

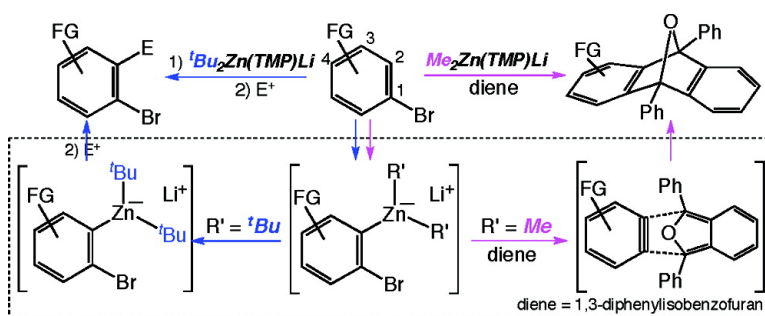
Article

Generation and Suppression of 3-/4-Functionalized Benzyne Using Zinc Ate Base (TMP–Zn–ate): New Approaches to Multisubstituted Benzenes

Masanobu Uchiyama, Yuri Kobayashi, Taniyuki Furuyama, Shinji Nakamura, Yumiko Kajihara, Tomoko Miyoshi, Takao Sakamoto, Yoshinori Kondo, and Keiji Morokuma

J. Am. Chem. Soc., **2008**, 130 (2), 472-480 • DOI: 10.1021/ja071268u

Downloaded from <http://pubs.acs.org> on February 8, 2009



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 6 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

[View the Full Text HTML](#)

Generation and Suppression of 3-/4-Functionalized Benzyne Using Zinc Ate Base (TMP–Zn–ate): New Approaches to Multisubstituted Benzenes

Masanobu Uchiyama,^{*,†,‡,§} Yuri Kobayashi,[†] Taniyuki Furuyama,^{†,§}
Shinji Nakamura,[†] Yumiko Kajihara,[‡] Tomoko Miyoshi,[‡] Takao Sakamoto,[‡]
Yoshinori Kondo,[‡] and Keiji Morokuma^{*,#}

Contribution from the Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, The Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Aoba-ku, Sendai 980-8578, Japan, Advanced Elements Chemistry Laboratory, Institute of Physical and Chemical Research, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan and the Cherry L. Emerson Center for Scientific Computation and Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received February 22, 2007; E-mail: uchiyama@mol.f.u-tokyo.ac.jp; morokuma@euch.chem.emory.edu

Abstract: We present full details of our new methods for preparing functionalized benzyne with lithium di-alkyl(2,2,6,6-tetramethylpiperidino)zincate ($R_2Zn(TMP)Li$) through deprotonative zincation as a key reaction. In this system, by choosing appropriate ligands for the zincate, either regioselective zincation of functionalized haloaromatics or the generation of substituted benzyne can be controlled in good yields with excellent chemoselectivity, using the same substrate. Zincation with $tBu_2Zn(TMP)Li$ followed by electrophilic trapping or zincation with $Me_2Zn(TMP)Li$ followed by nucleophilic or diene trapping is shown to be a powerful tool for the chemoselective preparation of 1,2,3-/1,2,4-trisubstituted benzene derivatives. These methods offer far greater generality than previous methods for the synthesis of multifunctionalized benzenes. Computational/theoretical studies of the reaction mechanism of this unique benzyne formation indicated that preferential coordination of the dialkylzinc moiety of zincate to halogen is the reason for the reduced activation energy of the elimination, that is, for the formation of the benzyne. The role of the ligands on Zn in accelerating/decelerating the elimination is also discussed.

Introduction

Aromatic rings are key structural elements of organic molecules, and hence chemo- and regiocontrolled synthesis of multisubstituted benzenes remains one of the central issues in organic synthesis. However, the variety of available derivatives is still quite limited. Inter-/intramolecular reaction, such as cycloaddition and nucleophilic addition, of substituted benzyne is, in principle, one of the most effective ways for introducing multiple functional groups on aromatic rings.¹ In particular, substituents on benzyne can control the regioselectivity of incoming reagents through electronic, steric, and chelation effects. Such regioselectivity is important in theoretical chemistry as well as for organic synthesis.² However, functionalized benzyne chemistry has not been well developed, mainly because of the lack of efficient preparation methods compatible with

various functional groups on the benzyne. Several methods for generating functionalized benzyne bearing limited substituents such as alkyl, alkoxy, or halogen groups have been reported.³ These methods require 1,2,3-(or 1,2,4-)trisubstituted benzenes as precursors (in which two of the substituents are in ortho positions),³ and therefore application of these conventional methods to the enhancement of benzyne bearing electrophilic substituents suffers from significant limitations in two respects: (1) poor availability of the starting highly substituted benzenes, and (2) restricted compatibility with the remaining functional groups. Thus, a new method for generating regiocontrolled functionalized benzyne with high functional group compatibility is highly desirable.

In this article, we present full details of our new approach to the preparation of functionalized benzyne (Figure 1) and

[†] The University of Tokyo.

[‡] Tohoku University.

[§] RIKEN.

[#] Emory University.

- (1) (a) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, England, 1991; Vol. 8, Chapter 4.4 and references cited therein. (b) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, England, 1991; Vol. 8, Chapter 2.3 and references cited therein.
- (2) (a) Johnson, W. T. G.; Cramer, C. J. *J. Am. Chem. Soc.* **2001**, *123*, 923–928. (b) Dkhar, P. G. S.; Lyngdoh, R. H. D. *Proc. Indian Acad. Sci., Chem. Sci.* **2000**, *112*, 97–108 (CAN 133:104683).

