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

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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.

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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 ethers⁸ 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

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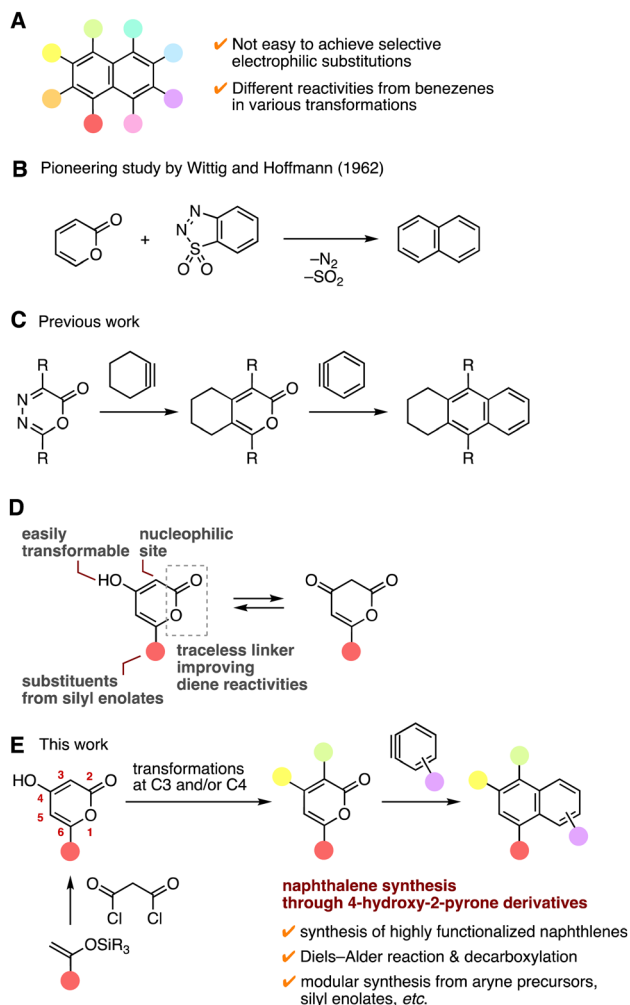


Fig. 1 (A) Multisubstituted naphthalenes. (B) A pioneering study by Wittig and Hoffmann. (C) Our previous study. (D) Features of 4-hydroxy-2-pyrone. (E) Overview of this work.

(Fig. 1D).¹⁰ (1) A wide variety of 6-substituted 4-hydroxy-2-pyrone 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-pyrone. Thus, we expected that a wide variety of highly functionalized naphthalenes would be synthesized from diverse *o*-silylaryl triflates and 2-pyrone 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.

Results and discussion

First, we prepared a wide range of di- or trisubstituted 2-pyrone from 6-substituted 4-hydroxy-2-pyrone in accordance with various reports¹⁰ with minor modifications (Fig. 2). Divergent synthetic methods using common intermediates are beneficial

