Synthetic Methods

DOI: 10.1002/anie.201100360

ortho-Selective Nucleophilic Addition of Primary Amines to Silylbenzynes: Synthesis of 2-Silylanilines**

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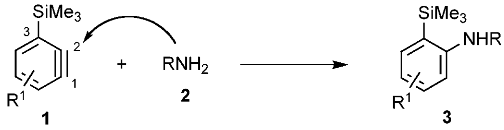
One of the most notable discoveries in aromatic chemistry was that of benzyne intermediates.[1,2] This achievement has opened the way for designing new molecules as a result of the unique and extraordinary reactivity of benzynes. Among the various reactions of benzynes, nucleophilic addition has been one of the most important and widely used in modern organic synthesis.[3,4] However, the regioselectivity of the nucleophilic addition to unsymmetrically substituted benzynes has been a longstanding challenge. High selectivity has been limited to the reaction of benzynes having chlorine or fluorine,[5a,b] alkoxy,[5b,c] alkylamino,[5a] phenyl,[5f] and bulky groups[5d,e] at the C3 position, in which the nucleophiles react at the C1 position to give the *meta*-disubstituted arenes. These results are thought to result from the inductive electron-withdrawing effect and/or steric effect of the substituents.[6] On the contrary, the inductive electron-donating effect of the substituent of the benzyne may prefer the nucleophilic addition at its *ortho* position. However, the repulsive steric interaction between the substituent and the nucleophile significantly hampers this reaction, and therefore, the preferential preparation of the *ortho*-disubstituted arenes has seldom been achieved.[3] The only example of the *ortho*-selective nucleophilic addition was reported by Meyers and co-workers, which was attained by the coordinative interaction of organolithium compounds and 3-oxazolinylbenzyne, while similar addition reactions of the dialkylcuprates with the same benzyne took place at the *meta* position.[4a]

Our research group has recently reported that a silyl group attached at the C3 position of benzynes effectively controlled the regiochemistry of their Diels–Alder reaction with substituted furans to give adducts possessing the silyl group and the substituents of the furans in a remote position on the ring.[7] Because the silyl groups on aromatic compounds are stable under ordinary conditions and can be replaced with various functional groups including halo, hydroxy, aryl, and alkyl groups,[8] the silyl-group-control strategy should be widely applicable in providing a solution for the problem of controlling the regioselectivity of various reactions of substituted benzynes. Herein, we report the first *ortho*-selective nucleophilic addition reaction of amines to 3-substituted benzynes. Despite a large trimethylsilyl group, primary amines **2** attacked the C2 position of 3-silylbenzynes **1**, which are generated under mild reaction conditions using a fluoride ion, to produce 2-silylanilines **3** (Scheme 1).

The 3-(trimethylsilyl)benzynes **1** have been generated from 2-bromo-6-(trimethylsilyl)phenyl triflates **4** using *n*BuLi in THF or toluene at −78 °C. Besides our Diels–Alder reactions,[7] **1** has been applied to [3+2] cycloaddition reactions[9] and nucleophilic addition reactions of carbanions.[10] These reactions also took place regioselectively probably as a result of the steric and/or electronic nature of the silyl group. In particular, the latter addition reactions proceeded preferentially at the *meta* position of the silyl group. According to these precedents, we began this project by carrying out the reaction of 5-methyl-3-(trimethylsilyl)benzyne **1a**, generated from 2-bromo-4-methyl-6-(trimethylsilyl)phenyl triflate **4a** using *n*BuLi, with *n*-butylamine **2a** in THF at −78 °C. The reaction provided the *meta*-silylaniline derivative **5a** exclusively in 45 % yield (Table 1, entry 1). On the other hand, we found that **1a**, generated from 2,6-bis(trimethylsilyl)-4-methylphenyl triflate **6a** using Bu_4NF (TBAF), reacted with **2a** at −40 °C to give the *ortho*-silylaniline derivative **3a** preferentially (Table 1, entry 5), although there must have been significant steric repulsion between the bulky trimethylsilyl group and the approaching **2a**. This result was in stark contrast to similar addition reactions of **2a** with 3-isopropyl-



Scheme 1. *ortho*-Selective nucleophilic addition of primary amines **2** to silylbenzynes **1**.

