Experimental and Theoretical Studies on Regiocontrol of Benzyne Reactions Using Silyl and Boryl Directing Groups

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Abstract: The silyl- and boryl-directed regiocontrol of benzyne reactions and their theoretical analyses using density functional theory (DFT) are described herein. The Diels–Alder reactions of both 3-silyl- and 3-borylbenzynes with substituted furans and the [3+2] cycloadditions of 3-silylbenzynes with 1,3-dipoles predominantly produced distal cycloadducts, whereas the [3+2] cycloadditions of the borylbenzynes exclusively produced proximal cycloadducts. Moreover, primary amines selectively underwent nucleophilic addition reactions at the more hindered *ortho*-position of the silyl group of the benzynes. The origin of these anomalous regiochemistries was theoretically evaluated using the natural bond orbital and reaction pathway analyses including the transition states of these reactions. On the basis of DFT calculations, it is proposed that the reactions of the borylbenzynes were controlled by the electrostatic effect of the boryl group, whereas those of the silylbenzynes were primarily governed by the steric effect of the silyl group.

1. Introduction

o-Benzyne, which is formally generated by the abstraction of two adjacent hydrogen atoms from benzene, has been long known as one of the most important reaction intermediates in organic synthesis and has been extensively studied.¹ Although the existence of this molecule as a highly reactive intermediate was a mere speculation around a century ago,² its existence was later confirmed,³ and then, it has been proven to be isolable in a matrix at low temperature.⁴ The distortion of the triple bond in the six-membered ring system of benzyne triggers its distinctive reactions, among which the Diels–Alder (DA) reactions have been extensively utilized to build benzo-fused ring systems in single steps.¹ Since the development of the fluoride-ion-mediated mild preparation of benzyne from *o*-(trimethylsilyl)phenyl triflate by Kobayashi and co-workers,⁵ a wide variety of unprecedented benzyne reactions, such as transition-metal-catalyzed reactions,^{1b} insertion reactions,¹ and multi-component coupling reactions,^{1c} have been developed (Figure 1).¹ Therefore, it is clear that benzyne chemistry is now in another rapidly developing era and has been attracting the interest of synthetic, organometallic, bioorganic, and medicinal chemists.

Benzyne chemistry has nevertheless been plagued by a serious long-recognized problem in that the reactions of unsymmetrically substituted benzynes generally produce mixtures of two possible regioisomers in varying ratios. For example, the DA reactions⁶ of benzynes appended with an alkyl ($R^1 = \text{Me}$, *t*-Bu, Table 1, entries 5 and 6),^{7a,b} a carbamoyl ($R^1 = \text{CONEt}_2$, entry 7),^{7c} or a nitro group ($R^1 = \text{NO}_2$, entry 8)^{7g} at the 3 position provided mixtures of the proximal and distal adducts in varying ratios, and their regioselectivities were hardly predictable, although those having inductively electron-withdrawing groups, such as fluoro ($R^1 = \text{F}$, entries 1 and 2)^{7d} and alkoxy groups ($R^1 = \text{OMe}$, entries 3 and 4),^{7e,f} produced cycloadducts with good-to-excellent proximal selectivities.

Figure 1. Various types of benzyne reactions.

Table 1. Regioselectivities in DA reactions of 3-substituted benzynes with furans.

Entry	R ¹	R ²	<i>distal</i> : <i>proximal</i>	Yield (%)	Ref ^a
1	F	Me	36 : 64	61	7d
2	F	<i>t</i> -Bu	10 : 90	59	7d
3	OMe	<i>t</i> -Bu	15 : 85	34	7f
4	OMe	OMe	1 : >99	75	7e
5	Me	Me	42 : 58	74	7b
6	<i>t</i> -Bu ^b	<i>t</i> -Bu	65 : 35	57	7a
7	CONEt ₂	Me	50 : 50	60	7c
8	NO ₂	Me	36 : 64	74	7g

^aReference. ^b3,5-Di(*tert*-butyl)benzyne was used.

The use of semi-metallic silyl and boryl substituents as regio-directing groups has become one of the major tools in various reactions.^{8,9} In the case of benzyne reactions, Suzuki and co-workers first reported the regioselective cycloaddition reactions of 3-silylbenzynes with nitrones.^{10,11} Herein, we present our very recent results on the regiocontrol of benzyne reactions using silyl^{12,13a} and boryl groups.^{14,15} Given that the silyl and boryl substituents of the products can be converted into a variety of carbon-, oxygen-, and nitrogen-substituents, the current method provides a new and reliable alternative means of synthesizing multisubstituted aromatic compounds. The mechanism underlying the regioselective reactions of the silyl- and boryl-benzynes is also discussed herein based on DFT calculations.

2. Experimental Results

2.1 Diels-Alder Reactions of 3-Silylbenzynes with Furans

Based on our interest in the development of a new method of synthesizing 1-arylnaphthalenes and their derivatives,¹⁶ the DA reaction of 3-phenylbenzyne **5a**, generated *in situ* by the treatment of a precursor **1a** with *n*-BuLi at -78°C , and *tert*-butylfuran **4a** was preliminarily investigated. The reaction gave rise to a mixture of two regioisomers, *distal*-**8a** and *proximal*-**8a**, in 70% total yield; however, the regioselectivity was quite low (*distal*/*proximal*=43:57, Table 2, entry 1). Considering another of our experimental results (*distal*-**9a**/*proximal*-**9a**=63:37, Table 2, entry 2) and other reports,¹⁷ it appears that simple steric bulkiness was largely ineffective for controlling the regiochemistry of the DA reaction of the benzynes.

The focus was subsequently turned to 3-silylbenzynes^{10,11} as substrates for the synthesis of 1-arylnaphthalenes, given that the lower electronegativity of silicon relative to that of carbon (Allred-Rochow electronegativities, Si: 1.7, C: 2.5) should exert an electrostatic effect on the benzyne nucleus, thereby producing a distinction between C1 and C2, thus enabling control of the regiochemistry of the DA reaction. The possible transformation of the silyl groups to various aryl groups using Hiyama couplings^{18,19} was another motivating factor for examining the use of 3-silylbenzynes as new dienophiles for the DA reaction. Combination of the DA and

Hiyama reactions was expected to enable the regioselective synthesis of various 1-arylnaphthalenes and their derivatives.

