NJC

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *New J. Chem.*, 2023, 47, 18762

Multisubstituted naphthalene synthesis from 4-hydroxy-2-pyrones through [4+2] cycloaddition with *o*-silylaryl triflates†

Koyo Numata,[a] Shinya Tabata,[a] Akihiro Kobayashi[ab] and Suguru Yoshida *[a]

Received 16th August 2023,
Accepted 15th September 2023

DOI: 10.1039/d3nj03831a

rsc.li/njc

An efficient synthetic method for multisubstituted naphthalenes from 4-hydroxy-2-pyrones through cycloaddition with aryne intermediates is disclosed. Various highly functionalized 2-pyrones were synthesized through 4-hydroxy-2-pyrones in short steps. The resulting 2-pyrones reacted smoothly with a wide range of aryne intermediates generated from *o*-silylaryl triflates to provide multisubstituted naphthalenes by the Diels–Alder reaction and following decarboxylative aromatization. The aryne reaction of 2-pyrones served in the synthesis of diverse naphthalenes having 1,2,3-triazole moieties by combination with triazole formation of 4-azido-2-pyrones.

Introduction

Multisubstituted naphthalenes are a widely used class of compounds in various research areas such as pharmaceutical sciences, agrochemistry, and materials chemistry.[1] Despite the significance of highly functionalized naphthalenes, it is still challenging to prepare multisubstituted naphthalenes efficiently due to the problematic reactivity and selectivity control in various transformations such as electrophilic aromatic substitutions (Fig. 1A).[2] Herein, we describe an efficient method to synthesize multisubstituted naphthalenes by an aryne reaction with a broad range of 2-pyrones prepared through 4-hydroxy-2-pyrones.

Remarkable advances in synthetic aryne chemistry have improved the accessibility of multisubstituted arenes having a variety of functional groups.[3] Since a broad range of functionalized arynes served in arene synthesis and recent studies allowed us to synthesize *o*-silylaryl triflates bearing various functionalities in good efficiencies, we paid attention to dienes as arynophiles for naphthalene synthesis.[4] In general, the Diels–Alder reactions of diverse electron-rich furans with arynes easily take place, since aryne intermediates show a highly electron-deficient nature.[5] A range of naphthalenes were prepared by further deoxygenative aromatization of the cycloadducts between arynes and furans.[6] Due to the poor accessibility of functionalized furans and limitations in reductive aromatizations, facile synthetic methods of multisubstituted naphthalenes are still desired.

In this study, we conceived an idea of facile naphthalene synthesis by reaction of 2-pyrones with arynes. A pioneering study on naphthalene synthesis was reported by Wittig and Hoffmann in 1962, where the Diels–Alder reaction of 2-pyrone with benzyne and subsequent retro Diels–Alder reactions removing carbon dioxide proceeded smoothly to afford naphthalene (Fig. 1B).[7a] We paid attention to the cyclic ester moiety as a traceless linker that would improve the diene reactivity by fixing the s-*cis* structure. Although various 2-pyrones served as electron-deficient dienes in the inverse electron-demand Diels–Alder reactions with electron-rich dienophiles such as vinyl ethers[8] and a range of substituted 2-pyrones have served in the reaction with benzyne in recent studies,[7] only limited naphthalenes have been synthesized probably due to the electronic demands as both arynes and 2-pyrones are electron-deficient classes of skeletons, in which substituted arynes were not examined and the effects of substituents on the arynes and pyrones are still unclear.[7] Also, theoretical studies of the aryne reaction with 2-pyrones are sought after.

Recently, we developed an efficient method to prepare tetrahydroanthracene derivatives by the reaction of arynes *via* pyrones (Fig. 1C).[9a] Indeed, treatment of oxadiazinones and cycloalkyne precursors with fluoride ions provided tetrasubstituted 2-pyrones. The resulting 2-pyrones reacted with arynes to furnish tetrahydroanthracene derivatives. Similar transformations of oxadiazinones with cycloalkynes and arynes were also reported by Garg and coworkers.[9b,c]

For the synthesis of highly functionalized naphthalenes, we focused on 4-hydroxy-2-pyrones as intermediates for di- or trisubstituted 2-pyrones because of the following three features

---

[a] *Department of Biological Science and Technology, Faculty of Advanced Engineering, Tokyo University of Science, 6-3-1 Niijuku, Katsushika-ku, Tokyo 125-8585, Japan. E-mail: s-yoshida@rs.tus.ac.jp*

[b] *Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan*

† Electronic supplementary information (ESI) available. See DOI: **https://doi.org/10.1039/d3nj03831a**

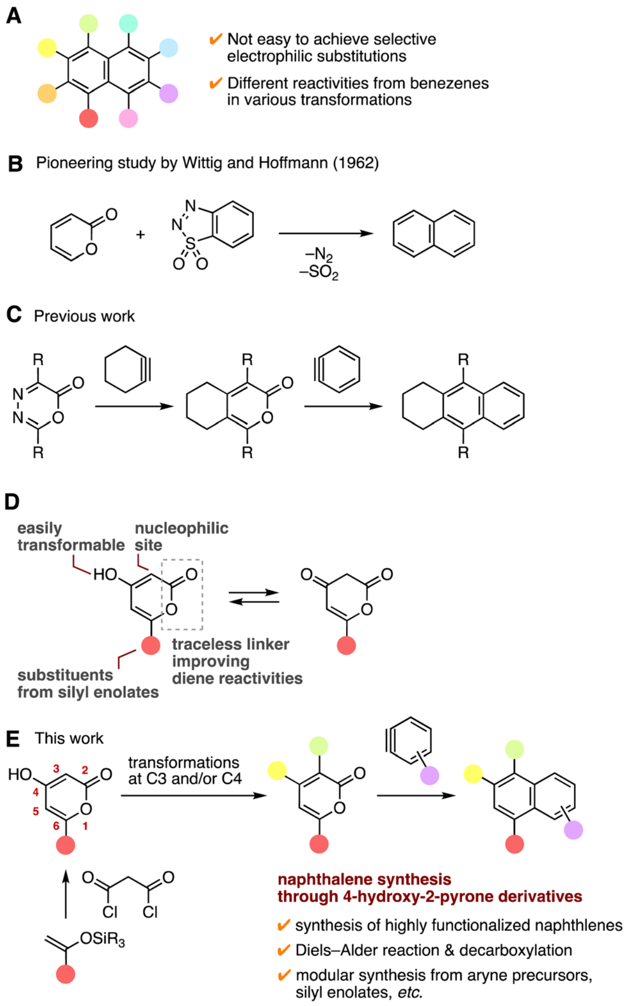


Fig. 1 (A) Multisubstituted naphthalenes. (B) A pioneering study by Wittig and Hoffmann. (C) Our previous study. (D) Features of 4-hydroxy-2-pyrones. (E) Overview of this work.

