JOC Article

Three-Component Coupling Using Arynes and Aminosilanes for ortho-Selective Double Functionalization of Aromatic Skeletons

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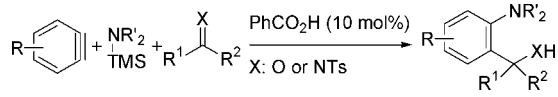

Arynes were found to couple with aminosilanes and carbonyl compounds in the presence of benzoic acid to provide 2-aminobenzhydrols. Sulfonylimines could also be applied to the reaction, enabling amino and aminomethyl moieties to be incorporated into contiguous positions of aromatic skeletons. Only a small amount of the three-component coupling product was obtained in the absence of benzoic acid, which confirms its vital role in the present reaction.

1. Introduction

Synthetic application of arynes to constructing polysubstituted arenes and/or benzo-annulated cyclic compounds, which are difficult to obtain by conventional methods, has attracted considerable attention.[1] Among these, multicomponent coupling reactions would be very beneficial from a synthetic standpoint for generating molecular complexity and diversity, and we have already disclosed that iminoisobenzofuran,[2a] iminoisoindoline[2b] or benzoxazinone[2c] derivatives can directly be synthesized based upon the three-component coupling using arynes. The reaction proceeds through following three steps: (1) formation of zwitterions resulting from nucleophilic attack of such unsaturated nucleophiles as isocyanides or imines to arynes, (2) capture of the resulting zwitterions by electrophiles,[3] (3) intramolecular cyclization.[4] The third step is triggered by the unsaturation in the cationic site of intermediate A, and thus we envisaged that the use of saturated nucleophiles in lieu of unsaturated ones should result in a different type of three-component coupling, in which the intramolecular cyclization is impeded entirely (Scheme 1).[5] We report herein new methods for simultaneous introduction of two functionalities into neighboring positions of aromatic skeletons based upon a three-component coupling using arynes and aminosilanes.[6] By employing such carbon electrophiles as carbonyl compounds or sulfonylimines, diverse multisubstituted arenes containing

(1) For reviews, see: (a) Biehl, E. R.; Khanapure, S. P. *Acc. Chem. Res.* **1989**, *22*, 275–281. (b) Kessar,S. V. In *Comprehensive Organic Synthesis* Trost,B. M. , Fleming,I. , Semmelhack,M. F. , Eds.; Pergamon: Oxford ,1991; Vol. 4, pp 483−515. (c) Pellissier, H.; Santelli, M. *Tetrahedon* **2003**, *59*, 701–730. (d) Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093–4112. For recent examples, see: (e) Hamura, T.; Ibusuki, Y.; Uekusa, H.; Matsumoto, T.; Siegel, J. S.; Baldridge, K. K.; Suzuki, K. *J. Am. Chem. Soc.* **2006**, *128*, 10032–11033. (f) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 223–232. (g) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559.

(2) Aryne-isocyanide-aldehyde: (a) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew.Chem., Int. Ed.* **2004**, *43*, 3935–3938. Aryne-isocyanide-imine: (b) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2004**, *45*, 8659–8662. Aryne-imine-CO_2: (c) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040–11041. See also: (d) Yoshida, H.; Fukushima, H.; Morishita, T.; Ohshita, J.; Kunai, A. *Tetrahedron* **2007**, *63*, 4793–4805.

(3) Formation of monosubstituted arenes by proton abstraction: (a) Sato, Y.; Toyooka, T.; Aoyama, T.; Shirai, H. *J. Org. Chem.* **1976**, *41*, 3559–3564. (b) Nakayama, J.; Takeue, S.; Hoshino, M. *Tetrahedron Lett.* **1984**, *25*, 2679–2682. (c) Hayashi, S.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 642–644. (d) Ramtohul, Y. K.; Chartrand, A. *Org. Lett.* **2007**, *9*, 1029–1032. (e) Kolomeitsev, A. A.; Vorobyev, M.; Gillandt, H. *Tetrahedron Lett.* **2008**, *49*, 449−454. For a review on insertion reactions of arynes into element−element σ-bond, see: Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3578−3581. For examples, see: (f) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int.Ed.* **2002**, *41*, 3247–3249. (g) Liu, Z. J.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112–13113. (h) Yoshida, H.; Terayama, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2004**, 1980–1981. (i) Yoshida, H.; Minabe, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3454–3456. (j) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292–3294. (k) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729–6731. (l) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505–1507. (m) Tamber, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341. (n) Tamber, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752–11753. (o) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Lett.* **2005**, *34*, 1538–1539. (p) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405–2407. (q) Beltrán-Rodil, S.; Peña, D.; Guitián, E. *Synlett* **2007**, *8*, 1308–1310. (r) Toledo, F. T.; Margues, H.; Comasseto, J. V.; Raminelli, C. *Tetrahedron Lett.* **2007**, *48*, 8125–8127.

