

Intramolecular Anionic Diels–Alder Reactions of
1-Aryl-4-oxahepta-1,6-diyne Systems in DMSOTakayuki Kudoh,[†] Tomoko Mori,[†] Mitsuhiro Shirahama,[†] Masashi Yamada,[†]
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Abstract: Base-promoted cycloaddition reactions of 1-aryl- or 1-aryl-7-substituted-4-oxahepta-1,6-diyne systems in DMSO have proven to involve an anionic intramolecular Diels–Alder process taking place even at room temperature in spite of the reaction suffering from temporary disruption of aromaticity. Although initially formed α -aryllallenide anion can be protonated by DMSO, it can be back to the allenide anion probably because of a small acidity difference between α -aryllallene and DMSO. The α -aryllallenide anion in combination with the α -aryl substituent can constitute an anionic diene structure that undergoes the intramolecular Diels–Alder reaction involving the C(6)-yne part, a very fast process probably because of the increased HOMO–1 level of the anionic diene, as shown by DFT calculations. Diversified substituted naphthalenes, benzofurans, phenanthrenes, and quinolines, including biaryl architectures, are available from 4-oxahepta-1,6-diynes in a highly expeditious way.

Introduction

The power of Diels–Alder reactions¹ has been highlighted in transforming a simple combination of diene and dienophile into cyclohexene rings in a myriad of contexts for 80 years after its discovery.² A lot of versions of the Diels–Alder reaction have been explored to establish valuable and irreplaceable ways for constructing complex molecules.³ In particular, the Lewis acid-promoted Diels–Alder reaction, with dienophiles bearing an electron-withdrawing group capable of making complexes with Lewis acids, has provided diverse opportunities in organic synthesis including asymmetric synthesis.⁴ An extraordinary rate acceleration effected by the Lewis acid in the Diels–Alder reaction⁵ can be rationalized as a result of lowering an energy-level of dienophile LUMO by such a coordination of the Lewis acid to the dienophile.⁶

On the other hand, for the base-promoted Diels–Alder reaction, only limited reports concerned with two-representative systems have appeared so far. One typical example is that the Diels–Alder reaction between 9(10*H*)-anthracenone (anthrone) and *N*-methylmaleimide (NMM) extremely rapidly proceeds in hydrogen bond acceptor solvents such as DMF, pyridine, or triethylamine; in DMF, the reaction is complete within a few minutes, affording an almost quantitative yield of **adduct-1**, whereas in CDCl₃ it affords only 14% of the **adduct-1** after 68 h at 25 °C. These results were reasoned by a mechanism involving highly reactive oxido diene provided through a base-promoted enolization process as shown in Scheme 1, which they referred to as catalytic oxyanion acceleration mechanism.⁷

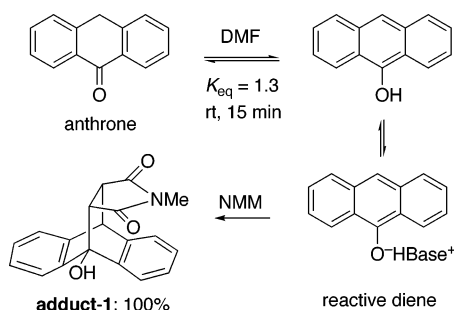
Similar oxyanion acceleration systems involving a dienolate available through kinetically favored deprotonation of cyclohexenone with LDA was demonstrated to react with methyl acrylate to give bicyclo[2.2.2]nonane framework (**adduct-2**) in 90% yield under the given reaction conditions, as shown in Scheme 2.⁸ Although the reaction can be rationalized as a [4 + 2] cycloaddition process, a conceivable stepwise mechanism involving domino Michael pathway was suggested on the basis of the very mild conditions under which the reaction occurred.⁹

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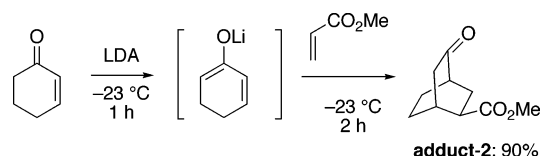
- (1) For reviews or monographs, see (a) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 4.1, pp 315–399. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 4.1, pp 513–550. (c) Fringuelli, F.; Taticchi, A. *The Diels–Alder Reaction: Selected Practical Methods*; John Wiley & Sons: New York, 2002.
- (2) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1926**, 450, 237–254; Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1927**, 460, 98–122.
- (3) For a leading review, see: Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, 41, 1668–1698.
- (4) (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, 41, 1650–1667. (b) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. III, Chapter 33.1, pp 1178–1235.
- (5) Yates, P.; Eaton, P. J. *Am. Chem. Soc.* **1960**, 82, 4436–4437.
- (6) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, 95, 4094–4096.

(7) Koerner, M.; Rickborn, B. J. *Org. Chem.* **1989**, 54, 9–10.(8) (a) Lee, R. A. *Tetrahedron Lett.* **1973**, 3333–3336. See also (b) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1977**, 3929–3930. (c) White, K. B.; Reusch, W. *Tetrahedron* **1978**, 34, 2439–2443. (d) Ihara, M.; Toyota, M.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1984**, 25, 2167–2170. (e) Tamura, Y.; Sasho, M.; Nakagawa, K.; Tsugoshi, T.; Kita, Y. *J. Org. Chem.* **1984**, 49, 473–483. (f) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kametani, T. *Kabuto, C. J. Am. Chem. Soc.* **1988**, 110, 1963–1964. (g) Marchand, A. P.; Annappurna, P.; Watson, W. H.; Nagl, A. *Chem. Commun.* **1989**, 281–282.