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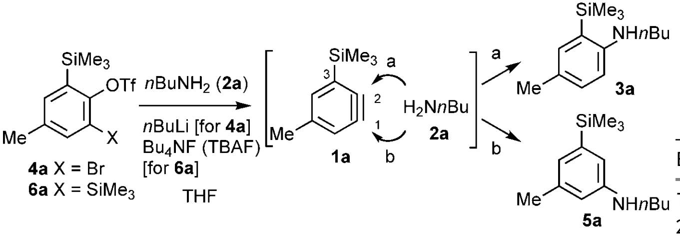
[**] This work was supported by Grants-in-Aid for Scientific Research (KAKENHI; no. 21790020) and a Grant-in-Aid for the Global COE Program from the MEXT (Japan). T.I. also thanks the Daicel Chemical Industry award in Synthetic Organic Chemistry (Japan).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201100360.

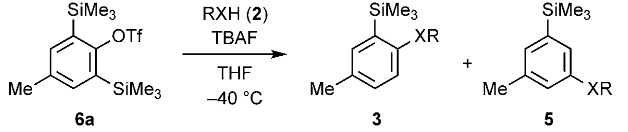
Table 1: Nucleophilic addition of butylamine **2a** to the 3-(trimethylsilyl)benzyne **1a**, generated from the precursors (**4a** or **6a**).



Entry	Precursor	*T* [°C]	*t* [h]	**3a**/**5a**[a]	Yield [%][b]
1[c]	**4a**	−78	0.5	1.0:>50	45
2[d]	**6a**	60	0.5	2.0:1.0	91
3[d]	**6a**	25	0.5	2.7:1.0	89
4[d]	**6a**	0	1.0	3.7:1.0	88
5[d]	**6a**	−40	5	7.7:1.0	92
6[d,e]	**6a**	−40	48	6.5:1.0	17[f]
7[d,g]	**6a**	−40	48	8.6:1.0	16[f]
8[d]	**6a**	−78	12	10:1.0	31[f]

[a] Determined by ^{1}H NMR analysis (500 MHz) of a crude reaction mixture and also by the yield of isolated product. [b] Total yield of isolated **3a** and **5a**. [c] Reaction conditions: **4a** (1.0 equiv), **2a** (3.0 equiv), *n*BuLi (5.0 equiv) at −78 °C in THF (0.20 M) under nitrogen. [d] Reaction conditions: **6a** (1.0 equiv), **2a** (3.0 equiv), TBAF (2.0 equiv) in THF (0.10 M) under nitrogen. [e] KF and 18-crown-6 were used instead of TBAF. [f] Total yield of **3a** and **5a** determined by ^{1}H NMR analysis. [g] CsF in MeCN was used instead of TBAF in THF. Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

Table 2: Nucleophilic addition of various nucleophiles **2** to the 3-(trimethylsilyl)benzyne **1a**, generated from **6a**.[a]



Entry	**2**, RX	*t* [h]	Products	**3**/**5**[b]	Yield [%][c]
1	**2b**, H_2N	9	**3b**, **5b**	12:1.0	63 (79)[d]
2	**2c**, MeNH	3	**3c**, **5c**	6.2:1.0	62
3	**2d**, $nC_{10}H_{21}NH$	7	**3d**, **5d**	7.6:1.0	86
4	**2e**, $CH_2{=}CHCH_2NH$	3	**3e**, **5e**	6.6:1.0	83
5	**2f**, $PhCH_2NH$	3	**3f**, **5f**	7.3:1.0	73
6	**2g**, *t*BuNH	3	**3g**, **5g**	1.0:>50	78
7	**2h**, 4-MeC_6H_4NH	6.5	**3h**, **5h**	1.0:1.6	78
8	**2i**, Et_2N	12	**3i**, **5i**	1.0:1.2	80
9[e]	**2j**, EtO	8.5	**3j**, **5j**	10:1.0	41

