Construction of N-Heterocycles Fused with a Highly Substituted Benzene Ring by a Benzyne-Mediated Cyclization/Functionalization Cascade Reaction and Its Application to the Total Synthesis of Marine Natural Products

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This account summarizes the development of a benzyne-mediated cyclization/functionalization protocol for the versatile construction of highly substituted benzene derivatives fused with an N-heterocyclic ring such as indolines, indoles, and related nitrogen-containing heterocycles. The protocol comprises sequential reactions initiated by generating a benzyne species and subsequent cyclization via addition of magnesium amide to the benzyne, followed by trapping of the resultant magnesium compound in situ with various electrophiles. The substituent scope was expanded by conducting a transmetalation on a copper species to introduce alkyl, aryl, and alkenyl substituents. The utility of the sequential reaction was demonstrated in the synthesis of a carbazole natural product (heptaphylline), pyrrolo[4,3,2-de]quinoline alkaloids (batzellines), and pyrrolo[2,3-c]carbazole alkaloids (dictyodendrines).

Key words benzyne; heterocycle; cascade reaction; total synthesis; alkaloid

Introduction
Numerous biologically active natural products and pharmaceuticals consist of a highly substituted benzene ring fused with an N-heterocyclic ring as their main framework (Fig. 1). So far, synthetic methodologies for constructing these structural motifs have been thoroughly developed. However, many of these methods are generally unsuitable for the synthesis of highly substituted compounds. Thus, the introduction of substituents on the benzene ring after the construction of the benzene-fused N-heterocyclic ring often suffers from a regiochemical problem and low chemical yield, which becomes more severe as the number of introduced substituents increases because of steric constraints and electronic factors (Chart 1, A). For example, the introduction of substituents on the benzene ring by conventional cross-coupling or aromatic electrophilic substitution reactions into a highly congested position is often difficult. In addition, ortho-metalation and C–H activation processes usually possess a narrow substrate scope. Moreover, functional group compatibility and difficulty to undergo cyclization at a sterically hindered position hamper the ring-forming reaction of a substrate possessing a highly substituted benzene ring (Chart 1, B). This account focuses on the development of a protocol for constructing highly substituted benzene derivatives fused with an N-heterocyclic ring by a benzyne-mediated cyclization and in situ functionalization cascade sequence and its application to the total syntheses of highly functionalized marine alkaloids.

Fig. 1. Marine Alkaloids Possessing an N-Heterocyclic Ring Fused with a Highly Substituted Benzene Ring

This review of the author’s work was written by the author upon receiving the 2015 Pharmaceutical Society of Japan Award for Divisional Scientific Promotion.

This paper is dedicated to Professor Ei-ichi Nakamura (The University of Tokyo) on the occasion of his 70th birthday.

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1. Development of a Protocol for Constructing 7-Substituted Indolines by a Benzyne-Mediated Cyclization/Functionalization Cascade Sequence

Chart 2 displays our working hypothesis for constructing an N-heterocyclic ring fused to a highly substituted benzene ring, which comprises a benzyne-mediated cyclization and subsequent functionalization by in situ reaction with electrophiles. Accordingly, the treatment of ortho-halo aminoethylbenzene 4 with a strong base would generate benzyne species 6 by β-elimination of a hydrogen halide. Then, intramolecular nucleophilic addition of the generated amide anion to the benzyne and trapping of the resultant sp² metal species 7 with an electrophile (E⁺) would furnish indoline 8 having a substituent at the 7-position.

The aforementioned hypothesis was examined by treating bromobenzene derivative 9 with five equivalents of lithium 2,2,6,6-tetramethylpiperazide (LiTMP) at −78 °C. Then, the reaction temperature was raised to 0 °C, and the reaction was terminated by adding a D₂O solution of DCl. Although the desired cyclization product was obtained in 80% chemical yield, the ratio of deuteration/protonation product (10/11 = 62/38) was unsatisfactory (Table 1, entry 1). We reasoned that the undesired protio-compound 11 could result from the protonation of C(sp²)–Li species 13 with 2,2,6,6-tetramethylpiperazine (H-TMP) generated by the initial deprotonation (Chart 3). Fortunately, we found that the use of Mg(TMP)₂·2LiCl instead of LiTMP was effective to prevent undesired protonation, possibly due to the generation of a more stable C(sp²)–Mg bond. Further screening of various magnesium amides revealed that the use of Mg(TMP)₂·2LiBr resulted in low yields and low ratio of the deuterated product (Table 1, entries 2–4).