(Fig. 1D).[10] (1) A wide variety of 6-substituted 4-hydroxy-2-pyrones can be synthesized easily from silyl enolates and malonyl chloride. (2) Due to the equilibrium structures between an enol form and a keto form, electrophilic substitution easily takes place at C3 selectively. (3) Transformations at C4 involving halogenation and subsequent substitutions lead to various 4-substituted 2-pyrones. Thus, we expected that a wide variety of highly functionalized naphthalenes would be synthesized from diverse *o*-silylaryl triflates and 2-pyrones by the Diels–Alder reaction followed by decarboxylative aromatization (Fig. 1E). Detailed scope and limitations, applications to prepare triazoles, and theoretical studies on naphthalene synthesis have been performed.

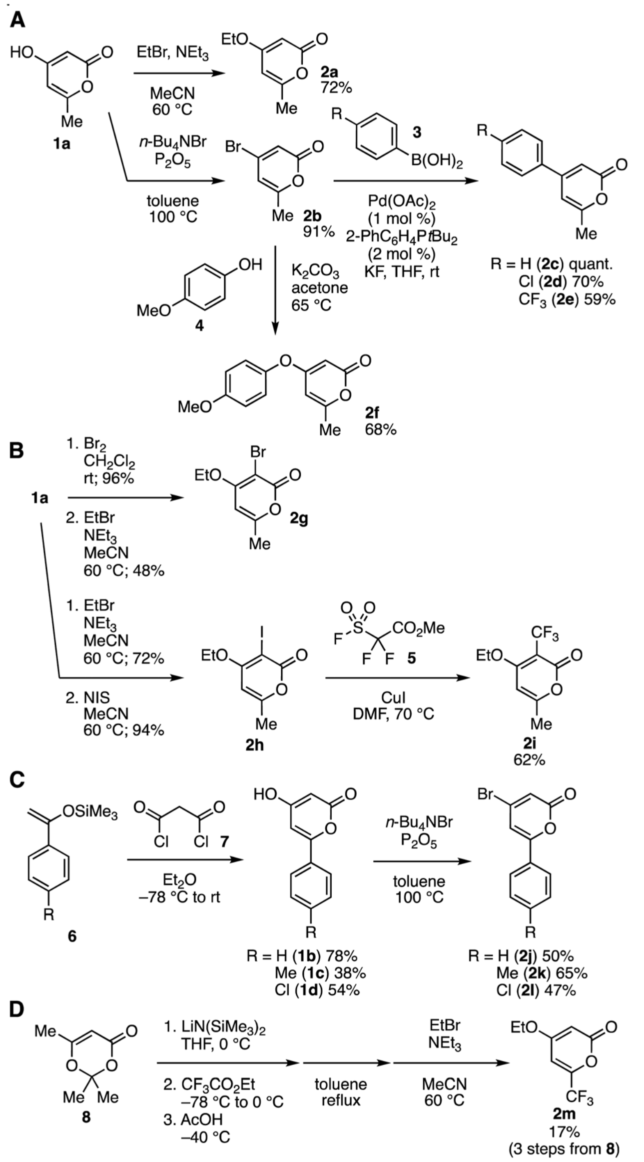


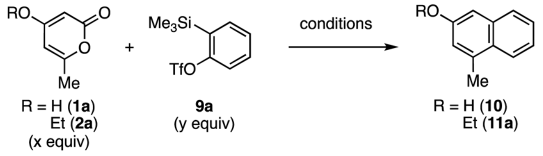
Fig. 2 (A) Synthesis of **2a–2f**. (B) Synthesis of **2g–2i**. (C) Synthesis of **2j–2l**. (D) Synthesis of **2m**. See ESI† for details.

Results and discussion

First, we prepared a wide range of di- or trisubstituted 2-pyrones from 6-substituted 4-hydroxy-2-pyrones in accordance with various reports[10] with minor modifications (Fig. 2). Divergent synthetic methods using common intermediates are beneficial in preparing multisubstituted naphthalenes. For example, *O*-alkylation[10g] and dehydrative bromination[10k] of 4-hydroxy-6-methyl-2-pyrone (**1a**) smoothly took place to provide **2a** and **2b** in good yields (Fig. 2A). Suzuki–Miyaura cross-coupling reactions of **2b** with arylboronic acids **3** in the presence of a catalytic amount of palladium acetate and JohnPhos efficiently proceeded to afford 4-arylated pyrones **2c**–**2e**.[10e] We also succeeded in the synthesis of ether **2f** by treatment of bromide **2b** with 4-methoxyphenol (**4**) in the presence of potassium carbonate.[10h] These results clearly indicate that a wide variety of 4-substituted pyrones can be prepared easily from 4-hydroxypyrone **1a** and simple starting materials such as arylboronic acids and phenols. A variety of substituents were successfully installed at nucleophilic C3 of 4-hydroxy-6-methyl-2-pyrone (**1a**) (Fig. 2B).[10g] Bromination or iodination followed by *O*-ethylation furnished trisubstituted 2-pyrone **2g** or **2h**, respectively.[10g] We accomplished further trifluoromethylation of **2h** to give **2i** in good yield according to the reported method by McGlacken and coworkers.[10g] Synthesis of 6-aryl-4-bromo-2-pyrones **2j–2l** was realized from silyl enolates **6** and malonyl chloride (**7**) and subsequent dehydrative bromination (Fig. 2C).[10c] In addition, we achieved the preparation of 6-trifluoromethyl-substituted 2-pyrone **2m** through trifluoroacetylation of acetyl acetone derivative **8** without purification of intermediates (Fig. 2D).[10d]