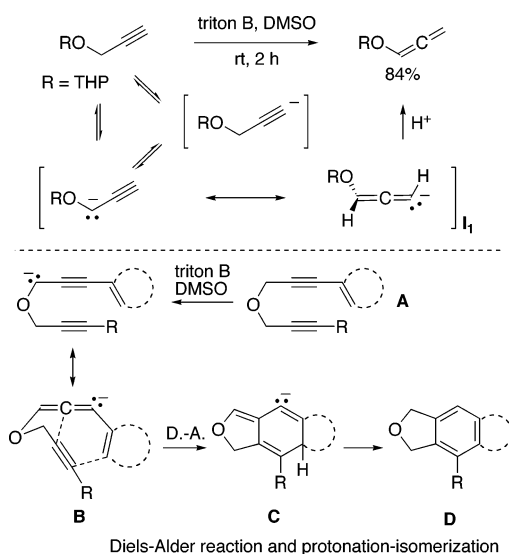
Scheme 1



Scheme 2

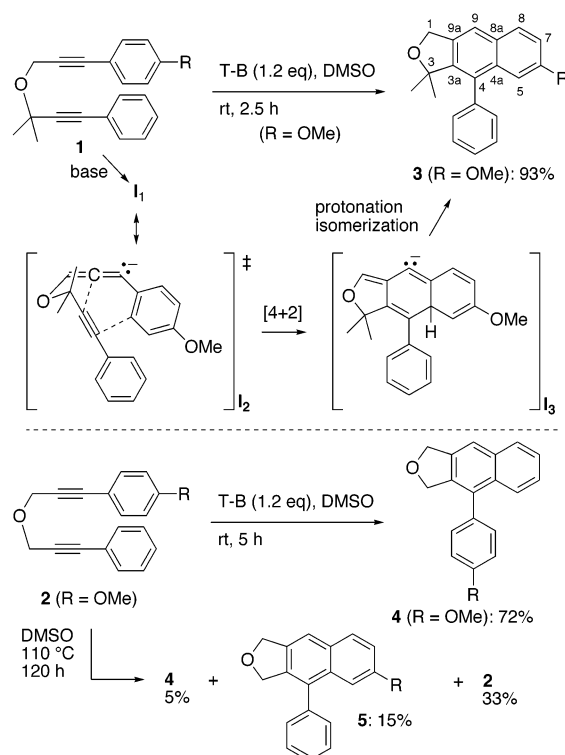


Scheme 3



Thus, the anionic Diels–Alder reactions have been studied less extensively and limited to oxyanion versions as outlined in Schemes 1 and 2. To the best of our knowledge, no reaction involving anionic dienes of those previous types or new ones has been developed since 1990, when the last report^{8f} pertinent to Scheme 2 was published. Meanwhile, we found that *O*-(tetrahydropyranyl)-2-propynol gives (tetrahydropyranyloxy)allene in high yields (84%) when such an ether was treated with $(\text{C}_6\text{H}_5\text{CH}_2)(\text{CH}_3)_3\text{N}^+\text{OH}^-$ (Triton B) in DMSO (rt, 2 h) (Scheme 3).¹⁰ This finding strongly motivated us to design new anionic dienes consisting of allenide and neighboring any carbon–carbon double bonds (**B** in Scheme 3). These considerations lead to 4-oxa-1,6-diyne systems as a substrate (**A** in Scheme 3) which, on treatment with Triton B in DMSO, is expected to give anionic Diels–Alder system (**B**) followed by cycloaddition leading to an initial adduct (**C**), an immediate precursor for final product (**D**) via protonation–isomerization.

Scheme 4

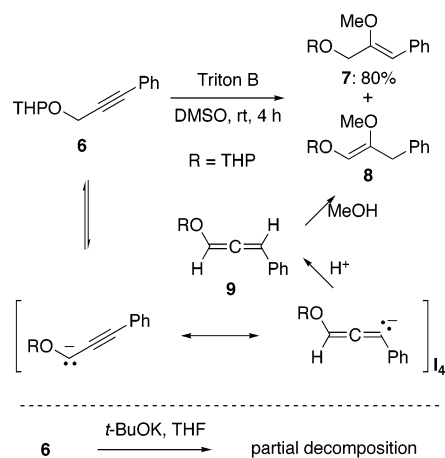


This idea was realized by preliminary experiments employing **1** and **2**¹¹ with interesting results (Scheme 4). The transition state of this intramolecular anionic Diels–Alder reaction, such as **I**₂ involving the canonical form of initially formed 2-propynide **I**₁, is expected via deprotonation of **1**, and **1** indeed led to a cycloadduct such as biaryl (**3**: 6-methoxy-3,3-dimethyl-4-phenyl-1,3-dihydronaphtho[2,3-*c*]furan) in high yield (93%) on treatment with Triton B (40% in MeOH: 1.2 equiv) in DMSO at room temperature for 2.5 h. More interestingly, substrate **2**, which is missing geminal dimethyl groups at C(3), exclusively afforded **4** in 72% yield as an only isolable cycloadduct in spite of the possible formation of isomer **5**.

Furthermore, in marked contrast to these anionic processes, the thermal conditions (DMSO, 110 °C) exhibited extremely sluggish rates and gave rise to rather **5** as a major product but in low yield (15%), together with minor **4** (5%), and left **2** (33%) unchanged. Thus, the base-promoted process is capable of providing favorable situation for [4 + 2] cycloaddition to proceed even at room temperature in spite of the reaction suffering from temporary disruption of aromaticity. After intensive additional experiments, it was strongly suggested that the reaction should constitute the intramolecular Diels–Alder reaction (IMDAR) system (**I**₂) involving the anionic diene at transition state to give the vinyl anion intermediate (**I**₃) as an immediate precursor for **3**. Generality, applicability, and mechanism for this anionic IMDAR of 1-aryl- or 1-aryl-7-substituted-4-oxahepta-1,6-diyne systems promoted by a base (Triton B or NaH) in DMSO at room temperature will be disclosed.

- (9) Reactions of enolates, generated from α,β -unsaturated ketones, with electron-deficient olefins such as α,β -unsaturated esters or ketones might be the anionic Diels–Alder reaction. However, stepwise mechanism involving a double-Michael process cannot be ruled out: see ref 1c, pp 7–8 and references cited therein.
- (10) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* **2003**, *68*, 3702–3705.

- (11) Soon after we had embarked on this work, three papers pertinent to our work were found: (a) Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1964**, *12*, 1094–1100. (b) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc. Perkin I* **1975**, 1315–1320. (c) Garratt, P. J.; Neoh, S. B. *J. Org. Chem.* **1979**, *44*, 2667–2674. These reports were not concerned with IMDAR featuring anionic dienes at all. For mechanisms they had proposed, see the text.

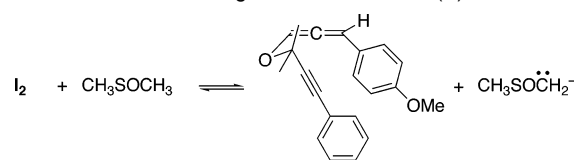
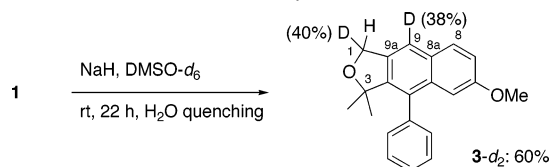
Scheme 5. Allenide Generation

Results and Discussion

Generation of Allenide Anion from 3-Substituted-2-propynyl Ethers. Similarly to the case of *O*-(tetrahydropyranyl)-2-propyn-1-ol (Scheme 3), *O*-(tetrahydropyranyl)-3-phenyl-2-propynol (**6**) led to endiol ether such as **7** in 80% yield together with its constitutional isomer **8** in a very small amount on treatment with Triton B (40% in MeOH) in DMSO at room temperature for 4 h (Scheme 5).

This result indicates that **6** indeed led to allene (**9**), as a precursor for **7**, to which MeOH, presented in the medium, added. Thus, 3-substituted 2-propynyl ethers such as **6** can produce allenes via deprotonation-protonation processes as shown in Scheme 5 [**6** to resonance hybrid of 1-alkoxy-2-propynide and 3-alkoxyallene (**I₄**) to **9**], providing strong support for the generation of allenide anion from 4-oxahepta-1,6-diyne systems (Scheme 4) under the conditions employed (Triton B, DMSO, rt).