The substituents and leaving group on the benzene ring were found to strongly affect the smooth generation of benzyne species. Thus, the bromo group was superior as a leaving group compared with other halogens (Chart 4). In addition, for the initial deprotection, the target proton should be located between the halogen and methoxy groups. Thus, 3-bromo-4-methoxyphenethylamine derivative 16 gave only a trace amount of cyclized product 11. Substrate 17–20, without oxygen functionality at the meta-position of the halogen provided trace to low yields of the corresponding cyclized product 21 (Chart 4). These results suggested that the presence of oxygen functionality increases the acidity of the sp² C–H bond due to an inductive effect or stabilization of the resulting anion.

Because the protocol for the benzyne-mediated cyclization/

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**Biography**

Hidetoshi Tokuyama received his Ph.D. from the Tokyo Institute of Technology in 1994 under the direction of Prof. Ei-ichi Nakamura. He spent one year (1994–1995) at the University of Pennsylvania as a JSPS postdoctoral fellow with Prof. Amos B. Smith III. He then joined the group of Prof. Tohru Fukuyama at the University of Tokyo in 1995 and was appointed as an associate professor in 2003. In 2006, he moved to Tohoku University, where he is currently a professor. His research interests are the development of synthetic methodologies and the total synthesis of natural products. Prof. Tokuyama is a recipient of the Alan R. Katritzky Junior Award in Heterocyclic Chemistry (2015) and the Pharmaceutical Society of Japan Award for Divisional Scientific Promotion (2015).
protonation has been established, the scope of the substituents at the 7-position of the indoline product was investigated using various electrophiles (Table 2). Indoline products 22–24 having Br, Cl, and I groups at the 7-position were synthesized by terminating the reaction with Br(CCl₂)₂Br, ClTf, and I₂, respectively (Table 2, entries 1–3). Similarly, acetyl, cyano, azide, and phenylthio groups were introduced by adding acetic anhydride, p-toluenesulfonyl cyanide, p-toluenesulfonyl azide, and diphenyl disulfide, to furnish 25–28, respectively (entries 4–7). Furthermore, quenching the reaction with B(OMe)₃ and subsequent treatment with alkaline hydrogen peroxide provided 7-hydroxyindoline derivative 29.

The scope of protective groups on the amino group was also evaluated (Chart 5). In addition to substrate 9 having t-butoxycarbonyl (Boc) group, 30 and 31 bearing 2,4,6-triisopropylbenzenesulfonyl (Tris) and benzyl groups were suitable for the benzyne-mediated cyclization-functionalization cascade sequence. In contrast, reaction of unprotected primary amine resulted in a complex mixture.

The introduction of sp² carbon substituents was executed via a palladium-catalyzed cross-coupling reaction after transmetalation of the organomagnesium intermediate to a copper species (Chart 6). In addition, the transmetalation to a copper species, followed by an S_N2 reaction was effective to introduce sp³ carbon substituents. Thus, after the benzyne-mediated cyclization, copper iodide was added to the reaction mixture to promote transmetalation of the 7-magnesiiodindole intermediate to the copper species. Then, the one-pot cross-coupling reaction with iodobenzene derivatives or iodoalkane proceeded in the presence of a palladium catalyst to provide 7-arylindolines 34–36 or 7-alkenylindoline 37, respectively. The introduction of sp³ carbon substituents was conducted via the reaction of the copper species with excess alkyl halides such as iodomethane or allyl bromide to furnish 38 or 39, respectively. The established cascade reaction terminated by S_N2 reaction was applied to a formal total synthesis of a hepatitis C virus (HCV) RNA polymerase inhibitor 40 (Chart 7).
Thus, 2,6-dibromobenzene derivative 41 was subjected to Mg(TMP)₂·2LiCl mediated benzyne generation and subsequent transmetalation to cupper species. Finally, S₂₂ reaction with iodomethene provided indoline product 42 with one of two bromo group untouched. In addition to the precursor of the HCV RNA polymerase inhibitor 43, a several derivatives were synthesized divergently by functionalization of the remaining bromo group of 42.