(4) Other three-component couplings using neutral nucleophiles: (a) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, *6*, 4049–4051. (b) Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2006**, 2454–2456.

(5) (a) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1983**, *24*, 4935–4938. (b) Meyers, A. I.; Pansegrau, P. D. *J Chem. Soc., Chem. Commun.* **1985**, 690–691. (c) Tripathy, S.; LeBlanc, R.; Durst, T. *Org. Lett.* **1999**, *1*, 1973–1975.

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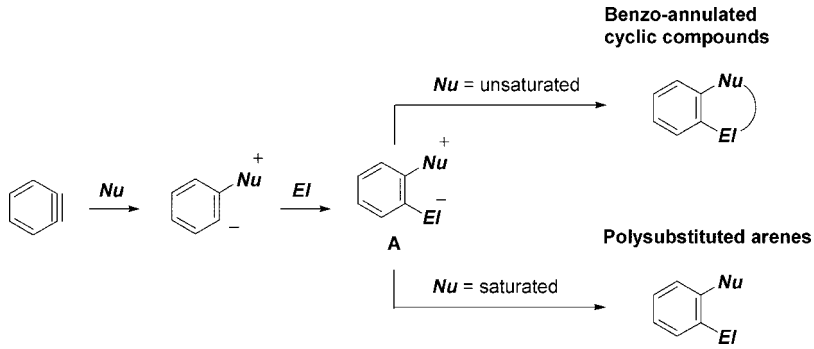
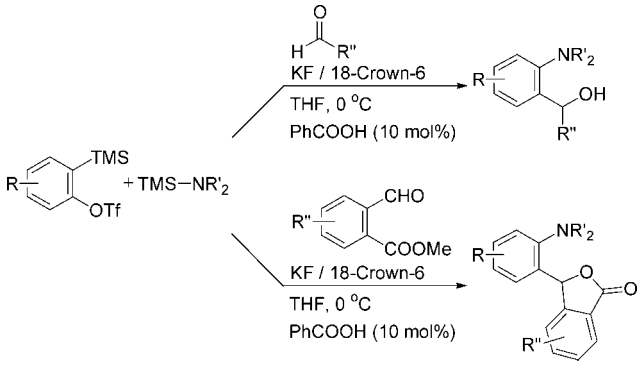
SCHEME 1



SCHEME 2. Three-Component Coupling of Arynes, Aminosilanes and Aldehydes

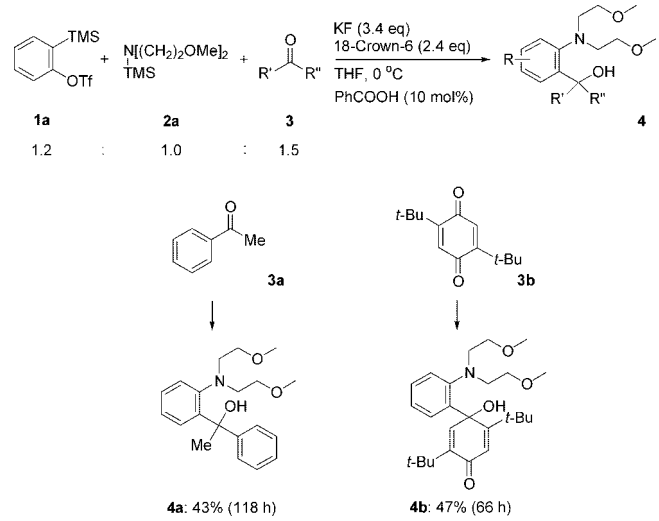


amino and hydroxymethyl (or aminomethyl) moieties can be synthesized all in one pot.[7,8]