Role of DMSO, Deuterium Scrambling Experiments, and Mechanism. Interestingly, other base/solvent system such as *tert*-BuOK/THF did not effect the formation of any allenide-based products from **6** at all (Scheme 5) and only resulted in the recovery and partial decomposition of **6** (rt, 2 h). Furthermore, **1** did not undergo IMDAR at all and recovered unchanged on treating with *tert*-BuOK in *tert*-BuOH (rt, 6.5 h). Therefore, DMSO can play a crucial role for the production or stabilization of allenides. Judging from the reported pK_a values of DMSO (35.1)¹² and expected increasing acidity of Csp^2-H bond of allene as a result of an α phenyl substitution,¹³ there would exist facile equilibrium between DMSO and initially formed allenide intermediate as indicated in Scheme 6. If this were the case, it would increase the chance of the existence of the **I₂** intermediate (Scheme 4), which undergoes the fast intramolecular anionic Diels–Alder reaction, whereas the *tert*-BuOK/*tert*-BuOH system can shift the equilibrium far to the right because of higher acidity of *tert*-BuOH than DMSO. Thus, no expected IMDAR took place under such conditions (vide supra).

Scheme 6. Proton Exchange between Allenide (**I₂**) and DMSO**Scheme 7.** Deuterium Transfer Experiments

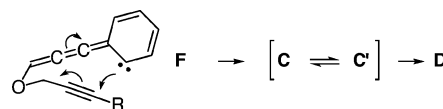
The occurrence of such proton exchange process was supported by deuterium incorporation observed when **1** was treated with NaH as a base in DMSO- d_6 as a solvent (Scheme 7). The reaction required 22 h for the disappearance of **1** on TLC diagnosis, and, after quenching the reaction by H_2O , careful ^{13}C and 1H NMR experiments showed that cycloadduct **3** (60% yield) contains deuterium atoms at both C(9) (38% deuterium) and C(1) positions (40% deuterium per one hydrogen).¹⁴ The existence of one deuterium on these carbons was definitely observed as $^{13}C-D$ triplets appeared at 0.3 ppm upper field from the corresponding non-deuterated ^{13}C -signals.¹⁴

As a control experiment, the same experiment was conducted employing DMSO as a solvent, NaH as a base, and D_2O quenching. The reaction was completed in a much shorter time (2.5 h) than that in DMSO- d_6 (22 h) as judged by the disappearance of **1** on TLC and gave **3** (60% yield), which had no deuterium in it.¹⁴ These significant results allowed us to formulate the mechanism as shown in Scheme 8, which can explain how deuteriums were incorporated into the specified position of **3** (Scheme 7).

According to above-mentioned Schemes 3 and 4, deprotonation of **1** with a base leads to resonance hybrid of **I₁** and **I₂**. If this anion is followed by cycloaddition process involving the anionic diene and internal alkyne, the reaction would afford **I₃** as an initial adduct because the process may be very fast,¹⁵ probably due to the increased energy level of diene HOMO by involving anionic sp^2 -carbon. It is quite reasonable that **I₃** can deprotonate DMSO to give rise to intermediate (**I₅**) and methylsulfinylmethide ($CH_3SOCH_2^-$); the latter can easily deprotonate highly acidic proton attaching to triallylmethyl-type carbon located at the ring-fused position, which triggers

(14) Supporting Information gives a full detail for how we have determined deuterium distribution in cycloadduct **3** obtained from anionic IMDAR of **1** in DMSO- d_6 with NaH at rt.

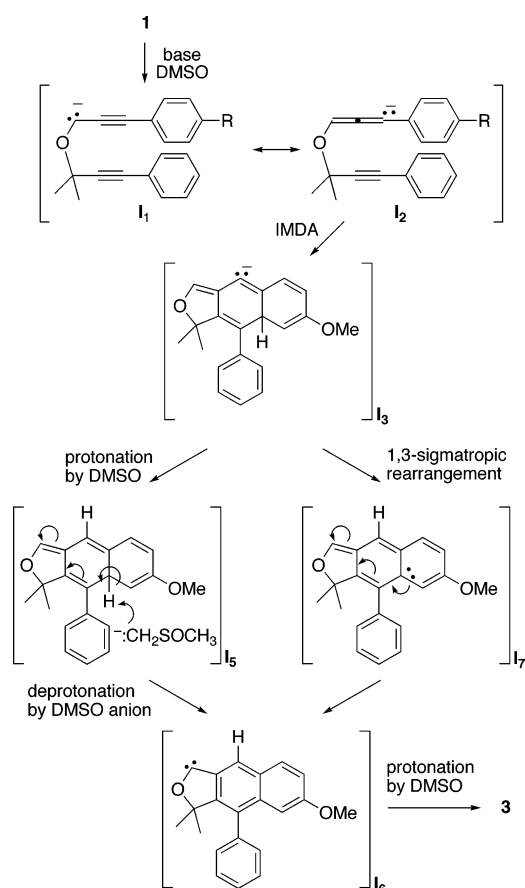
(15) Intramolecular dehydro Diels–Alder reactions of *N*-propargyl phenylpropionamides proceeds at 160 °C via 1,2,4-cyclohexatriene intermediates, strained cyclic allenes, to give a mixture of benzo[*f*]isoindol-1-ones and benzo[*e*]isoindol-1-ones (see Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Am. Chem. Soc.* **2001**, *123*, 9178–9179 and the references cited therein). In light of the very high temperature required unexceptionally for the Diels–Alder reactions of such class, the heightening of diene HOMO should be a predominant reason for the present IMDAR to take place at “room temperature”. A cumulene form (**F**) as a canonical structure of **B** might be ruled out for the formation of **D** because of its symmetrically forbidden 8-electron system.



(12) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

(13) To the best of our knowledge, no report for pK_a values of allene or substituted allenes has been available. We thought, however, that we could estimate the plausible pK_a values of $C_{\alpha}-H$ bond of α -phenyl substituted allene to be around 33–40 on the basis of pK_a value of ethylene or propylene (**44**) and acidifying effects of phenyl substituent as ΔpK_a 4.4–10.6. For acidifying effects of phenyl substituent, see Bordwell, F. G.; Bares, J. E.; Bartmess, J. E.; McCollum, G. J.; Puy, M. V. D.; Vanier, N. R.; Matthews, W. S. *J. Org. Chem.* **1977**, *42*, 321–325.