Efficient synthesis of disubstituted naphthalene **11a** by the reaction of pyrone **2a** with *o*-silylphenyl triflate **9a** was accomplished (Table 1). While the desired naphthalene **10** was not obtained when using 4-hydroxy-6-methyl-2-pyrone (**1a**) (entry 1), we succeeded in the preparation of naphthalene **11a** by the reaction of 4-ethoxy-6-methyl-2-pyrone (**2a**) with benzyne generated from *o*-silylphenyl triflate **9a** with cesium fluoride in acetonitrile at room temperature (entry 2). Although the efficiency was not improved by changing the activators for generating benzyne from **9a** (entries 3–5), we successfully synthesized naphthalene **11a** in high yield when the reaction was conducted at 50 °C (entry 6). After modifying the ratio between pyrone **2a** and *o*-silylphenyl triflate **9a** (entries 7–9), naphthalene **11a** was prepared efficiently from **2a** (1.0 equiv.) and **9a** (1.5 equiv.) (entry 9) and the yield was slightly decreased when using 2.0 equivalents of **9a** (entry 10). We also succeeded in naphthalene synthesis on a 1 mmol scale, obviously showing good scalability of the protocol.

Table 1 Screening of the reaction conditions



Entry	OR	*x*	*y*	Conditions	Product, yield[a] (%)
1	OH	2.0	1.0	CsF (2.0 equiv.), MeCN, rt, 24 h	**10**, 0
2	OEt	2.0	1.0	CsF (2.0 equiv.), MeCN, rt, 24 h	**11a**, 35[b]
3	OEt	2.0	1.0	CsF (2.0 equiv.), 18-crown-6 (2.0 equiv.) MeCN, rt, 24 h	**11a**, 20[c]
4	OEt	2.0	1.0	KF (2.0 equiv.), 18-crown-6 (2.0 equiv.) THF, rt, 24 h	**11a**, 39[c]
5	OEt	2.0	1.0	Cs$_2$CO$_3$ (2.0 equiv.), 18-crown-6 (2.0 equiv.) THF, rt, 24 h	**11a**, 17[c]
6	OEt	2.0	1.0	CsF (2.0 equiv.), MeCN, 50 °C, 24 h	**11a**, 72
7	OEt	2.0	1.0	CsF (2.0 equiv.), MeCN, 80 °C, 24 h	**11a**, 58
8	OEt	1.0	1.0	CsF (2.0 equiv.), MeCN, 50 °C, 24 h	**11a**, 61
9	OEt	1.0	1.5	CsF (2.0 equiv.), MeCN, 50 °C, 24 h	**11a**, 76[d] [70][de]
10	OEt	1.0	2.0	CsF (3.0 equiv.), MeCN, 50 °C, 24 h	**11a**, 65

[a] Yields based on ^{1}H NMR analysis. Reactions were performed in 0.1 mmol scale unless otherwise noted. [b] Aryne precursor **9a** (50%) was recovered. [c] Aryne precursor **9a** was consumed. [d] Isolated yield. [e] The reaction was conducted using 1.0 mmol of **2a**.

A wide range of multisubstituted 2-pyrones **2** reacted with benzyne generated from *o*-silylphenyl triflate **9a** providing naphthalenes having various functionalities (Fig. 3). For example, 3-bromo-1-methylnaphthalene (**11b**) was prepared by the reaction of 4-bromo-6-methyl-2-pyrone (**2b**) with benzyne in good yield. The Diels–Alder reaction and following decarboxylative aromatization of 4-aryl-6-methyl-2-pyrones **2c–2e** with benzyne took place, in which lactone intermediates without decarboxylation were not observed. We also succeeded in the efficient synthesis of 1-methyl-3-(4-methyoxyphenyloxy)naphthalene (**11f**) from 2-pyrone **2f.** These results clearly show that diverse naphthalenes can be prepared from 2-pyrones **2**, aryne precursor **9a**, and arylboronic acids or phenols. Furthermore, 3-substituted 2-pyrones **11g–11i** participated in the naphthalene synthesis without damaging the ethoxy, methyl, bromo, iodo, and trifluoromethyl group. We also accomplished naphthalene synthesis using 6-aryl-4-bromo-2-pyrones **2j–2l** prepared from the corresponding silyl enolates. It is worth noting that 6-trifluoromethyl-substituted 2-pyrone **2m** smoothly reacted with benzyne to provide 1-trifluoromethyl-substituted naphthalene **11m** in moderate yield. Since various naphthalenes bearing a range of functional groups were efficiently synthesized from the corresponding 2-pyrones in which further

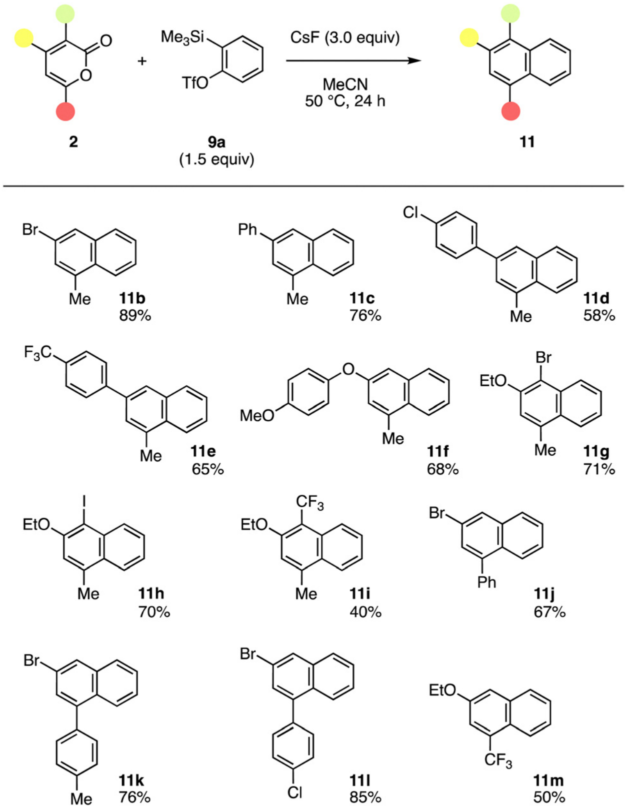


Fig. 3 Synthesis of naphthalenes **11** using various 2-pyrones **2**. Reactions were performed on a 0.1 mmol scale unless otherwise noted.

activation was not required for the decarboxylation, diverse naphthalenes would be prepared by the aryne reaction of multi-substituted 2-pyrones prepared from silyl enolates in short steps. Of note, 2-pyrones having electron-withdrawing substituents including bromo and trifluoromethyl groups participated in the naphthalene synthesis.