The initial reaction of 3-(trimethylsilyl)benzyne **7A γ** , generated *in situ* from the precursor **3A γ** using *n*-BuLi, and **4a** predominantly generated the *distal* adduct *distal*-**10A γ a** along with *proximal*-**10A γ a** (*distal*/*proximal*=98:2) in 63% total yield (Table 2, entry 3). Similar reactions of 3-(*tert*-butyldimethylsilyl)benzyne **7B γ** and 3-(allyldimethylsilyl)benzyne **7C γ** respectively furnished *distal*-**10B γ a** and *distal*-**10C γ a** as exclusive products (entries 4 and 5). These data provide conclusive evidence that the silyl groups have an outstanding ability to effectively control the regioselectivity of benzyne reactions.

The scope and limitation of the *distal* selective DA reaction of variously substituted **7B** or **7C** and furans **4** were explored (Table 3). The ratios of *distal*-**10B** to *proximal*-**10B** and those of *distal*-**10C** to *proximal*-**10C** ranged from 71:29 to >99:1, and the ratios were slightly affected by the substituents (R^1 and SiR^2Me_2) of **7B** or **7C**. For example, the reaction of 3-(*tert*-butyldimethylsilyl)-5-methylbenzyne **7B γ** ($\text{R}^1=\text{Me}$, $\text{R}^2=t\text{-Bu}$) with 2-butylfuran **4b** ($\text{R}^3=n\text{-Bu}$, $\text{R}^4=\text{H}$) gave an 85:15 mixture of *distal*-**10B γ b** and *proximal*-**10B γ b**, and the reaction of 3-(*tert*-butyldimethylsilyl)-5-fluorobenzyne **7B δ** ($\text{R}^1=\text{F}$, $\text{R}^2=t\text{-Bu}$) provided **10B δ b** in a slightly higher ratio (*distal*/*proximal*=91:9). On the other hand, the bulkier R^3 group at the 2 position of **4** significantly improved the *distal* selectivity, and the R^4 group at the 3 position of **4** ($\text{R}^3=\text{H}$, $\text{R}^4=\text{Me}$) also induced *distal* selectivity (for details, see Scheme 4). Various functional groups, such as fluoro, methoxy, (tetrahydropyranyloxy, trimethylsilyl, and tributylstannyl groups, were tolerated under the given reaction conditions.

In contrast, similar reactions of 4-methoxy-2-siloxyfuran **11** with **7B** or **7C** respectively generated *proximal*-**12B** or **12C** as the predominant products. Because these adducts were

Table 2. DA reactions of benzynes **5–7** with 2-(*tert*-butyl)furan **4a**.

Reaction scheme showing the synthesis of 1-arylnaphthalene isomers (8-10) from 3-substituted-5-bromo-2-OTf benzynes (1-3) and 2-(tert-butyl)furan (4a) using *n*-BuLi in toluene at -78 °C for 15–30 min.

The reaction proceeds via a mixture of **5–7** and **4a** intermediates, leading to the formation of **distal-8–10** and **proximal-8–10** isomers.

1, 5, 8: $\text{R}^1 = \text{Ph}$
2, 6, 9: $\text{R}^1 = t\text{-Bu}$
3A, 7A, 10A: $\text{R}^1 = \text{SiMe}_3$
3B, 7B, 10B: $\text{R}^1 = \text{Si}(t\text{-Bu})\text{Me}_2$
3C, 7C, 10C: $\text{R}^1 = \text{Si(allyl)Me}_2$

Entry	R^1	R^2	1–3, 5–7	<i>distal</i> : <i>proximal</i>	8–10	Yield (%)
1	Ph	H	1a, 5a	43 : 57	8a	70
2	<i>t</i> -Bu	<i>t</i> -Bu	2b, 6b	63 : 37	9b	53
3	SiMe_3	Me	3Aγ, 7Aγ	98 : 2	10Aγa	63
4	$\text{Si}(t\text{-Bu})\text{Me}_2$	Me	3Bγ, 7Bγ	>99 : 1	10Bγa	69
5	Si(allyl)Me_2	Me	3Cγ, 7Cγ	>99 : 1	10Cγa	79

Table 3. DA reactions of 3-silylbenzynes (**7B** or **7C**) with furans **4**.

		<p>3B, 7B, 10B: $\text{R}^2 = t\text{-Bu}$ 3C, 7C, 10C: $\text{R}^2 = \text{allyl}$</p>	
Entry	Major Product	Results	
1		<p><i>distal</i>-10B/<i>proximal</i>-10B = 76 : 24 to >99 : 1 40–68% total isolated yield</p> <p>$\text{R}^1 = \text{H, Me, Ph, F, OMe, etc.}$ $\text{R}^3 = \text{Me, } n\text{-Bu, SiMe}_3, \text{SnBu}_3$ $\text{R}^4 = \text{H, Me}$</p>	
2		<p><i>distal</i>-10C/<i>proximal</i>-10C = 71 : 29 to >99 : 1 38–85% total isolated yield</p> <p>$\text{R}^1 = \text{H, Me, Ph, CH}_2\text{OTHP, etc.}$ $\text{R}^3 = \text{Me, } n\text{-Bu, SiMe}_3, \text{SnBu}_3$ $\text{R}^4 = \text{H, Me}$</p>	

unstable in air under ambient conditions, the corresponding naphthoquinones (*proximal*-**13B** and -**13C**) and the acetate *proximal*-**14B** were obtained after the treatment of the crude products with either ceric ammonium nitrate (CAN) or Ac₂O/pyridine, respectively (Table 4). The proximal selectivities were excellent in all cases.

Table 4. DA reactions of 3-silylbenzynes (**7B** or **7C**) with 4-alkoxy-2-siloxyfuran **11**.

Entry	Workup	Major Product	Results
1	CAN	 <i>proximal</i> - 13B or 13C / <i>distal</i> - 13B or 13C	= >10 : 1 31–82% total isolated yield R ¹ = H, Me, Ph, F, OMe, etc. R ² = <i>t</i> -Bu, allyl
2	Ac ₂ O pyridine	 <i>proximal</i> - 14B	<i>proximal</i> - 14B / <i>distal</i> - 14B = >10 : 1 56% total isolated yield

The Hiyama coupling of *distal*-**10B** with aryl iodides was achieved via intramolecular activation of the silyl group.²⁰ Following the regioselective 1,4-epoxy-ring opening of *distal*-**10B** using TsOH,²¹ the phenolic hydroxyl groups were coordinated to the silicon atom at the *peri*-position under basic conditions, which promoted the coupling reactions with aryl iodides to give 1-arylnaphthalenes **16**. Thus, the coupling reaction proceeded without the use of a fluoride ion (Scheme 1, Eq. 1).²² The fact that the silyl group was transferred to the neighboring oxygen atom during the reaction indicated the formation of pentacoordinate silicate intermediates. This is the first example of the Hiyama coupling using the robust (*tert*-butyldimethylsilyl)arenes.²³

Other useful transformations of *distal*-**10** for the synthesis of multisubstituted naphthalene derivatives are also shown in Scheme 1. The TMSI-promoted desilylation and epoxy-ring opening of *distal*-**10B** provided 1-naphthol **17** (Eq. 2). 1,8-Dihydroxynaphthalenes **18**,²⁴ which had previously been difficult to synthesize, were obtained by the Tamao oxidation²⁵ of *distal*-**10C**, followed by the regioselective epoxy-ring opening (Eq. 3).