Scheme 8



aromatization and migration of carbanion to the tetrahydrofuran ring (**I**₆) to be protonated again by DMSO leading to the final adduct **3**.¹⁶

A series of these processes can reasonably explain the observed deuterium distribution in **3**, which also provides direct evidence for the intervention of the allenide anion at least. The finding that no deuterium was incorporated in **3** when the reaction was conducted in DMSO and quenched with D₂O is also fully consistent with the proposed mechanism. More acidic solvent, such as *tert*-BuOH, than DMSO may probably quench the initial 2-propynide anions quickly to result in the total recovery of **1**, as mentioned above.

Another pathway from **I**₃ to **I**₆ (right-hand route in Scheme 8), which can be triggered by anionic 1,3-sigmatropic rearrangement leading to triallylmethide-type anion (**I**₇) as an immediate precursor for **I**₆, could not be ruled out. It should be pointed out that there is a possibility that the pathway from **I**₃ to **3** might be rate-determining because a kinetic solvent deuterium isotope effect, not quantitative but qualitative, was

Table 1. Anionic IMDA of 4-Oxahepta-1,6-diynes with 3,3-Dimethyl Substituent^a

entry	substrate: time	product: yield
1	1: 2.5 h	3 : 93%
2	10: 5 h	11 : 32%
3	12: 11 h	decomposition
4	13: 2 h	14 : 63%

^a Reagents and conditions: Triton B (40% MeOH solution, 120 mol %), DMSO, rt; for reaction time, see numerical values insetted beside the substrate numbers.

observed; as already mentioned above, the disappearance of **1** in DMSO-*d*₆ took much longer time (22 h) than in DMSO (2.5 h).¹⁷

Base-Promoted [4+2] Cycloaddition Reactions: (A) 1-Aryl-7-aryl'-3,3-dimethyl-4-oxahepta-1,6-diynes. As already shown in Scheme 4, **1** stands for one of the most reasonable designs for the intramolecular anionic Diels–Alder reaction of 4-oxahepta-1,6-diyne systems because the introduction of geminal dimethyl group at C(3) make it definitive that C(6)–C(7)–Ar moiety and C(1)–C(2) triple bond strictly play a role of diene and dienophile, respectively. Thus, **1** led to **3** (93% yield, room temperature, 2.5 h) in which 4-methoxyphenyl group is embedded in a naphthalene framework. Results pertinent to this design are presented in Table 1.

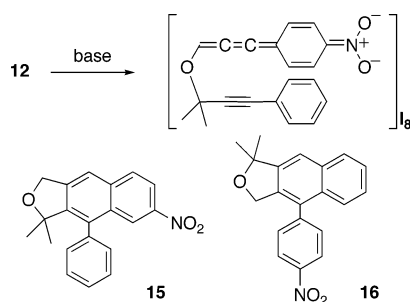
Substrate bearing electron-withdrawing substituent such as an NO₂ group (**12**; entry 3) afforded an unidentifiable mixture. Deprotonation of **12** might produce conjugated nitronate anion (Scheme 9: **I**₈) due to strong electron-accommodating ability of an NO₂-group, which might have undergone further reaction other than the expected pathway (Scheme 8) leading to **15** or **16** (Scheme 9). Small but clear formation of the expected cycloadduct (**11**: 32%) in the case of a CN group (entry 2) under the anionic conditions might be the reflection of weaker electron-withdrawing nature of this functional group than an NO₂ group.

(B) 4-Oxahepta-1,6-diynes with Aromatic Substituent at Both Ends. In Table 2 are listed the results for cycloaddition

(16) Products were isolated by means of simple gravity column chromatography over silica gel, and their structures were determined by NMR analysis and supplementary X-ray crystallographic analysis for representative products (for X-ray data of **27** and **56**, see Supporting Information). Commercial triton-B (40% MeOH solution) was used as received for convenience. Thus, reactions necessarily involved MeOH, which might serve as proton source or nucleophile. However, no addition product like **7** or **8** was detected at all. In cases in which chemical yields of cycloadducts were low, using NaH instead of triton-B sometimes remedied such a drawback, probably due to avoiding MeOH-based protonation, if any. This is the reason why we have conducted reactions employing NaH–DMSO conditions in some cases: see data in Tables listed with footnotes describing as such.

(17) Although the determination of exact value of *k*_H/*k*_D requires rate measurements, the existence of kinetic isotope effects of solvent is beyond doubt. When the reaction was commenced by using preformed methylsulfinylmethide-*d*₅ anion from NaH and DMSO-*d*₆ (the mixture was stirred at 50 °C for 1 h and 70 °C for 1 h, and cooled to rt), no rate enhancement was observed at all (TLC diagnosis indicated that disappearance of the substrate required 22 h). This result clearly showed that NaH is playing a role of base for the room temperature cycloaddition process in DMSO.

Scheme 9



reactions of **17–24** bearing aromatic substituents at both terminus and no 3,3-dimethyl group, which afforded substituted naphthalene or benzofuran derivatives (**25–32**) featuring biaryl architectures. On the basis of the mechanism shown in Scheme 8, whereas the one side of dissymmetric ethers is transformed to allenide, the other side should remain intact because it must work as a dienophile. Accordingly, acidity difference between 2-propynyl hydrogens, C(3)–H and C(5)–H, may play an important role for which side can serve as the anionic diene because of similar steric demand for both sides. Thus, an aromatic ring with more electron withdrawing substituent can be involved in the anionic diene functionality. In line with this interpretation, Scheme 4 and entries 1, 4, and 6–8 in Table 2 are providing a clear-cut trend to produce cycloadducts in which such aromatic rings are embedded in the naphthalene rings with very high selectivity; possible isomers incorporating the benzene ring bearing less electron withdrawing substituent into naphthalene ring have not been detected at all. This probably means that the process involves thermodynamically controlled formation of the anions followed by facile intramolecular cycloaddition processes.

In order for alkyne parts to serve as dienophiles, they are requested to stay intact. However, anion generation from them cannot be avoided, and therefore, delicate balance between acidity itself and acidity difference of both sides can affect not only reactivity but also product yields. A substituent, such as CN capable of making extended conjugation possible, would eventually break diene function to result in low yield in spite of its high reactivity (entry 6).

(C) 4-Oxahepta-1,6-diynes with Aromatic and Aliphatic Substituent Termini. In Table 3 are summarized results for the anionic IMDAR of 4-oxahepta-1,6-diynes bearing a benzene ring on one terminus and aliphatic substituent on the other terminus (**33–35**).