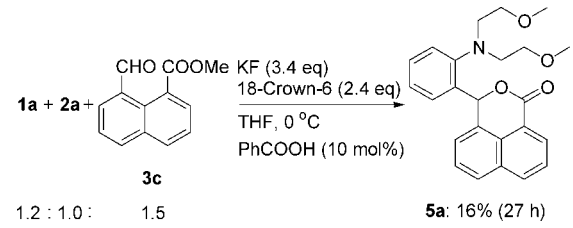
2. Results and Discussion

2.1. Three-Component Coupling of Arynes, Aminosilanes and Carbonyl Compounds. We previously reported on a three-component coupling using aldehydes as electrophiles, which gave 2-aminobenzyl alcohol (or phthalide) derivatives of structural diversity in a straightforward manner (Scheme 2).[9] On the basis of these results, we next conducted the three-component coupling using other carbonyl compounds (Scheme 3). First we carried out the reaction of benzyne, prepared in situ from 2-(trimethylsilyl)phenyl triflate (**1a**)[10] and a fluoride ion (KF/18-Crown-6), with [bis(2-methoxyethyl)amino]trimethylsilane (**2a**) and acetophenone (**3a**) in the presence of a substoichiometric amount of benzoic acid (10 mol %), in THF at 0 °C, and observed that a three-component coupling product, 1-{2-[bis(2-methoxyethyl)amino]phenyl}-1-phenylethanol (**4a**),

SCHEME 3. Three-Component Coupling of Benzyne, 2a and Ketones



SCHEME 4. Three-Component Coupling of Benzyne, 2a and Methyl 8-Formylnaphthoate



was formed in 43% yield. In marked contrast, no trace of the three-component coupling product was obtained with 2,2,2-trifluoroacetophenone, regardless of its highly electrophilic character. The present coupling was also applicable to 2,5-di-*tert*-butylbenzoquinone (**3b**), affording a 47% yield of **4b**. In addition, methyl 8-formylnaphthoate (**3c**) could also be applied to the present reaction to provide a 16% yield of (2-aminophenyl)benzo[*de*]isocoumarin **5a**, as were the cases with methyl 2-formylbenzoates (Scheme 4).[9]

2.2. Three-Component Coupling of Arynes, Aminosilanes and Sulfonylimines. Simultaneous introduction of amino and aminomethyl moieties into aromatic skeletons could also be achieved by employing sulfonylimines as electrophiles. Under reaction conditions similar to those described above, *N*-tosylbenzaldimine (**6a**) was coupled with benzyne and dialkylaminosilanes (**2b**−**2d**, **2g**) to give the respective 2-aminobenzhydrylamine derivatives (Table 1, entries 2−4, 7), although the yields were rather lower than those of 2-aminobenzhydrols

(6) The reaction of arynes with primary and secondary amines: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (b) Wickham, P. P.; Hazen, K. H.; Guo, H.; Jones, G.; Reuter, K. H.; Scott, W. J. *J. Org. Chem.* **1991**, *56*, 2045–2050.

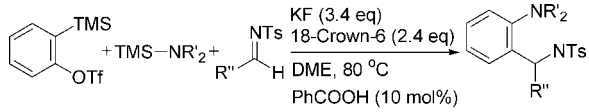
(7) The reaction of benzyne with benzaldehyde was reported to produce 2-(dimethylamino)benzhydrol (12% yield), whose dimethylamino moiety was derived from a benzyne precursor (1-(2-carboxyphenyl)-3,3-dimethyltriazene). However, this reaction was not developed as a useful synthetic procedure, because it required harsh conditions (160 °C) and excess aldehyde (∼39 equiv). Nakayama, J.; Yoshida, M.; Shimamura, O. *Chem. Lett.* **1973**, 451–454.

(8) Similar products can be synthesized by the direct ortho-lithiation of anilides followed by reaction with an electrophile, although the highly basic reaction conditions would limit the use of substrates bearing relatively sensitive functional groups. (a) Fuhrer, W.; and Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133–1136. (b) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798–4801.