2.2 Diels-Alder Reactions of 3-Borylbenzynes with Furans and Pyrroles

The potential of boronic acids and boronates not only as synthetic intermediates²⁶ but also as functional molecules²⁷

Scheme 1. Synthesis of substituted naphthalenes **16–18** by transformations of *distal*-**10B** or **10C**.

and drug candidates has garnered significant attention.²⁸ Thus, efficient synthetic protocols for generating aryl boronic acids have been sought by organic chemists. The approach to the novel synthesis of aryl boronates used by the authors was based on the construction of carbon frameworks from benzyne containing boronic functionalities. However, prior to the initiation of this project, there had been no prior reports of borylbenzynes.

Initially, the preparation of 3-silylbenzynes **7** was applied to the preparation of 3-borylbenzyne **21γ** (R¹ = Bpin, R² = Me), and its generation was evaluated by the DA reaction with *n*-butylfuran **4b**. However, the use of various alkylolithiums resulted in low yields of the cycloadduct **22γb** (R¹ = Bpin, R² = Me). Extensive trials revealed that the efficiency of **21α** generation was significantly enhanced by the reaction of 2-boryl-6-iodophenyl triflate **20α** (R¹ = Bpin, R² = H) with *i*-PrMgCl·LiCl²⁹ in Et₂O at –78 °C, which produced a 90:10 mixture of *distal*-**22αb** and *proximal*-**22αb** in 88% total yield (Table 5, entry 2). Such a high distal regioselectivity of the DA reaction of **21** was noteworthy considering that a similar reaction of *tert*-butylbenzyne **6γ** (R¹ = *t*-Bu, R² = Me) prepared

Table 5. DA reactions of benzyne (**6** or **21**) with 2-*n*-butylfuran **4b**.

Entry	R ¹	R ²	6 , 19–21	<i>distal</i> : <i>proximal</i>	9 or 22	Yield (%)
1	<i>t</i> -Bu	Me	19γ , 6γ	52 : 48	9γb	71
2	Bpin	H	20α , 21α	90 : 10	22αb	88
3 ^a	Bpin	H	20α' , 21α	91 : 9	22αb	29

^a **20α'** was used instead of **20α**.

from **19γ** produced a 1:1 mixture of *distal*-**9γb** and *proximal*-**9γb** (Table 5, entry 1). The use of an alternative precursor, **20α'**, in which the positions of the iodo and sulfonyloxy groups were interchanged, generated a mixture of *distal*-**22αb** and *proximal*-**22αb** in the same ratio (*distal*-**22αb**/*proximal*-**22αb**=91:9, entry 3) as that of entry 2, although the total yield of **22αb** was lower than that from **20α**. These results provided strong evidence to support the formation of the borylbenzyne **21α**.

The invention of the benzyne precursor **20** also offered the added benefit of facilitating the preparation of precursors with various labile functional groups without the use of strong bases such as *n*-BuLi.³⁰ Thus, the DA reaction of various borylbenzynes **21**, generated from **20**, with 2-substituted furans **4** was investigated (Table 6). Under the optimized reaction conditions, the cycloaddition products **22** (X=O) were produced in 40–99% yields with high *distal* selectivities (*distal*-**22**/*proximal*-**22**=82:18 to >99:1, entry 1). Substituents such as ester, acyl, cyano, and bromo groups, were compatible under the reaction conditions. Surprisingly, the reaction of **4** appended with either an electron-withdrawing (R²=CO₂Me) or an electron-donating (R²=OMe) group at the 2 position resulted in similar *distal* selectivities (entry 1). Similar reactions with *N*-protected pyrroles **23** also produced cycloadducts **24**, in which the *distal* adducts were again major products (entry 2). These results represented the first examples of regioselective DA reactions of substituted benzynes and pyrroles **23**.³¹

Table 6. DA reaction of 3-borylbenzynes **21** with furans **4** or pyrroles **23**.

Entry	Major Product	Results
1		<i>distal</i> - 22 / <i>proximal</i> - 22 = 82 : 18 to >99 : 1 40–99% total isolated yield R ¹ = Me, Br, CO ₂ Me R ² = Me, Bu, SnBu ₃ , OMe, CO ₂ Me, etc.
2		<i>distal</i> - 24 / <i>proximal</i> - 24 = 87 : 13 to >99 : 1 58–72% total isolated yield R ¹ = Me, Br, CO ₂ Me, R ² = Et, Br R ⁴ = Boc, Ts

Interestingly, **20γ** reacted with either 3-methylfuran **4c** or 3-methylpyrrole **23c** to produce the corresponding products, *proximal*-**22γc** and *proximal*-**24γc**, with high regioselectivities, in which the methyl group derived from **4c** and **23c** was located close to the boryl group (Scheme 2). This high level of regioselectivity is outstanding compared with the known DA

Scheme 2. DA reactions of 3-borylbenzyne, generated from **20γ**, with 3-methylfuran **4c** or 3-methylpyrrole **23c**.

reactions of substituted benzynes and 3-substituted furans.^{21a}

The boryl group of *distal*-**22γ** was transformed into amino (Scheme 3, conditions A) and hydroxyl groups (conditions B), while leaving the 1,4-epoxy-1,4-dihydronaphthalene frame intact. Following the acid-catalyzed isomerization of *distal*-**22γ** and *distal*-**24γ**, Suzuki–Miyaura coupling with aryl iodides gave the biaryl compounds **27** and **28** (Scheme 3). Thus, this series of reactions, namely, the regioselective DA reaction of the borylbenzynes **21** and the transformation of the boryl group of the adducts, provided a reliable method for the synthesis of multisubstituted benzo-fused compounds.

Scheme 3. Transformations of *distal*-**22γ** and *distal*-**24γ**.