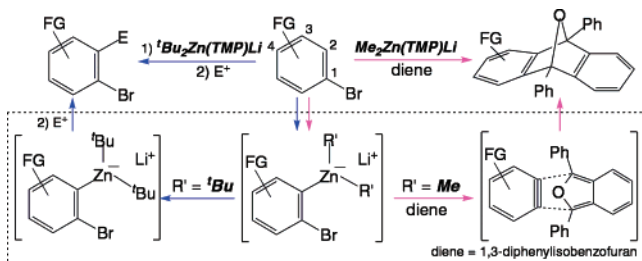
- (3) (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (b) H. Hart. In *The Chemistry of Triple-Bonded Functional Groups*; S. Patai, Ed.; John Wiley & Sons Ltd.: Chichester, U.K., 1994; Suppl. C2, Chapter 18. (c) Gilchrist, T. L. In *The Chemistry of Functional Groups*; Patai, S., Rappaport, Z., Eds.; Wiley: Chichester, U.K., 1983; Suppl. C, Chapter 11. For examples of the preparation of benzyne, see: (d) Kitamura, T.; Yamane, M.; Inoue, K.; Tokuda, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674–11679. (e) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735–6736. (f) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99–102.

Table 1. Ligand Screening of Zincate for Direct Generation of Benzyne^a

entry	FG	Zn-ate	temp	diene	yield (%)	Diene
1	H (1a)	^t Bu ₃ ZnLi	room temp	A	0	 A
2	H (1a)	ⁿ Bu ₃ ZnLi	room temp	A	trace	
3	H (1a)	Me ₃ ZnLi	room temp	A	99 (4a)	
4	H (1a)	Me ₃ ZnLi	0 °C	A	96 (4a)	 B
5	H (1a)	Me ₃ ZnLi	0 °C	B	79 (4a-B)	
6	CON ^t Pr ₂ (1b)	Me ₃ ZnLi	0 °C	A	86 (4b)	
7	H (1a)	Me ₄ ZnLi ₂	-78 °C	A	99 (4a)	

^a Unless otherwise noted, the iodine-zinc exchange reaction was carried out using zincate (2.2 equiv) and substrate **1** (1 equiv) in THF in the presence of 1,3-diphenylisobenzofuran (2.2 equiv). ^b Isolated yield. ^c FG = functional group.

multiply substituted benzenes.⁴ A new zinc ate base (lithium di-methyl(2,2,6,6-tetramethylpiperidino)zincate: Me₂Zn(TMP)-Li), which functions both as a base for directed ortho metalation on functionalized benzenes and as a promoter for the benzyne formation, was developed for direct chemo- and regioselective benzyne formation reaction. This reagent provides a new, efficient, and simple method for preparing trisubstituted benzene derivatives, and we describe several synthetic applications, including preparation of substituted arylsilanes and a biphenyl derivative. By selecting appropriate ligands for the zincate, generation and suppression of benzyne formation in this system can be controlled to afford desired products in good yield with excellent chemoselectivity, using the same substrate.

**Figure 1.** Summary of the reactions described here (FG = functional group).

Detailed second-order Møller-Plesset perturbation (MP2) and ONIOM2 (MP2:HF) studies were also performed for these unique benzyne formation reactions. Mechanistic studies on benzyne formation from *o*-metallohalobenzenes (metal = Li, Na, Mg, ...) are still lacking, despite the fact that knowledge of the reaction pathways and the elimination mechanism would aid rational design to improve the yield and selectivity of the benzyne formation and to develop more efficient metal reagents. The purposes of our computational/theoretical study were as follows: (1) to investigate the reaction pathways of benzyne formation reactions using zincate; (2) to investigate the geometrical features of the transition structure, intermediates, and products of the present benzyne formation; and (3) to analyze the role of the ligands on zinc in the generation of benzyne.

Results and Discussion

Organolithiums and Grignard reagents have been widely used as powerful metalating reagents of aromatic rings and also for

benzyne formation.^{5,6} However, their use has been limited because these reagents or the resulting intermediary aromatic metal species undergo reaction with electrophilic functional (directing) groups.⁷ Our approach capitalizes on the high chemoselectivity of organozincate reagents, which allows flexible design and fine-tuning by modifying the ligation environment.⁸ To date, little attention has been paid to benzyne formation using zinc ate complexes, except for a single report by Harada et al.,⁹ because of their mild reactivity. One naturally expects that the elimination of a metal-stabilized anion and a leaving group would require high activation energy. However, in 1999, Harada et al. overcame this drawback of zincates by the use of a strong leaving group (trifluoromethylsulfonyl (TfO-)), and the successive homologation reactions with zincate to afford butylphenylzinc species were reported to proceed smoothly. However, only a limited number of examples of the homologation reactions have been examined, and their generality remains unclear. Thus, we systematically investigated the ability of organozinc ate complexes to show high reactivity and selectivity in the benzyne formation reaction *without the occurrence of successive homologation reactions*.

Direct Benzyne Formation Reaction Through Halogen–Zinc Exchange Reaction. Optimization of the Ligation Environment of Zincates and Reaction Conditions. As a preliminary model reaction, the iodine–zinc exchange reaction of 2-haloiodobenzenes with various zincates was investigated. The results are summarized in Table 1. We first speculated that it might be possible to develop benzyne formation reactions by using ^tBu₃ZnLi,^{8d} the most chemoselective halogen–metal

- (4) A part of the results concerning the 3-functionalized benzyne described here was reported as a preliminary Communication: Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514–8515.
- (5) For reviews on directed ortho metalation, see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. (b) Gschwend, H. W.; Rodriguez, H. R. *Heteroat. Facilitated Lithiations. Org. React. (N.Y.)* **1979**, *26*, 1–360.
- (6) For examples of nonlithio-aromatic species, see: (a) Armstrong, D. R.; Clegg, W.; Dale, S. H.; Hevia, E.; Hogg, L. M.; Honeyman, G. W.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3775–3778. (b) Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4364–4366.
- (7) Upton, C. J.; Beak, P. *J. Org. Chem.* **1975**, *40*, 1094–1098.
- (8) (a) Review: Uchiyama, M.; Kondo, Y. *Synth. Org. Chem. Jpn.* **2006**, *64*, 1180–1190. (b) Kondo, Y.; Takazawa, N.; Yamazaki, C.; Sakamoto, T. *J. Org. Chem.* **1994**, *59*, 4717–4718. (c) Kondo, Y.; Matsudaira, T.; Sato, J.; Murata, N.; Sakamoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736–738. (d) Kondo, Y.; Fujinami, M.; Uchiyama, M.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 799–800.
- (9) Harada, T.; Chiba, M.; Oku, A. *J. Org. Chem.* **1999**, *64*, 8210–8213.

