ChemComm
Chemical Communications

This article can be cited before page numbers have been issued, to do this please use: X. Ji, W. Feng, B. Wan, C. Cheng and Y. Zhang, *Chem. Commun.*, 2020, DOI: 10.1039/D0CC00872A.

ROYAL SOCIETY OF CHEMISTRY
View Article Online
DOI: 10.1039/D0CC00872A

Journal Name

COMMUNICATION

Palladium-Catalyzed Intermolecular C–H Silylation Initiated by Aminopalladation

eceived 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

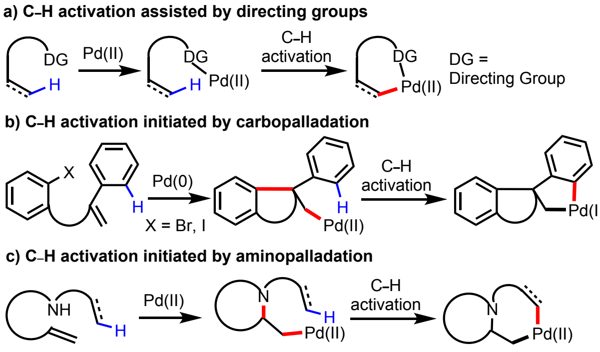
www.rsc.org/

Xiaoming Ji, Feng Wei, Bing Wan, Cang Cheng, Yanghui Zhang*

A Pd(II)-catalyzed intermolecular C–H silylation reaction initiated by aminopalladation has been developed. The C–H bonds were activated by an alkylPd(II) species generated through aminopalladation and then disilylated with hexamethyldisilane to form disilylated indolines as the final products. The reaction provides a new method for the introduction of silyl groups into complex organic molecules.

Transition metal-catalyzed direct C–H functionalization represents a powerful method for the construction of carbon–carbon and carbon–heteroatom bonds.[1] One of the major challenges in C–H functionalization reactions is to activate target C–H bonds selectively. Currently, the most common strategy to achieve site-selective C–H functionalization is to utilize directing groups that usually contain coordinating heteroatoms (Scheme 1a).[2] In the presence of directing groups, only C–H bonds proximal to the directing groups can be activated. Although this strategy has achieved great success, it has drawbacks including preinstallation and removal of directing groups. Furthermore, the strategy is limited to the activation of proximal C–H bonds and restricts the development of C–H functionalization. Notably, a variety of innovative methods have been developed to activate C–H bonds remote from directing groups, including U-shaped template-enabled *meta*/*para*-C–H functionalization,[3] norbornene-enabled *meta*-C–H activation,[4] and Cu or Ru-catalyzed *meta*-C–H acitvation.[5] Furthermore, remote C–H bonds can be activated through intramolecular carbopalladation (Scheme 1b).[6] However, these reactions still require the preinstallation of directing groups. It is highly desirable to develop new C–H activation strategies to expand the scope of C–H functionalization reactions.

C–H functionalization reactions initiated by aminopalladation have been developed by the groups of Yang,[7] Mhaske[8] and Liu.[9] This type of reaction starts with intramolecular aminopalladation to generate σ-alkylpalladium intermediates. The resulting Pd(II) species then active C–H bonds at appropriate positions to form *C*,*C*-palladacycles as the intermediates (Scheme 1c). In this reaction, C–H bonds that are distal to the nitrogen-containing group are activated through cascade reactions. Furthermore, the nitrogen atom is combined into the final product and the removal or conversion of directing groups is avoided. The reaction represents an innovative and atom-economical strategy for C–H activation. In all the current reactions, the resulted *C*,*C*-palladacycles underwent intramolecular cyclization, and intermolecular functionalization reactions with external reagents have not been reported yet.[10]



Scheme 1. Selective C–H functionalization.