(9) Yoshida, H.; Morishita, T.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2007**, *9*, 3367–3370.

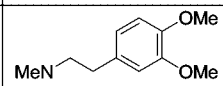
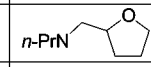
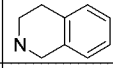
(10) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, *12*, 1211–1214.

TABLE 1. Three-Component Coupling of Benzyne, Aminosilanes and Sulfonylimines[a,b]



1.2 : 1.0 : 1.5

1a **2** **6** **7**

entry	R'		R"		Time (h)	Yield (%)[b]	7
1	$N[(CH_2)_2OMe]_2$	**2a**	Ph	**6a**	20	56	**7a**
2	NEt_2	**2b**	Ph	**6a**	21	26	**7b**
3	N*n*-Bu_2	**2c**	Ph	**6a**	14	45	**7c**
4	NCyMe	**2d**	Ph	**6a**	18	36	**7d**
5		**2e**	Ph	**6a**	18	40	**7e**
6		**2f**	Ph	**6a**	21	50	**7f**
7	NMe_2	**2g**	Ph	**6a**	23	30	**7g**
8		**2h**	Ph	**6a**	19	29	**7h**
9		**2i**	Ph	**6a**	22	25	**7i**
10		**2j**	Ph	**6a**	19	21	**7j**
11	$N[(CH_2)_2OMe]_2$	**2a**	4-$MeOC_6H_4$	**6b**	63	55	**7k**
12	$N[(CH_2)_2OMe]_2$	**2a**	4-$CF_3C_6H_4$	**6c**	21	59	**7l**
13	$N[(CH_2)_2OMe]_2$	**2a**	1-Naphthyl	**6d**	22	51	**7m**
14	$N[(CH_2)_2OMe]_2$	**2a**	2-Thienyl	**6e**	46	59	**7n**
15	$N[(CH_2)_2OMe]_2$	**2a**	2,4-$Me_2C_6H_3$	**6f**	23	23	**7o**
16	$N[(CH_2)_2OMe]_2$	**2a**	Mesityl	**6g**	27	8	**7p**

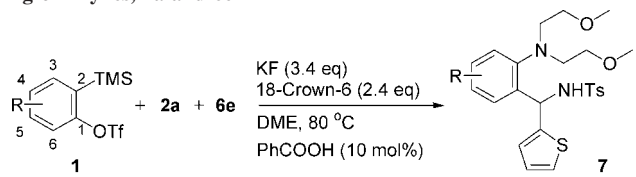
[a] The reaction was carried out in DME (1 mL) at 80 °C using **1a** (0.18 mmol), **2** (0.15 mmol), **6** (0.23 mmol), PhCOOH (0.015 mmol), KF (0.51 mmol) and 18-Crown-6 (0.36 mmol). [b] Isolated yield based on **2**.

(cf. ref 9). Alkoxy-substituted aminosilanes (**2a**, **2e** or **2f**) provided moderate yields of products **7a**,**7e** or **7f** (entries 1, 5 and 6), whereas the reaction using cyclic aminosilanes (**2h**−**2j**) resulted in low yield (entries 8−10). In addition, sulfonylimines bearing an electron-donating (**6b**) or electron-withdrawing (**6c**) substituent at the para position underwent the reaction to give **7k** or **7l** in 55% or 59% yield, respectively (entries 11 and 12), and the reaction of 1-naphthyl (**6d**) or 2-thienylsulfonylimine (**6e**) afforded a 51% or 59% yield of the product as well (entries 13 and 14). Steric bulk around the imine carbon of **6f** or **6g** inhibited the course of the reaction, leading to lowering the yield (entries 15 and 16).