Divergent *o*-silylaryl triflates **9** bearing electron donating or withdrawing substituents smoothly reacted with 4-bromo-6-methyl-2-pyrone (**2b**) furnishing tri- and tetra-substituted naphthalenes **11n**–**11t** (Fig. 4). When using 3-methoxy-2-(trimethylsilyl)phenyl triflate (**9b**) as a 3-methoxybenzyne precursor, a regioisomeric mixture of naphthalenes **11n** and **11n′** was obtained, where 1-methyl-3-bromo-5-methoxynaphthalene (**11n**) was a major product in moderate selectivity. We achieved the efficient synthesis of naphthalene **11o** by the reaction of 2-pyrone **2b** with 4,5-dimethylbenzyne generated from **9c** triggered by cesium fluoride. The reaction of 4,5-difluorobenzyne with 2-pyrone **2b** also proceeded smoothly to afford naphthalene **11p** in a good yield leaving bromo and fluoro groups untouched. Dimethoxy-substituted naphthalene **11q** was successfully prepared in good yields using *o*-silylaryl triflate **9e** as a 4,5-dimethoxybenzyne precursor. Ring-fused naphthalenes **11r** and **11s** were also synthesized by the reaction of 2-pyrone **2b** with fused arynes generated from *o*-silylaryl triflates **9f** and **9g**, respectively. In addition, 3-bromo-1-methylanthracene (**11t**) was prepared by the reaction of 2,3-naphthalene in moderate yield, in which overreactions of anthracene **11t** also proceeded as a side reaction.

The naphthalene synthesis using 2-pyrones and aryne intermediates and triazole formations allowed us to prepare various triazolyl naphthalenes (Fig. 5). Indeed, we realized the synthesis of 4-azido-6-methyl-2-pyrone (**2n**)[10a] by azidation of bromide **2b** with sodium azide. Treatment of azide **2n** with *o*-silylphenyl triflate **9a** with cesium fluoride in acetonitrile at 50 °C provided triazole-substituted naphthalene **12** in an excellent yield by aryne reactions at the 2-pyrone and azide moieties.[11] Triazole formation of azide **2n** with terminal alkyne **13** catalyzed by copper also took place efficiently to furnish 1,2,3-triazole **2o** in high yield.[12] Further aryne reaction of 2-pyrone **2o** using *o*-silylaryl triflate **9f** smoothly proceeded affording highly functionalized naphthalene **14**. The broad scope of the click reaction using various alkynes enabled us to synthesize a wide range of multisubstituted naphthalenes having 1,2,3-triazole moieties from easily available starting materials. This result clearly demonstrates the advantage of this study: diverse pyrones and *o*-silylaryl triflates with a wide range of functional groups, including alkoxy, fluoro, bromo, iodo, trifluoromethyl, and triazole moieties, are applicable over conventional aryne reactions of pyrones.

We then investigated theoretical aspects of the aryne reaction of 2-pyrones (Fig. 6 and 7). Optimized structures of benzyne (**III**), electron-rich dienes **15a**–**15c**, and 2-pyrones **2** having various functionalities were obtained by DFT calculations (B3LYP, 6-311+G(d,p)) (Fig. 6). These results show that electron-deficient benzyne (**III**) has a low LUMO energy level, and furan (**15a**), 2,5-dimethylfuran (**15b**), and *N*-phenylpyrrole (**15c**) have high HOMO energy levels, leading to good reactivities as electron-rich dienes in Diels–Alder reactions with a benzyne intermediate. Compared to these electron-rich heteroaromatics **15a**–**15c**, theoretical calculations of substituted 2-pyrones **2** indicate that simple 2-pyrone (**2p**) has low LUMO and HOMO levels, and the HOMO energy levels are significantly affected by a variety of functional groups such as ethoxy, methyl, bromo, phenyl, and trifluoromethyl groups. To our surprise, the energy gaps between the LUMO of benzyne (**III**) and the HOMOs of 2-pyrones **2** were significantly

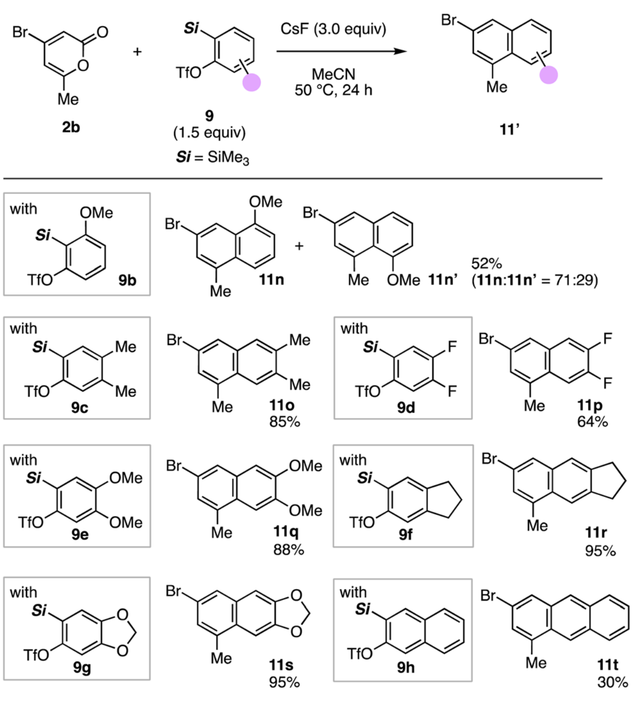


Fig. 4 Synthesis of naphthalenes **11** using various *o*-silylaryl triflates **9**. Reactions were performed on a 0.1 mmol scale unless otherwise noted.

