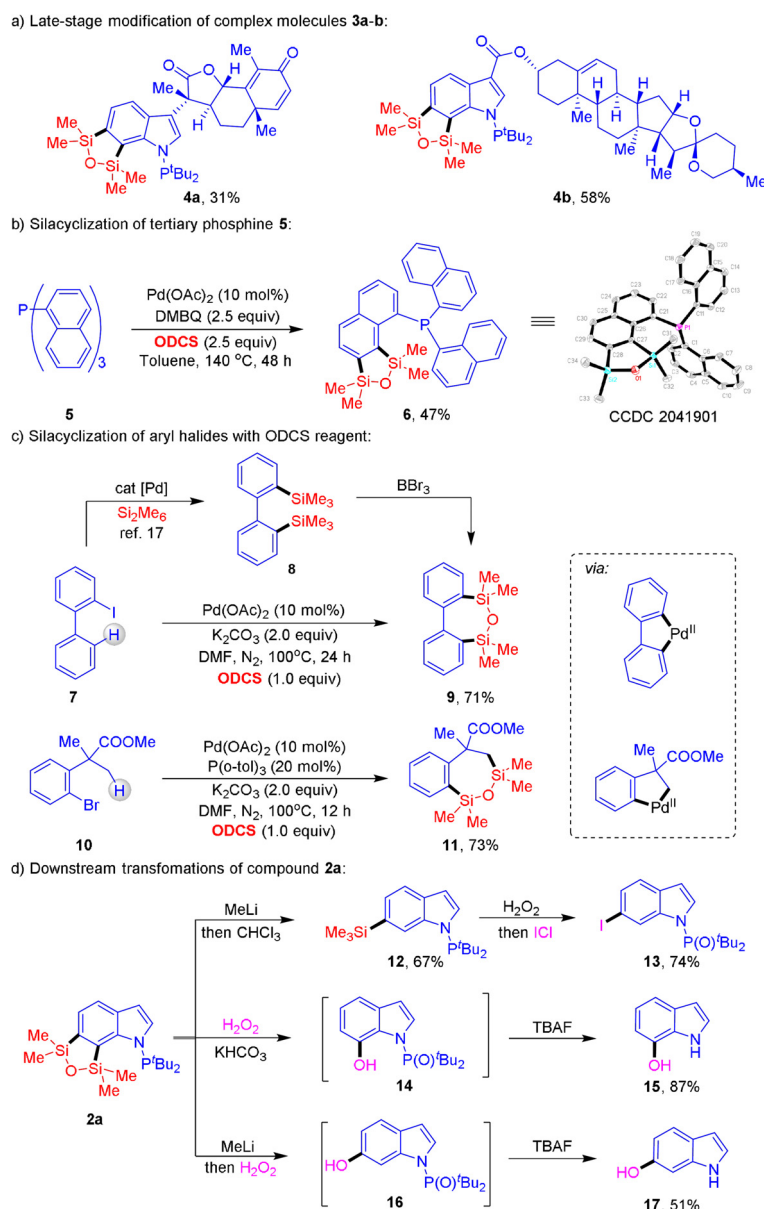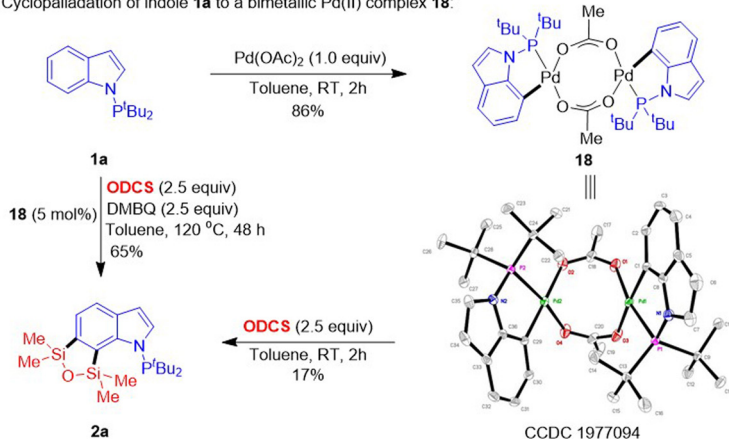
Scheme 2. Additional silacyclization studies.