Organosilicon compounds are widely applied in organic chemistry,[11] materials science[12] and medicinal chemistry,[13] due to their unique chemical, physical and bioactive properties. Therefore, the development of new strategies for the construction of C–Si bonds is of great significance. Recently, it has been revealed that *C*,*C*-palladacycles react efficiently with hexamethyldisilane and can be disilylated very efficiently.[14] Our group has been interested in the intermolecular functionalization of *C*,*C*-palladacycles obtained

---

School of Chemical Science and Engineering, Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University, 1239 Siping Road, Shanghai, 200092, P. R. China. E-mail: zhangyanghui@tongji.edu.cn;

† Footnotes relating to the title and/or authors should appear here.

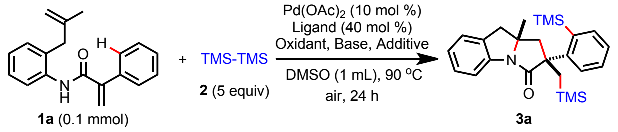
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/D0CC00872A

by C–H activation.[15] Since C–H activation via aminopalladation also form *C,C*-palladacycles as the intermediates, we envisioned that the *C,C*-palladacycles could also be disilylated with hexamethyldisilane. However, in all the current disilylation reactions, aryl halides were used as the substrates. Mechanistically, the reactions were initiated by the oxidative addition of aryl halides to Pd(0) and involved Pd(0)-Pd(0) catalytic cycle. For the aminopalladation-initiated C–H activation reactions, the catalytic cycle starts with Pd(II) and ends up with Pd(0). Therefore, a new catalyst system should be developed and extensive studies should be conducted to find suitable reaction conditions. Herein, we report a new Pd(II)-catalyzed intermolecular C–H silylation reaction initiated aminopalladation. The reaction represents an innovative method for the introduction of silyl groups into complex organic molecules.

We commenced our study by investigating the model reaction of 2-phenylacrylamide **1a** with hexamethyldisilane (**2**) (Table 1). To our delight, the desired disilylation product **3a** was obtained in 7% yield in the presence of $Pd(OAc)_2$ (10 mol%), Ag_2CO_3 (2 equiv), K_2CO_3 (2 equiv) in DMSO at 90 °C under an air atmosphere (entry 1). The reaction did not proceed in toluene or DMF, and only a trace amount of **3a** was obtained in 1,4-dioxane (entries 2-4). Subsequently, other oxidants were investigated, such as AgOAc, AgTFA and O_2 (entries 5-7). The results revealed that AgTFA was the most efficient and **3a** was not observed in the absence of a silver salt. Next, we examined the impact of bases on the reaction, including $NaHCO_3$, KOAc and $KHCO_3$ (entries 8-10). We found that replacing K_2CO_3 with $KHCO_3$ resulted in a slight increase in yield (entry 9). The yield was improved to 40% by using 40 mol % of pyridine as the ligand (entry 11) and further enhanced to 50% by adding 8 equiv of H_2O (entry 12). By increasing the amount of hexamethyldisilane **2** and $KHCO_3$, the yield was improved to 62% and 65%, respectively (entries 13 and 14), and the addition of 20 mol % of 2,5-DMBQ afforded product **3a** in 72% yield (entry 15). Finally, the reaction was more effective in 2 mL of DMSO and a yield of 81% was obtained (entry 16). Under N_2 atmosphere, the yield decreased to 25% (entry 17).

Table 1. Optimization of reaction conditions.