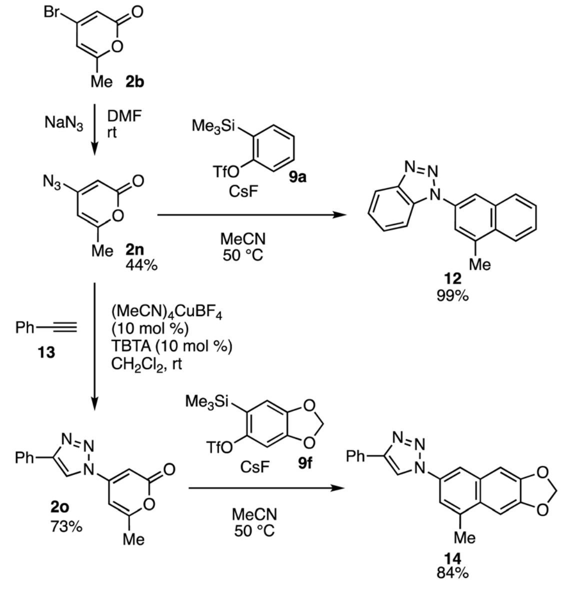
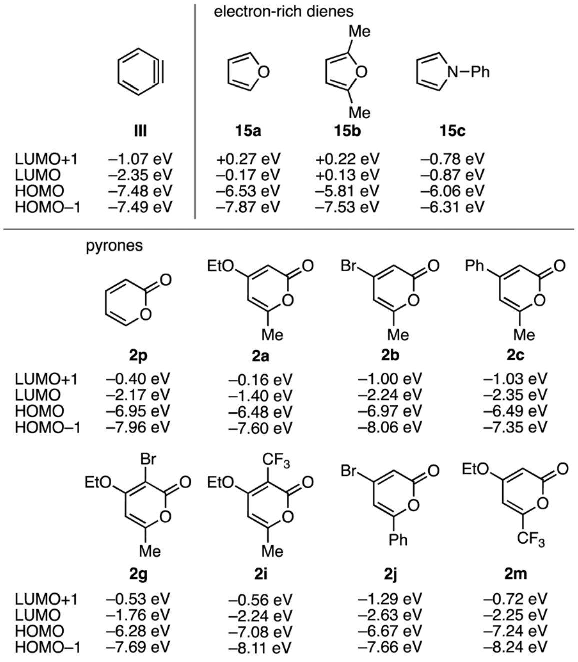


Fig. 5 Synthesis of 1,2,3-triazoles **12** and **14**. Reactions were performed on a 0.1 mmol scale unless otherwise noted.



	III	15a	15b	15c
LUMO+1	−1.07 eV	+0.27 eV	+0.22 eV	−0.78 eV
LUMO	−2.35 eV	−0.17 eV	+0.13 eV	−0.87 eV
HOMO	−7.48 eV	−6.53 eV	−5.81 eV	−6.06 eV
HOMO−1	−7.49 eV	−7.87 eV	−7.53 eV	−6.31 eV

	2p	2a	2b	2c
LUMO+1	−0.40 eV	−0.16 eV	−1.00 eV	−1.03 eV
LUMO	−2.17 eV	−1.40 eV	−2.24 eV	−2.35 eV
HOMO	−6.95 eV	−6.48 eV	−6.97 eV	−6.49 eV
HOMO−1	−7.96 eV	−7.60 eV	−8.06 eV	−7.35 eV

	2g	2i	2j	2m
LUMO+1	−0.53 eV	−0.56 eV	−1.29 eV	−0.72 eV
LUMO	−1.76 eV	−2.24 eV	−2.63 eV	−2.25 eV
HOMO	−6.28 eV	−7.08 eV	−6.67 eV	−7.24 eV
HOMO−1	−7.69 eV	−8.11 eV	−7.66 eV	−8.24 eV

Fig. 6 Frontier orbital energies of benzyne and dienes.

smaller than those between the HOMO of benzyne and the LUMOs of 2-pyrones **2**. It is worth noting that 2-pyrones **2** bearing not only electron-donating groups but also electron-withdrawing groups such as a trifluoromethyl group reacted with benzyne to furnish the corresponding naphthalenes, suggesting that the efficiencies in the Diels–Alder reaction between benzyne and pyrones and subsequent decarboxylative aromatization are not significantly affected by electron donating and withdrawing functional groups.

Further DFT calculations successfully provided transition state structures **TS1A–C** and **TS2A–C** for the reactions between benzyne (**III**) and 2-pyrones **2p**, **2a**, and **2m** and subsequent decarboxylation (Fig. 7). As a result, the calculated activation energies for the Diels–Alder reactions of benzyne (**III**) with simple 2-pyrone (**2p**), 4-ethoxy-6-methyl-2-pyrone (**2a**), and 4-ethoxy-6-trifluoromethyl-2-pyrone (**2m**) and subsequent decarboxylations are found to be lower than 20 kcal mol^{-1}, which obviously supports the experimental results that the Diels–Alder reaction proceeded smoothly at room temperature. Judged from the obtained calculated activation energies, the effects of electron-donating and electron-withdrawing functional groups on Diels–Alder reactions and decarboxylations were insignificant. The low calculated activation energies for the following decarboxylative aromatization are in good accordance with the fact that intermediates without decarboxylation were not observed in the aryne reactions of 2-pyrones. These reaction pathways obtained by DFT calculations would serve to predict the efficiencies of aryne reactions providing highly functionalized naphthalenes.