2.3 Differences between 3-Silylbenzynes and 3-Borylbenzynes in Diels–Alder Reactions with Furans

As discussed above, in this work, we have demonstrated that silyl and boryl groups effectively control the regioselectivity of the DA reactions of benzynes with furans and with pyrroles. Here, we present a brief comparison of the regioselectivities of the DA reactions of silylbenzynes **7Bγ** with those of borylbenzynes **21γ** (Scheme 4). The reactions of both **7Bγ** and **21γ** with 2-substituted furans (**4a** and **4d**) preferentially generated the *distal* adducts **10Bγ** and **22γ**, in which the larger R² substituent of **4** exhibited the higher *distal* selectivities. On the other hand, we found the following differences between the reactions of **7Bγ** and those of **21γ**. (1) Whereas the steric bulkiness of the substituent of **4** (*t*-Bu vs. Me) exerted a marked influence on the regioselectivity of **7Bγ**, the steric effect of the substituents of **21γ** was less pronounced (Scheme 4, Eq. 1). (2) The reaction of 3-methylfuran **4c** with **7Bγ** preferentially furnished the *distal* adduct **10Bγc** (*distal*

Scheme 4. Differences between the regiochemistries of the DA reactions of silylbenzynes **7Bγ** and those of borylbenzynes **21γ**.

proximal=67:33), whereas the reaction with **21γ** selectively produced *proximal*-**22γc** (*distal/proximal*=13:87) (Eq. 2). (3) Although the reaction of **7Bγ** with 2-methoxyfuran **4e** preferentially produced **29Bγe** with low selectivity (**29Bγe/31Bγe**=62:38) after immediate opening of the 1,4-epoxy ring of the cycloadducts, a similar reaction of **21γ** with **4e** exclusively provided **30γe** (Eq. 3). These results clearly demonstrate that the effect of the silyl group on the regioselectivity of the DA reactions is different from that of the boryl group; the former appears to be caused mainly by steric factors, and the latter, by electrostatic factors.

2.4 [3+2] Cycloadditions of 3-Silylbenzynes and 3-Borylbenzynes with 1,3-Dipoles

One of the most important methods for the synthesis of benzo-fused azole derivatives³² is the [3+2] cycloaddition of benzynes with 1,3-dipolar compounds. Since Yamamoto and Jin reported the synthesis of 1*H*-indazoles by means of the [3+2] cycloaddition of benzynes with diazo compounds in 2007,^{33a} this research area has developed rapidly.³³ However, the reactions of unsymmetrically substituted benzynes generally generated mixtures of two regioisomers with low selectivities.^{32d} With this background, we addressed the issue of the regiocontrolled synthesis of benzo-fused heteroaromatics using the silyl **7** and borylbenzynes **21**.¹⁵

Because the abovementioned methods for generation of **7** and **21** were not applicable to the [3+2] cycloaddition reactions with various 1,3-dipolar compounds, the initial challenge was the development of milder and more effective conditions using other benzyne precursors. Extensive studies finally revealed

Table 7. Regioselective [3+2] cycloadditions of 3-silylbenzynes **7** or 3-borylbenzynes **21** with 1,3-dipolar compounds **34–36**.

<p>33A: SiR₃ = SiMe₃ 33B: SiR₃ = Si(<i>t</i>-Bu)Me₂</p>			<p>40</p>				
Entry	Major Product	Result	Entry	Major Product	Result	Entry	Major Product & Result
1	 <i>distal</i> - 37A	<i>distal</i> - 37A/proximal - 37A = 77 : 23 to 93 : 7 44–81% total isolated yield R ¹ = H, Me, Cl, F R ² = Bn, CH ₂ CO ₂ Et, CHPh ₂ , C ₁₀ H ₂₁ , Ph, C ₆ H ₃ -2,6-Br ₂ , C ₆ H ₃ -2,4-(OMe) ₂ , C ₆ H ₅ -4-CO ₂ Et etc.	3	 <i>distal</i> - 38γ	SiR ₃ = SiMe ₃ : <i>distal</i> - 38Aγ/proximal - 38Aγ = 58 : 42 98% total isolated yield SiR ₃ = Si(<i>t</i> -Bu)Me ₂ : <i>distal</i> - 38Bγ/proximal - 38Bγ = 77 : 23 99% total isolated yield	5	 39Aγ (M = SiMe ₃) <i>distal</i> - 39Aγ/proximal - 39Aγ = 95 : 5 94% total isolated yield
2	 <i>proximal</i> - 41	only <i>proximal</i> - 41 65–89% isolated yield R ¹ = H, Me R ² = Bn, CH ₂ CO ₂ Et, CHPh ₂ , C ₁₀ H ₂₁ , Ph, C ₆ H ₄ -2-Br, C ₆ H ₃ -2,4-(OMe) ₂ , C ₆ H ₄ -2-Cl, CH ₂ C ₆ H ₄ -2-CN, CH ₂ C ₆ H ₄ -2-CO ₂ Me etc.	4	 <i>proximal</i> - 42γ	only <i>proximal</i> - 42γ 54% isolated yield	6	 43γ (M = Bpin) only <i>distal</i> - 43γ 64% isolated yield

Scheme 5. Syntheses of vorozole **45** and its regioisomer **47** using complementary regioselective [3+2] cycloadditions of silyl- and boryl-benzynes generated from **33Bε** and **40ε**.

that the reaction of 2,6-bis(trimethylsilyl)phenyl triflates **33A** with Bu₄NF and the reaction of 2-boryl-6-iodophenyl 2,4,5-trichlorobenzenesulfonate **40** with *i*-PrMgCl·LiCl were suitable for generating **7** and **21**, respectively, in the presence of 1,3-dipolar compounds. Under these conditions, **7Aγ** (SiR₃ = SiMe₃, R¹ = Me), which was generated *in situ*, immediately reacted with 4-(*tert*-butyl)phenyl azide **34a** [R² = C₆H₄-4-(*t*-Bu)] to selectively provide *distal*-**37Aγa** [R¹ = Me, R² = C₆H₄-4-(*t*-Bu)] (*distal/proximal* = 10:1, Table 7, entry 1), whereas a similar reaction of **21** furnished sterically unfavorable *proximal*-**41γa** [R¹ = Me, R² = C₆H₄-4-(*t*-Bu)] exclusively (entry 2).

