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Generation of Functionalized Asymmetric Benzynes with TMP-Zincates. Effects of Ligands on Selectivity and Reactivity of Zincates

Masanobu Uchiyama,*[,†,§] Tomoko Miyoshi,[‡] Yumiko Kajihara,[‡] Takao Sakamoto,[‡] Yuko Otani,[†]
Tomohiko Ohwada,[†] and Yoshinori Kondo[‡]
Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku,
Tokyo 113-0033, Japan, and Graduate School of Pharmaceutical Sciences, Tohoku University,
Aobayama, Aoba-ku, Sendai 980-8578, Japan

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Benzyne is among the most important intermediates in organic chemistry and has an unique structure, with two double bonds and one triple bond in a planar six-membered ring.[1] While unsubstituted benzyne has a symmetric triple bond, substituents on the benzyne break this symmetry, leading to different reactivities of the individual carbon atoms (Figure 1), i.e., substituents on benzyne can control the regioselectivity of incoming reagents through electronic, steric, and chelation effects. Therefore, such regioselectivity is important for organic synthesis[2] as well as for theoretical chemistry.[3] However, the potential of functionalized (asymmetric) benzynes has not yet been realized mainly due to the lack of efficient generation methods compatible with various functional groups, particularly electrophilic substituents such as ester, amide, and cyano groups, on the benzyne.

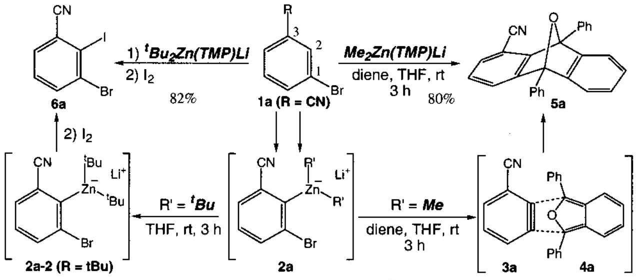
Figure 1. Asymmetric benzynes.

Several methods for generating functionalized benzynes bearing restricted substituents such as alkyl, alkoxy, or halogen groups have been reported.[1] These methods require (1,2,3- or 1,2,4-) trisubstituted benzenes as precursors, in which two of the substituents are in ortho positions, and they are eliminated upon the generation of the substituted benzynes.[1] However, the applicability of these conventional methods to generation of benzynes bearing electrophilic substituents is limited in two respects: (1) poor availability of the starting highly substituted benzenes, and (2) restricted compatibility with the remaining electrophilic functional groups. Thus, a method for generating asymmetric benzynes with high functional group compatibility is highly desirable.

Taking the availability of precursors and general applicability into consideration, deprotonative metalation seems to be advantageous to generate (multi-)functionalized benzynes.[4] Herein, we will report new methods to generate functionalized benzynes through deprotonative zincation as a key reaction, using lithium dialkyltetramethylpiperidino-zincates ($R_2Zn(TMP)Li$),[5] and we also describe dramatic effects of the ligands on Zn upon the benzyne formation.

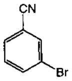
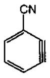
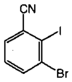
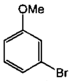
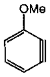
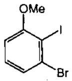
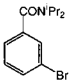
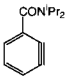
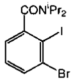
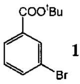
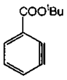
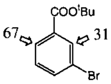
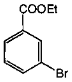
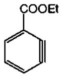
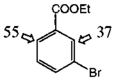
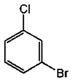
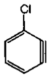
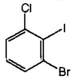
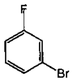
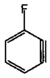
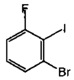
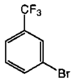
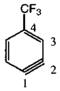
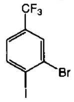
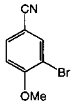
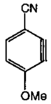
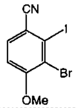
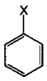
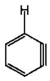
As a model reaction, the deprotonative zincation of 3-cyanobromobenzene (**1a**) with various $R_2Zn(TMP)Li$ was first investigated by focusing on the nature of TMP-zincates (Scheme 1). While deprotonative metalation of meta-substituted benzenes such as **1** can take place in three positions, the metalations with TMP-zincates

Scheme 1



diene = 1,3-diphenylisobenzofuran (**4a**)

Table 1. Chemoselective Deprotonative Metalation and Generation of Benzynes

Entry	Substrate		$Me_2Zn(TMP)Li$		${}^tBu_2Zn(TMP)Li$	
			Regioselectivity	Yield of **5** (%)	Regioselectivity	Yield of **6** (%)
1		**1a**		(reflux, 12 h) 90		(0°C, 3 h) 96
2		**1b**		(rt, 12 h) 100		(-30°C, 12 h) 95
3		**1c**		(reflux, 12 h) 100		(0°C, 3 h) 84
4		**1d**		(reflux, 6 h) 88		(rt, 3 h) *Iodination*
5		**1e**		(reflux, 3 h) 55		(rt, 3 h) *Iodination*
6		**1f**		(rt, 48 h) 72		(-30°C, 24 h) 77
7		**1g**		(60°C, 15 h) 71		(-30°C, 24 h) 93
8		**1h**		(rt, 12 h) 100		(rt, 3 h) 77
9		**1i**		(reflux, 3 h) 79		(0°C, 3 h) 74
10	 X = Br	**1j**	 **3j**	(reflux, 12 h) 100		
11	X = Cl	**1k**		(reflux, 12 h) 99		
12	X = F	**1l**		(reflux, 12 h) 99		
13	X = OTf	**1m**		(rt, 12 h) 100		

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* Corresponding author. E-mail: uchiyama@mol.f.u-tokyo.ac.jp.
[†] The University of Tokyo.
[‡] Tohoku University.
[§] PRESTO, Japan Science and Technology Corporation (JST).

