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Three-Component Coupling of Arynes, Aminosilanes, and Aldehydes

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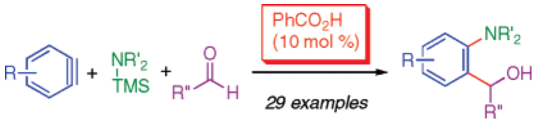
ABSTRACT



A three-component coupling of arynes, aminosilanes, and aldehydes enables diverse amino and hydroxymethyl groups to be incorporated directly into 1,2-positions of aromatic rings.

The development of a convenient and powerful method for functionalization of aromatic rings endowed with high chemo- and regioselectivities has been an essential subject in synthetic organic chemistry.[1] In particular, a synchronous introduction of two different functional groups into the aromatic rings would have higher synthetic significance, because the reaction enables various multisubstituted arenes to be constructed in a straightforward manner. In this context, we have recently disclosed ortho-selective double functionalization via insertion reactions of arynes into nucleophilic−electrophilic σ-bonds[2,3] and three-component couplings using arynes.[4,5] Although a variety of functional groups can be introduced through the reactions, versatility of this functionalization would further be enhanced by novel coupling reactions with use of arynes. We report herein a new method for simultaneous introduction of two functionalities (amino and hydroxymethyl moieties) into aromatic rings based on a three-component assembly of arynes, aminosilanes, and aldehydes, which gives 2-aminobenzyl alcohol derivatives of structural diversity in a straightforward manner.[6]

We first examined the reaction of in situ generated benzyne (from **1a**[7] and KF/18-Crown-6), (diethylamino)trimethylsilane (**2a**), and benzaldehyde (**3a**) in the presence of benzoic acid (10 mol %), and observed that the three-component coupling product, 2-(diethylamino)benzhydrol (**4a**), was formed in 76% yield (Table 1, entry 1). No trace of **4a** was obtained in the absence of benzoic acid, which confirms its vital role in the present reaction (vide infra). Dialkylaminosilanes (**2b** or **2c**), alkoxy-substituted aminosilanes (**2d** or **2e**), or an aminosilane bearing a tetrahydrofuranyl moiety

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[1] Reviews: (a) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley & Sons: Chichester, UK, 1990. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.

[2] Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.

[3] Our recent results: (a) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405. (b) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505. (c) Yoshida, H.; Tanino, K.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 5678. (d) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292.

[4] Three-component coupling of arynes with nucleophiles and electrophiles: (a) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, *128*, 11040. (b) Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2006**, 2454. (c) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2004**, *45*, 8659. (d) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3935.

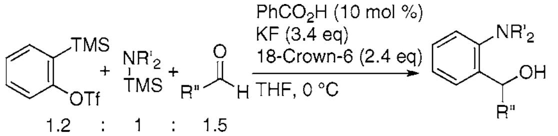
[5] Transition metal-catalyzed three-component coupling of arynes: (a) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426. (b) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 2921. (c) Chatani, N.; Kamitani, A.; Oshita, M.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 12686. (d) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173.

[6] 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 (ca. 39 equiv): Nakayama, J.; Yoshida, M.; Simamura, O. *Chem. Lett.* **1973**, 451.

[7] Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

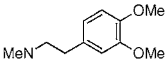
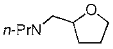
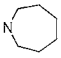
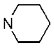
10.1021/ol071347a CCC: $37.00

Table 1. Three-Component Coupling of Benzyne, Aminosilanes, and Aldehydes[a]