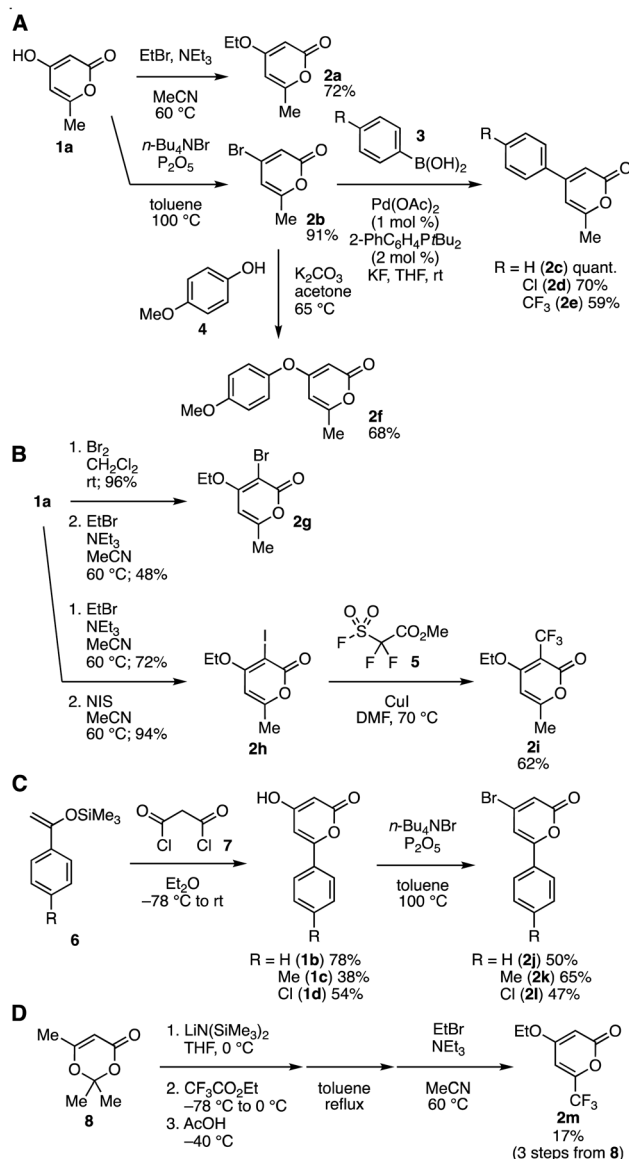


Fig. 2 (A) Synthesis of 2a–2f. (B) Synthesis of 2g–2i. (C) Synthesis of 2j–2l. (D) Synthesis of 2m. See ESI† for details.

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-hydroxypyrene 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.)

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 ¹H 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**.

(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.

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-methoxyphenoxy)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

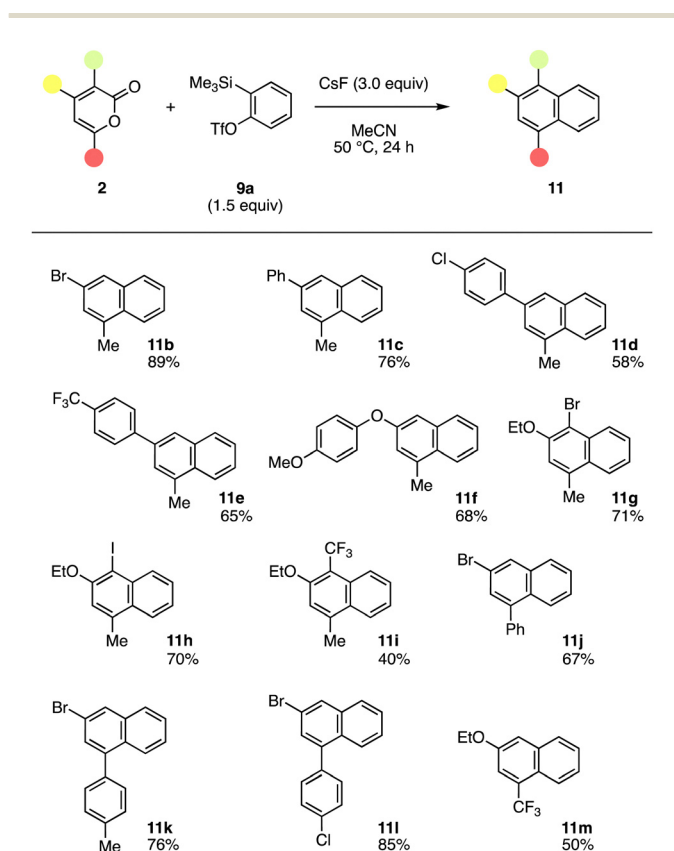


Fig. 3 Synthesis of naphthalenes **11** using various 2-pyrones **2**. Reactions were performed on a 0.1 mmol scale unless otherwise noted.