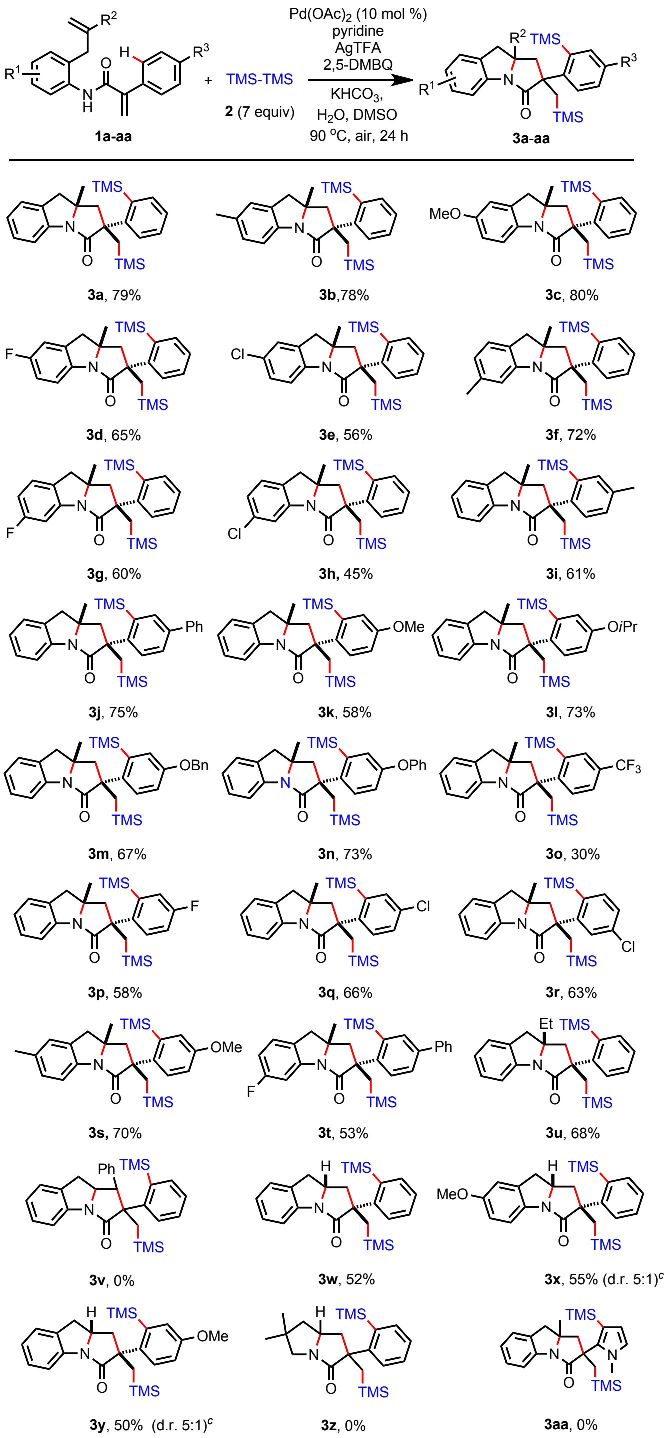
Entry	Ligand	Oxidant (equiv)	Base (equiv)	Solvent	Yield (%)[a]
1	/	Ag_2CO_3 (2)	K_2CO_3 (2)	DMSO	7
2	/	Ag_2CO_3 (2)	K_2CO_3 (2)	Toluene	0
3	/	Ag_2CO_3 (2)	K_2CO_3 (2)	Dioxane	trace
4	/	Ag_2CO_3 (2)	K_2CO_3 (2)	DMF	0
5	/	AgOAc (2)	K_2CO_3 (2)	DMSO	6
6	/	AgTFA (2)	K_2CO_3 (2)	DMSO	20
7	/	O_2	K_2CO_3 (2)	DMSO	0
8	/	AgTFA (2)	KOAc (2)	DMSO	6
9	/	AgTFA (2)	$KHCO_3$ (2)	DMSO	25
10	/	AgTFA (2)	$NaHCO_3$ (2)	DMSO	7
11	Pyridine	AgTFA (2)	$KHCO_3$ (2)	DMSO	40
12[b]	Pyridine	AgTFA (2)	$KHCO_3$ (2)	DMSO	50
13[b,c]	Pyridine	AgTFA (2)	$KHCO_3$ (3)	DMSO	62
14[b,c]	Pyridine	AgTFA (2)	$KHCO_3$ (4)	DMSO	65
15[b,c,d]	Pyridine	AgTFA (2)	$KHCO_3$ (4)	DMSO	72
16[b,c,d,e]	Pyridine	AgTFA (2)	$KHCO_3$ (4)	DMSO	81(79)[f]
17[b,c,d,e,g]	Pyridine	AgTFA (2)	$KHCO_3$ (4)	DMSO	25

[a] The yields were determined by ^1H NMR analysis of the crude reaction mixture using $CHCl_2CHCl_2$ as the internal standard. [b] H_2O (8 equiv) was added. [c] TMS-TMS (7 equiv). [d] 20 mol % of 2, 5-DMBQ was added. [e] DMSO (2 mL). [f] Isolated yield. [g] Under N_2 atmosphere. 2,5-DMBQ = 2,5-dimethyl-*p*-benzoquinone, TMS-TMS = 1,1,1,2,2,2-hexamethyldisilane.