Meanwhile, the synthesis of 7-alkynylindoline 44 bearing an sp substituent was conducted by applying Knochel’s oxidative coupling condition of the copper species with lithium acetylide in the presence of chloranil (45) as an oxidant (Chart 8).

This protocol applied also to other nitrogen-containing heterocyclic ring systems. The carbazole skeleton was constructed by subjecting 2-bromo-2'-aminobiphenyl derivative 46 to the Mg(TMP)₂-mediated benzyne generation conditions (Chart 9). Protonation, bromination, and transmetalation followed by in situ palladium-catalyzed cross-coupling reaction with p-iodoanisole furnished the corresponding functionalized carbazoles 47–49 in good to excellent yields.

Although conventional oxidation of the corresponding indoline precursors can synthesize indole derivatives, the present benzyne-mediated cyclization cascade reaction enabled the direct formation of the indole skeleton using dehydrophenylalanine derivative 50 (Chart 10).

2. Application to the Total Synthesis of Heptaphylline

A concise total synthesis of highly substituted carbazole alkaloid, heptaphylline, demonstrated the utility of the established benzyne-mediated cyclization/functionalization protocol. This compound was isolated by Joshi et al. in 1967 from Clausena heptaphylla and was reported to possess antitumor activity. Joshi et al. also reported the first total synthesis of this compound via functionalization of 2-hydroxycarbazole (53) (Chart 11). They encountered a regiochemical problem during the introduction of formyl and prenyl groups via the classical electrophilic substitution reaction. They reported that Vilsmeier-type formylation provided a mixture of the desired 3-formyl product 54 and 1-formyl product 55. In addition, the subsequent prenylation of the separated 3-formyl-2-hydroxycarbazole 54 gave a mixture of heptaphylline (2), 6-prenyl isomer 56, and N-prenyl isomer 57.

![Chart 8. Introduction of an sp Carbon Substituent](image)

![Chart 9. Application of the Protocol to the Construction of Substituted Carbazoles](image)

![Chart 10. Application of the Protocol to the Construction of the Indole Skeleton](image)

![Chart 11. The First Total Synthesis of Heptaphylline (2) by Joshi et al.](image)

![Chart 12. Five-Step Regioselective Total Synthesis of Heptaphylline (2)](image)
In this study, we accomplished a five-steps regioselective total synthesis of heplaphylline (2) in an overall 16% yield from benzaldehyde 58 using a benzyne-mediated carbazole synthesis/one-pot prenylation sequence (Chart 12). The substrate of the cascade cyclization was assembled in a three-step sequence comprising the regioselective iodination of benzaldehyde 58,20) and subsequent Suzuki–Miyaura cross-coupling with boronic acid pinacol ester 59,21) and conversion of the resultant biaryl compound 60 to diisopropyl acetal 61.22) The key construction of the carbazole skeleton starting from the benzyne-mediated cyclization, transmetalation to cupper species, and trapping with prenyl bromide furnished prenylcarbazole 62, which was then treated under acidic condition in situ to provide carbazole 63 in an 60% overall yield from 61. Finally, the deprotection of both Boc and phenolic methyl groups with a combination of BCl₃ and n-Bu₄NI completed the total synthesis of heptaphylline (2).23)

3. Application to the Total Synthesis of Pyrrolo[4,3,2-de]quinoline Marine Natural Products 24–26)

A series of pyrrolo[4,3,2-de]quinoline alkaloids such as damirones,27) batzellines,28) makaluvamines,29) makaluvone,29) and isobatzellines 30) have been isolated from marine sources, and some of these compounds have been demonstrated to possess a broad range of medicinally important activities such as antitumor activity,29) inhibitory activity against topoisomerase II,29) antimalarial activity,31) and inhibitory activity against envelope-mediated cell fusion of human immunodeficiency virus type 128) (Fig. 2). Therefore, these compounds have attracted interest as synthetic targets.32–37)

