## Three-Component Coupling of Arynes, Aminosilanes, and Aldehydes

## Hiroto Yoshida,\* Takami Morishita, Hiroyuki Fukushima, Joji Ohshita, and Atsutaka Kunai

Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, Higashi-Hiroshima 739-8527, Japan

yhiroto@hiroshima-u.ac.jp

Received June 7, 2007



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.<sup>1</sup> 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  $\sigma$ -bonds<sup>2,3</sup> and three-component couplings using arynes.<sup>4,5</sup> 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.<sup>6</sup>

ORGANIC LETTERS

2007 Vol. 9, No. 17

3367-3370

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

<sup>(1)</sup> 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.

<sup>(2)</sup> Peña, D.; Pérez, D.; Guitián, E. Angew. Chem., Int. Ed. 2006, 45, 3579.

<sup>(3)</sup> 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.

<sup>(4)</sup> 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.

<sup>(5)</sup> 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.

<sup>(6)</sup> 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.

<sup>(7)</sup> Himeshima, Y.; Sonoda, T.; Kobayashi, H. Chem. Lett. 1983, 1211.

 Table 1.
 Three-Component Coupling of Benzyne,

 Aminosilanes, and Aldehydes<sup>a</sup>
 1

				PhCO <sub>2</sub> H (10 mol %)		
	• TMS		~	KF (3.4 eq)	NR'2	
ſ		NR'2	Ö	18-Crown-6 (2.4 eq)		
	、 川 ・ * -	ſMS <sup>+</sup> Β"	╨╻		$\sim \sim^0$	н
	V OTf	п	П	1111,00	 	
	1.2 :	1 :	1.5			
	1a	2	3		4	
entry	NR'2		2	R"	yield/time	: 4
•					$(\%/h)^{b}$	
1	NEt <sub>2</sub>		2a	Ph ( <b>3a</b> )	76/19	4a
2	Nn-Bu <sub>2</sub>		2b	Ph ( <b>3a</b> )	77/18	4b
3	NCyMe		2c	Ph (3a)	68/15	4c
4	N[(CH <sub>2</sub> ) <sub>2</sub> ON	$[4e]_2$	2d	Ph (3a)	85/7	4d
		∽_OMe				
5			2e			
U	MeN <sup>2</sup> V	MeN <sup>2</sup> V V VOMe		Ph ( <b>3a</b> )	71/19	4e
6	$\sim^{\circ}$	<				
6	<i>n</i> -PrN <sup>*</sup>	/	21	Ph ( <b>3a</b> )	80/22	4f°
7	NMe <sub>2</sub>		2g	Ph(3a)	30/13	<b>4</b> σ
	$\sim$		8	1 ((()))	00,10	
8	N ]		2h			
	$\smile$			Ph ( <b>3a</b> )	46/15	4h
0	N		<b>c</b> :			
"			21	Ph ( <b>3a</b> )	35/17	4i
10	N[(CH <sub>2</sub> ) <sub>2</sub> ON	$[4e]_2$	2d	$4-NO_2C_6H_4$ (3b)	82/23	4j
11	N[(CH <sub>2</sub> ) <sub>2</sub> ON	$4e_{12}$	2d	$4-\text{MeOC}_6\text{H}_4(3c)$	80/28	4k
12	N[(CH <sub>2</sub> ) <sub>2</sub> ON	$[1e]_2$	2d	Mesityl (3d)	77/19	41
13	N[(CH <sub>2</sub> ) <sub>2</sub> ON	$[4e]_2$	2d	9-Phenanthryl (3e)	76/26	4m
14	N[(CH <sub>2</sub> ) <sub>2</sub> ON	$4e_{12}$	2d	$4-NCC_{6}H_{4}(3f)$	88/14	4n
15	N[(CH <sub>2</sub> ) <sub>2</sub> ON	$\sqrt{1e_{j_2}}$	2d	$4-MeO_2CC_6H_4(3g)$	87/14	40
16	N[(CH <sub>2</sub> ) <sub>2</sub> ON	$4e_{12}$	2d	$3-BrC_6H_4(3h)$	62/16	4p
17	N[(CH <sub>2</sub> ) <sub>2</sub> ON	$[4e]_2$	2d	2-Thienyl (3i)	81/25	4q
18	N[(CH <sub>2</sub> ) <sub>2</sub> ON	/le] <sub>2</sub>	2d	<i>t</i> -Bu ( <b>3j</b> )	35/20	4r
19	N[(CH <sub>2</sub> ) <sub>2</sub> ON	/le] <sub>2</sub>	2d	(E)-Cinnamyl (3k)	80/20	4s

<sup>*a*</sup> 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). <sup>*b*</sup> Isolated yield based on **2**. <sup>*c*</sup> 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-iresulted 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



<sup>*a*</sup> 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). <sup>*b*</sup> Isolated yield based on **2d**. <sup>*c*</sup> **4z**:**4**'z = 50:50. <sup>*d*</sup> **4** $\alpha$ :**4**' $\alpha$  = 67:33. <sup>*e*</sup> **4** $\beta$ :**4**' $\beta$  = 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  $4\gamma$  having the amino moiety at the meta position of the methoxy moiety (entry 10).<sup>9</sup>

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

<sup>(8)</sup> Unfortunately, the reaction of such an enolizable aldehyde as propanal resulted in the formation of a complex mixture.

<sup>(9)</sup> Similar regioselectivities were observed in other electrophilic couplings of these unsymmetrical arynes. See refs 3 and 4.



benzyne, 2d, and 3a gave only aminosilylated product 5 in place of three-component coupling product 4d (eq a),<sup>10</sup> 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).<sup>11</sup>

These results prompt us to propose a plausible reaction pathway, where in situ generated amine **6** (from aminosilane **2** and benzoic acid)<sup>12</sup> 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**.<sup>13</sup> The resulting silyl ether would be transformed into **4** via a workup process.<sup>14</sup>

Finally, utility of the three-component coupling has also been demonstrated by construction of heterocycles (Scheme 3). Thus, treatment of methyl 2-formylbenzoate (3l-n) with benzyne and 2d afforded phthalide 9a-c, which would be

(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.



formed through the above-mentioned coupling followed by intramolecular cyclization between the resulting alkoxide and the ester moieties.<sup>15</sup>



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

<sup>(10)</sup> Yoshida, H.; Minabe, T.; Ohshita, J.; Kunai, A. Chem. Commun. 2005, 3454.

<sup>(11)</sup> A significant amount of *N*,*N*-diethylaniline was formed as a byproduct 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 acidi 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.

<sup>(15)</sup> 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.

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

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

<sup>(18)</sup> 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<sup>16</sup> and squalene synthase inhibitors.<sup>17</sup> Moreover, the coupling, in combination with intramolecular cyclization, is applicable to assembly of phthalide skeletons. Studies on multicomponent coupling of arynes directed toward orthoselective double functionalization of aromatic rings are in progress.<sup>18</sup>

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. OL071347A