Subsequent investigation of various [3+2] reactions of **7** and **21** with diverse dipoles **34–36** (Table 7) demonstrated that the reactions of **7** with **34** and **35** selectively produced *distal* products (**37** and **38**) (entries 1 and 3), whereas similar reactions of **21** generally provided *proximal* products (**41** and **42**) (entries 2 and 4). These complementary selectivities provide useful protocols for the preparation of both regioisomers of a range of benzo-fused heterocycles.

Some other features of these reactions are worth noting. (1) Many functional groups such as ester, bromo, chloro, and cyano groups were tolerated under the reaction conditions. (2) The use of 3-(*tert*-butyldimethylsilyl)benzynes **7B** instead of **7A** increased the *distal* selectivity (entry 3). (3) The substituents R¹ (H, Me, F, and Cl) at the 5 position of the benzynes had little effect on the selectivities of the [3+2] cycloaddition reactions of **7** or **21** with various azides **34** (entries 1 and 2). (4) The [3+2] cycloaddition of **7γ** with TMSCHN₂ **35**^{32a} selectively provided indazole *distal*-**38γ** (entry 3), and similar reactions of **21γ** exclusively furnished *proximal*-**42γ** (entry 4). (5) The [3+2] cycloadditions of **7** or **21γ** with nitron **36**³⁴ are the only exceptions; both reactions exhibited the same regioselectivity to give *distal*-**39Aγ** and *distal*-**43γ** exclusively (entries 5 and 6), whereas all other reactions of **7** and **21d** with 1,3-dipoles (**34** and **35**) exhibited opposite selectivities (entries 1–4).

The developed methods were then applied to the synthesis of vorozole **45**, an aromatase inhibitor,³⁵ and its regioisomer **47**. Starting from suitably functionalized precursors (**33Bε** and **40ε**), *distal*-**37Bεb** and *proximal*-**41εb** were respectively obtained, each with high regioselectivity. These adducts were easily converted into **45** and **47**, respectively (Scheme 5). Therefore, the complementary synthesis of diverse benzo-fused heterocycles such as *distal*-**37** and *proximal*-**41** should

serve as useful synthetic tools for drug discovery.

2.5 Nucleophilic Addition to 3-Silylbenzynes

The silyl group also produced the regioselective nucleophilic addition of primary amines **48** to **7A**.¹³ Despite possible steric repulsion between the approaching **48** and the bulky trimethylsilyl group, the reaction occurred preferentially at the 2 position of **7A** to furnish *ortho*-**49A** (Scheme 6). This unique *ortho*-selectivity was widely demonstrated by the reactions of various **7A** with **48**, and a range of functional groups such as fluoro, chloro, silyloxy, furyl, hydroxyl, amino, and carbamoyl groups, were tolerated.

Scheme 6. *ortho*-Selective nucleophilic additions of amines **48** to silylbenzynes **7A**.

3. Discussion^{12b,14b,15}

The origin of the regioselectivities in the DA reactions, [3+2] cycloaddition reactions, and nucleophilic addition reactions of silyl- and boryl-benzynes (**7** and **21**) were theoretically evaluated based on DFT calculations at the B3LYP/6-31G(d) level using the Gaussian09 program package.³⁶

Initially, the electron densities at C1 and C2 of some 3-substituted benzynes (**7Aα**, **7Bα**, **7Bγ**, **7Dα**, **21α**, **21γ**, **50**, **51**, and **6α**) were calculated using the natural bond orbital (NBO) method^{37,38} in order to evaluate the electrostatic effect of the substituents. It was found that the electron densities at C1 of **7s** and **21s** were higher than those at C2, whereas those of **50** and **51** exhibited the opposite trend. In the case of **6α**, these two carbons had almost the same electron density. On the other hand, the substituents (H and Me) at the 5 position of benzynes had little influence on the electron densities (Figure 2).

Figure 2. Electron densities at C1 and C2 of various benzyne (**7Aα**, **7Bα**, **7Bγ**, **7Dα**, **21α**, **21γ**, **50**, **51**, and **6α**) and those at C2 and C5 of furans (**4a**, **4d**–**4f**) calculated by NBO method.

In a similar manner, it was found that alkyl and alkoxy groups at the 2 position of furans **4a**, **4d**, **4e**, and **4f** enhanced the electron density at C5 compared to C2, and the presence of a methoxycarbonyl group made C5 more electron-deficient.

The electrostatic interactions between benzyne (**7Bγ** and **21γ**) and furans (**4d** and **4e**) roughly account for the experimentally favorable orientation of their DA reactions (Figure 3). However, this explanation is inadequate to describe a similar interaction between **21γ** and **4f** for the preferential formation of *distal*-**22γf**. The DA reaction of **21γ** and **4f** was also evaluated based on theoretical analysis using the frontier orbital theory;³⁹ however, the HOMO–LUMO interaction of these reactants did not provide an adequate platform for understanding its anomalous orientation. These results clearly indicated that the electrostatic and/or orbital interaction of the reactants were not sufficient for a global and quantitative explanation of the experimental regioselectivity.

In order to rationalize the origin of the regioselectivities, reaction pathway analysis of the DA reactions, including the transition states (TSs),⁴⁰ was subsequently executed. The TS could be determined for nine reactions of silylbenzyne **7B** with **4**. For example, *distal*-TS10Bγd leading to *distal*-**10Bγd** is 0.82 kcal/mol lower than *proximal*-TS10Bγd leading to *proximal*-**10Bγd**, which theoretically indicates an 80:20 distal selectivity (Figure 4A) and is in excellent agreement with the experimental result (*distal*-**10Bγd**/*proximal*-**10Bγd**=80:20, Scheme 4, Eq. 1). We could also identify the TSs for fourteen

Figure 3. Electrostatic interaction between benzyne (**7Bγ** and **21γ**) and furans **4d**–**4f** by natural bond orbital (NBO) analysis. Numerals beside orbital lobes indicate electron density of the NBO. The distal-to-proximal ratio of each reaction indicates the experimental result.

reactions of borylbenzyne **21** with either **4** or pyrroles **23**. All theoretical distal-to-proximal ratios of the adducts (**10** and **22**) based on the potential energy differences between *distal*-TSs and *proximal*-TSs were in good agreement with the experimentally determined ratios. Thus, the reliability of the theoretically determined TSs was deemed acceptable. These results also suggested that the regioselectivities of the DA reactions were critically controlled by the TSs.