Indeed, the expected cycloadducts such as **36–38** were obtained in moderate yields but accompanied with substituted furans (**39–41**) in a considerable amount, in particular for those (**34** and **35**) with a tetrahydropyranyloxymethyl group. Accordingly, deprotonation from such a group should be responsible for the side reaction of this class. To examine this possibility, 8-(tetrahydropyranyloxy)-4-oxa-1,6-octadiyne (**42**) was submitted to the same reaction conditions as those for **33–35** to give a similar furan derivative (**43**: 36%), whereas unchanged **42** was recovered in 31%, as shown in Scheme 10, in which a plausible mechanism for the formation of furan derivatives is indicated. Initial deprotonation leading to ammonium allenide (**I₉**) would trigger an intramolecular carbometallation-type addition reaction toward the remaining acetylenic bond to give **I₁₀** followed by successive 1,3- and 1,4-prototropic rearrange-

Table 2. Anionic IMDA of 4-Oxahepta-1,6-diynes with Aromatic Substituents at Both C(1) and C(7)^a

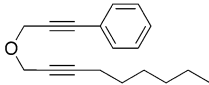
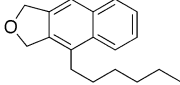
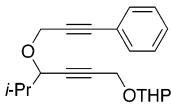
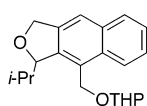
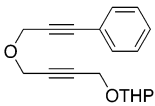
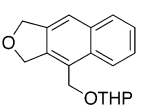
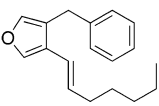
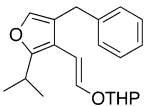
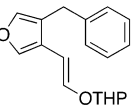
entry	substrate: time	product: yield
1	 17 : 0.5 h	 25 : 90%
2	 18 : 24 h ^b	 26 : 75% ^c
3	 19 : 22 h	 27 : 65%
4	 20 : 3 ^d	 28 : 54% ^e
5	 21 : 0.5 ^f	 29 : 64% ^g
6	 22 : 0.5 h ^h	 30 : 34% ⁱ
7	 23 : 0.5 h	 31 : 41%
8	 24 : 0.5 h	 32 : 81%

^a Reagents and conditions: Triton B (40% MeOH solution, 120 mol %), DMSO, rt unless otherwise indicated; for reaction time, see numerical values inserted beside the substrate numbers. ^b If conducted at 50 °C for 44 h, **26** was obtained in 94%. ^c 77% (NaH, rt, 32 h). ^d NaH. ^e 39% for Triton B. ^f NaH. ^g 18% for Triton B. ^h NaH. ⁱ 10% for Triton B.

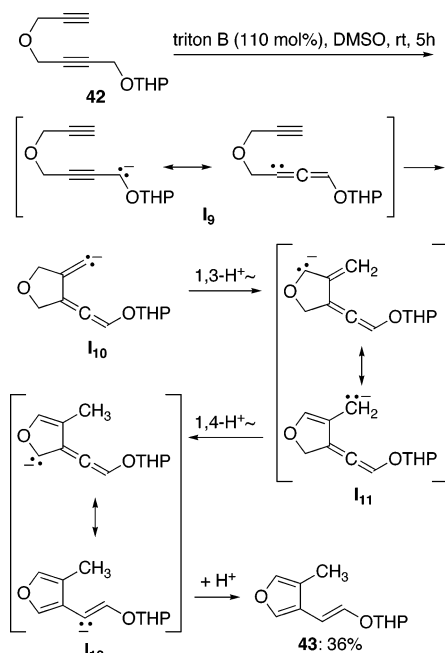
ments, ending up with **I₁₂** via **I₁₁**, the immediate precursor for **43**. The same process as this should compete with the anionic IMDAR process commenced by deprotonation from other oxymethylene groups for **33–35**.

(D) 1-Aryl-4-oxahepta-1,6-diynes: No Substituent at C(6). For substrates bearing aromatic or heteroaromatic substituents at C(1) (**44–51**), the same [4 + 2] reaction uniformly took place to give substituted naphthalene, phenanthrene, or benzofuran derivatives (**52–58**) on treatment with Triton-B or NaH in DMSO at room temperature (Table 4). Both electron-withdraw-

Table 3. Anionic IMDAR of 1-Phenyl-6-alkyl-4-oxahepta-1,6-diynes^a

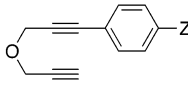
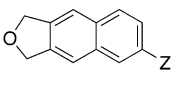
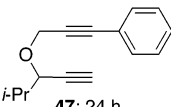
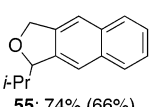
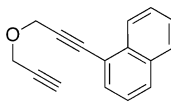
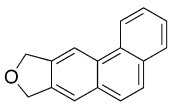
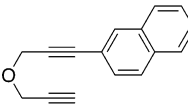
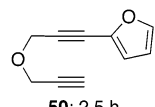
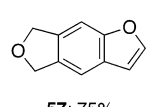
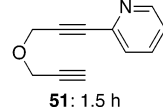
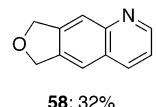
entry	substrate: time	product: yield
1	 33 : 39 h	 36^b : 68%
2	 34 : 4 h	 37^c : 72%
3	 35 : 17 h	 38^d : 41%
<hr/>		
	 39 : 5%	 40 : 24%
	 41 : 27%	

^a Reagents and conditions: Triton B (40% MeOH solution, 120 mol %), DMSO, rt; for reaction time, see numerical values insetted beside the substrate numbers. ^b 3-Benzyl-4-[(*E*)-heptenyl]furan (**39**: 5%) as a byproduct. ^c 4-Benzyl-2-isopropyl-3-[(*E*)-tetrahydropyranyloxyethenyl]furan (**40**: 24%) as a byproduct. ^d 3-Benzyl-4-[(*E*)-tetrahydropyranyloxyethenyl]furan (**41**: 27%).

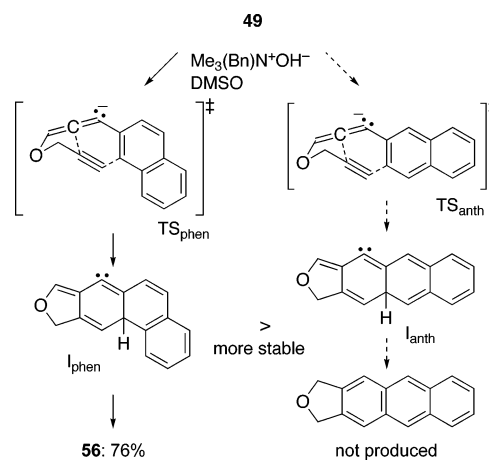
Scheme 10. Furan Formation: Results and Mechanism

ing and -donating substituents (entries 2 and 3) resulted in less yields of adducts, whereas additional substituent at C(5) (entry 4) led to much better yield. Other aromatic substituents, such as 1- or 2-naphthyl and 2-furyl groups (entries 5–7), exhibited good activity as a part of diene. Particularly interesting is that both 1- and 2-naphthyl groups (entries 5 and 6) led to the same phenanthrene derivative (**56**) in high yields though **49** has an opportunity to produce an anthracene backbone. As shown in Scheme 11, intermediate (*I*_{phen}), leading to **56**, should be more

Table 4. Anionic IMDAR of 1-Aryl-4-oxahepta-1,6-diynes^a

entry	substrate: time	product: yield ^b
1	 44 Z = H: 20 h	 52 Z = H: 59%
2	45 Z = OCH ₃ : 25 h	53 Z = OCH ₃ : 42%
3	46 Z = Cl: 3 h	54 Z = Cl: 25% (32%)
4	 47 : 24 h	 55 : 74% (66%)
5	 48 : 2 h	 56 : 85% (from 48) 76% (from 49)
6	 49 : 3 h	
7	 50 : 2.5 h	 57 : 75%
8	 51 : 1.5 h	 58 : 32%

^a Reagents and conditions: Triton B (40% MeOH solution, 120 mol %), NaH (60% in oil)/DMSO/rt; for reaction time, see numerical values insetted beside substrate numbers. ^b Yield in parenthesis for NaH as a base.