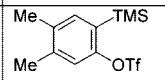
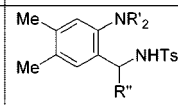
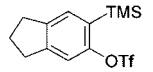
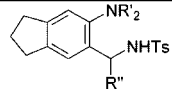
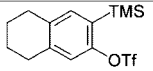
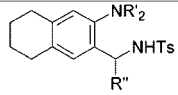
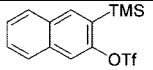
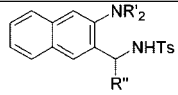
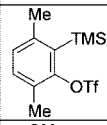
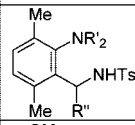
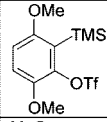
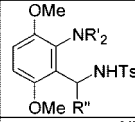
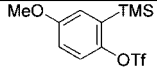
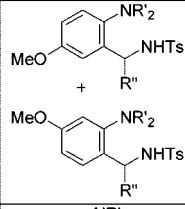
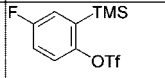
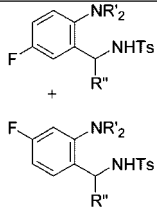
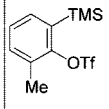
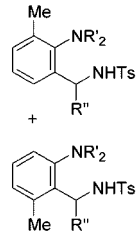
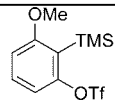
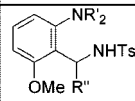
Variously substituted 2-aminobenzhydrylamine derivatives were readily synthesized by the reaction of substituted arynes. As shown in Table 2, such symmetrical arynes as 4,5-dialkylated arynes (**1b**−**1d**) or 2,3-naphthalyne (**1e**) reacted with **2a** and **6e** to afford products **7q**−**7t** in moderate yield (entries 1−4). Sterically congested arynes (**1f** and **1g**) could also participate in the reaction, giving **7u** or **7v** in 56% or 39% yield, respectively (entries 5 and 6). Furthermore, almost the same regioselectivities as those with an aldehyde were observed in the reaction using unsymmetrical arynes: 4-methoxybenzyne (**1h**) produced equal amounts of regioisomers (**7w** and **7′w**), and **7x** or **7y** was obtained as the major product in the reaction of 4-fluorobenzyne or 3-methylbenzyne (entries 7−9). Exclusive formation of **7z**, which bears the amino moiety at the meta position of the methoxy group, was observed in the reaction of 3-methoxybenzyne (entry 10).

2.3. Reaction Pathway. We next investigated the reaction pathway as depicted in Scheme 5. In the absence of benzoic acid, the reaction of benzyne, **2a** and benzaldehyde gave only aminosilylated product **8**[11] in place of the three-component coupling product (**9**) (eq 1), and a similar reaction using sulfonylimine **6a** afforded a small amount of **7a** (eq 2).

TABLE 2. Three-Component Coupling of Arynes, 2a and 6e[a,b,c,d,e]