In order to further evaluate the origin of the regioselectivities, the structures of these TSs were extensively characterized. They were also compared with the TSs of the DA reactions of **7** or **21** with unsubstituted furan **4g** as standard references. The following findings are noteworthy:

(1) The results of characterization of the TSs (TS10Dαg, TS10Aαg, TS10Bαg, and TS22αg) of the DA reactions of some silyl- (**7Dα**, **7Aα**, and **7Bα**) and boryl-benzyne **21α** with unsubstituted furan **4g**, including vibration, indicated that all reactions proceeded via the non-synchronous concerted mechanism (Figure 5). Although the charge distribution of silylbenzyne **7Aα** and that of borylbenzyne **21α** are quite similar (Figure 2), the structures of TS10Aαg and TS22αg are very different. In the case of TS10Aαg, the distance between C2 of **7Aα** and **4g** is longer than that between C1 and **4g**, whereas in TS22αg, the distance between C2 of **21α** and **4g** is

Figure 4. Two most possible transition states of the DA reaction between silylbenzyne **7Bγ** and 2-substituted furans [2-methylfuran **4d** (Fig. 4A) and 2-*tert*-butylfuran **4a** (Fig. 4B)].

Figure 5. Transition states (**TS10Dαg**, **TS10Aαg**, **TS10Bαg** and **TS22αg**) of DA reactions between silylbenzynes **7α** or borylbenzynes **21α** and unsubstituted furan **4g**.

Figure 6. Two most possible transition states of the DA reaction between borylbenzynes **21γ** and 2-substituted furans [2-methylfuran **4d** (Fig. 6A), 2-*tert*-butylfuran **4a** (Fig. 6B), 2-methoxyfuran **4e** (Fig. 6C), and 2-(methoxycarbonyl)furan **4f** (Fig. 6D)].

much shorter than that between C1 and **4g** (Figure 5). The structures of **TS10Aαg** and **TS10Bαg** show a large steric repulsion between the silyl groups and the hydrogen of **4g**, while the structure of **TS22αg** clearly reflects the inherent electron density of **21α**.

(2) In *proximal*-**TS10Bγd** and *proximal*-**TS10Bγa** (Figures 4A and 4B), the steric repulsion between the silyl group and the substituents at the 2 position of furans (**4d** or **4a**) is even greater, thus enlarging the potential energy difference between the distal and proximal TSs. In particular, in *proximal*-**TS10Bγa** bearing the bulkier *t*-butyl group, the potential energy difference is much larger. On the other hand, in the case of borylbenzynes **21γ** (Figures 6A and 6B), the structural difference between *proximal*-**TS22γd** and *proximal*-**TS22γa** is relatively small, and the potential energy differences between the distal and proximal TSs are also small. These contrasting results

clearly indicate that the regioselectivities of the DA reactions of the silylbenzynes **7** are mainly determined by the steric repulsion between **7** and **4** in addition to their inherent electrostatic interactions, whereas those of borylbenzynes **21** are mainly determined by their electrostatic interactions with **4**.

(3) The DA reaction of borylbenzynes **21γ** with 2-methoxyfuran **4e** and that with 2-(methoxycarbonyl)furan **4f** were both distal selective (Table 6, entry 1), among which the latter cannot be accounted for by the electrostatic interaction between **21γ** and **4f** (Figure 3). In *proximal*-**TS22γf** (Figure 6D), which is electrostatically more favorable than *distal*-**TS22γf**, the length (2.64 Å) of the forming bond at the 2 position of **21γ** is much shorter than those in *proximal*-**TS22γa** (2.94 Å) and *proximal*-**TS22γe** (2.93 Å) (Figures 6B and 6C). Therefore, *proximal*-**TS22γf** is susceptible to the large steric repulsion between the boryl and the methoxycarbonyl groups and is

Figure 7. Transition state of the [3+2] cycloaddition reaction between benzyl azide **34c** and benzyne **52** (Fig. 7A). Two most possible transition states of the [3+2] cycloaddition reactions between benzyl azide **34c** and benzyne **7Aγ** (Fig. 7B), **7Dγ** (Fig. 7C), and **21γ** (Fig. 7D).

quite unstable. Consequently, the alternative *distal*-**TS22γf**, which is electrostatically less favorable, becomes relatively more stable.

The TSs (**TS53**, **TS37Aγc**, **TS37Dγc**, and **TS41γc**) of the [3+2] cycloaddition reactions between benzyne (**52**, **7Aγ**, **7Dγ**, and **21γ**) and benzyl azide **34c** (Figure 7) were also analyzed. **TS53** shows the nature of the electrostatic interaction between 5-methylbenzyne **52** and **34c**, in which the bond distance (2.41 Å) between the internal nitrogen of **34c** and the carbon of the benzyne is shorter than that (2.77 Å) between the terminal nitrogen and the carbon of the benzyne (Figure 7A). *Proximal*-**TS37Aγc**, in which the distance (2.51 Å) between the internal nitrogen and the C2 of the benzyne is greater than the corresponding distance in **TS53**, demonstrates that there is a very large steric repulsion between the trimethylsilyl group and the benzyl group (Figure 7B). This makes the electrostatically favorable *proximal*-**TS37Aγc** less stable than *distal*-**TS37Aγc**, thereby resulting in the preferential production of *distal*-**37Aγc**. The potential energy difference (1.11 kcal/mol) corresponds to 87:13 *distal* selectivity, which is reasonable in the context of our experimental result (*distal*-**37Aγc**/*proximal*-**37Aγc**=77:23). Analysis of two TSs (*distal*-**TS37Dγc** and *proximal*-**TS37Dγc**) derived from a virtual benzyne **7Dγ** possessing a SiH₃ group demonstrated that the potential energy difference between these two TSs was very small (0.14 kcal/mol) (Figure 7C). These results suggest that the steric bulkiness of the silyl groups has a significant adverse influence on the electrostatically favorable *proximal* TSs, and that steric repulsion is the governing factor for the production of *distal* adducts in the [3+2] cycloaddition reaction of **7**.

In the [3+2] cycloaddition reaction of **21γ** with **34c**, *proximal*-**TS41γc** is 2.58 kcal/mol lower than *distal*-**TS41γc** (Figure 7D), which theoretically corresponds to 1:>99 *proximal* selectivity and is in good agreement with our experimental

result (*distal*-**41γc**/*proximal*-**41γc**=1:>99). The structure of *proximal*-**TS41γc**, where the electrostatic combination of the reacting atoms is well matched, is very close to that of **TS53** (Figures 7A and 7D). This implies that the boryl group exerts little adverse steric effect on *proximal*-**TS41γc** and governs the formation of *proximal*-**41γc**.