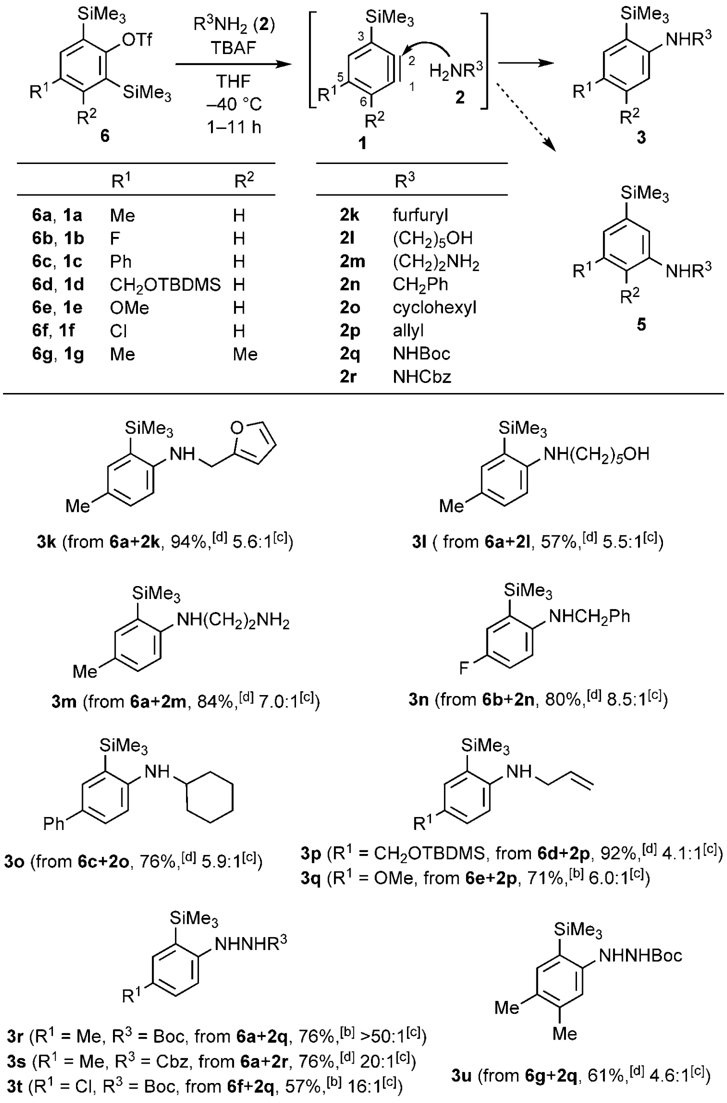
[a] Reaction conditions: **6a** (1.0 equiv), **2** (3.0 equiv), TBAF (2.0 equiv) in THF (0.10 M) under nitrogen. [b] Determined by ^{1}H NMR analysis (500 MHz) for a crude reaction mixture and also by the yield of isolated product. [c] Total yield of isolated **3** and **5**. [d] Yield getermined by GC. [e] 4.0 equiv of TBAF was used.

benzyne **7** that exhibited high *meta* selectivity,[11] although the steric size of the isopropyl group (A value = 2.2) is slightly smaller than that of the trimethylsilyl group (A value = 2.5).[12] The *ortho* regioselectivity was higher at lower temperature, and led us to suggest that this reaction was kinetically controlled (Table 1, entries 2–5 and 8). The reaction at around −40 °C seemed to be the best conditions and gave **3a** in 81 % yield along with its regioisomer **5a** (11 %; Table 1, entry 5). The conversion of the reaction dropped down to about 30 % at −78 °C even after 12 hours (Table 1, entry 8). Notably, the use of TBAF was the key in carrying out the reaction effectively at such a low reaction temperature like −40 °C. This was because the use of common fluoride sources, such as KF/18-crown-6 and CsF, for the generation of **1a** from **6a**, resulted in very slow reactions probably owing to their poor solubility (Table 1, entries 5–7).