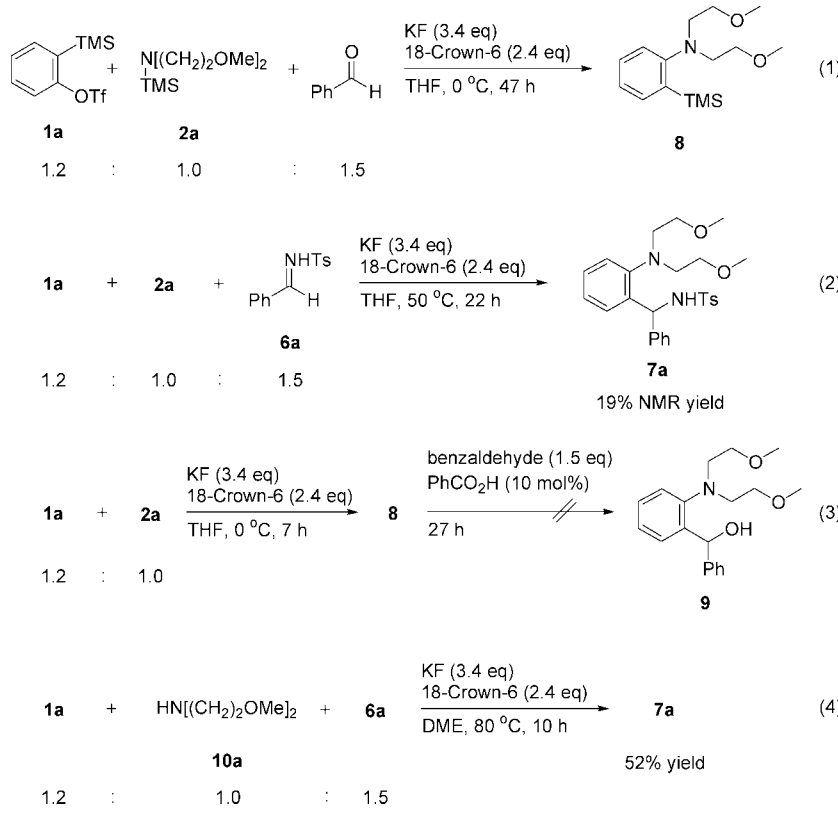


1.2 : 1.0 : 1.5

entry	1		7		Time (h)	Yield (%)[b]
1		**1b**		**7q**	47	50
2		**1c**		**7r**	49	37
3		**1d**		**7s**	47	46
4		**1e**		**7t**	40	40
5		**1f**		**7u**	50	56
6		**1g**		**7v**	56	39
7		**1h**		**7w** **7'w**	43	49[c]
8		**1i**		**7x** **7'x**	42	52[d]
9		**1j**		**7y** **7'y**	48	46[c]
10		**1k**		**7z**	48	28

[a] The reaction was carried out in DME (1 mL) at 80 °C using **1** (0.18 mmol), **2a** (0.15 mmol), **6e** (0.23 mmol), PhCOOH (0.015 mmol), KF (0.51 mmol) and 18-Crown-6 (0.36 mmol). [b] Isolated yield based on **2a**. [c] **7w**:**7′w** = 1:1. [d] **7x**:**7′x** = 63:37. [e] **7y**:**7′y** = 62:38.

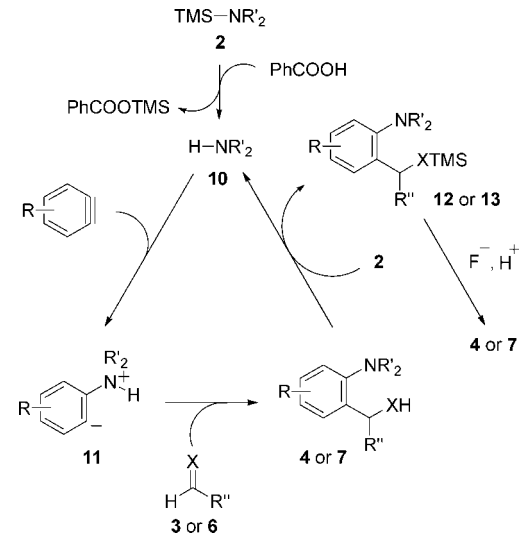
SCHEME 5. Mechanistic Studies



Moreover, **9** was not formed at all in the reaction of benzaldehyde with **8** (eq 3), showing that the aminosilylated product is not an intermediate in the three-component coupling. In marked contrast to the cases of an aminosilane (eqs 1 and 2), treatment of an amine (**10a**) with benzyne and **6a** was found to produce **7a** without added benzoic acid (eq 4).[12]

These results prompted us to propose a plausible reaction pathway, where in situ generated amine **10** (from aminosilane **2**and benzoic acid)[13] serves as an actual nucleophile to afford zwitterion **11** through action with an aryne (Scheme 6). Subsequent nucleophilic coupling of **11** with an electrophile (carbonyl compound **3** or sulfonylimine **6**),[14] furnished **4** or **7**, which then reacts with **2** to give silylether **12** or silylamine **13**

SCHEME 6. Plausible Pathway



with regeneration of amine **10**.[15] The resulting silylether (or silylamine) would be transformed into **4** (or **7**) via the workup process.[16]

Owing to a strong electron-withdrawing inductive effect of fluoro substituent, the negative charge at the meta position of the fluoro moiety in the transition state would be stabilized for the addition of amine to 4-fluorobenzyne, which results in the preferential formation of **7x** (Scheme 7).[17] In contrast, a methoxy substituent in 4-methoxybenzyne exerts little effect on the

(11) The TMS group in aminosilylated product **8** was demonstrated to derive not from **1** but from **2a**. See ref 3i.