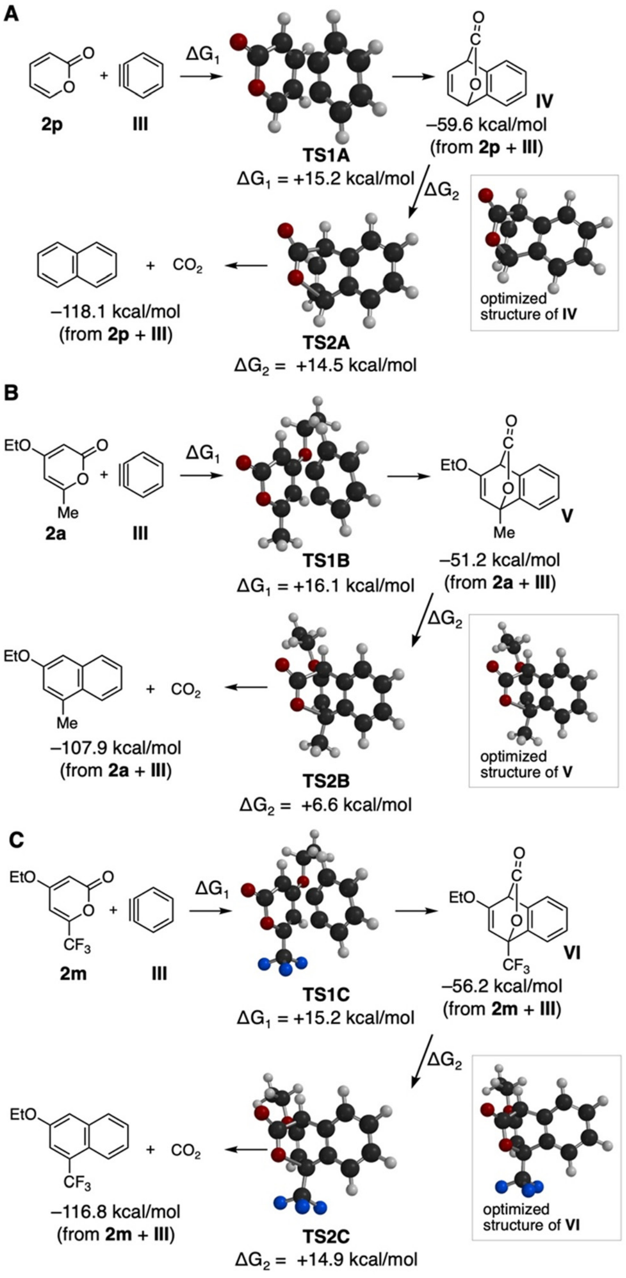


Fig. 7 (A) Calculated reaction pathways of the reaction between **2p** and **III**. (B) Calculated reaction pathways of the reaction between **2a** and **III**. (C) Calculated reaction pathways of the reaction between **2m** and **III**. Atoms in **TS1A–C** and **TS2A–C**: black = C; grey = H; red = O; blue = F. See the ESI† for details.

Conclusions

In conclusion, we have developed an efficient method to synthesize multisubstituted naphthalenes from 2-pyrones and *o*-silylaryl triflates. A wide variety of 2-pyrones were synthesized using easily accessible starting materials such as silyl enolates, arylboronic acids, and phenols through 4-hydroxy-substituted 2-pyrones. Since substituent effects on the aryne reactions of 2-pyrones were not significant and further transformations including triazole formations served in the preparation of diverse 2-pyrones, a wide range of highly functionalized naphthalenes will be prepared from 2-pyrones in a modular synthetic manner. Detailed theoretical calculations supported the reaction mechanisms involving Diels–Alder reaction and decarboxylative aromatization, in which interactions between the HOMOs of 2-pyrones and the LUMO of benzyne would contribute to the [4+2] cycloaddition. Further studies such as the synthesis of diverse triazole-substituted naphthalenes from azide-substituted 2-pyrones are in progress in our group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank Central Glass Co., Ltd. for providing Tf_2O. This work was supported by JSPS KAKENHI Grant Number JP22H02086 (S. Y.); The Uehara Memorial Foundation (S. Y.); Tokuyama Science Foundation (S. Y.); The Ube Foundation (S. Y.); and Inamori Research Grants (S. Y.).

Notes and references

1 (*a*) S. Makar, T. Saha and S. K. Singh, Naphthalene, a versatile platform in medicinal chemistry: Sky-high perspective, *Eur. J. Med. Chem.*, 2019, **161**, 252; (*b*) S. V. Bhosale, M. A. Kobaisi, R. W. Jadhav, P. P. Morajkar, L. A. Jones and S. George, Naphthalene diimides: perspectives and promise, *Chem. Soc. Rev.*, 2021, **50**, 9845; (*c*) A. Saeed, S. Ashraf, M. Aziz, P. A. Channar, S. A. Ejaz, A. Fayyaz, Q. Abbas, F. A. Alasmary, A. M. Karami, A. Tehzeeb, A. Mumtaz and H. R. El-Seedi, Design, synthesis, biochemical and in silico characterization of novel naphthalene-thiourea conjugates as potential and selective inhibitors of alkaline phosphatase, *Med. Chem. Res.*, 2023, **32**, 1077.

2 (*a*) C. B. de Koning, A. L. Rousseau and W. A. L. van Otterlo, Modern methods for the synthesis of substituted naphthalenes, *Tetrahedron*, 2003, **59**, 7; (*b*) S. Prévost, Regioselective C–H Functionalization of Naphthalenes: Reactivity and Mechanistic Insights, *ChemPlusChem*, 2020, **85**, 476.

3 *Modern Aryne Chemistry*, ed. A. T. Biju, Wiley-VCH, Weinheim, 2021.