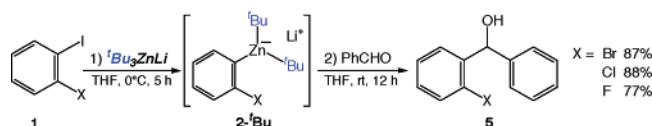


Figure 2. Electrophilic trapping of the intermediary zincates (2).

exchange reagent in our group. Despite excellent reactivity and selectivity in the iodine–zinc exchange reaction (Figure 2), the reagent did not mediate benzyne formation reaction at all at room temperature (Table 1, entry 1). Even when the reaction was carried out at higher temperature (40 °C–reflux), unsatisfactory results were obtained (yields < 30%). With benzaldehyde as the electrophile instead of diene, 2-halobenzhydrol derivatives were obtained in high yields, and this result clearly indicates that only regio-/chemoselective zincation proceeded *without the following benzyne formation* (Figure 2). We then evaluated the influence of other alkyl ligands on zinc upon benzyne formation. In the case of using ^tBu₃ZnLi, only trace amounts of **4a** were obtained at room temperature, along with byproducts obtained by the homologation reaction of the intermediary benzyne and zincate (Table 1, entry 2). Finally, we found that the use of Me₃ZnLi produced Diels–Alder adducts (**4a** or **4a-B**) in satisfactory yields in THF at over 0 °C (Table 1, entries 3–5).¹⁰ Other solvents, such as Et₂O, toluene, and CH₂Cl₂, gave less satisfactory results. It is noteworthy that this benzyne formation method was also applicable to the electrophilic functional group-containing *o*-bromiodobenzene (**1b**) (Table 1, entry 6). Furthermore, when Me₄ZnLi₂ was employed in THF, **4a** was obtained quantitatively even at –78 °C (Table 1, entry 7), supporting our previous findings that dianion-type ate complexes display increased reactivity relative to the monoanion-type ones.¹¹

In other words, we found a significant switching of the reactivity of the arylalkylzincate intermediates (2–R). This drastic change of reaction modes (metalation (no elimination; ^tBu) or generation of benzyne (facile elimination; Me)) depending on the alkyl-ligation environment is a feature of zincates and is potentially useful from the synthetic viewpoint.

Direct Benzyne Formation Reaction Through Deprotonative Zincation Reaction by Using Zinc Ate Base. Development of Me₂Zn(TMP)Li. Having optimized the ligation environment of the arylzincates for benzyne formation and suppression, we next focused on the application to the synthesis of multiply substituted benzyne and benzene. Taking the availability of precursors and general applicability into consideration, deprotonation is expected to be advantageous for the preparation of (multi-)functionalized benzyne. Similar ligand effects might operate in the deprotonative zincation. Thus, we designed Me₂Zn(TMP)Li as a new zinc ate base

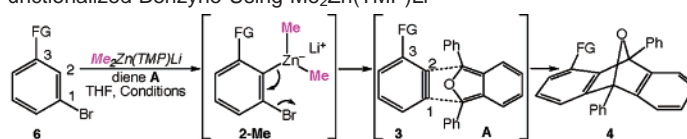
for benzyne synthesis, and the deprotonative zincation was investigated using 3-cyanobromobenzene (**6c**) as a representative substrate (see Supporting Information, Figure S-1, for details).¹²

While deprotonative metalation of 3-substituted benzenes such as **6c** can take place at three positions, the metalation using zincate bases proved to occur regioselectively at the C2 position.⁴ As expected, in the reaction using the newly designed Me₂Zn(TMP)Li, the directed zincation and the subsequent generation of 3-cyanobenzyne (**3c**) proceeded smoothly at room temperature, and the resulting benzyne reacted with 1,3-diphenylisobenzofuran to give the corresponding Diels–Alder adduct (**4c**)¹³ in 80% yield. On the other hand, when ^t-Bu₂Zn(TMP)Li¹⁴ was used under the same conditions, only zincation occurred regio-/chemoselectively *without the formation of benzyne*, and the resulting arylzincate (**2c-t**-Bu) was treated with I₂ to give 3-bromo-2-iodobenzonitrile (**1c**) in 82% yield.

I. Generation of 3-Functionalized Benzyne Using Me₂Zn(TMP)Li. As shown in Table 2, deprotonative zincation with Me₂Zn(TMP)Li proved effective for the one-pot generation of various 3-functionalized benzyne.⁴ Not only alkoxy groups, but also a variety of electrophilic functional groups, including amide, cyano, ester, and various halogens (runs 1–8), are compatible with Me₂Zn(TMP)Li, and neither destruction of functional groups nor self-condensation was observed. The generation of a disubstituted asymmetric benzyne also caused no problem (run 10). The trifluoromethyl group works as an exclusively para-metalating directing group, and the generation of benzyne proceeded smoothly at the 4-position (run 9), although the mechanism of this peculiar metalation is not clear. Thus, this benzyne formation reaction has a high compatibility with functional groups, presumably because of the soft nucleophilicity of zincates. Finally, deprotonative zincation of various halobenzenes (or their analogues) using Me₂Zn(TMP)Li was then investigated to examine the scope of the present method (runs 11–13); various groups such as fluoro, chloro, and triflyl (except for iodo¹⁵) turned out to work well as both ortho-directing and -leaving groups in benzyne formation.