(12) A large amount of *N*,*N*-diethylaniline was formed as a byproduct in this reaction, which demonstrates an advantage of the use of aminosilanes in the three-component coupling. The existence of only a catalytic amount of amines, generated from aminosilanes and benzoic acid, in the reaction mixture would decrease aniline derivatives. For N-arylation of amines by the use of arynes, see: (a) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *5*, 4673–4675. (b) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198–3209.

(13) An amine and a silyl carboxylate are readily formed in the reaction of an aminosilane and a carboxylic acid: (a) Wissner, A. *Tetrahedron Lett.* **1978**, *19*, 2749–2752. (b) Ruhlmann, K. *Chem. Ber.* **1961**, *94*, 1876–1878.

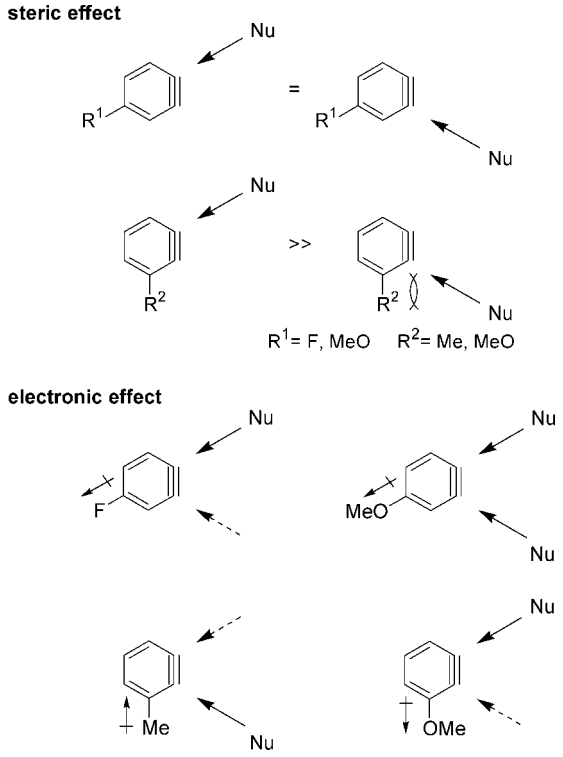
(14) A reviewer pointed out that there may be an attractive hydrogen bonding between the amine H in **11** and an electrophile, which enhances the electrophilicity of **3** or **6**.

(15) Various alcohols are readily transformed into the respective silyl ethers via action with aminosilanes: (a) Shirini, F.; Mollarazi, E. *Synth. Commun.* **2006**, *36*, 1109–1115. (b) Gautret, P.; El-Ghammarti, S.; Legrand, A.; Couturier, D.; Rigo, B. *Synth. Commun.* **1996**, *26*, 707–717.

(16) Because there was an excess of fluoride in the reaction mixture, three-component coupling products would exist as silicates, amides or alkoxides before a workup process. Therefore, we could only detect trace amounts of silyl ether **12** or silylamine **13** in crude products. For protodesilylation of silyl ethers with a fluoride ion, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; Chapter 2, pp 113−148.

(17) Preferential nucleophilic attack at a para position of a chlorine atom also occurred in electrophilic coupling reactions of 4-chlorobenzyne: (a) Bunnett, J. F.; Pyun, C. *J. Org. Chem.* **1969**, *34*, 2035–2037. (b) Bunnett, J. F.; Kim, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 2254–2259.

SCHEME 7. Regioselectivities in the Nucleophilic Addition of Amine



regioselectivity of the nucleophilic attack, resulting in equal formation of two regioisomers. Exclusive production of **7z** in the reaction of 3-methoxybenzyne can be attributed to an electron-withdrawing inductive effect of a methoxy moiety together with a steric repulsion between the methoxy moiety and an incoming nucleophile, both of which direct the nucleophilic attack toward the meta position of the methoxy moiety. In the case of 3-methylbenzyne, the steric effect would be in conflict with an electron-donating inductive effect which favors the generation of the anion at the meta position, and a mixture of regioisomers is yielded.