1.2 : 1 : 1.5

1a **2** **3** **4**

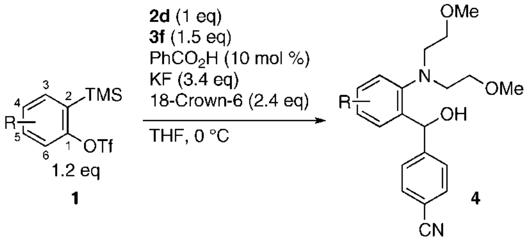
entry	NR'$_2$	**2**	R"	yield/time (%/h)[b]	**4**
1	NEt$_2$	**2a**	Ph (**3a**)	76/19	**4a**
2	N*n*-Bu$_2$	**2b**	Ph (**3a**)	77/18	**4b**
3	NCyMe	**2c**	Ph (**3a**)	68/15	**4c**
4	N[(CH$_2$)$_2$OMe]$_2$	**2d**	Ph (**3a**)	85/7	**4d**
5		**2e**	Ph (**3a**)	71/19	**4e**
6		**2f**	Ph (**3a**)	80/22	**4f**[c]
7	NMe$_2$	**2g**	Ph (**3a**)	30/13	**4g**
8		**2h**	Ph (**3a**)	46/15	**4h**
9		**2i**	Ph (**3a**)	35/17	**4i**
10	N[(CH$_2$)$_2$OMe]$_2$	**2d**	4-NO$_2$C$_6$H$_4$ (**3b**)	82/23	**4j**
11	N[(CH$_2$)$_2$OMe]$_2$	**2d**	4-MeOC$_6$H$_4$ (**3c**)	80/28	**4k**
12	N[(CH$_2$)$_2$OMe]$_2$	**2d**	Mesityl (**3d**)	77/19	**4l**
13	N[(CH$_2$)$_2$OMe]$_2$	**2d**	9-Phenanthryl (**3e**)	76/26	**4m**
14	N[(CH$_2$)$_2$OMe]$_2$	**2d**	4-NCC$_6$H$_4$ (**3f**)	88/14	**4n**
15	N[(CH$_2$)$_2$OMe]$_2$	**2d**	4-MeO$_2$CC$_6$H$_4$ (**3g**)	87/14	**4o**
16	N[(CH$_2$)$_2$OMe]$_2$	**2d**	3-BrC$_6$H$_4$ (**3h**)	62/16	**4p**
17	N[(CH$_2$)$_2$OMe]$_2$	**2d**	2-Thienyl (**3i**)	81/25	**4q**
18	N[(CH$_2$)$_2$OMe]$_2$	**2d**	*t*-Bu (**3j**)	35/20	**4r**
19	N[(CH$_2$)$_2$OMe]$_2$	**2d**	(*E*)-Cinnamyl (**3k**)	80/20	**4s**

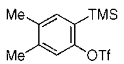
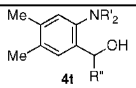
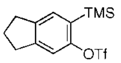
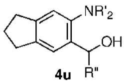
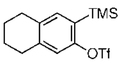
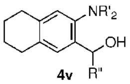
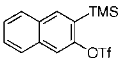
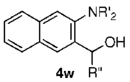
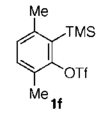
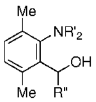
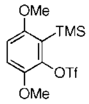
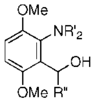
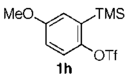
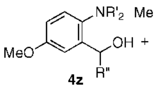
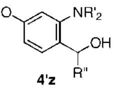
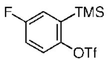
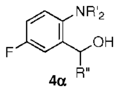
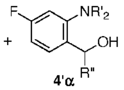
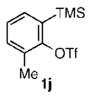
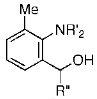
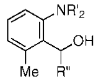
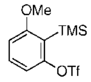
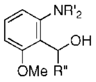
[a] The reaction was carried out at 0 °C in THF (1 mL) with **1a** (0.18 mmol), **2** (0.15 mmol), **3** (0.23 mmol), KF (0.51 mmol), and 18-crown-6 (0.36 mmol) in the presence of benzoic acid (0.015 mmol). [b] Isolated yield based on **2**. [c] Mixture of two diastereomers (ratio = 1:1).

(**2f**) also reacted smoothly to give high yields of respective products **4b**−**f** (entries 2−6), whereas the reaction of **2g**−**i** resulted in moderate yield (entries 7−9). In addition, electron-deficient (**3b**), electron-rich (**3c**), or sterically congested aromatic aldehydes (**3d** or **3e**) were applicable to the reaction, affording the products (**4j**−**m**) in 76−82% yield (entries 10−13). It is worth noting the excellent chemoselectivity of the reaction: treatment of cyano- (**3f**), methoxycarbonyl- (**3g**), or bromo-substituted benzaldehyde (**3h**) with benzyne and **2d** provided **4n**−**p** exclusively, leaving these functional groups intact (entries 14−16). A heteroaromatic aldehyde (**3i**) or an aliphatic aldehyde (**3j**)[8] could also participate in the reaction (entries 17 and 18), and furthermore, (*E*)-cinnamaldehyde (**3k**) underwent 1,2-addition to give an 80% yield of **4s**, whose stereochemistry was retained unchanged (entry 19).