tertiary phosphines (Scheme 2 b). For example, twofold C−H silylation of tri-1-naphthylphosphine (**5**) produced a new ligand **6** in one step. Third, the ODCS reagent has the potential to conduct other types of silacyclization reactions (Scheme 2 c). Disiloxane-bridged biphenyl **9** is a widely studied OLED material[16] that was previously synthesized from iodoarene **7** by palladium-catalyzed disilylation (**8**), followed by cyclization with a BBr₃ reagent.[17] Using the ODCS reagent for the direct silacyclization of substrate **7** could afford product **9** in a good yield in the presence of a palladium salt, shortening the reaction path. Moreover, aryl halide **10** could undergo silacyclization to form product **11** through activation of an aliphatic C−H bond. Finally, molecular scaffolds bearing disiloxane are known to undergo a variety of downstream transformations (Scheme 2 d). For instance, treatment of compound **2a** with a MeLi reagent furnishes C6-silylated indole **12**, which could further form
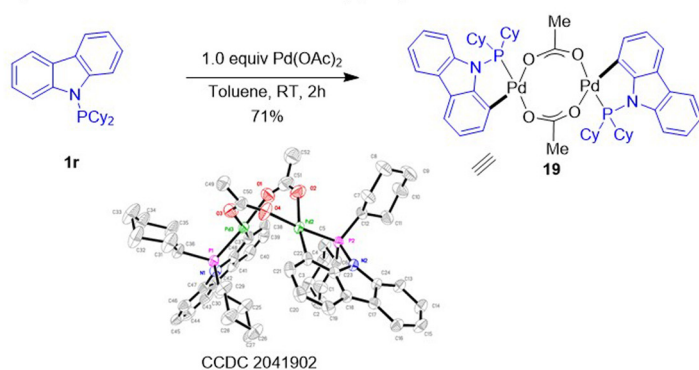
iodo-substituted indole **13**. Interestingly, Tamao-Fleming oxidation[18] of indole **2a** with or without MeLi reagent was found to selectively produce C7- and C6-hydroxy indoles **14** and **16**, which further underwent one-pot deprotection with TBAF to generate N-free indoles **15** and **17**, respectively.

Several experiments were carried out to elucidate the C−H activation process (Scheme 3). First, a stoichiometric reaction of indole **1a** with Pd(OAc)₂ was found to produce a bimetallic Pd^{II} complex **18** chelation by N-P^{t}Bu group, as characterized by X-ray analysis (Scheme 3 a).[19] The use of either complex **18** as a catalyst or the starting material with the ODCS reagent was found to yield the desired product **2a**, indicating the C−H metalation complex **18** as a possible intermediate in the reaction. Similarly, the reaction of carbazole **1r** with stoichiometric Pd(OAc)₂ afforded the dimer complex **19**, as confirmed by X-ray analysis (Scheme 3 b). In addition, a KIE of 1.45 between indoles **1a** and
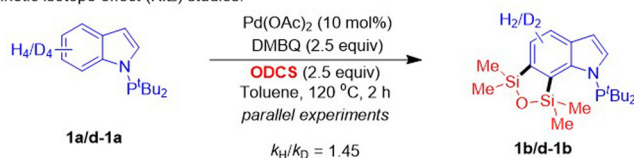
a) Cyclopalladation of indole **1a** to a bimetallic Pd(II) complex **18**:

b) Cyclopalladation of carbazole **1r** to a bimetallic Pd(II) complex **19**:

c) Kinetic isotope effect (KIE) studies:

$k_H/k_D = 1.45$

Scheme 3. Mechanistic experiments.

group, forming a 14-membered intermediate **INT5A** to release ring strain and tension. In the presence of DMBQ and the in situ-formed AcOH, the palladium center is oxidized to regenerate the Pd catalyst and form the intermediate **INT6A**, whereas the alternative pathway involving the insertion of the catalyst into the Si–Si bond is less favorable. The insertion of the Pd catalyst into the Si–Si bond of **INT6A** requires a free energy of 33.8 kcal mol^{-1} to form the intermediate **INT7A**. The calculated energy profile shows that the oxidative addition of the Pd^{II} species to the Si–Si bond of **INT6A** is the rate-determining step in the overall reaction pathway. The second C–H metalation proceeds with an activation barrier of 30.2 kcal mol^{-1} via a CMD process to form the intermediate **INT8A**. The second reductive elimination results in the formation of the desired product **3 aa** and the Pd species **INT9A**. Finally, the active palladium catalyst can be regenerated in the presence of DMBQ and the in situ-generated AcOH. Detected by high-resolution electrospray ionization mass spectrometry (ESI-HRMS), the reaction mixture showed a clearly signal for the byproduct **20** (ESI-HRMS [*M*+K]$^+$ calculated for $C_{20}H_{30}KO_5Si_2$: 445.1263, found: 445.1262.).