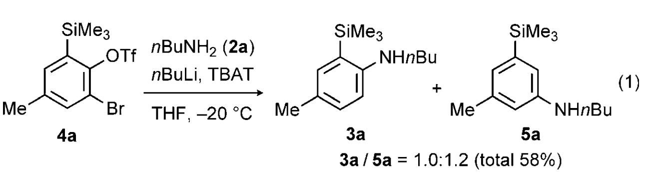
Under the optimal reaction conditions (Table 1, entry 5), various nucleophiles **2** were subjected to the regioselective addition reaction with the silylbenzyne **1a** (Table 2). The reactions of various primary amines **2c**–**f** selectively produced 2-silylanilines **3c**–**f** in good yields (Table 2, entries 2–5).[13,14] Notably, the smallest nucleophile, ammonia **2b**, exhibited even higher regioselectivity and gave the silylated aniline **3b** (Table 2, entry 1).[15] The diarylation product was not observed in this reaction probably because the bulky trimethylsilyl group interfered with the second addition reaction of **3b** with another molecule of **1a**. To the best of our knowledge, this is the first example of the addition of ammonia to benzyne without using NH_2^-.[16] Interestingly, the less nucleophilic ethanol **2j** was also available to produce the ethyl 2-silylphenyl ether **3j** with high selectivity (Table 2, entry 9). On the other hand, the adducts of an aromatic amine **2h** (Table 2, entry 7) and a secondary amine **2i** (Table 2, entry 8) were obtained with low selectivities. The reaction of *tert*-butylamine **2g** exclusively gave the *meta*-addition product **5g** owing to its bulkiness (Table 2, entry 6).

The versatile applicability of the *ortho* selectivity was further demonstrated with the successful addition of various functionalized amines **2k**–**r** to 3-silylbenzynes **1** (Scheme 2). The exclusive N arylation of furfurylamine **2k** with **1a** took place and gave **3k**, with the furan framework intact.[17] Notably, the amino alcohol **2l** and the diamine **2m** reacted with **1a** in a one-to-one ratio with high fidelity and provided **3l** and **3m**, respectively. The *ortho* selectivity has not been significantly affected by substituents such as fluoro (**1b**, generated from **6b**), phenyl (**1c**, from **6c**), methoxy (**1e**, from **6e**) and chloro (**1f**, from **6f**) groups at the C5 position of **1**. Interestingly the OTBDMS group of the product **3p** was tolerant under the reaction conditions when using TBAF at −40 °C.[18] The nucleophilic addition reaction of the *tert*-butyl carbazate **2q** and the benzyl carbazate **2r** exclusively gave the amination products (**3r**–**u**) instead of the amidation products which were selectively obtained by the palladium-[19a] and copper-catalyzed[19b] coupling reactions. Moreover, the *ortho* regioselectivities of the reactions using the carbazates (**2q** and **2r**) were higher than those of the primary amines (**2a**–**f** and **2k**–**p**). Although two kinds of benzynes could have been generated from the unsymmetrical benzyne precursor **6g**, 5,6-dimethyl-3-(trimethylsilyl)benzyne **1g** was selectively generated to give **3u**. This result is worth noting because the fluoride ion preferentially attacked at the congested trimethylsilyl group of **6g**.

It was of interest to discover what kind of effects determined the regioselectivity of the nucleophilic addition of **2** to **1**. In the presence of 2 equivalents of a fluoride source, tetrabutylammonium triphenyldifluorosilicate (TBAT),[20] the reaction of **2a** and **1a**, generated from **4a** using *n*BuLi, gave a significant amount of **3a** along with **5a** [Eq. (1)]. This result



Scheme 2. Nucleophilic addition of amines **2** to 3-(trimethylsilyl)benzynes **1**, generated from the precursors **6**.[a] [a] Reaction Conditions: **6** (1.0 equiv), **2** (3.0 equiv), TBAF (2.0 equiv) in THF (0.10 M) under nitrogen. [b] Yield of isolated **3**. [c] Ratio of **3** to **5** determined by ^{1}H NMR analysis (500 MHz) for a crude reaction mixture and also by the yield of isolated product. [d] Total yield of isolated **3** and **5**. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, TBDMS = *tert*-butyldimethylsilyl.



suggested that the fluoride ion played an important role in the *ortho*-selective nucleophilic addition reaction.