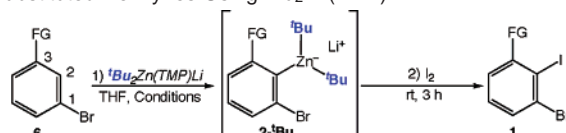
- (10) In the case of using Me₃ZnLi, even when the reaction was carried out at higher temperature (40 °C–reflux), no homologation product (methyl-adduct) was detected. On the other hand, when the reaction of *o*-bromiodobenzene (**1a**) with ^tBu₃ZnLi was performed under reflux for 16 hours in the presence of diene (**A**), the Diels–Alder adduct (**4a**) was obtained in 50% yield.
- (11) (a) Uchiyama, M.; Furuyama, T.; Kobayashi, M.; Matsumoto, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 8404–8405. (b) Uchiyama, M.; Matsumoto, Y.; Nakamura, S.; Ohwada, T.; Kobayashi, N.; Yamashita, N.; Matsumiya, A.; Sakamoto, T. *J. Am. Chem. Soc.*, **2004**, *126*, 8755–8758. (c) Uchiyama, M.; Kondo, Y.; Miura, T.; Sakamoto, T. *J. Am. Chem. Soc.* **1997**, *119*, 12372–12373. (d) Uchiyama, M.; Koike, M.; Kameda, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 8733–8734.

- (12) R₂Zn(TMP)Li (R = Me or ^tBu) can be prepared simply by mixing dialkylzinc and LTMP in a 1:1 molar ratio in THF at room temperature for 1 hour. See Supporting Information for details. On the basis of our computational analysis,^{14c,d} the deprotonation of aromatic compounds using R₂Zn(TMP)Li is endothermic in most cases, so excess zincate (2.2 equiv) was used for the deprotonation reaction in this study. Iodine or benzaldehyde was used as a representative electrophile in this study, but intermediary arylzincate species are known to be able to react with various electrophiles (see refs 8, 11, and 14).
- (13) A series of recent studies has expanded the utility of rigid oxabicyclic compounds: (a) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437–1447. (b) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884–14892. (c) Lautens, M.; Fagnou, K.; Hiebert, S. *J. Am. Chem. Soc.* **2003**, *125*, 48–58. (d) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043–8053. (e) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834–6839. (f) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170–7171. (g) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1803–1804.
- (14) (a) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539–3540. (b) Imahori, T.; Uchiyama, M.; Sakamoto, T.; Kondo, Y. *Chem. Commun.* **2001**, 2450–2451. (c) Uchiyama, M.; Matsumoto, Y.; Nobuto, D.; Furuyama, T.; Yamaguchi, K.; Morokuma, K. *J. Am. Chem. Soc.* **2006**, *128*, 8748–8750. (d) Uchiyama, M.; Matsumoto, Y.; Usui, S.; Hashimoto, Y.; Morokuma, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 926–929. (e) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802–3824. (f) Kondo, Y.; Morey, J. V.; Morgan, J. C.; Naka, H.; Nobuto, D.; Raithby, P. R.; Uchiyama, M.; Wheatley, A. E. H. *J. Am. Chem. Sol.* **2007**, *129*, ASAP.
- (15) The iodine–zinc exchange may occur preferentially over the deprotonation.

Table 2. Direct Generation of 3-Functionalized Benzyne Using $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}^a$ 

Run	Substrate	Benzyne	Conditions	Yield of 4 (%) ^b	Run	Substrate	Benzyne	Conditions	Yield of 4 (%) ^b
1			refl., 12 h	100	8			60°C, 15 h	71
2			refl., 12 h	100	9			rt, 12 h	100
3			refl., 12 h	90	10			refl., 3 h	79
4			refl., 6 h	88	11			refl., 12 h	99
5			refl., 3 h	55	12			refl., 12 h	99
6			rt, 12 h	100	13			rt, 12 h	100
7			rt, 48 h	72					

^a The reaction was carried out using $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}$ (2.2 equiv) and substrate (1 equiv) in THF in the presence of 1,3-diphenylisobenzofuran (2.2 equiv).
^b Isolated yield.

Table 3. Deprotonative Zincation of 3-Substituted Benzyne Using $^t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}^a$ 

Run	Substrate	Product (1)	Conditions	Yield (%) ^b	Run	Substrate	Product (1)	Conditions	Yield (%) ^b
1			0°C, 3 h	84	6			-30°C, 24 h	77
2			0°C, 3 h	96	7			-30°C, 24 h	93
3			rt, 3 h	98	8			rt, 3 h	77
4			rt, 3 h	92	9			0°C, 3 h	74
5			-30°C, 12 h	95					

^a The reaction was carried out using $^t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}$ (2.2 equiv) and substrate (1 equiv) in THF. ^b Isolated yield. ^c FG = functional group.