Having developed an efficient protocol for Pd(II)-catalyzed oxidative double cyclization/disilylation reaction, we next investigated the substrate scope of this transformation (Table 2). First, we examined the performance of acrylamides bearing different substituents on the benzene rings of the anilines. The substrates bearing a 4-methyl or methoxy group were suitable (**3b** and **3c**), and the fluoro and chloro groups were tolerated under the standard conditions (**3d** and **3e**). In these reactions, the corresponding disilylated products were formed in moderate or high yields. 5-Substituted substrates by methyl, fluoro or chloro were also reactive (**3f**-**3h**), and the reactions were slightly less effective than those of the corresponding 4-substituted substrates. The structure of **3h** was unambiguously confirmed by single-crystal X-ray structural analysis.[16] The methyl group is *cis* to the (trimethylsilyl)methyl group. Next, the compatibility of functionalities on the other phenyl group was examined. The substrates containing a methyl or phenyl group at *para*-positions underwent the domino reaction smoothly (**3i** and **3j**). The phenoxy group and a range of alkoxy groups were compatible, and moderate yields were obtained (**3k**-**3n**). The presence of electron-withdrawing trifluoromethyl group led to a low yield (**3o**). Fluoro and chloro groups were well tolerated, and the reactions gave the desired products in moderate yield (**3p**-**3r**). The reaction selectively took place at the less hindered position for *meta*-substituted **1r**. The substrates bearing substituents on both of the benzene rings could also be disilylated with hexamethyldisilane (**3s** and **3t**). The impact of substituents on the allyl groups was also examined. Ethyl-substituted alkene **1u** was disilylated in 68% yield (**3u**). The reaction did not occur in the presence of a terminal phenyl group (**3v**). It should be mentioned that unsubstituted alkene (**1w-1y**) also underwent the disilylation reaction (**3w-3y**), and the potential side products from β-hydride elimination were not observed. The NOESY spectrum of **3w** indicates that the α-proton of the amide group is *cis* to the (trimethylsilyl)methyl group. An alkylamine was not compatible and failed to give the desired product (**3z**). The substrate containing a pyrrole ring was not reactive and the starting material was recovered (**3aa**).

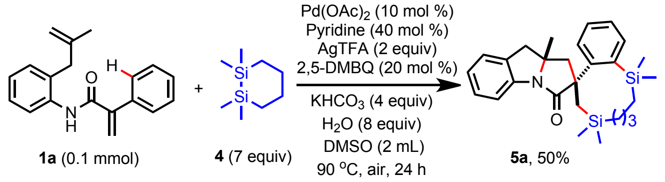
View Article Online
DOI: 10.1039/D0CC00872A

Table 2. Substrate scope of the disilylation reaction.[a,b]

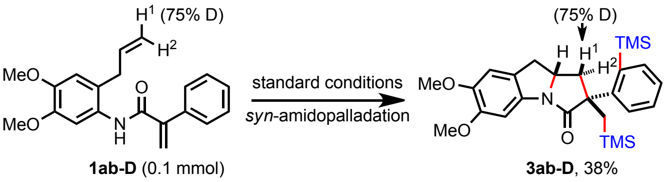


[a] Reaction conditions: 2-phenylacrylamide **1** (0.1 mmol), TMS-TMS **2** (7 equiv), $Pd(OAc)_2$ (10 mol %), pyridine (40 mol %), AgTFA (2 equiv), $KHCO_3$ (4 equiv), 2,5-DMBQ (20 mol %), H_2O (8 equiv) in DMSO (2 mL) at 90 °C for 24 h. [b] Yields of the isolated products. [c] Ratio determined by ^1H NMR analysis; the major diastereomer is depicted.