Plausible mechanisms of these *ortho*-selective nucleophilic reactions are as follows: The inductively electron-donating effect of the silicon causes the benzyne's triple bond to become polarized, in which the C2 position has a positive electric charge.[9] Moreover, in the presence of the fluoride ion that coordinates to the silicon center to generate a silicate-like complex **8**, the magnitude of the charge could have been increased. For nucleophilic attack at the benzyne compounds, steric factors favor *meta* selectivity, which have been observed in the reactions of 3-silylbenzynes **1**, generated from the precursors with either *n*BuLi (this experiment) or *sec*BuLi (Schlosser and co-workers).[10] This enhancement of the polarization was also demonstrated by the DFT calculations [B3LYP/6-31G(d)][21] of the natural atomic charge of **1h** and **8** (Figure 1). The amines **2** would preferentially approach the more positive C2 carbon atom to give the *ortho*-adducts **3**, although the steric demand of the pentavalent silicate complex **8** might be larger than that of the tetravalent silicon complex **1h**. In either case, the electronic effect should override the steric disadvantage.

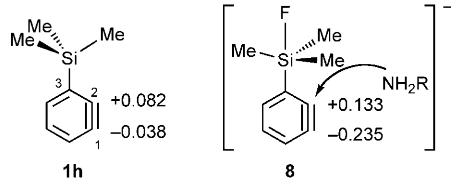


Figure 1. Natural atomic charge of the tetravalent silylbenzyne **1h** and the pentavalent silylbenzyne **8** calculated with the B3LYP/6-31G(d) method.

In summary, the rare *ortho* selectivity of the nucleophilic addition of primary amines **2** to 3-silylbenzynes **1** has been accomplished as a result of the strong inductive effect of the silicate, coordinated by a fluoride ion, to give 2-silylaniline derivatives **3**. Therefore, the use of the 3-silylbenzynes could offer a solution to the problematic regioselectivity issue in benzyne chemistry. Exploring the detailed reaction mechanism and studying the application of this method are in progress.

Experimental Section

General procedure for the *ortho*-selective nucleophilic addition reactions of primary amines **2** to 3-(trimethylsilyl)benzynes **1** (Table 1, Table 2, Scheme 2): An oven-dried flask was charged with **6** (1.0 equiv) and capped with a rubber septum and then evacuated and back-filled with nitrogen. Anhydrous THF (0.10 M) was added using a syringe and the mixture cooled to −40 °C. After 5 min, **2** (3.0 equiv) and TBAF (1.0 M THF solution, 2.0 equiv) were added in this order, and the reaction mixture was stirred at −40 °C for a given reaction time. The mixture was filtered through a short pad of silica gel. The filtrate was concentrated under reduced pressure and further purified by flash column chromatography on silica gel (hexanes/ethyl acetate or dichloromethane/methanol) to give the 2-(trimethylsilyl)-aniline derivative **3**.

Received: January 15, 2011
Revised: March 28, 2011
Published online: May 9, 2011

Please note: Minor changes have been made to this manuscript since its publication in *Angewandte Chemie* Early View. The Editor.

Keywords: amines · benzynes · nucleophilic addition · regioselective reactions · silicon

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[1] For selected early papers on experimental proof of benzynes, see: a) G. Wittig, *Naturwissenschaften* **1942**, *30*, 696–703; b) J. D. Roberts, H. E. Simmons, L. A. Carlsmith, C. W. Vaughan, *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291; c) R. Huisgen, H. Rist, *Naturwissenschaften* **1954**, *41*, 358–359.