Scheme 11

stable than that (*I*_{anth}), leading to the anthracene backbone, because the former has a 6 π aromatic system whereas the latter has no such a system. Consequently, transition state TS_{phen} would be lower in energy than TS_{anth}, which must be responsible for the highly selective formation of **56** from **49**.

Similarly to the case of entry 8 in Table 2, a furan ring (entry 7) served as a part of diene, and thus, **50** led to benzofuran derivative (**57**: 75%). Also, a pyridine ring turned out to be incorporated into the diene part, and quinoline derivative (**58**:

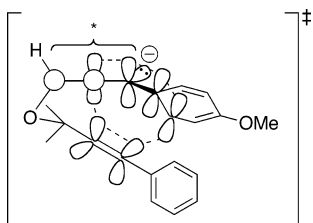


Figure 1. Transition state model featuring p-orbital array [allene-p-orbital part indicated by asterisk (*)].

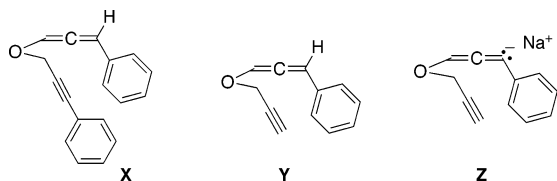


Figure 2. Model intermediates: allenyne (**X**), allene (**Y**), and allenide anion (**Z**).

32%) was furnished, though in low yield, which stands for the first example of pyridine-based quinoline synthesis.

Transition State. Because the allenide moiety involves the sp^2 -hybridized carbon, the anion exists in one of sp^2 -hybridized orbitals, and therefore, 1,3-diene p-orbitals and the anion orbital are orthogonal to each other at the transition state, as indicated in Figure 1 for **1** as a representative case. Under such situation, an electron-withdrawing substituent on the phenyl group, such as $-\text{NO}_2$ or $-\text{CN}$, lowers the negative charge density of the diene p-orbitals to result in an unfavorable transition state for the cycloaddition reaction of normal electron demand although they can stabilize the anion by an electron-withdrawing inductive effect. On the other hand, an electron-releasing substituent such as CH_3O -group can not only heighten the negative-charge density of the diene p-orbitals to result in favorable transition state for the cycloaddition reaction but also stabilize the anion by an electron-withdrawing inductive effect.

In general, rate acceleration of the Diels–Alder reaction would be expected by heightening an energy level of a diene HOMO. The anionic nature of **I**₂ should probably result in heightening the energy level of the diene HOMO, which considerably enhances the Diels–Alder reaction to rapidly proceed even at room temperature, though the process is accompanied with the disruption of aromaticity. To obtain supporting evidence for this idea, we have attempted to synthesize a model intermediate allenyne (**X**)¹⁸ in vain to be submitted to the reaction at elevated temperature (Figure 2). Hence, we turned our attention to DFT-evaluation of specific orbital energies¹⁹ for both an arylallene model (**Y**) and the corresponding sodium allenide intermediate model (**Z**)²⁰ (Figure

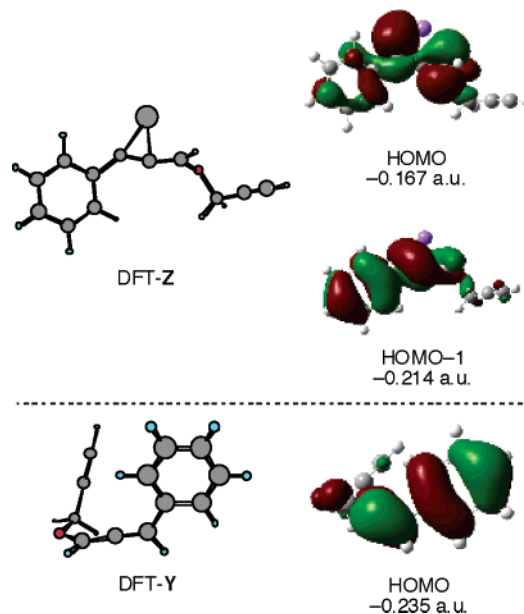
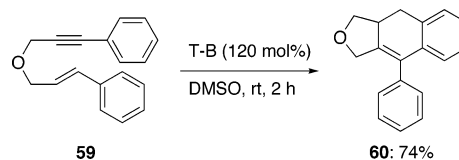


Figure 3. DFT-structures and specific orbitals for model intermediates allene (**Y**) and allenide anion (**Z**).

Scheme 12. Anionic IMDAR for an Enyne System (**1**)



2) to discuss about their reactivity difference in terms of specific orbital energies.

The results of DFT–HOMO or HOMO–1 calculations for **Y** and **Z** are shown in Figure 3 together with their frontier orbitals by the GaussView.²¹ In line with the above argument concerned with the raise of HOMO-level by transforming **Y** to **Z**, the calculations indicated that the HOMO of **Z** has much higher energy than the HOMO of **Y** by 0.067 au (42.0 kcal/mol). Apparently, the frontier orbital view of the HOMO of **Z** tells us that it would not work as a diene part and is quite different from that of the HOMO of **Y**, which should be appropriate as a diene part for IMDAR. However, it turned out that the HOMO–1 of **Z** has a reasonable orbital coefficient that may play a role of a diene part. In addition, the HOMO–1 has still higher energy than the HOMO of **Y** by 0.021 au (13.2 kcal/mol), supporting the feasibility of IMDAR involving the anionic diene.