Notably, a cyclic disilane was also an effective disilylating reagent. As shown in Scheme 2, **1a** could react with 1,1,2,2-tetramethyl-1,2-disilacyclohexane (**4**) to form ten-membered cyclic product **5a**. The reaction provides an efficient method for the construction of medium-sized cyclic compounds containing silicons.

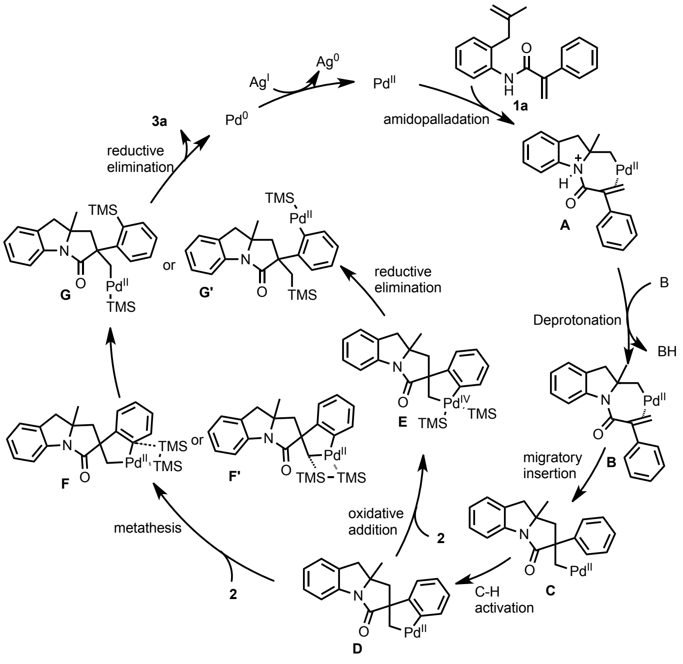


Scheme 2. Disilylation Reaction with a Cyclic Disilane.



Scheme 3. Deuterium-Labeling Experiment on the Determination of Stereochemistry in the Aminopalladation Step.

Aminopalladtion may proceed via a *syn*- or *anti*-pathway.[17] To determine the stereochemical course of the aminopalladation step in the disilylation reaction, we prepared substrate **3ab-D** with 75% deuterium incorporated into the H^1. Under the standard conditions, product **3ab-D** was obtained with 75% deuterium incorporated into the H^1 positions, which indicates a *syn*-amidopalladation pathway (Scheme 3).



Scheme 4. Proposed Mechanism for the Disilylation Reaction.

Based on the above experimental results and previous reports,[9,13] we proposed a tentative mechanism for the Pd(II)-catalyzed oxidative double cyclization/disilylation reaction. As

View Article Online
DOI: 10.1039/D0CC00872A

shown in Scheme 4, substrate **1a** undergoes intramolecular aminopalladation to form *σ*-alkylpalladium intermediate **A**, in which the double bond might coordinate to the alkyl-Pd(II) species. The N–H deprotonation by a base generates intermediate **B**. The subsequent intramolecular olefin insertion yields a second alkyl-Pd(II) intermediate **C**. The resulting Pd(II) cleaves an aryl C–H bond to give palladacycle **D**. **D** can react with hexamethyldisilane via either an oxidative addition/reductive elimination or σ-bond metathesis pathway.[18] In these steps, an alkyl-Pd(II) or aryl-Pd(II) intermediate may be formed. Finally, the reductive elimination of **G** or **G'** generates product **3a** and releases Pd(0) species. The catalytic cycle is completed by the regeneration of Pd(II) from Pd(0) with Ag(I) as the oxidant.

In conclusion, we have developed a new Pd(II)-catalyzed intermolecular C–H silylation reaction initiated by aminopalladation. The reaction formed disilylated indolines as the final products in moderate to good yields, providing a novel and straightforward method for the introduction of silyl groups into complex organic molecules.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ The work was supported by the National Natural Science Foundation of China (No.216721626) and Shanghai Science and Technology Commission (14DZ2261100).