[2] For recent reviews on benzynes, see: a) H. Pellissier, M. Santelli, *Tetrahedron* **2003**, *59*, 701–730; b) H. H. Wenk, M. Winkler, W. Sander, *Angew. Chem.* **2003**, *115*, 518–546; *Angew. Chem. Int. Ed.* **2003**, *42*, 502–528; c) A. M. Dyke, A. J. Hester, G. C. Lloyd-Jones, *Synthesis* **2006**, 4093–4112; d) D. Peña, D. Pérez, E. Guitián, *Heterocycles* **2007**, *74*, 89–100; e) R. Sanz, *Org. Prep. Proced. Int.* **2008**, *40*, 215–291.

[3] For a review on nucleophilic additions to benzynes, see: *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B. M. Trost, I. Fleming, M. F. Semmelhack), Pergamon, Oxford, **1992**, pp. 483–515.

[4] For selected examples of nucleophilic addition to benzynes, see: a) P. D. Pansegrau, W. F. Rieker, A. I. Meyers, *J. Am. Chem. Soc.* **1988**, *110*, 7178–7184; b) M. Beller, C. Breindl, T. H. Riermeier, A. Tillack, *J. Org. Chem.* **2001**, *66*, 1403–1412; c) H. Yoshida, S. Sugiura, A. Kunai, *Org. Lett.* **2002**, *4*, 2767–2769; d) Z. Liu, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 3198–3209; e) Y. K. Ramtohul, A. Chartrand, *Org. Lett.* **2007**, *9*, 1029–1032; f) S. M. Bronner, K. B. Bahnck, N. K. Garg, *Org. Lett.* **2009**, *11*, 1007–1010.

[5] a) G. B. R. de Graaff, H. J. Hertog, W. C. Melger, *Tetrahedron Lett.* **1965**, *6*, 963–968; b) E. R. Biehl, E. Nieh, K. C. Hsu, *J. Org. Chem.* **1969**, *34*, 3595–3599; c) A. Razzuk, E. R. Biehl, *J. Org. Chem.* **1987**, *52*, 2619–2622; d) H. Hart, T. Ghosh, *Tetrahedron Lett.* **1988**, *29*, 881–884; e) T. Ghosh, H. Hart, *J. Org. Chem.* **1988**, *53*, 3555–3558; f) P. P. Wickham, K. H. Hazen, H. Guo, G. Jones, K. H. Reuter, W. J. Scott, *J. Org. Chem.* **1991**, *56*, 2045–2050.

[6] During the preparation of this manuscript, an impressive paper was published that explained the origin of the regioselectivity in the nucleophilic addition to substituted benzynes, see: a) P. H.-Y. Cheong, R. S. Paton, S. M. Bronner, G-Y. J. Im, N. K. Grag, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 1267–1269; b) G.-Y. J. Im, S. M. Bronner, A. E. Goetz, R. S. Paton, P. H.-Y. Cheong, K. N. Houk, N. K. Grag, *J. Am. Chem. Soc.* **2010**, *132*, 17933–17944.

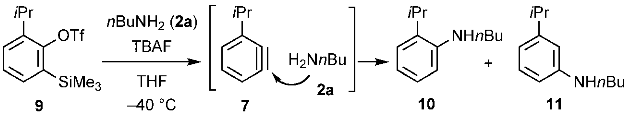
[7] S. Akai, T. Ikawa, S. Takayanagi, Y. Morikawa, S. Mohri, M. Tsubakiyama, M. Egi, Y. Wada, Y. Kita, *Angew. Chem.* **2008**, *120*, 7787–7790; *Angew. Chem. Int. Ed.* **2008**, *47*, 7673–7676.