For the divergent synthesis of these compounds, we planned to apply the developed benzyne-mediated cyclization/function-alization cascade sequence (Chart 13). Various pyrrolo[4,3,2-de]quinoline alkaloids possessing the p-iminoquinone skeleton, such as makaluvamine A (70) and D (72), isobatzelline C (75), or the o-quinone skeleton including damirone B (65), makaluvone (66), and batzelline C (69), could be obtained from tetrahydropyrrolo[4,3,2-de]quinoline 76 via oxidative transformations. Meanwhile, the key intermediate 76 could be constructed by the benzyne-mediated cyclization/functionalization cascade sequence using 4-haloindoline 78 followed by protonation or halogenation of the generated aryl anion species.

First, we optimized conditions for the key benzyne-mediated cyclization of tetrahydroquinoline skeleton and functionalization using 4-iodoindoline derivative 79, which was prepared from 2-bromo-5-methoxyaniline by a five-step sequence.38) While the condition using Mg(TMP)₂·2LiBr or Mg(TMP)₂·2LiCl provided the desired compound 80 in low yield, benzyne-generation using five equivalents of LiTMP and termination of the reaction by protonation, chlorination, or bromination afforded tetrahydropyrrolo[4,3,2-de]quinolines 80–82 in good yields 24,25) (Chart 14).

The key tetrahydropyrrolo[4,3,2-de]quinoline intermediate 80 was then converted to makaluvamine A (70) and D (72) and damirone B (65) divergently using conventional transformations 25) (Chart 15). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation of 80 to the corresponding indole derivative and subsequent removal of Boc and ethoxycarbonyl groups provided indole derivative 84.37) Makaluvamine A (70) was obtained via methylation on the indole...
N-1 position, followed by oxidation with salcomine under an oxygen atmosphere to \(p\)-iminoquinone and replacement of the methoxy group with ammonia. Meanwhile, the oxidation of indole 84 with Fremy's salt afforded the corresponding \(p\)-iminoquinone 85, which was then converted to damirone B (65) by \(N\)-methylation, followed by a concomitant demethylative isomerization to \(o\)-quione. In addition, makaluvamine D (72) was obtained from the addition–elimination displacement of the methoxy group with tyramine.

Halogenated congeners were also synthesized similarly from 81 (E = Cl) or 82 (E = Br) (Chart 16). A four-step sequence including DDQ oxidation to indole, deprotection of the two protective groups, and oxidation with Fremy's salt provided \(p\)-iminoquinone derivatives 87 or 88. After \(N\)-methylation of 87 or 88, the cleavage of the resulting methyl ether by treatment with BBr₃ and concomitant isomerization to \(o\)-quinoine furnished batzelline C (69),24,25 or makaluvone (66),25 respectively. \(N\)-Methylation of 87 and subsequent addition–elimination-type displacement of the methoxy group with ammonia furnished isobatzelline C (75).24,25

Total synthesis of congeners bearing methylthio group was more difficult.39,40 The sensitivity of the alkylthio group toward oxidants hindered the synthesis of the key pyrroloquinoline intermediate and the final oxidation of the benzene ring to the corresponding \(p\)-iminoquinone or \(o\)-quinone skeletons while leaving the methylthio group intact. Therefore, we planned to construct highly substituted pyrroloquinoline intermediate 89 or 90 having methylthio group by utilizing the benzyne-mediated cyclizationfunctionalization protocol using 4-bromo-2-methylthiotryptamine derivative 91 (Chart 17). For the preparation of hexasubstituted indole 91, we extended the scope of nucleophiles in our ring-expansion reaction of benzocyclobutanone oxime sulfonate to provide 2-substituted indoles41 (Chart 18). The benzocyclobutanone oxime sulfonate would be easily prepared via \([2 + 2]\) reaction of benzene 94 and cyclic ketene silyl acetal 95.