1 (a) J.-Q. Yu and Z. Shi, *C–H Activation*, Springer, Berlin, 2010; (b) Y. Zhang, G. Shi and J.-Q. Yu, in *Comprehensive Organic Synthesis*, ed. P. Knochel and G. A. Molander, Elsevier, Oxford, 2014, 2nd, vol. 3, pp 1101-1209; (c) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi and A. Lei, *Chem. Rev.*, 2015, **115**, 12138; (d) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900; (e) G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48**, 1007; (f) R. Shang, L. Ilies and E. Nakamura, *Chem. Rev.*, 2017, **117**, 9086; (g) M. Moselage, J. Li and L. Ackermann, *ACS Catal*., 2016, **6**, 498; (h) O. Baudoin, *Acc. Chem. Res.,* 2017, **50**, 1114.

2 (a) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (b) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res*., 2012, **45**, 788; (c) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front*., 2015, **2**, 1107.

3 (a) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518; (b) S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera and D. Maiti, *J. Am. Chem. Soc*., 2015, **137**, 11888; (c) A. Dey, S. K. Sinha, T. K. Achar and D. Maiti, *Angew. Chem.*, *Int. Ed.*, 2019, **58**, 10820; (d) L. Zhang, C. Zhao, Y. Liu, J. Xu, X. Xu and Z. Jin, *Angew. Chem., Int. Ed.,* 2017, **56**, 12245; (e) Li, S. H. Wang, Y. Weng and G. Li, *Angew. Chem.*, *Int. Ed*., 2019, **58**, 18502.

4 (a) J. Wang and G. Dong, *Chem. Rev*., 2019, **119**, 7478; (b) H.-G. Cheng, S. Chen, R. Chen and Q. Zhou, *Angew. Chem*., *Int. Ed*., 2019, **58**, 5832; (c) X.-C. Wang, W. Gong, L.-Z. Fang, R.-Y. Zhu, S. Li, K. M. Engle and J.-Q. Yu, *Nature*, 2015, **519***,* 334; (d) Z. Dong, J. Wang and G. Dong, *J. Am. Chem. Soc*., 2015, **137**, 5887; (e) J. Han, L. Zhang, Y. Zhu, Y. Zheng, X. Chen, Z.-B. Huang, D.-Q. Shi and Y. Zhao, *Chem. Commun*., 2016, **52**, 6903.

5 (a) R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593; (b) J. A. Leitch and C. G. Frost, *Chem. Soc. Rev.*, 2017, **46**, 7145; (c) O. Saidi, J. Marafie, A. E. W. Ledger, P. M. Liu, M. F. Mahon, G. Kociok-Kohn, M. K. Whittlesey and C. G. Frost, *J. Am. Chem. Soc*., 2011, **133**, 19298; (d) N. Hofmann and L. Ackermann, *J. Am. Chem. Soc*., 2013, **135**, 5877.

6 (a) V. P. Mehta and J.-A. García-López, *ChemCatChem*, 2017, **9**, 1149; (b) J. Ye, Z. Shi, T. Sperger, Y. Yasukawa, C. Kingston, F. Schoenebeck and M. Lautens, *Nat. Chem*., 2017, **9**, 361; (c) Y. Hyung, *Angew. Chem*., *Int. Ed*., 2017, **56**, 10920; (d) H. Zheng, Y. Zhu and Y. Shi, *Angew. Chem*., *Int. Ed*., 2014, **53**, 11280; (e) T. Piou, L. Neuville and J. Zhu, *Angew. Chem*., *Int. Ed*., 2012, **51**, 11561; (f) M. Wang, X. Zhang, Y.-X. Zhuang, Y.-H. Xu and T.-P. Loh, *J. Am. Chem. Soc*., 2015, **137**, 1341; (g) M. Pérez-Gómez and J.-A. García-López, *Angew. Chem*., *Int. Ed*., 2016, **55**, 14389; (h) X. Luo, Y. Xu, G. Xiao, W. Liu, C. Qian, G. Deng, J. Song, Y. Liang and C. Yang, *Org. Lett*., 2018, **20**, 2997; (i) P. Li, Q. Li, H. Weng, J. Diao, H. Yao and A. Lin, *Org. Lett*., 2019, **21**, 6765.