In summary, a silicon reagent (ODCS) has been developed for the silacyclization of (hetero)-arenes through twofold C–H silylation. ODCS is a credible reagent for the direct transfer of a disiloxane-bridged unit to diverse substrates, including indoles, carbazoles, tertiary phosphines and aryl halides, by Pd catalysis. The mechanistic features of this silacyclization process have been investigated. An investigation of the general use of the ODCS reagent for other organic substrates is ongoing and will be reported in due course.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

d-1a with the ODCS reagent showed that the C–H cleavage step was fast and did not function as a rate-determining step.[20]

Density functional theory (DFT) calculations were conducted to elaborate the detailed reaction mechanism (Figure 2).[21] Initially, an active Pd catalyst associates with indole **1a** to generate **INT1**, which preferentially deprotonates the C7 position of **1a** to form the C–H metalated palladacycle **INT2A** through a concerted metalation deprotonation (CMD) pathway[22] with a 12.7 kcal mol^{-1} energy barrier. Dimerization of **INT2A** to form the intermediate **18** is exothermic by 10.2 kcal mol^{-1}, suggesting that the active catalyst is in a rest state. Oxidative addition of **INT2A** with the ODCS reagent forms the 7-membered palladacycle **INT3A** through the transition state **TS3A** with an energy barrier of 18.7 kcal mol^{-1}. Subsequent reductive elimination results in the formation of the first C–Si bond at the indole C7 position with an energy demand of 10.7 kcal mol^{-1}, leading to the formation of **INT4A**. The intermediate **INT4A** easily undergoes further reductive elimination to transfer the silicon connected with the palladium atom to the O of the acetoxy
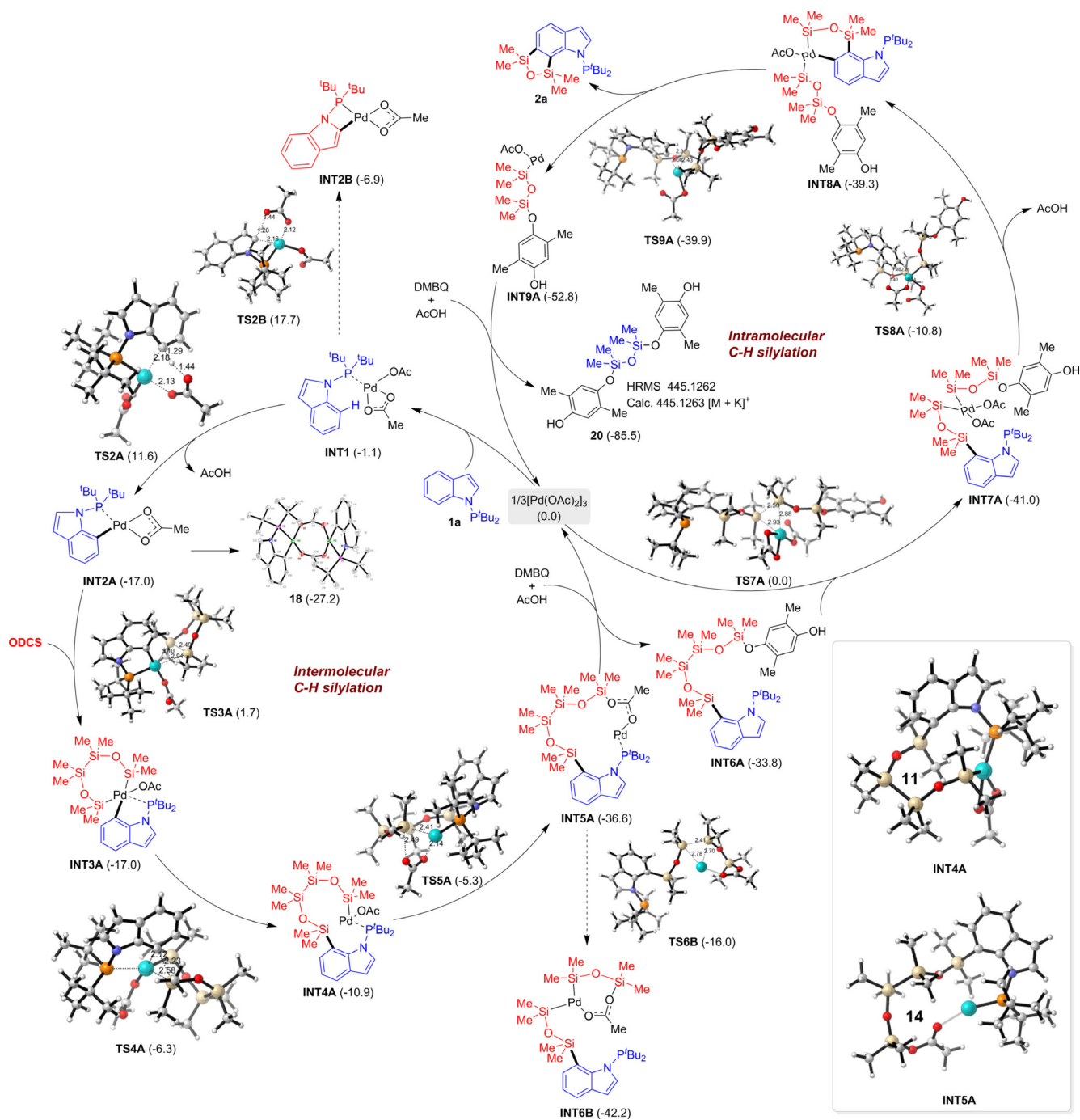
Figure 2. Plausible reaction mechanism and free energy profiles for silacyclization of indole **1a** with ODCS reagent; bond lengths are in Å.