The preparation of hexasubstituted indole 91 started with the \([2 + 2]\) cycloaddition of ketene silyl acetal 95 with a benzene species generated from 1-bromo-3,4-dimethoxybenzene 99.26 (Chart 19). The resultant tricyclic hemiacetal product was treated with aqueous hydrogen fluoride to afford the desired benzocyclobutanone 93 with a perfect orientational selectivity. After installation of the amino group and regioselective bromination, oxime sulfonate 92 was obtained in three steps involving condensation with hydroxylamine, reattachment of the Boc group on the nitrogen, and sulfonylation. The planned ring-expansion reaction proceeded upon treatment with sodium methylthiolate to furnish 2-methylthiotryptamine derivative 102 in 86% yield. Finally, methylation of the indole N-1 position provided the desired hexasubstituted indole 91.

At this stage, 91 was subjected to the key benzyne-mediat-
ed cyclization/functionalization cascade sequence to construct a pyrrolo[4,3,2-de]quinoline structure (Chart 20). Thus, the cascade reaction was initiated by treatment of 87 with LiTMP, and the reaction was terminated by adding aqueous ammonium chloride or hexachoroethane to provide 1-methyl-2-methylthio-pyrroloquinoline derivative or its 6-chloro derivative, respectively. Then, deprotection of the Boc group afforded the corresponding pyrroloquinoline derivatives 103 and 105. The remaining tasks for the completion of the total syntheses of isobatzelline A (73) and B (74) were the selective oxidation of the benzene ring to p-iminoquinone skeleton and the introduction of amino group. Oxidation of 103 using ceric ammonium nitrate (CAN) provided a complex mixture including 21% of the desired p-iminoquinone 104 and 36% of 103. The unexpected conversion of 6-chloro-pyrroloquinoline derivative 105 to the desired p-iminoquinone 104 with trifluoroacetic acid circumvented this unsuccessful oxidation. This redox-neutral process started with protonation at the ipso-position of the chloro group, followed by elimination of the chloride ion and formation of the p-iminoquinone structure upon hydrolysis. Finally, isobatzelline B (74) was obtained by the displacement of the methoxy group with ammonia via an addition–elimination process. Meanwhile, oxidation of 6-chloropyrroloquinoline derivative 105 with manganese dioxide in acetic acid provided the corresponding p-iminoquinone 106 in good yield, which was converted to isobatzelline A (73) by treating with ammonium chloride in methanol.

4. Application to the Total Synthesis of Dictyodendrins

Dictyodendrins (107–111), which were first isolated from the marine sponge Dictyodendrilla verongiformis, possess an inhibitory activity against telomerase (Fig. 3). Because telomerase is expressed in most tumor cell lines and has proved to be associated with cell proliferation, telomerase is a potential target for cancer chemotherapy. In addition to its important biological activity, the highly substituted pyrrolo[2,3-c]carbazole core has attracted attention as a synthetic target. After Fürstner’s first total synthesis of dictyodendrin B (108), C (109), and E (111), Iwao and Ishibashi accomplished the second total synthesis of dictyodendrin B (108). We recently reported a divergent total synthesis of dictyodendrins A (107), B (108), C (109), D (110), and E (111) by utilizing the benzene-mediated cyclization/functionalization protocol as the key process.

Chart 21 shows a retrosynthetic analysis of dictyodendrin A (107). The pyrrolo[2,3-c]carbazole skeleton, the common framework of dictyodendrins, would be constructed by the intramolecular C–H insertion of a nitrene intermediate generated from azide 112, which would be obtained by the cross-coupling reaction of 4-bromoindole derivative 113 with an aryl azide segment and installation of the substituent at
the 2-position by Friedel–Crafts alkylation. For constructing 4-bromoindole 113, we planned to apply the benzyne-mediated cyclization/cross-coupling cascade process to dibromo-benzene derivative 116. Oxidative conversion of the resulting indoline product 114 to indole and alkylation at the indole N-1 position with a p-anisylethyl halide would afford the key intermediate 113. Dictyodendrin B (108) and E (111) would also be synthesized similarly via the installation of the corresponding substituent at the 2-position. Furthermore, dictyodendrins C (109) and D (110) possessing a highly oxidized framework could be obtained from the common intermediate 113 via the final oxidation of the pyrrolo[2,3-c]carbazole skeleton.