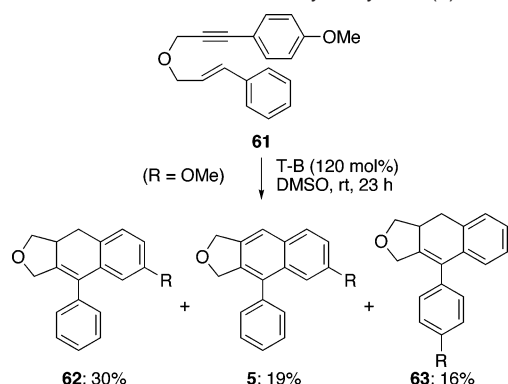
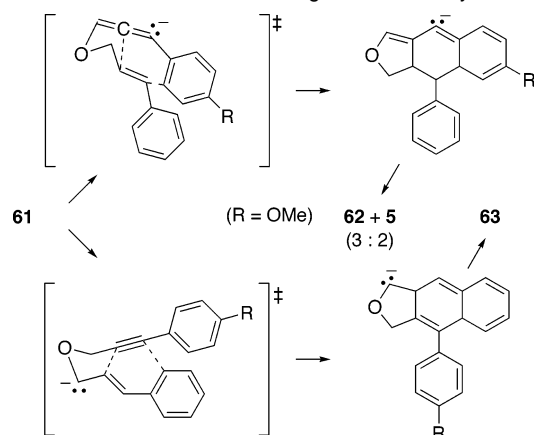
Alkene as a Dienophile. Expanding applicability of the anionic IMDAR in organic synthesis would make sense in terms of the establishment of synthetic method diversification. Toward one of such a goal, the scope of the dienophile was examined using an alkene group as in 1,6-diphenyl-4-oxahept-1-en-6-yne **59** as shown in Scheme 12. Interestingly, the room temperature anionic IMDAR again proceeded to give dihydronaphthalene derivative **60** (74%), which, however, left behind ambiguity that which of the unsaturated bonds, the double or triple bond, was taken up as an anionic diene part. To make this point clear, enyne **61** bearing a *p*-MeO group in the C(6)-phenyl group was

(18) We have attempted to prepare model allenyne (**X**) through two routes: one involved 6-(*tert*-butyldimethylsiloxy)-1-phenyl-4-oxa-1-hexyne as a starting compound, which was treated with *tert*-BuOK in THF (rt, 2 h) to afford the corresponding 1,2-hexadiene derivative. However, deprotection of the TBS-group resulted in intramolecular trapping of an allene function (the 1,2-diene part) by thus-liberated hydroxy group. The other route involved a cobalt mono-complex of **19** as a starting compound, which was treated with *tert*-BuOK in THF (rt, several hours) followed by decomplexation protocol (CAN, acetone rt): no sign of the formation of **X** was obtained.

(19) All DFT calculations were performed with the Gaussian 03 suite of programs at the B3LYP/6–31+G(d,p) theory level. Frisch, M. J.; et al. *Gaussian 03*, revision B.05; Gaussian, Inc.: Pittsburgh PA, 2003.

(20) We have attempted DFT calculation for ammonium and tetramethylammonium allenides in the first place. However, these systems resulted in the formation of **Y** + NH_3 and **Y** + $(\text{CH}_3)_4\text{N}^+\text{Me}_3$, respectively, that was the reason why we employed sodium allenide (**Z**) as a model.

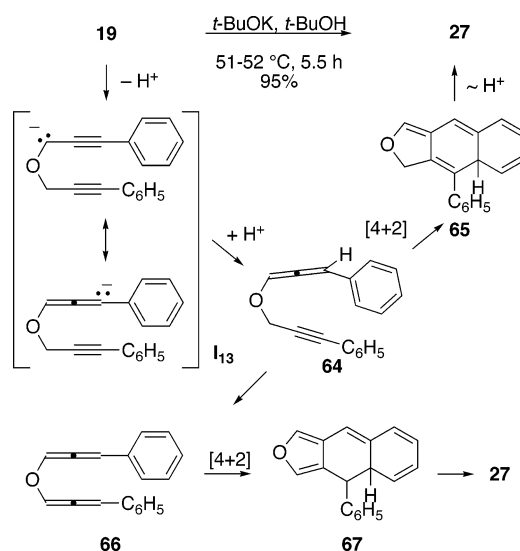
(21) Dennington, R., II.; Keith, T.; Millam, J.; Eppinnett, K.; Hovell, W. L.; Gilliland, R. *GaussView*, version 3.0; Semichem, Inc.: Shawnee Mission, KS, 2003.

Scheme 13. Anionic IMDAR for an Enyne System (2)**Scheme 14.** Anionic IMDAR Involving Allenide or Allylic Anions

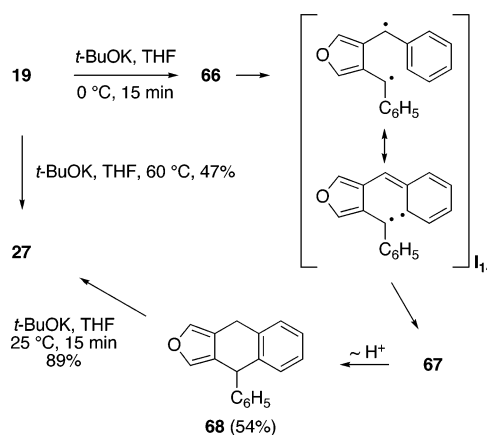
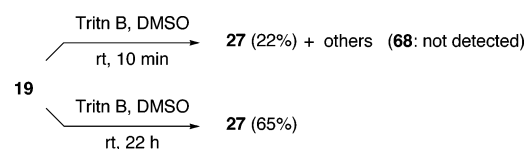
submitted to the anionic IMDAR, giving rise to a mixture of **62** (30%), **5** (19%), and **63** (16%) (Scheme 13). The result clearly indicated that both the styryl group and *p*-methoxyphenylethynyl group were able to play a role of the anionic diene. A mechanism capable of explicating the formation of these cycloadducts is indicated in Scheme 14. This result also provided the new aspect of the anionic IMDAR that when allylic anion constitutes a part of dienophile as a combination with benzene ring, it can effect the room temperature anionic IMDAR nicely.

Previous Mechanism. Iwai and Ide^{11a} reported the first example of a base-promoted formal [4 + 2] cycloaddition reaction in 1964, which is outlined in Scheme 15. For instance, they found **19** led to **27** on treatment with *tert*-BuOK in *tert*-BuOH at 51–52 °C for 5.5 h. They proposed a mechanism for this process involving allene derivative (**64**) as the first intermediate, generated through deprotonation (**I**₁₃)–protonation process, capable of undergoing thermal [4 + 2] cycloaddition reaction with the disruption of aromaticity to give the second intermediate (**65**) followed by 1,5-prototropic rearrangement, ending up with the formation of **27** with a biaryl unit. They also proposed the second possibility of formal [4 + 2] process of **66** generated from **64** to result in adduct (**67**), a reasonable precursor for **27** via isoaromatization from 6 π to 10 π system.²²

Garratt and Neoh reported in 1979 that **19** led to a furan derivative (**68**) (54% yield under the conditions employing *tert*-BuOK in THF at 0 °C for 15 min) (Scheme 16).^{11c} When the reaction was conducted at elevated temperature (60 °C), **19** led to **27** (47%). In addition, they confirmed that **68** could be