II. Synthesis of 1,2,3-Functionalized Benzenes Using $^t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}$. On the other hand, zincation with $^t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}$ followed by electrophilic trapping (with I_2) proved a powerful tool for the preparation of 1,2,3-trisubstituted aromatic

compounds.^{4,16} The substrate scope and limitations are summarized in Table 3. With amide, cyano, methoxy, and various halides containing *m*-bromobenzenes, both the chemical yield and the *regioselectivity* were good to excellent. A 1,2,4-

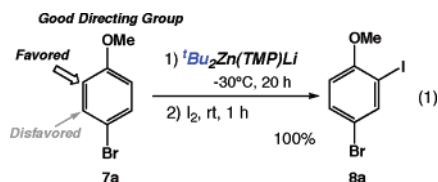
Table 4. Direct Generation of 4-Functionalized Benzyne Using $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}^a$

Run	Substrate	Benzyne	Conditions	Yield of 9 (%) ^b	Run	Substrate	Benzyne	Conditions	Yield of 9 (%) ^b
1			refl., 3 days	81	5			rt, 13 h	91
2			rt, 16 h	52	6			rt, 24 h	83
3			rt, 15 h	56	7			rt, 8 h	100
4			refl., 12 h	80	8			refl., 8 h	80

^a The reaction was carried out using $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}$ (2.2 equiv) and substrate (1 equiv) in THF in the presence of 1,3-diphenylisobenzofuran (2.2 equiv).
^b Isolated yield. ^c FG = functional group.

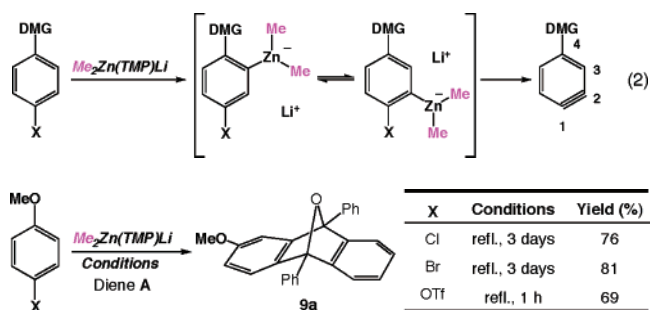
substituted substrate could be used, and a 1,2,3,4-tetrasubstituted product was obtained with high chemo-/regioselectivity. The trifluoromethyl group also functions as an exclusively para-metalating directing group, affording the 1,2,4-substituted benzene derivative.

Application to Preparation of Various 4-Functionalized Benzyne and 1,2,4-Functionalized Benzenes. Having established effective procedures for the generation of 3-functionalized benzyne, we then considered 4-functionalized benzyne. However, deprotonative metalation has so far been regarded as a difficult reaction to use for the synthesis of 4-substituted benzyne, because of its apparently unfavorable regioselectivity. In fact, in the reaction of 4-methoxybromobenzene (**7a**) with $^t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}$ and the successive iodination, the deprotonative zincation proceeded at the ortho position of the methoxy group (a good directing group) selectively to give 1-methoxy-2-iodo-4-bromobenzene (**8a**) in a quantitative yield (eq 1).¹⁷



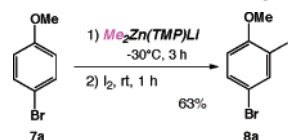
However, we hypothesized that the generation of 4-substituted benzyne could be realized by using the zincate shift reaction from the ortho position of the directed metalation group (DMG) to that of leaving group (eq 2). As expected, when the reaction

temperature was increased and/or reaction time was extended, the reaction proceeded slowly but afforded the desired products (**9**) in high yields (Figure 3). Additionally, when a strong directed leaving group, such as a TfO group, was used, the reaction time was shortened.

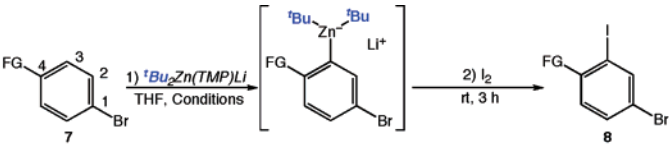
**Figure 3.** Reaction of 4-haloanisole with $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}$.

With optimized conditions in hand, we studied the scope of this new protocol, and representative results are summarized in Table 4. Substrates containing methoxy, bromo, trifluoromethyl, phenyl, and *tert*-butyl groups on the benzene ring can be utilized by employing $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}$, affording 4-substituted benzyne (**10**) through displacement of the phenyl anion equilibrium (runs 1 and 5–8). No double benzyne formation was observed in run 5, although the double benzyne formation often occurs in alkyllithium- or Grignard reagent-mediated reactions of 1,4-dihalobenzene derivatives.^{1,2} In the case of substrates having

(17) In the deprotonation reaction of **7a** with $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}$ under similar reaction conditions, **8a** was also obtained as a single product.

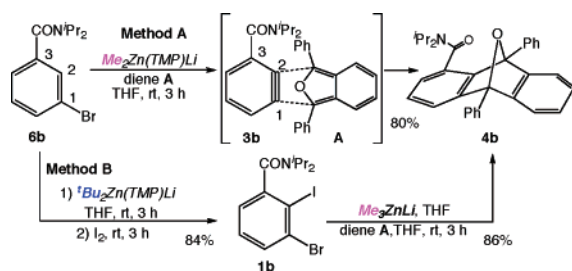


(16) Generally, when traditional reagents, such as alkyllithiums and lithium amides, are used, the desired 1,2,3-trisubstituted benzene derivatives are not obtained in high yields under usual conditions because of the instability of these reagents and/or intermediary aryllithium species with various electrophilic substituents or neighboring bromine (including the formation of benzyne). Indeed, the 2,6-disubstituted iodobenzene derivatives shown in Table 3 are all new compounds.

Table 5. Deprotonative Zincation of Functionalized 4-Substituted Benzenes Using $t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}^a$


Run	Substrate	Product (8)	Conditions	Yield (%) ^b	Run	Substrate	Product (8)	Conditions	Yield (%) ^b
1			-30°C, 20 h	100	4			0°C, 3 h	99
2			-30°C, 2 h	92	5			-30°C, 24 h	83
3			rt, 3 h	97	6			-30°C, 2 h	84

^a The reaction was carried out using $t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}$ (2.2 equiv) and substrate (1 equiv) in THF. ^b Isolated yield. ^c FG = functional group.