First, the common indole intermediate 113 was synthesized via the key benzyne-mediated cyclization/functionlalization protocol (Chart 22). Dibromomiodobenzene derivative 118, which was obtained in six steps from p-nitrophenol (117),59 was treated with n-BuLi in toluene at −78 °C to promote the iodine-selective halogen–lithium exchange reaction and subsequent Michael addition to nitroalkene 119. The nitro group of the resulting compound 120 was then selectively reduced, and Boc protection of the primary amine product afforded 121. The key benzyne-mediated cyclization proceeded smoothly using Mg(TMP)2·2LiBr, followed by in situ transmetalation to a copper species 122 and palladium-catalyzed cross-coupling reaction with p-iodoanisole to furnish 7-anisyl indoline product 123 in 93% yield. The key indole intermediate 113 was obtained upon removal of the Boc group, DDQ oxidation, and installation of the p-anisylethyl group on the indole N-I position.

With the key indole intermediate 113 in hand, a series of dictyodendrins A–E (107–111) was synthesized divergently via the construction of the pyrrolo[2,3-c]carbazole skeleton and the introduction of substituents at the indole 2-position. First, Friedel–Crafts alkylation using bromide 125 and AgOTf as an activating agent attached the methyl p-anisylacetate unit30 (Chart 23). The pyrrolo[2,3-c]carbazole derivative 128 was then constructed in three steps comprising palladium-catalyzed pinacolborylation, Suzuki–Miyaura coupling42,43 with 126 to incorporate the azidephenyl group, and subsequent intramolecular C–H insertion of a nitrene species generated from azide 127 under heating. The total synthesis of dictyodendrin A (107) was completed by using a modification of Fürstner’s protocol.47,48 After the cleavage of the t-butyl ether using boron trichloride in the presence of pentamethylenebenzene,54,55 the resulting phenol was converted to trichloroethyl-sulfamate 129. Finally, five methoxy groups and the trichloro-ethyl group were cleaved to furnish dictyodendrin A (107).56

The total syntheses of dictyodendrin B (108) and E (111) were also accomplished via the introduction of a p-methoxybenzyl group and a p-methoxybenzyl group, respectively, at the 2-position and construction of the pyrrolo[2,3-c]carbazole skeleton (Chart 24). Thus, Friedel–Crafts acylation of 113 with p-anisic chloride (130) provided ketone 131,57 which was then subjected to seven-step transformations to accomplish the total synthesis of dictyodendrin B (108) (12% overall yield from 117 over 21 steps). Friedel–Crafts alkylation using a combination of p-methoxybenzyl trichloroacetimide and scandium triflate initiated the endgame of the total synthesis of dictyodendrin E (111).58 Then, eight steps, including the construction of the pyrrolo[2,3-c]carbazole skeleton and the final DDQ oxidation, furnished dictyodendrin E (111) (7.4% overall yield from 117 over 22 steps). Similarly, dictyodendrin C (109) was synthesized via the construction of the pyrrolo[2,3-c]carbazole skeleton and final oxidation using hydrogen peroxide. In addition, dictyodendrin D (110) was synthesized by modification of the synthetic route of dictyodendrin C (109) (Chart not shown).

**Conclusion**

We have developed a benzyne-mediated cyclization/functionlalization protocol that enables direct access to highly substituted nitrogen-containing heterocycles fused with a benzene ring, such as indole, indole, carbazole, pyrroloindoline, and pyrroloindole. Although numerous benzyne-mediated approaches for the synthesis of these heterocycles have been reported, there are few examples of cascade processes includ-
We have solved this problem by selecting Mg(TMP)₂·2LiBr or Li-TMP as the appropriate base, which smoothly generates the benzene species and the metal salt of the heterocycles possessing reasonable reactivity toward functionalization with a broad range of functional group compatibility. The generality of the cascade reaction regarding the scope of the substituents introduced and high functional group compatibility was demonstrated by performing a divergent total synthesis of dictyodendrin compounds and a series of functionalized heterocycles.

Conflict of Interest

The author declares no conflict of interest.

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