The DFT analyses of the ground and transition state structures of the benzyne reactions proved to be quite effective for quantitative interpretation of the intriguing and characteristic properties of the silyl and boryl groups. The electrostatic attractive interactions of the two reactants and the steric repulsion between the approaching substituents were found to be the most significant factors dominating the regioselectivities. Thus, the DA reactions of both silyl and borylbenzyne were controlled by the synergy of the electrostatic and steric effects. On the other hand, in the [3+2] cycloaddition reactions, the silylbenzyne were determined to be more susceptible to steric effects, whereas the reactions of the borylbenzyne were more electrostatically dominated.

4. Conclusion

A novel method for the regiocontrol of benzyne reactions was developed using silyl and boryl substituents. Similar regioselectivities were observed in the DA reactions of both silyl and borylbenzyne. On the other hand, complementary regioselectivities were exhibited by these two species in the [3+2] cycloaddition reactions. Given that the silyl and boryl groups of the products are convertible into carbon-, oxygen-, and nitrogen-substituents as well as hydrogen, the developed protocol serves as a useful preparation strategy for developing multisubstituted benzo-fused compounds. The regioselectivities of these reactions were quantitatively interpreted on the basis of analysis of the transition state structures obtained from DFT calculations, revealing that steric effects governed

the reactions of the silyl groups, whereas the reactivity of the boryl group was exclusively governed by electrostatic effects.

Thus, the current account provides insight into certain longstanding problems related to the regioselectivity of benzyne reactions. However, the selectivities and reactivities of other benzyne remain uninvestigated. Further studies towards these goals are currently underway in our laboratory.

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References

- For recent reviews: (a) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem. Int. Ed.* **2003**, *42*, 502. (b) Worlikar, S. A.; Larock, R. C. *Curr. Org. Chem.* **2011**, *15*, 3214. (c) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (d) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550.
- Bachmann, W. E.; Clarke, H. T. *J. Am. Chem. Soc.* **1927**, *49*, 2089.
- (a) Wittig, G. *Naturwissenschaften* **1942**, *30*, 3209. (b) Roberts, J. D.; Simmons, Jr., H. E.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290.
- (a) Chapman, O. L.; Mattes, K.; McIntosh, C. L.; Pacansky, J.; Calder, G. V.; Orr, G. *J. Am. Chem. Soc.* **1973**, *95*, 6134. (b) Chapman, O. L.; Chang, C. C.; Kolc, J.; Rosenquist, N. R.; Tomioka, H. *J. Am. Chem. Soc.* **1975**, *97*, 6586.
- (a) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211. (b) Peña, D.; Cobas, A.; Pérez, D.; Guitián, E. *Synthesis* **2002**, 1454. Our recent contribution to benzyne generation, see: (c) Ikawa, T.; Nishiyama, T.; Nosaki, T.; Takagi, A.; Akai, S. *Org. Lett.* **2011**, *13*, 1730.
- A recent review of synthetic methods for naphthalenes: de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7.
- (a) Anderson, J. E.; Franck, R. W.; Mandella, W. L. *J. Am. Chem. Soc.* **1972**, *94*, 4608. (b) Newman, M. S.; Kannan, R. *J. Org. Chem.* **1976**, *41*, 3356. (c) Shankaran, K.; Snieckus, V. *Tetrahedron Lett.* **1984**, *25*, 2827. (d) Gribble, G. W.; Keavy, D. J.; Branz, S. E.; Kelly, W. J.; Pals, M. A. *Tetrahedron Lett.* **1988**, *29*, 6227. (e) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735. (f) Giles, R. G. F.; Hughes, A. B.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1571. (g) Nishiyama, T.; Okada, M.; Miyazawa, M. *Reports of Kyushu School of Engineering, Kinki University* **2000**, *28*, 37.
- Selected silyl-directed reactions: (a) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534. (b) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068.
- Selected boryl-directed reactions: (a) Auvinet, A.-L.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 2769. (b) Kirkham, J. D.; Butlin, R. J.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 6402.
- Matsumoto, T.; Sohma, T.; Hatazaki, S.; Suzuki, K. *Synlett* **1993**, 843.
- The DA reaction between 3-fluoro-6-(trimethylsilyl)benzyne and 2-(trimethylsilyl)furan was reported to exclusively generate 1,5-bis(trimethylsilyl)-1,4-epoxy-8-fluoro-1,4-dihydronaphthalene. However, the DA reaction of the simple 3-(trimethylsilyl)benzyne was not examined, see: Masson, E.; Schlosser, M. *Eur. J. Org. Chem.* **2005**, 4401.
- Regioselective DA of silylbenzyne, see: (a) Akai, S.; Ikawa, T.; Takayanagi, S.; Morikawa, Y.; Mohri, S.; Tsubakiyama, M.; Egi, M.; Wada, Y.; Kita, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 7673. (b) Ikawa, T.; Takayanagi, S.; Morikawa, Y.; Mohri, S.; Takagi, A.; Aoyama, Y.; Tsubakiyama, M.; Itoh, Y.; Tokiwa, H.; Ishikawa, Y.; Kita, Y.; Akai, S. submitted for publication.
- Regioselective nucleophilic additions of silylbenzyne, see: (a) Ikawa, T.; Nishiyama, T.; Shigeta, T.; Mohri, S.; Morita, S.; Takayanagi, S.; Terauchi, Y.; Morikawa, Y.; Takagi, A.; Ishikawa, Y.; Fujii, S.; Kita, Y.; Akai, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 5674. (b) Bronner, S. M.; Mackey, J. L.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, ASAP.
- Regioselective DA of borylbenzyne, see: (a) Ikawa, T.; Takagi, A.; Kurita, Y.; Saito, K.; Azechi, K.; Egi, M.; Kakiguchi, K.; Kita, Y.; Akai, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 5563. (b) Takagi, A.; Ikawa, T.; Kurita, Y.; Saito, K.; Azechi, K.; Egi, M.; Itoh, Y.; Tokiwa, H.; Kita, Y.; Akai, S. submitted for publication.
- Regioselective [3+2] cycloadditions of silyl- and borylbenzyne, see: Ikawa, T.; Takagi, A.; Goto, M.; Aoyama, Y.; Ishikawa, Y.; Itoh, Y.; Fujii, S.; Tokiwa, H.; Akai, S. submitted for publication.
- (a) Baudoin, O.; GuHritte, F. *Stud. Nat. Prod. Chem.* **2003**, *29*, 355. (b) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (c) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801. (d) Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13326.
- Some other examples of the DA reactions of benzyne having a bulky group: (a) Franck, R. W.; Leser, E. G. *J. Org. Chem.* **1970**, *35*, 3932. (b) Anderson, J. E.; Franck, R. W.; Mandella, W. L. *J. Am. Chem. Soc.* **1972**, *94*, 4608. (c) Handal, J.; White, J. G.; Franck, R. W.; Yuh, Y. H.; Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 3345. (d) Anderson, J. E.; Franck, R. W. *J. Chem. Soc., Perkin Trans. 2*, **1984**, 1581. (e) Aikawa, H.; Takahira, Y.; Yamaguchi, M. *Chem. Commun.*, **2011**, 47, 1479.
- Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**.
- (a) Hiyama, T. *J. Organomet. Chem.* **2002**, *653*, 58. (b) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 75.
- (a) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* **2002**, *67*, 8450. (b) Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952.
- For some examples of acid-catalyzed opening of 1,4-epoxy-1,4-dihydronaphthalenes, see: (a) Batt, D. G.; Jones, D. G.; La Greca, S. *J. Org. Chem.* **1991**, *56*, 6704. (b) Schlosser, M.; Castagnetti, E. *Eur. J. Org. Chem.* **2001**, 3991. (c) Kaelin, D. E.; Sparks, S. M.; Plake, H. R.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 12994. (d) Nrgel, S. S.; Azap, C.; Reißig, H.-U. *Eur. J. Org. Chem.* **2006**, 4405.
- For examples of intermolecular fluoride-free Hiyama reactions, see: Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2006**, *348*, 2085.
- After the publication of our work, the following paper was published: Tsubouchi, A.; Matsuda, H.; Kira, T.; Takeda, T. *Chem. Lett.* **2009**, *38*, 1180.
- Synthesis of 1,8-dihydroxynaphthalene: Lurie, A. P.; Brown, G. H.; Thirtle, J. R.; Weissberger, A. *J. Am. Chem. Soc.* **1961**, *83*, 5015.
- (a) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983. (b) Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29.
- (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954.
- For selected examples, see: (a) Shinkai, S.; Takeuchi, M. *Biosens. Bioelectron.* **2004**, *20*, 1250. (b) Elfeky, S. A.; Flower, S. E.; Masumoto, N.; Dhooge, F.; Labarthe, L.; Chen, W.; Len, C.; James, T. D.; Fossey, J. S. *Asian J.* **2010**, *5*, 581.
- For recent examples, see: (a) Baker, S. J.; Zhang, Y.-K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W.; Alley, M. R. K.; Sanders, V.; Plattner, J. J. *J. Med. Chem.* **2006**, *49*, 4447. (b) Dorsey, B. D.; Iqbal, M.; Chatterjee, S.; Menta, E.; Bernardini, R.; Kanareggi, A.; Cassar, P. G.; D'Arasmo, G.; Ferretti, E.; De Munari, S.; Oliva, A.; Pezzoni, G.; Allievi, C.; Strepponi, I.; Ruggeri, B.; Ator, M. A.; Williams, M.; Mallamo, J. P. *J. Med. Chem.* **2008**, *51*, 1068.
- (a) Lin, W.; Chen, L.; Knochel, P. *Tetrahedron* **2007**, *63*, 2787. (b) Sapountzis, I.; Lin, W.; Fischer, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4364.
- The precursors **20** were generally prepared from the corresponding 2,6-diiodophenols **54** in five steps as shown below. The overall yields were fairly good [for example, **20a** (R¹=H) was obtained in 62% overall yield].