**Figure 4.** Two alternative methods for generation of functionalized benzenes.

electron-withdrawing groups such as cyano, ester, and 1,3-oxazolyl groups,¹⁸ a strong directed leaving group, such as a TfO moiety, was required for the benzyne formation to proceed chemoselectively (runs 2–4).

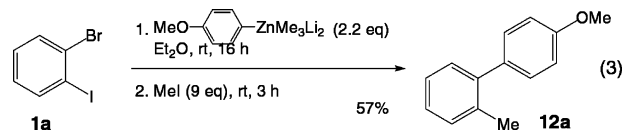
On the other hand, the deprotonative zincation of 4-substituted benzenes using $t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}$ was found to be regio- and chemoselective *with no formation of benzyne*, and the reaction was tolerant of both electron-donating group, such as methoxy, and electron-withdrawing groups, such as cyano, 1,3-oxazolyl, ester, bromo, and trifluoromethyl groups (Table 5).

In summary, deprotonative zincation of various 3-/4-substituted halobenzenes using $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}$ proved effective for the one-pot generation of various 3-/4-functionalized benzenes, particularly those with electrophilic substituents, such as ester, amide, and cyano. On the other hand, zincation with $t\text{Bu}_2\text{Zn}(\text{TMP})\text{Li}$, followed by electrophilic trapping (with I_2) proved a powerful tool for the preparation of 1,2,3-/1,2,4-trisubstituted aromatic compounds *without the formation of benzyne*. As mentioned in Table 1, the resultant trisubstituted benzenes (**1** or **8**) are available as precursors for the generation of 3-/4-substituted benzenes by iodine–zinc exchange reaction. Thus, we have provided two new tools for generating various functionalized benzenes and heterynes (Figure 4). Facile method A (direct benzyne synthesis from halobenzenes) should make reactions involving benzenes more synthetically useful. With dienes having any acidic proton, method B (stepwise benzyne synthesis using halogen–metal exchange reaction) would be

effective and advantageous. These methods offer far greater generality than previous methods for the synthesis of functionalized asymmetric benzenes and multifunctionalized aromatic compounds (Figure 4).

Silylzincation and Carbozincation of Functionalized Unsymmetrical Benzenes. We then demonstrated, as shown in Table 6 and eq 3, that the unsymmetrically functionalized benzyne intermediates we have obtained can be utilized as an electrophilic foundation for further functionalization of the benzene rings. After extensive experimentation, we found that $\text{Me}_2\text{Zn}(\text{SiMe}_2\text{Ph})\text{Li}$ is the best complex for iodine–zinc exchange, benzyne formation, and successive silylzincation reaction¹⁹ with high chemoselectivity. In 3-substituted benzenes, when a coordinative group (DMG) such as methoxy, methoxymethyl, or carbonyl group is present, the silylzincation occurs regioselectively at the meta carbon atom, mainly because of the coordination of DMG to the cation moiety of the zincate (which results in the stabilization of the resultant zincate)²⁰ (runs 2–5). On the other hand, the regiocontrol of incoming reagents is more difficult in 4-substituted benzenes (runs 6–8). In the case of 4-trifluorobenzene, the inductive effect of the functional group seems to be more important for the regioselectivity of the silylzincation (run 8).

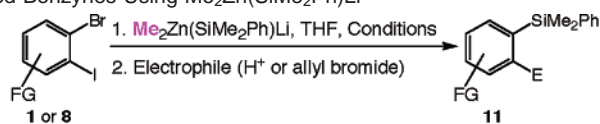
This methodology should be also applicable for synthesis of 4-substituted biphenyl derivatives, that is, cross biaryl coupling (eq 3).²¹



Computational/Theoretical Investigation of Generation and Suppression of 3-/4-Functionalized Benzenes Using Zinc Ate Base (TMP–Zn–ate). Theoretical calculations were performed to investigate the reaction pathway and to understand the origin of the reactivity and unique selectivity achieved through changing the alkyl ligand on zincates in the organozincate-mediated benzyne formation reaction.

Computational Methods and Chemical Models. All calculations were done using the Gaussian 03 program package.²²

(18) For review see: Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837–860.

Table 6. Silylzincation of Functionalized Benzenes Using $\text{Me}_2\text{Zn}(\text{SiMe}_2\text{Ph})\text{Li}^a$ 

Run	Substrate	Product	Yield (%) ^b (Conditions)	Run	Substrate	Product	Yield (%) ^b (Conditions)
1			100 (rt, 16 h)	5 ^c			75 (0°C, 16 h)
2			87 (0°C, 16 h)	6			83 (rt, 16 h) (m : p = 1.2 : 1)
3			86 (0°C, 16 h)	7			71 (refl., 16 h) (m : p = 1 : 1)
4			64 (refl., 12 h)	8			63 (refl., 16 h) (m : p = 1 : 2.7)

^a The reaction was carried out using $\text{Me}_2\text{Zn}(\text{SiPhMe}_2)\text{Li}$ (3.3 equiv) and substrate (1 equiv) in THF. ^b Isolated yield. ^c Treated with 7 equiv of allyl bromide after silylzincation and stirred for 24 h at room temperature. ^d FG = functional group.