4 (*a*) P. M. Tadross and B. M. Stoltz, A Comprehensive History of Arynes in Natural Product Total Synthesis, *Chem. Rev.*, 2012, **112**, 3550; (*b*) A. Bhunia, S. R. Yetra and A. T. Biju, Recent advances in transition-metal-free carbon–carbon and carbon–heteroatom bond-forming reactions using arynes, *Chem. Soc. Rev.*, 2012, **41**, 3140; (*c*) S. Yoshida and T. Hosoya, The Renaissance and Bright Future of Synthetic Aryne Chemistry, *Chem. Lett.*, 2015, **44**, 1450; (*d*) A. E. Goetz, T. K. Shah and N. K. Garg, Pyridynes and indolynes as building blocks for functionalized heterocycles and natural products, *Chem. Commun.*, 2015, **51**, 34; (*e*) S. S. Bhojgude, A. Bhunia and A. T. Biju, Employing Arynes in Diels–Alder Reactions and Transition-Metal-Free Multicomponent Coupling and Arylation Reactions, *Acc. Chem. Res.*, 2016, **49**, 1658; (*f*) J.-A. García-López and M. F. Greaney, Synthesis of biaryls using aryne intermediates, *Chem. Soc. Rev.*, 2016, **45**, 6766; (*g*) J. Shi, Y. Li and Y. Li, Aryne multifunctionalization with benzdiyne and benztriyne equivalents, *Chem. Soc. Rev.*, 2017, **46**, 1707; (*h*) F. I. M. Idiris and C. R. Jones, Recent advances in fluoride-free aryne generation from arene precursors, *Org. Biomol. Chem.*, 2017, **15**, 9044; (*i*) T. Roy and A. T. Biju, Recent advances in molecular rearrangements involving aryne intermediates, *Chem. Commun.*, 2018, **54**, 2580; (*j*) S. Yoshida, Controlled Reactive Intermediates Enabling Facile Molecular Conjugation, *Bull. Chem. Soc. Jpn.*, 2018, **91**, 1293; (*k*) T. Matsuzawa, S. Yoshida and T. Hosoya, Recent advances in reactions between arynes and organosulfur compounds, *Tetrahedron Lett.*, 2018, **59**, 4197; (*l*) H. Takikawa, A. Nishii, T. Sakai and K. Suzuki, Aryne-based strategy in the total synthesis of naturally occurring polycyclic compounds, *Chem. Soc. Rev.*, 2018, **47**, 8030; (*m*) Y. Nakamura, S. Yoshida and T. Hosoya, Recent Advances in Synthetic Hetaryne Chemistry, *Heterocycles*, 2019, **98**, 1623; (*n*) D. B. Werz and A. T. Biju, Uncovering the Neglected Similarities of Arynes and Donor–Acceptor Cyclopropanes, *Angew. Chem., Int. Ed.*, 2020, **59**, 3385.

5 (*a*) M.-X. Zhang, W. Shan, Z. Chen, J. Yin, G.-A. Yu and S. H. Liu, Diels–Alder reactions of arynes in situ generated from DA reaction between bis-1,3-diynes and alkynes, *Tetrahedron Lett.*, 2015, **56**, 6833; (*b*) S. S. Bhojgude, A. Bhunia and A. T. Biju, Employing Arynes in Diels–Alder Reactions and Transition-Metal-Free Multicomponent Coupling and Arylation Reactions, *Acc. Chem. Res.*, 2016, **49**, 1658; (*c*) F. García, D. Peña, D. Pérez and E. Guitián, Aryne Cycloadditions for the Synthesis of Functional Polyarenes, in *Modern Aryne Chemistry*, ed. A. T. Biju, Wiley-VCH, Weinheim, 2021, pp. 27–68.

6 (*a*) C. Bozzo and M. D. Pujol, Deoxygenation of 5,12-Epoxy-5,12-dihydro-5,12-dimethyl-1,4-benzodioxino[2,3-g]isoquinoline with Iron Compounds. Synthesis of Antitumour Agents, *Synlett*, 2000, 550; (*b*) J. L. Marshall, D. Lehnherr, B. D. Lindner and R. R. Tykwinski, Reductive Aromatization/Dearomatization and Elimination Reactions to Access Conjugated Polycyclic Hydrocarbons, Heteroacenes, and Cumulenes, *ChemPlusChem*, 2017, **82**, 967; (*c*) E. M. Serum, S. Selvakumar, N. Zimmermann and M. P. Sibi, Valorization of 2,5-furandicarboxylic acid. Diels–Alder reactions with benzyne, *Green Chem.*, 2018, **20**, 1448.

7 (*a*) G. Wittig and R. W. Hoffmann, Dehydrobenzol aus 1.2.3-Benzothiadiazol-1.1-dioxyd, *Chem. Ber.*, 1962, **95**, 2718; (*b*) C. May and C. J. Moody, A concise synthesis of the antitumour alkaloid ellipticine, *J. Chem. Soc., Chem. Commun.*, 1984, 926; (*c*) C. J. Moody, Diels–Alder reactivity of pyrano[3,4-b]indol-3-ones, stable analogues of indole-2,3-quinodimethanes, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2505; (*d*) J. F. P. Andrews, P. M. Jackson and C. J. Moody, Pyrrole-2,3-quinodimethane analogues in the synthesis of indoles. Part 2.1 Synthesis and Diels–Alder reactions of 1,6-dihydropyrano[4,3-b]pyrrol-6(1*H*)-ones, *Tetrahedron*, 1993, **49**, 7353; (*e*) S. Escudero, D. Pérez, E. Guitián and L. Castedo, A New Convergent Approach to the Polycyclic

Framework of Dynemicin A, *J. Org. Chem.*, 1997, **62**, 3028; (*f*) S. Escudero, D. Pérez, E. Guitián and L. Castedo, [4+2] Cycloadditions between 2-pyrones and benzyne. Application to the synthesis of binaphthyls, *Tetrahedron Lett.*, 1997, **38**, 5375; (*g*) Y. Kuninobu, H. Takata, A. Kawata and K. Takai, Rhenium-Catalyzed Synthesis of Multisubstituted Aromatic Compounds *via* C–C Single-Bond Cleavage, *Org. Lett.*, 2008, **10**, 3133; (*h*) P.-P. Yeh, D. S. B. Daniels, D. B. Cordes, A. M. Z. Slawin and A. D. Smith, Isothiourea-Mediated One-Pot Synthesis of Trifluoromethyl Substituted 2-Pyrones, *Org. Lett.*, 2014, **16**, 964; (*i*) T. K. Shah, J. M. Medina and N. K. Garg, Expanding the Strained Alkyne Toolbox: Generation and Utility of Oxygen-Containing Strained Alkynes, *J. Am. Chem. Soc.*, 2016, **138**, 4948; (*j*) J. Huang, L. Li, H. Chen, T. Xiao, Y. He and L. Zhou, Synthesis of 3-Aryl-2-pyrones by Palladium-Catalyzed Cross-Coupling of Aryl Iodides with Cyclic Vinyldiazo Ester, *J. Org. Chem.*, 2017, **82**, 9204; (*k*) A. Szlapa-Kula, S. Kula, M. Filapek, A. Fabianczyk, K. Bujak, M. Siwy, S. Kotowicz, H. Janeczek, K. Smolarek, S. Maćkowski, S. Krompiec and E. Schab-Balcerzak, Synthesis, electrochemistry and optical properties with electroluminescence ability of new multisubstituted naphthalene derivatives with thiophene and carbazole motifs, *J. Lumin.*, 2018, **196**, 244; (*l*) B. S. Chinta, D. Lee and T. R. Hoye, Coumarin (5,6-Benzo-2-pyrone) Trapping of an HDDA-Benzyne, *Org. Lett.*, 2021, **23**, 2189.