Keywords: heteroarenes · ODCS · palladium · silacyclization · silylation

[1] a) A. Showell, J. S. Mills, *Drug Discovery Today* **2003**, *8*, 551–556; b) A. K. Franz, S. O. Wilson, *J. Med. Chem.* **2013**, *56*, 388–405; c) D. Sun, Z. Ren, M. R. Bryce, S. Yan, *J. Mater. Chem.* **2015**, *3*, 9496–9508.

[2] M. Mortensen, R. Husmann, E. Veri, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 1002–1010.

[3] For reviews on C–H silylation, see: a) L. Omann, C. D. F. Königs, H. F. T. Klare, M. Oestreich, *Acc. Chem. Res.* **2017**, *50*, 1258–1269; b) J. F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864–873; c) C. Cheng, J. F. Hartwig, *Chem. Rev.* **2015**, *115*, 8946–8975.

[4] W. A. Gustavson, P. S. Epstein, M. D. Curtis, *Organometallics* **1982**, *1*, 884–885.

[5] a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 2375–2378; b) F. Zhang, D. R. Spring, *Chem. Soc. Rev.* **2014**, *43*, 6906–6919; c) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107–1295; d) C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, *47*, 6603–6743.

[6] a) H. Ihara, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 7502–7503; b) E. M. Simmons, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**,

7070 www.angewandte.org

© 2020 Wiley-VCH GmbH

Angew. Chem. Int. Ed. **2021**, *60*, 7066–7071

132, 17092–17095; c) Y. Hua, P. Asgari, T. Avullala, J. Jeon, *J. Am. Chem. Soc.* **2016**, *138*, 7982–7991; d) J. Wen, B. Dong, J. Zhu, Y. Zhao, Z. Shi, *Angew. Chem. Int. Ed.* **2020**, *59*, 10909–10912; *Angew. Chem.* **2020**, *132*, 11001–11004.

[7] a) A. Maji, S. Guin, S. Feng, A. Dahiya, V. K. Singh, P. Liu, D. Maiti, *Angew. Chem. Int. Ed.* **2017**, *56*, 14903–14907; *Angew. Chem.* **2017**, *129*, 15099–15103; b) A. Modak, T. Patra, R. Chowdhury, S. Raul, D. Maiti, *Organometallics* **2017**, *36*, 2418–2423; c) A. Dey, S. K. Sinha, T. K. Achar, D. Maiti, *Angew. Chem. Int. Ed.* **2019**, *58*, 10820–10843; *Angew. Chem.* **2019**, *131*, 10934–10958; d) G. Meng, N. Y. S. Lam, E. L. Lucas, T. G. Saint-Denis, P. Verma, N. Chekshin, J.-Q. Yu, *J. Am. Chem. Soc.* **2020**, *142*, 10571–10591.

[8] M. Cypryk, J. Chojnowski, J. Kurjata in *The Science and Technology of Silicones and Silicone-Modified Materials* (Eds.: S. J. Clarson, J. J. Fitzgerald, M. J. Owen, S. S. Smith, M. E. Van Dyke), American Chemical Society, Washington, **2007**, pp. 10–26.