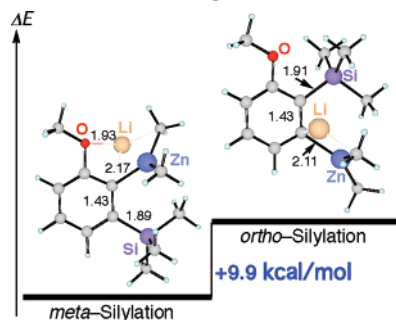
We employed $\text{Me}_2\text{Zn}(2\text{-BrAni})\text{Li}$ (Ani = anisole) and $\text{tBu}_2\text{Zn}(2\text{-BrAni})\text{Li}$ as chemical models for the arylzincate intermediates. The molecular structures and harmonic vibrational frequencies for $\text{Me}_2\text{Zn}(2\text{-BrAni})\text{Li}$ (**13**) were obtained using second-order Møller–Plesset perturbation theory (MP2).²³ We used Ahlrichs' SVP²⁴ all-electron basis set for the Zn and Br atoms and 6-31G* for the other atoms (denoted as 631SVPs in the text). Geometry optimization and vibrational analysis were performed at the same level. All stationary points were optimized without any symmetry assumptions and characterized by normal coordinate analysis at the same level of theory (the number of imaginary frequencies, NIMAG, was 0 for minima

and 1 for TSs). All the transition states structures and the reaction coordinates (Hessian eigenvectors with negative eigenvalues) were examined visually. The intrinsic reaction coordinate (IRC) method²⁵ was used to track minimum energy paths from transition structures to the corresponding local minima.

We used the ONIOM2 (MP2/631SVPs:HF/3-21G) method for the geometry optimization for $\text{tBu}_2\text{Zn}(2\text{-BrAni})\text{Li}$ (**14**). The ONIOM method divides the complex **14** into high- ($\text{C}_2\text{Zn}(2\text{-BrAni})\text{Li}$) and low-level layers (CH_3) connected at the interface by the link H atoms. For the final ONIOM optimized geometries, we performed single point energy calculations using MP2/631SVPs.²⁶

I. Pathway of Generation of Benzyne. We first investigated the reaction pathway of the benzyne formation from $\text{Me}_2\text{Zn}(2\text{-BrAni})\text{Li}$ (**13**) as a basic model reaction. Figure 5 shows the reaction course and the energy profile of the generation of the benzyne from **13** at the MP2/631SVPs level. The intermediate **13** involves a pseudotetrahedral arrangement around the Zn atom and Li bridging between the zincate and ortho MeO group. Among several possibilities for benzyne formation from **13**, we identified one TS, **TS1**, which involves a trigonal planar arrangement around Zn. To reach this TS, the orientation of the Zn atom has to change drastically so that the Lewis acidity of the Zn atom can effectively enhance the leaving ability of the Br atom, and the Zn–C₂ bond cleaves with an overall energy loss of 23.5 kcal/mol (MP2/631SVPs). The degree of shortening of the C₁–C₂ bond length (1.28 Å) in the TS (9%), as well as

- (19) (a) Nakamura, S.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 28–29. (b) Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2005**, *127*, 13116–13117. (c) Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2004**, *126*, 11146–11147.
(20) Comparison of the relative energies of the intermediary zincates based on MP2/631SVPs calculation. (See Computational Methods for details)



- (21) When THF was used as a solvent, the yield of **12a** was reduced, though no non-methylated protonation product could be detected.
(22) Frisch, M. J.; et al. *Gaussian 03*, revision B.04; Gaussian, Inc.: Pittsburgh, PA, 2003.
(23) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618–622.
(24) Schäfer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571–2577.

- (25) (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363–368. (b) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154–2161. Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523–5527.
(26) (a) Kwon, O.; Mckee, M. L. *J. Phys. Chem. A* **2001**, *105*, 10133–10138. (b) Irle, S.; Rubin, Y.; Morokuma, K. *J. Phys. Chem. A* **2002**, *106*, 680–688.

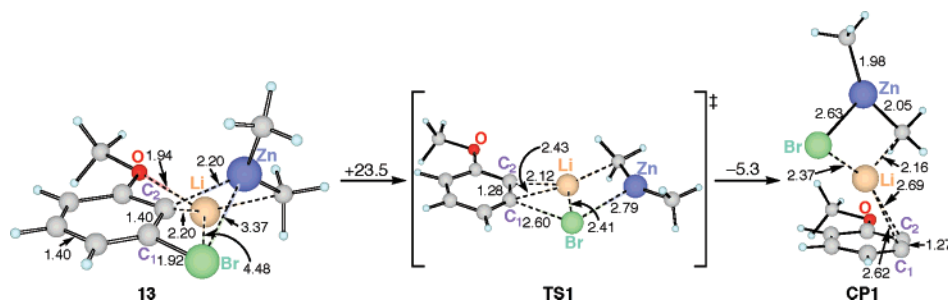


Figure 5. Intermediates, complexes, and TSs in the benzyne formation of $\text{Me}_2\text{Zn}(2\text{-BrAni})\text{Li}$. Bond lengths and energy changes at the MP2/631SVPs level are shown in Å and kcal/mol, respectively.

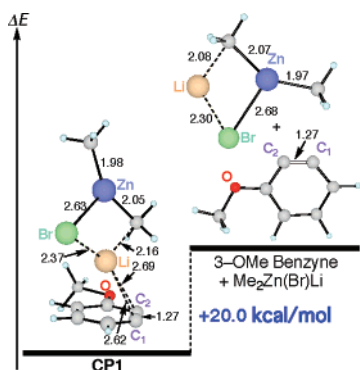


Figure 6. Dissociation of benzyne–zincate complex (**CP1** or **CP2**).

the elongation of the $\text{C}_1\text{-Br}$ (2.60 Å) and $\text{C}_2\text{-Li}$ (2.12 Å) bonds, clearly suggest that the TS is rather late. Since the elimination reaction is facilitated by the push–pull synergy of two heterometals in the zincate, the activation energy seems to be reasonably low. The interaction between dialkylzinc moiety and bromine is crucial for smooth benzyne formation.