8 (*a*) K. Afarinkia, V. Vinader, T. D. Nelson and G. H. Posner, Diels–Alder cycloadditions of 2-pyrones and 2-pyridones, *Tetrahedron*, 1992, **48**, 9111; (*b*) G. Huang, C. Kouklovsky and A. de la Torre, Inverse-Electron-Demand Diels–Alder Reactions of 2-Pyrones: Bridged Lactones and Beyond, *Chem. – Eur. J.*, 2021, **27**, 4760.

9 (*a*) T. Meguro, S. Chen, K. Kanemoto, S. Yoshida and T. Hosoya, Modular Synthesis of Unsymmetrical Doubly-ring-fused Benzene Derivatives Based on a Sequential Ring Construction Strategy Using Oxadiazinones as a Platform Molecule, *Chem. Lett.*, 2019, **48**, 582; (*b*) E. R. Darzi, J. S. Barber and N. K. Garg, Cyclic Alkyne Approach to Heteroatom-Containing Polycyclic Aromatic Hydrocarbon Scaffolds, *Angew. Chem., Int. Ed.*, 2019, **58**, 9419; (*c*) M. Ramirez, E. R. Darzi, J. S. Donaldson, K. N. Houk and N. K. Garg, Cycloaddition Cascades of Strained Alkynes and Oxadiazinones, *Angew. Chem., Int. Ed.*, 2021, **60**, 18201.

10 (*a*) M. Cervera, M. Moreno-Manas and R. Pleixats, 4-amino-6-methyl-2H-pyran-2-one. Preparation and reactions with aromatic aldehyde, *Tetrahedron*, 1990, **46**, 7885; (*b*) M. Sato, J.-i Sakaki, Y. Sugita, S. Yasuda, H. Sakoda and C. Kaneko, Two lactone formation reactions from 1,3-dioxin-4-ones having hydroxyalkyl group at the 6-position: Difference in ring opening and closure, *Tetrahedron*, 1991, **47**, 5689; (*c*) J. V. N. V. Prasad, K. S. Para, P. J. Tummino, D. Ferguson, T. J. McQuade, E. A. Lunney, S. T. Rapundalo, B. L. Batley, G. Hingorani, J. M. Domagala, S. J. Gracheck, T. N. Bhat, B. Liu, E. T. Baldwin, J. W. Erickson and T. K. Sawyer, Nonpeptidic Potent HIV-1 Protease Inhibitors: (4-Hydroxy-6-phenyl-2-oxo-2*H*-pyran-3-yl)thiomethanes That Span P1-P2′ Subsites in a Unique Mode of Binding, *J. Med. Chem.*, 1995, **38**, 898; (*d*) S. Gatti McArthur, E. Goetschi, W. S. Palmer, J. Wichmann and T. J. Woltering, Acetylenyl-pyrazolo-pyrimidine Derivatives as mGluR2 Antagonists, WO2006099972A1, 2006; (*e*) I. J. S. Fairlamb, L. R. Marrison, J. M. Dickinson, F.-J. Lu and J. P. Schmidt, 2-Pyrones possessing antimicrobial and cytotoxic activities, *Bioorg. Med. Chem.*, 2004, **12**, 4285; (*f*) T. Shinozuka, K. Shimada, S. Matsui, T. Yamane, M. Ama, T. Fukuda, M. Taki, Y. Takeda, E. Otsuka, M. Yamato and S. Naito, Arylamine based cathepsin K inhibitors: Investigating P3 heterocyclic substituents, *Bioorg. Med. Chem.*, 2006, **14**, 6807; (*g*) S. L. Clarke and G. P. McGlacken, Access to trifluoromethylated 4-alkoxy-2-pyrones, pyridones and quinolones, *Tetrahedron*, 2015, **71**, 2906; (*h*) K. Mackey, L. M. Pardo, A. M. Prendergast, M.-T. Nolan, L. M. Bateman and G. P. McGlacken, Cyclization of 4-Phenoxy-2-coumarins and 2-Pyrones via a Double C–H Activation, *Org. Lett.*, 2016, **18**, 2540; (*i*) Y. Zheng, S. Dong, K. Xu, D. Liu and W. Zhang, Pd-Catalyzed Asymmetric Allylic Substitution Cascade of Substituted 4-Hydroxy-2*H*-pyrones with *meso*-Allyl Dicarbonates, *Org. Lett.*, 2022, **24**, 3440; (*j*) R. Samala, M. K. Basu and K. Mukkanti, Regioselective functionalization of pyrones: Facile synthesis of 6-styrylpyrones via KHMDS-mediated aldol condensation, *Tetrahedron Lett.*, 2022, **88**, 153574; (*k*) M. Baak, B. Jaun, F. Belaj and R. Neier, Conformations of 4-tert-Butyloxy-, 4-(Trimethylsilyl)oxy- and 4-(Trimethylstannyl)oxy-6-methyl-2*H*-pyran-2-ones in the Crystalline State and in Solution, *Helv. Chim. Acta*, 2022, **105**, e202200029.

11 F. Shi, J. P. Waldo, Y. Chen and R. C. Larock, Benzyne Click Chemistry: Synthesis of Benzotriazoles from Benzynes and Azides, *Org. Lett.*, 2008, **10**, 2409.

12 (*a*) C. W. Tornøe, C. Christensen and M. Meldal, Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides, *J. Org. Chem.*, 2002, **67**, 3057; (*b*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; (*c*) T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Fokin, Polytriazoles as Copper(I)-Stabilizing Ligands in Catalysis, *Org. Lett.*, 2004, **6**, 2853.