[9] a) R. J. P. Corriu, J. J. E. Moreau, M. Pataud-Sat, *Organometallics* **1985**, *4*, 623–629; b) W. Setaka, K. Ebata, H. Sakurai, M. Kira, *J. Am. Chem. Soc.* **2000**, *122*, 7781–7786; c) B.-J. Pei, W.-H. Chan, A. W. M. Lee, *Org. Lett.* **2011**, *13*, 1774–1777; d) Y. Lin, K.-Z. Jiang, J. Cao, Z.-J. Zheng, Z. Xu, Y.-M. Cui, L.-W. Xu, *Adv. Synth. Catal.* **2017**, *359*, 2247–2252.

[10] L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673–714.

[11] a) B. Lu, J. R. Falck, *Angew. Chem. Int. Ed.* **2008**, *47*, 7508–7510; *Angew. Chem.* **2008**, *120*, 7618–7620; b) A. A. Toutov, W.-B. Liu, K. N. Betz, A. Fedorov, B. M. Stoltz, R. H. Grubbs, *Nature* **2015**, *518*, 80–84; c) Q.-A. Chen, H. F. T. Klare, M. Oestreich, *J. Am. Chem. Soc.* **2016**, *138*, 7868–7871; d) Y. Han, S. Zhang, J. He, Y. B. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 7399–7407.

[12] a) L. Ping, D. S. Chung, J. Bouffard, S.-g. Lee, *Chem. Soc. Rev.* **2017**, *46*, 4299–4328; b) J. A. Leitch, Y. Bhonoah, C. G. Frost, *ACS Catal.* **2017**, *7*, 5618–5627; c) Y. Yang, Z. Shi, *Chem. Commun.* **2018**, *54*, 1676–1685; d) C. N. Kona, Y. Nishii, M.

Miura, *Angew. Chem. Int. Ed.* **2019**, *58*, 9856–9860; *Angew. Chem.* **2019**, *131*, 9961–9965; e) I. Choi, A. M. Messinis, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 12534–12540; *Angew. Chem.* **2020**, *132*, 12635–12641.

[13] For some recent examples, see: a) X. Qiu, P. Wang, D. Wang, M. Wang, Y. Yuan, Z. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 1504–1508; *Angew. Chem.* **2019**, *131*, 1518–1522; b) J. Wen, D. Wang, J. Qian, D. Wang, C. Zhu, Y. Zhao, Z. Shi, *Angew. Chem. Int. Ed.* **2019**, *58*, 2078–2082; *Angew. Chem.* **2019**, *131*, 2100–2104; c) K. Fukuda, N. Iwasawa, J. Takaya, *Angew. Chem. Int. Ed.* **2019**, *58*, 2850–2853; *Angew. Chem.* **2019**, *131*, 2876–2879; d) Z. Zhang, T. Roisnel, P. H. Dixneuf, J.-F. Soulé, *Angew. Chem. Int. Ed.* **2019**, *58*, 14110–14114; *Angew. Chem.* **2019**, *131*, 14248–14252.

[14] a) A. J. Borah, Z. Shi, *J. Am. Chem. Soc.* **2018**, *140*, 6062–6066; b) X. Qiu, H. Deng, Y. Zhao, Z. Shi, *Sci. Adv.* **2018**, *4*, eaau6468.

[15] C. A. Salazar, K. N. Flesch, B. E. Haines, P. S. Zhou, D. G. Musaev, S. S. Stahl, *Science* **2020**, *370*, 1454–1460.

[16] H. Kai, J. Ohshita, S. Ohara, N. Nakayama, A. Kunai, I.-S. Lee, Y.-W. Kwak, *J. Organomet. Chem.* **2008**, *693*, 3490–3494.

[17] A. Lu, X. Ji, B. Zhou, Z. Wu, Y. Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 3233–3237; *Angew. Chem.* **2018**, *130*, 3287–3291.

[18] I. Fleming, R. Henning, D. C. Parker, H. E. Plaut, P. E. J. Sanderson, *J. Chem. Soc. Perkin Trans. 1* **1995**, 317–337.

[19] T. W. Lyons, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 4455–4464.

[20] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066–3072; *Angew. Chem.* **2012**, *124*, 3120–3126.

[21] Y. Kim, Y. Park, S. Chang, *ACS Cent. Sci.* **2018**, *4*, 768–775.

[22] L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345.