3. Conclusion

We have developed a convenient and general method for introducing nitrogen and carbon functional groups into adjacent positions of aromatic rings. The ortho-selective double functionalization procedure enables 2-aminobenzhydrols or 2-aminobenzhydrylamines, which are hardly accessible by conventional methods, to be assembled straightforwardly and, thus, would have high synthetic significance.

Experimental Section

Three-Component Coupling of Arynes, Aminosilanes, and Carbonyl Compounds: A General Procedure. To a THF solution (1 mL) of an aryne precursor (0.18 mmol), an aminosilane (0.15 mmol), a carbonyl compound (0.23 mmol), benzoic acid (1.8 mg, 0.015 mmol) and 18-crown-6 (0.095 g, 0.36 mmol), KF (0.030 g, 0.51 mmol) was added, and the resulting mixture was stirred at 0 °C for the period as specified in Schemes 3 and 4. The mixture was diluted with ethyl acetate, filtered through a Celite plug, and concentrated. After a hexane (or toluene) solution (5 mL) of the residue was treated with aluminum oxide (2.5 g) containing a 75 μL of water at room temperature overnight,[18] the resulting mixture was filtered through a Celite plug. Evaporation of the solvent followed by silica-gel column chromatography (dichloromethane/ethyl acetate as an eluent) gave the corresponding product.

1-{2-[Bis(2-methoxyethyl)amino]phenyl}-1-phenylethanol (4a). Isolated in 43% yield as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3 H), 2.28−2.48 (m, 2 H), 2.77−2.86 (m, 1 H), 2.92−3.01 (m, 1 H), 3.07 (s, 3 H), 3.18−3.46 (m, 7 H), 7.09−7.17 (m, 1 H), 7.18−7.39 (m, 7 H), 7.54 (d, J = 7.7 Hz, 1 H), 8.14 (s, 1 H);^{13}C NMR ($CDCl_3$) δ 32.5, 55.0, 55.4, 58.4, 58.8, 69.5, 69.8, 70.5, 125.2, 125.5, 125.7, 126.1, 127.8, 127.9, 128.1, 143.7, 149.3, 150.8; HRMS Calcd for $C_{20}H_{27}NO_3$: M^+, 329.1991. Found: m/z 329.1989.

Three-Component Coupling of Arynes, Aminosilanes, and Sulfonylimines: A General Procedure. To a DME solution (1 mL) of an aryne precursor (0.18 mmol), an aminosilane (0.15 mmol), a sulfonylimine (0.23 mmol), benzoic acid (1.8 mg, 0.015 mmol), 18-crown-6 (0.095 g, 0.36 mmol), and KF (0.030 g, 0.51 mmol) was added, and the resulting mixture was stirred at 80 °C for the period as specified in Tables 1 and 2. The mixture was diluted with ethyl acetate, filtered through a Celite plug, and concentrated. Silica-gel column chromatography (hexane/ethyl acetate as an eluent) followed by gel permeation chromatography gave the corresponding product.

***N*-*p*-Tosyl-2-[bis(2-methoxyethyl)amino)benzhydrylamine (7a).** Isolated in 56% yield as a white solid: mp 77−78 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 2.45−2.57 (m, 2 H), 2.75−2.90 (m, 2 H), 2.97−3.14 (m, 4 H), 3.27 (s, 6 H), 5.62 (d, J = 8.9 Hz, 1 H), 6.95−7.30 (m, 11 H), 7.55 (d, J = 8.2 Hz, 2 H), 8.15 (d, J = 8.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.26, 21.31, 21.36, 21.41, 54.3, 58.49, 58.52, 60.1, 60.6, 60.7, 61.2, 70.1, 125.0, 126.2, 126.4, 126.5, 126.9, 128.0, 128.5, 128.8, 137.6, 138.5, 142.0, 142.1, 150.0; Anal. Calcd for $C_{26}H_{32}N_2O_4S$: C, 66.64; H, 6.88; N, 5.98. Found: C, 66.58; H, 7.16; N, 5.82.

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Supporting Information Available: Experimental procedure and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800761B

(18) Feixas, J.; Capdevila, A.; Guerero, A. *Tetrahedron* **1994**, *50*, 8539–8550.