Similarly to the cases with simple benzyne, 4,5-disubstituted arynes (from **1b**−**d**) or 2,3-naphthalyne (from **1e**) efficiently reacted with **2d** and **3f** to furnish **4t**−**w** in high yield, and even 3,6-disubstitued arynes (from **1f** or **1g**) could be applied to the reaction, despite the steric congestion around the triple bond (Table 2, entries 1−6). The reaction

Table 2. Three-Component Coupling of Arynes, **2d** and **3f**[a]



entry	1	4	time (h)	yield (%)[b]
1	 **1b**	 **4t**	67	85
2	 **1c**	 **4u**	52	76
3	 **1d**	 **4v**	98	76
4	 **1e**	 **4w**	66	61
5	 **1f**	 **4x**	70	60
6	 **1g**	 **4y**	28	46
7	 **1h**	 **4z** +  **4'z**	86	67[c]
8	 **1i**	 **4α** +  **4'α**	53	58[d]
9	 **1j**	 **4β** +  **4'β**	55	64[e]
10	 **1k**	 **4γ**	52	47

[a] The reaction was carried out at 0 °C in THF (1 mL) with **1** (0.18 mmol), **2d** (0.15 mmol), **3f** (0.23 mmol), KF (0.51 mmol), and 18-crown-6 (0.36 mmol) in the presence of benzoic acid (0.015 mmol). [b] Isolated yield based on **2d**. [c] **4z**:**4′z** = 50:50. [d] **4**α:**4′**α = 67:33. [e] **4**β:**4′**β = 60:40.

of such unsymmetrical arynes as 4-methoxy- (from **1h**), 4-fluoro- (from **1i**), or 3-methylbenzyne (from **1j**) resulted in the formation of a mixture of regioisomers (entries 7−9), whereas 3-methoxybenzyne (from **1k**) yielded exclusively **4**γ having the amino moiety at the meta position of the methoxy moiety (entry 10).[9]

We next investigated the reaction pathway as depicted in Scheme 1. In the absence of benzoic acid, the reaction of

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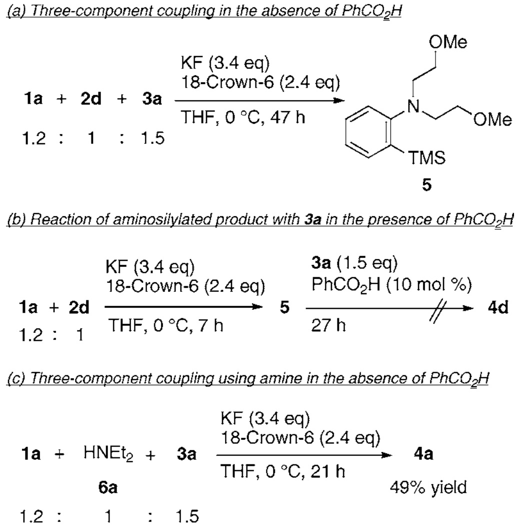
[8] Unfortunately, the reaction of such an enolizable aldehyde as propanal resulted in the formation of a complex mixture.

[9] Similar regioselectivities were observed in other electrophilic couplings of these unsymmetrical arynes. See refs 3 and 4.

Scheme 1

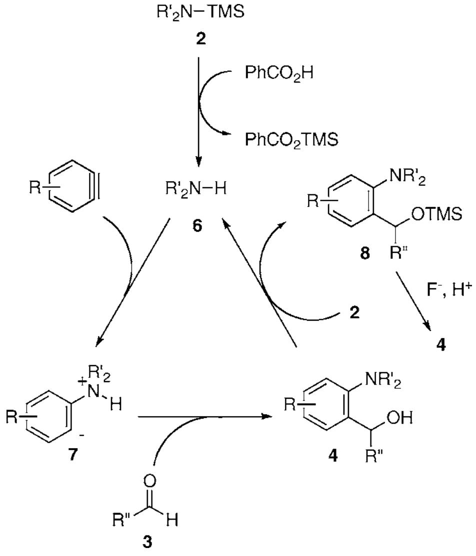


benzyne, **2d**, and **3a** gave only aminosilylated product **5** in place of three-component coupling product **4d** (eq a),[10] and moreover, **4d** was not formed at all in the reaction of **3a** with **5** (eq b), showing that an aminosilylated product is not an intermediate species in the three-component coupling. In marked contrast to the case of an aminosilane, treatment of an amine (**6a**) with benzyne and **3a** was found to produce **4a** without added benzoic acid (eq c).[11]