[8] a) E. W. Colvin in *The Chemistry of Organic Silicon Compounds*, *Part 2* (Eds.: Z. Rappoport, Y. Apeloig, Wiley, Chichester, **1998**, pp. 1667–1685; b) T. Hiyama, E. Shirakawa in *Handbook of Organopalladium Chemistry for Organic Synthesis*, *Vol. 1* (Ed.: E.-i. Negishi), Wiley, Hoboken, **2002**, pp. 285–309; c) S. E. Denmark, R. F. Sweis in *Metal-Catalyzed Cross-Coupling Reactions*, *2nd ed.*, *Vol. 1* (Eds.: A. De Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp. 163–216; d) T. H. Chan, D. Wang, *Chem. Rev.* **1992**, *92*, 995–1006; e) G. R. Jones, Y. Landais, *Tetrahedron* **1996**, *52*, 7599–7662.

[9] Suzuki reported the regioselective [3+2] cycloaddition reactions between 3-silylbenzynes, generated from the 2-bromo-6-silylphenyl triflates **4** using *n*BuLi, and nitrones, see: T. Matsumoto, T. Sohma, S. Hatazaki, K. Suzuki, *Synlett* **1993**, 843–846.

[10] Schlosser and co-workers reported the *meta*-selective nucleophilic addition reaction to the 3-silylbenzyne, see: a) C. Heiss, F. Cottet, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 5236–5241; b) C. Heiss, F. Leroux, M. Schlosser, *Eur. J. Org. Chem.* **2005**, 5242–5247; c) V. Diemer, M. Begaud, F. R. Leroux, F. Colobert, *Eur. J. Org. Chem.* **2011**, 341–354.

[11] The nucleophilic addition of **2a** to 3-isopropylbenzyne **7**, generated from **9**, preferentially gave the 3-isopropylaniline derivative **11** with high selectivity.



10 / **11** = 1.0:5.0 (total 75%)

[12] For the A value, see: E. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry*, University Science books, Sausalito, CA, **2005**, p. 104.

[13] The synthesis of 2-silylanilines from benzynes was reported by the aminosilylation using aminosilanes; however, it produced only tertiary anilines: see: H. Yoshida, T. Minabe, J. Ohshita, A. Kunai, *Chem. Commun.* **2005**, 3454–3456.

[14] Silicon-containing biologically active compounds are becoming more important, see: a) S. Gately, R. West, *Drug Dev. Res.* **2007**, *68*, 156–163; b) K. Eshima, S. Fukaya, A. Sugimoto, T. Mori, H. Yokoi, Y. Yamamoto, S. Sugiura, S. Honda, N. Masuko, K. Murakami, Y. Yamasaki, H. Kagechika, *Tumor Biol.* **2009**, *30*, 1–7.

[15] For the synthesis of primary anilines using ammonia, see: a) Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 10028–10029; b) D. S. Surry, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 10354–10355; c) N. Xia, M. Taillefer, *Angew. Chem.* **2009**, *121*, 343–345; *Angew. Chem. Int. Ed.* **2009**, *48*, 337–339.

[16] For selected examples of addition of NH_2^-, see: a) J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, D. A. Semenow, *J. Am. Chem. Soc.* **1956**, *78*, 611–614; b) J. F. Bunnett, J. K. Kim, *J. Am. Chem. Soc.* **1973**, *95*, 2254–2259.

[17] The reaction of *N*-Boc-furfurylamine and the benzyne **1a** selectively gave the corresponding Diels–Alder product (unpublished result).

[18] For selective desilylation at low temperature, see: a) J. A. Lafontaine, D. P. Provencal, C. Gardelli, J. W. Leahy, *J. Org. Chem.* **2003**, *68*, 4215–4234; b) T. Ikawa, T. Nishiyama, T. Nosaki, A. Takayi, S. Akai, *Org. Lett.* **2011**, *13*, 1730–1933.

[19] a) Z. Wang, R. T. Skerlj, G. J. Bridger, *Tetrahedron Lett.* **1999**, *40*, 3543–3546; b) M. Wolter, A. Klapars, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 3803–3805.

[20] The use of TBAF provided a 3-bromoaniline derivative, which was probably derived from the generation of 3-bromobenzyne.

[21] Gaussian 03 (Revision C.02), M. J. Ferisch et al., see the Supporting Information for full citation.