After the TS, the Br anion migrates to the Zn atom, and the resultant new zincate ($\text{Me}_2\text{Zn}(\text{Br})\text{Li}$) becomes attached to the benzyne residue to produce a weak complex (**CP1**) through cation–p (benzyne; endocyclic p orbital) interaction. As judged from the $\text{C}_1\text{-C}_2$ bond length (1.27 Å) in the CP, we can consider the CP to be the benzyne complex. Dissociation of the benzyne–zincate complex (**CP1**)²⁷ into a naked benzyne and $\text{Me}_2\text{Zn}(\text{Br})\text{Li}$ occurs with ca. 20 kcal/mol endothermicity (Figure 6), which indicates lower stability than **TS1** (Figure 5). These findings suggest that the reactivity and selectivity of the benzyne intermediate can be tuned through modification of the metal complex (zincate) moiety, in accordance with experimental observations.²⁸ Although the stabilization energies from TS to CP are rather small (ca. 5 kcal/mol), it is probable that **CP1** reacts smoothly with a diene or a nucleophile to gain further stabilization.

II. Suppression of the Benzyne Formation. It has been experimentally clarified that a *t*-Bu ligand on Zn inhibits benzyne formation and hence the zincation with a *t*-Bu–Zn–ate, and subsequent electrophilic trapping provides a powerful tool for the synthesis of 1,2,3-/1,2,4-trisubstituted aromatic compounds *without the formation of benzyne*. To examine the reaction selectivity in relation to the nature of the ligand on Zn, we next examined the benzyne formation of $\text{t}\text{-Bu}_2\text{Zn}(2\text{-BrAni})\text{Li}$ (**14**) by using the ONIOM2 (MP2/631SVPs:HF/3-21G) method.

We can expect a priori that two *t*-Bu ligands strongly hinder the metal (Zn or Li) site from accessing the Br atom, because of the bulkiness of the *t*-Bu ligand, and indeed, this was the case (Figure 7). The activation energy for benzyne formation in *t*-Bu–zincate **14** is sufficiently high, and in accordance with the experimental facts, is much higher than the barrier of the Me–zincate (**13**).²⁹

Conclusion

The zinc ate base, $\text{Me}_2\text{Zn}(\text{TMP})\text{Li}$, has been developed as a novel multifunctional base reagent, allowing highly chemo- and regioselective deprotonative zincation of meta-/para-functionalized aromatic compounds, and successive 3-/4-benzyne formation. This simple and straightforward method provides direct and efficient access to various unsymmetrical functionalized benzenes, which are valuable synthetic intermediates. We also demonstrated Diels–Alder cycloaddition, silylzincation, and phenylzincation with the resultant functionalized benzenes. On the other hand, zincation with $\text{t}\text{-Bu}_2\text{Zn}(\text{TMP})\text{Li}$ followed by electrophilic trapping is a powerful tool for the chemoselective preparation of 1,2,3-/1,2,4-trisubstituted aromatic compounds.

A detailed theoretical/computational mechanistic investigation of the reaction pathway of benzyne formation in this system was conducted, and the structure of the benzyne–zincate complex and the origin of the remarkable selectivity for generation/suppression of benzyne depending upon the ligands

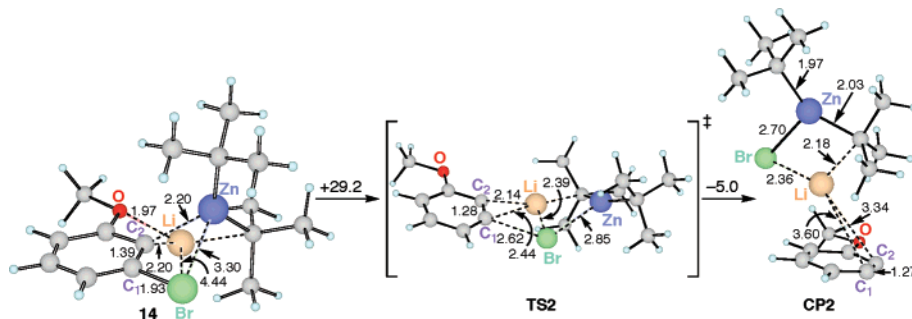


Figure 7. Reaction pathway of benzyne formation of the di-*tert*-butylarylzincate intermediate (**14**). Bond lengths at the ONIOM2(MP2/631SVPs:HF/3-21G) level and energy changes at the MP2/631SVPs/ONIOM2(MP2/631SVPs:HF/3-21G) level are shown in Å and kcal/mol, respectively.

on the zincate have been elucidated. With the comprehensive mechanistic knowledge acquired in this research, improvement of the reaction system and the logical design of a new chemoselective base reagents are in progress in our laboratory.

Acknowledgment. This research was partly supported by the Astellas Foundation, the Sumitomo Foundation, a Grant-in-Aid for Young Scientists (A) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (to M. U.), and

- (27) We identified another complexes **CP2** in which a benzyne and the zincate coordinate through cation–p (benzyne; exocyclic p bond) interaction. The energy difference between **CP1** and **CP2** is only 1.2 kcal/mol and hence they may be in equilibrium.
- (28) Retbøll, M.; Edwards, A. J.; Rae, A. D.; Willis, A. C.; Bennett, M. A.; Wenger, E. *J. Am. Chem. Soc.* **2002**, *124*, 8348–8360.
- (29) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067.

a JSPS Research Fellowship for Young Scientists (to T.F.). M. U. is also the recipient of a Visiting Fellowship at the Cherry L. Emerson Center of Emory University. The calculations were performed on the RIKEN Super Combined Cluster (RSCC). We thank Prof. T. Ohwada and Prof. Y. Otani (The University of Tokyo) for their valuable comments.

Supporting Information Available: Complete ref 22; details of the experimental procedures, spectral and theoretical data (Cartesian coordinates and total electron energies for the optimized stationary points at each level of theory). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA071268U