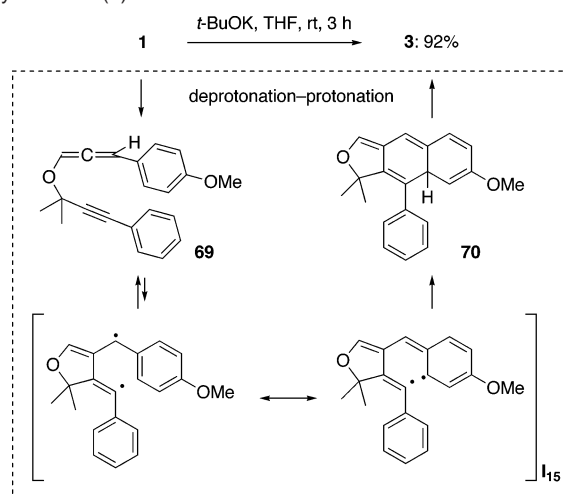
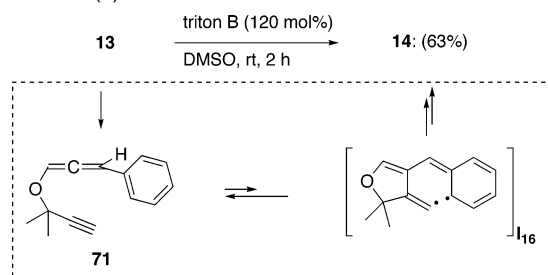
Scheme 15. First Base-Promoted [4 + 2] Cycloaddition Reaction^{11a}**Scheme 16.** Radical Cyclization Mechanism

Garratt–Neoh mechanism; 1979

**Scheme 17.** Initial Products from **19** under Triton B in DMSO

converted to **27** on treatment with *tert*-BuOK in THF at 25 °C for 15 min as indicated in Scheme 16.^{11c} On the basis of these results, they proposed a plausible mechanism involving the initial product, 4-oxahepta-1,2,5,6-tetraene (diallenyl ether: **66**), produced from **19** through a repeated deprotonation and protonation, to undergo radical cyclization forming a furan ring through a carbon–carbon bond between the allene central carbons and thus-formed biradical intermediate (**I**₁₄) could cyclize to the second intermediate (**67**) followed by isomerization to **68**, the immediate precursor for **27**. Because the base (*tert*-BuOK) was regenerated at this stage and could promote isomerization of **68** to **27**, probably through deprotonation (formation of an allylic anion)—protonation accompanied by the disruption of the furan ring, which could be compensated by the concomitant formation of a naphthalene ring.

(22) Iwai, I. In *Mechanism of Molecular Migrations*, Vol. 2; Thyagarajan, B. S., Ed.; Interscience: New York, 1969; pp 73–116.

Scheme 18. Hypothetical Radical Mechanism Including Unstable Vinyl Radical (1)**Scheme 19.** Hypothetical Radical Mechanism Including Unstable Vinyl Radical (2)

Radical Mechanism is Not Valid for the Conditions using Triton B in DMSO. In marked contrast to these previous results outlined in Schemes 15 and 16, when **19** was treated with Triton B in DMSO, none of **68** was detected at all, even at the initial stage of the reaction (room temperature, 10 min), and **27** was the only isolable product (22%), and **19** eventually afforded **27** in 65% yield after 22 h at the same temperature, as shown in Scheme 17.

Interestingly, **1** uneventfully led to **3** in 92% yields under the Garratt-Neoh conditions (110 mol % $t\text{-BuOK}$, THF, rt, 3 h) (Scheme 18). Because **1** has no chance to form diallenyl ether-type intermediate like **66** due to the presence of geminal 3,3-dimethyl groups, if a radical mechanism is operating, allenyne intermediate (**69**) must be converted to biradical intermediate (I_{15}) in which one part is a stable allylic radical but another part is an unstable vinyl radical. This is quite different from the Garratt-Neoh biradical intermediate I_{14} consisted of two stable allylic radicals. However, the radical mechanism cannot completely be ruled out as a result of such an interpretation because the vinyl radical involved in I_{15} might have a chance to be stabilized by means of conjugation with the phenyl ring depending on its special arrangement. It should be mentioned that **13** afforded cycloadduct **14** under almost the same conditions as those for **1** [120 mol % Triton B, DMSO, rt, 2 h (**13**) and 2.5 h (**1**)] (Table 1). If the reaction of **13** proceeds

via the radical mechanism, biradical intermediate (I_{16}) involving a highly unstable, non-substituted vinyl radical moiety must be produced in this case (Scheme 19). Thus, the radical mechanism should be much more unlikely for **13** than for **1**. Therefore, more reasonable mechanism capable of uniformly explaining the reactivity of both **1** and **13** must be required. The anionic Diels–Alder mechanism should be the most appropriate choice because only this mechanism can explain almost the same level of reactivity of **1** and **13** under the present conditions.²³

Concluding Remarks

A method capable of embedding aromatic or heteroaromatic rings into substituted naphthalene or benzoheteroaromatic backbones has been developed, relying on base-promoted IMDAR of 4-oxahepta-1,6-diyne systems in DMSO. Any aromatic compounds substituted by 3-alkoxy-1-propynyl groups can serve as the anionic diene functions in which carbon–carbon double bonds of the any aromatic systems and the carbon–carbon double bond of allene generated in the side chain by the action of base in DMSO. Even benzene substituted by 3-alkoxy-1-propenyl group was demonstrated to constitute such a case in which allylic anion was involved as a part of diene, indicating the generality of the present strategy. Although the prototype of this reaction was reported 40 years ago,^{11,24} its synthetic potential has been veiled since then. Replacement of early solvent with DMSO seems to be a key to unveiling the synthetic potential of base-promoted rearrangement of the 1-aryl-4-oxahepta-1,6-diynes through the anionic intramolecular Diels–Alder process.

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Supporting Information Available: Representative experimental procedures, physical properties, and ^1H and ^{13}C NMR charts for representative compounds; X-ray structural data for **27** and **56** in CIF format; complete ref 19. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (23) To make a final decision as to the intervention of the anionic diene intermediate at the transition state, we need to know about thermal stability for **69** or **71**. If these hypothetical intermediates were too stable to undergo IMDAR leading to **3** or **14** at elevated temperature, the anionic mechanism can be an appropriate choice. Toward this end, we have attempted the prepare **69** or **71** via alternative routes. To our disappointment, we have not succeeded in the synthesis of these allenynes yet.
- (24) A paper concerned with base-catalyzed (DBU, CDCl_3 , rt) cycloaromatization of symmetrical bis(π -conjugated propargyl)sulfones was published in 2000 (Braverman, S.; Zafrani, Y.; Gottlieb, H. E. *Tetrahedron Lett.* **2000**, *41*, 2675–2678) in which they discussed the mechanism on the basis of radical cyclization proposed by Garratt (ref 11c). One interesting result, however, in this report is that the corresponding sulfides, which remained unchanged even after 1 day, led to the expected product within 24 h on switching CDCl_3 to DMSO as a solvent. Those authors did not propose any idea about such a remarkable solvent effect.