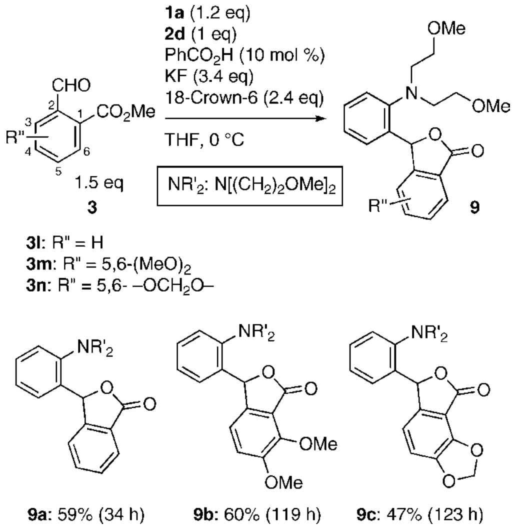
These results prompt us to propose a plausible reaction pathway, where in situ generated amine **6** (from aminosilane **2** and benzoic acid)[12] serves as an actual nucleophile to afford zwitterion **7** through action with an aryne (Scheme 2). Subsequent nucleophilic coupling of **7** with an aldehyde (**3**) furnishes **4**, which then reacts with **2** to give silyl ether **8** with regeneration of **6**.[13] The resulting silyl ether would be transformed into **4** via a workup process.[14]

Finally, utility of the three-component coupling has also been demonstrated by construction of heterocycles (Scheme 3). Thus, treatment of methyl 2-formylbenzoate (**3*l*−n**) with benzyne and **2d** afforded phthalide **9a−c**, which would be formed through the above-mentioned coupling followed by intramolecular cyclization between the resulting alkoxide and the ester moieties.[15]

Scheme 2



Scheme 3



In conclusion, we have demonstrated that diverse amino and hydroxymethyl moieties can be simultaneously introduced into adjacent positions of aromatic rings depending

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(10) Yoshida, H.; Minabe, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3454.

(11) A significant amount of *N*,*N*-diethylaniline was formed as a by-product in this reaction, which demonstrates an advantage of 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. (b) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198.

(12) 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**, 2749. (b) Ruhlmann, K. *Chem. Ber.* **1961**, *94*, 1876.

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

(14) Because there was an excess of fluoride in the reaction mixture, three-component coupling products would exist as silicates or alkoxides before a workup process. Therefore, we could only detect trace amounts of silyl ethers **8** 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.

(15) We also examined other protic acids and Lewis acids as additives; however, none of them improved the yield of **9a**. See the Supporting Information for details.

(16) Ejima, A.; Barford, S. C.; Kawakoshi, K.; Mitsuwa, T. Daiichi Seiyaku Co., Ltd., Japan, JP 11080141, 1999.

(17) Sugita, K.; Yokomizo, A.; Suzuki, M.; Ito, M.; Haginoya, N.; Usui, H. Daiichi Seiyaku Co., Ltd., Japan, JP 2007022943, 2007.

(18) A three-component coupling of arynes, aminosilanes, and sulfonylimines also proceeds to give 2-aminobenzylamine derivatives, which will be reported in due course.

upon the three-component coupling using arynes. The resulting 2-aminobenzhydrol derivatives comprise an important group of pharmacologically active compounds such as antitumors[16] and squalene synthase inhibitors.[17] Moreover, the coupling, in combination with intramolecular cyclization, is applicable to assembly of phthalide skeletons. Studies on multicomponent coupling of arynes directed toward ortho-selective double functionalization of aromatic rings are in progress.[18]

Acknowledgment. We thank Dr. Yoshiaki Nakao and Prof. Tamejiro Hiyama (Kyoto University) for HRMS measurement, and also the Central Glass Co Ltd. for a generous gift of trifluoromethanesulfonic anhydride.

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

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