- For the only example of a DA reaction of an unsymmetrically substituted benzyne with pyrrole, see: Gribble, G. W.; Kelly, W. J. *Tetrahe-*

dron Lett. **1985**, 26, 3779.

- 32) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell, 2000. (b) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon, 2000. (c) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH, 2003.
- 33) For selected examples for [3+2] cycloaddition of benzyne: (a) Jin, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, 46, 3323. (b) Spiteri, C.; Keeling, S.; Moses, J. E. *Org. Lett.* **2010**, 12, 3368. (c) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, 10, 2409. (d) Zhang, F. Z.; Moses, J. E. *Org. Lett.* **2009**, 11, 1587. (e) Lu, C.; Dubrovskiy, A. V.; Larock, R. C. *J. Org. Chem.* **2012**, 77, 2279. (f) Hong, D.; Chen, Z. B.; Lin, X. F.; Wang, Y. G. *Org. Lett.* **2010**, 12, 4608. (g) McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. *Org. Lett.* **2011**, 13, 3667.
- 34) The reaction of 3-silylbenzyne **7A** with nitrones **36**, which had been reported by Suzuki¹¹ and Danishefsky under harsh reaction conditions, also gave benzisoxazoles **39A** with high selectivity, see: Dai, M.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, 49, 6613.
- 35) (a) Prous, J.; Grant, J.; Castaner, J. *Drug Future* **1994**, 457. (b) Wood, P. M.; Lawrence, W., L. W.; Thomas, M. P.; Mahon, M. F.; Purohit, A.; Potter, B. V. L. *ChemMedChem* **2011**, 6, 1423.
- 36) Gaussian 09, Revision B.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2010**.
- 37) (a) Wiberg, K. B. *Tetrahedron* **1968**, 24, 1083. (b) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, 102, 7211. (c) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, 83, 735.
- 38) NBO 5.0, Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Bohmann, J. A.; Morales, C. M.; Weinhold, F. Theoretical Chemistry Institute, University of Wisconsin, Madison WI, **2001**.
- 39) Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* **2003**, 5, 3551.
- 40) Optimized structures of reactants, TSs, and products were characterized by analytical frequency calculations, and all total electronic energies of these species were included in the zero-point energy corrections at the same level. The calculated number of imaginary frequencies (NImag) determine whether the optimized structures are energy minima (NImag=0) or TSs (NImag=1) along the reaction pathway.

PROFILE

Takashi Ikawa is an Assistant Professor at the University of Shizuoka. He was born in Gifu, Japan, in 1977, and he received a Ph.D. degree (2005) from Gifu Pharmaceutical University. After two years of postdoctoral work (2005–2007) for Professor Stephen L. Buchwald at Massachusetts Institute of Technology, he joined the University of Shizuoka as an Assistant Professor in 2007. He received the Japanese Society for Process Chemistry Award for Excellence (2003) and the Daicel Chemical Industries, Ltd. Award in Synthetic Organic Chemistry, Japan (2008). His research interests are in the area of synthetic organic chemistry, organometallic chemistry, medicinal, and bioorganic chemistry.

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