7 (a) K.-T. Yip and D. Yang, *Org. Lett.,* 2011, **13**, 2134; (b) W. Du, Q. Gu, Z. Li and D. Yang, *J. Am. Chem. Soc*., 2015, **137**, 1130.

8 D. N. Garad and S. B. Mhaske, *Org. Lett*., 2016, **18**, 3862.

9 W. Zhang, P. Chen and G. Liu, *Angew. Chem*., *Int. Ed*., 2017, **56**, 5336.

10 Although σ-alkylpalladium generated by aminopalladation could activate C–H bonds of simple arenes intermolecularly, these have been found to preferentially cleave the C–H bonds of an external arene substrate, rather than a C–H bond tethered to the nitrogen atom of the substrate. C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc*., 2009, **131**, 9488.

11 (a) *Chemistry of Organosilicon Compounds*, vol. 3 (Eds.: Z. Rappoport and Y. Apeloig), Wiley-VCH, New York, 2001; (b) *Silicon in Organic*, *Organometallic and Polymer Chemistry* (Eds.: M. A. Brook), Wiley, New York, 2000.

12 (a) *Silicon Polymers* (Eds.: A. M. Muzafarov), Springer, Heidelberg, 2011; (b) *Silicon-Containing Polymers* (Eds.: R. G. Jones, W. Ando and J. Chojnowski), Kluwer Academic, Dordrecht, 2000.

13 (a) M. Mortensen, R. Husmann, E. Veri and C. Bolm, *Chem. Soc. Rev*., 2009, **38**, 1002; (b) A. K. Franz and S. O. Wilson, *J. Med. Chem*., 2013, **56**, 388; (c) S. M. Sieburth, T. Nittoli, A. M. Mutahi, L. Guo, *Angew. Chem*., *Int. Ed*., 1998, **37**, 812.

14 (a) A. Lu, X. Ji, B. Zhou, Z. Wu and Y. Zhang, *Angew. Chem.*, *Int. Ed*., 2018, **57**, 3233; (b) W. Lv, S. Wen, J. Yu and G. Cheng, *Org. Lett*., 2018, **20**, 4984; (c) W. Lv, J. Yu, B. Ge, S. Wen and G. Cheng, *J. Org. Chem*., 2018, **83**, 12683; (d) Y. Xu, X. Liu, W. Chen, G. Deng, Y. Liang and Y. Yang, *J. Org. Chem*., 2018, **83**, 13930; (e) W. Li, W. Chen, B. Zhou, Y. Xu, G. Deng, Y. Liang and Y. Yang, *Org. Lett*., 2019, **21**, 2718.

15 (a) D. Chen, G. Shi, H. Jiang, Y. Zhang and Y. Zhang, *Org. Lett*., 2016, **18**, 2130; (b) G. Shi, D. Chen, H. Jiang, Y. Zhang and Y. Zhang, *Org. Lett*., 2016, **18**, 2958; (c) C. Shao, Z. Wu, X. Ji, B. Zhou and Y. Zhang, *Chem. Commun*., 2017, **53**, 10429; (d) Z. Wu, D. Ma, B. Zhou, X. Ji, X. Ma, X. Wang and Y. Zhang, *Angew. Chem*., *Int. Ed*., 2017, **56**, 12288; (e) B. Zhou, Z., D. Ma, X. Ji and Y. Zhang, *Org. Lett*., 2018, **20**, 6440; (f) B. Zhou, A. Lu, C. Shao, X. Liang and Y. Zhang, *Chem. Commun*., 2018, **54**, 10598.

16 CCDC 2007063 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

17 P. Kočovský and J.-E. Bäckvall, *Chem. Eur. J.*, 2015, **21**, 36.

18 (a) T. Matsuda and H. Kirikae, *Organometallics*, 2011, **30**, 3923. (b) A. Deb, S. Singh, K. Seth, S. Pimparkar, B. Bhaskararao, S. Guin, R. B. Sunoj and D. Maiti, *ACS Catal.*, 2017, **7**, 8171.