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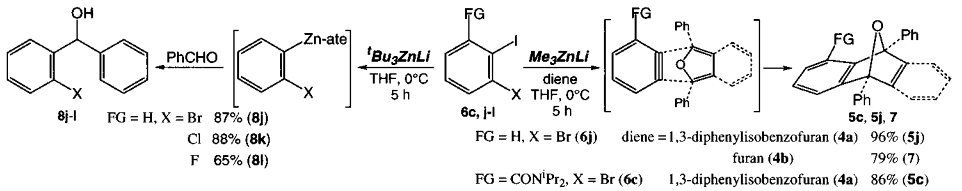
Scheme 2



proved to occur regioselectively at the C2 position.[4a] Furthermore, the nature of alkyl ligands on the zincates turned out to influence dramatically the reactivities of the resultant arylzincates (**2**). In the reaction with $^{t}Bu_2Zn(TMP)Li$,[5] zincation occurred regio-/chemoselectively without the formation of benzyne and the resulting arylzincate (**2a-2**) was treated with I_2 to give 1-bromo-2-cyano-3-iodobenzene (**6a**) in 82% yield. On the other hand, when $Me_2Zn(TMP)Li$ was used under the same conditions in the presence of diene (**4a**), the Diels−Alder adduct (**5a**) was obtained in 80% yield,[6] which indicates the generation of 3-cyanobenzyne (**3a**) through ready “elimination” of the arylzincate (**2a**). This drastic change of reaction modes (chemoselective metalation (inert “elimination”; *t*-Bu) or generation of benzyne (facile elimination; Me)) dependent on the alkyl-ligation environment is a feature of zincates, interesting and potentially useful from the synthetic viewpoint.

Then, deprotonative zincations of various meta-substituted bromobenzenes with $R_2Zn(TMP)Li$ were investigated (Table 1). Deprotonative zincation with $Me_2Zn(TMP)Li$ proved effective for the one-pot generation of various 3-functionalized benzynes. On the other hand, zincation with $^{t}Bu_2Zn(TMP)Li$ followed by electrophilic trapping (with I_2) proved a powerful tool for the preparation of 1,2,3-trisubstituted aromatic compounds.[7] The resultant 1,2,3-trisubstituted benzenes (**6**) are available as precursors for generation of 3-substituted benzynes by halogen−zinc exchange reactions (vide infra).

The trifluoromethyl group works as an exclusively para-metalating directing group, and the metalation and the generation of benzyne proceeded smoothly at the 4-position (Entry 8).

To expand the applicability of the present method, deprotonative zincation of various halobenzenes (or their analogues) with $Me_2Zn(TMP)Li$ was then investigated (Entries 10−13); various groups such as fluoro, chloro, and triflate (except for iodo[8]) turned out to work well as both ortho-directing and leaving groups in benzyne formation.

Similar benzyne intermediates can reasonably be formed by the halogen−zinc exchange reaction of *o*-dihalobenzene analogues (Scheme 2).[9,10] In the reaction of *o*-bromoiodobenzene (FG = H; **6j**) with Me_3ZnLi,[10a,b] the metalation and following “elimination” proceeded smoothly, and the resulting benzyne reacted with dienes (**4a**,**b**) to give the corresponding bicyclo compounds (**5j**, **7**) in high yields.[6] On the other hand, when $^{t}Bu_3ZnLi$[10c] was used under the same conditions, zincation proceeded without the formation of benzyne, and the arylzincate was trapped by an electrophile, e.g., benzaldehyde, to give the corresponding 2-halobenzhydrol derivatives (**8j**−**l**) in high yields. These results supports the intermediary formation of arylzincates (**2**) in deprotonative zincation by TMP-zincates. As a matter of course, 3-substituted benzynes can also be generated by using the iodine−zinc exchange reactions of the 1,2,3-trisubstituted benzenes (**6**) shown in Table 1; the reaction of *N*,*N*-diisopropyl-3-bromo-2-iodobenzamide (FG = $CON^{i}Pr_2$; **6c**) with Me_3ZnLi proceeded smoothly, and the benzyne reacted with diene (**4a**) to give the desired bicyclo compound (**5c**) in 86% yield. Thus, we have provided two new tools, which would be applicable for generating various functionalized benzynes and heterynes.

In conclusion, a chemo-/regioselective directed zincation of meta-functionalized haloaromatics and a versatile generation of 3-substituted benzynes could be achieved by utilizing the drastic ligand effects in zincates. While the role of nonreacting (i.e., dummy or spectator) ligands of ate complexes has been discussed, general application of their influence has not yet been realized. The present work underlines the utility of dummy ligands on the central metal of ate complexes as a tunable functionality in the development of new ate complex-promoted reactions. On the basis of the simplicity of the procedure, the absence of a requirement for tedious multistep synthesis of the precursor, and high chemo-/regioselectivity, we consider that the present methods represent a valuable extension of the aryne chemistry.

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Supporting Information Available: Experimental procedures and characterizations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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