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

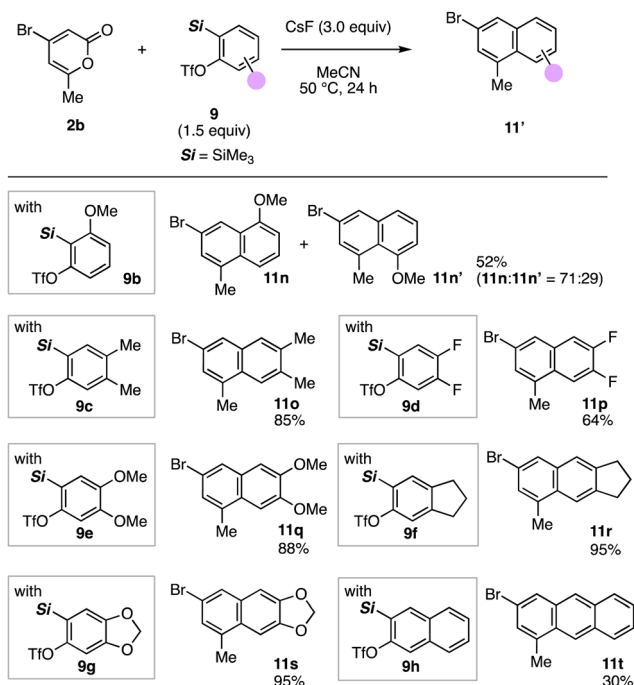


Fig. 4 Synthesis of naphthalenes **11** using various *o*-silylaryl triflates **9**. Reactions were performed on a 0.1 mmol scale unless otherwise noted.

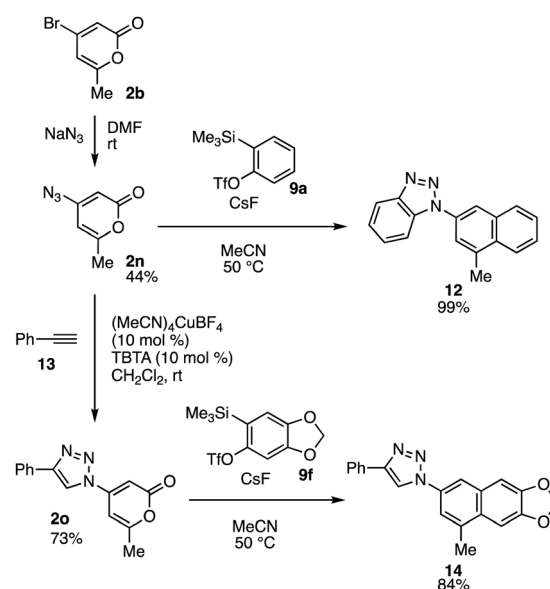


Fig. 5 Synthesis of 1,2,3-triazoles **12** and **14**. Reactions were performed on a 0.1 mmol scale unless otherwise noted.



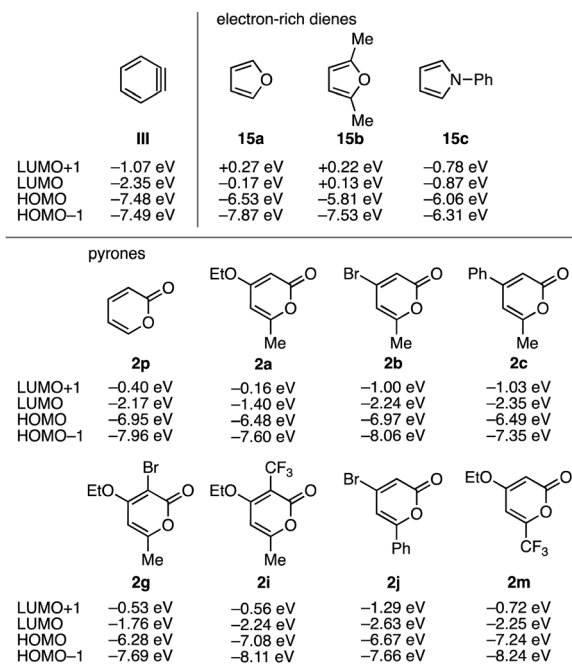


Fig. 6 Frontier orbital energies of benzyne and dienes.

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.

Conclusions

In conclusion, we have developed an efficient method to synthesize multisubstituted naphthalenes from 2-pyrones and

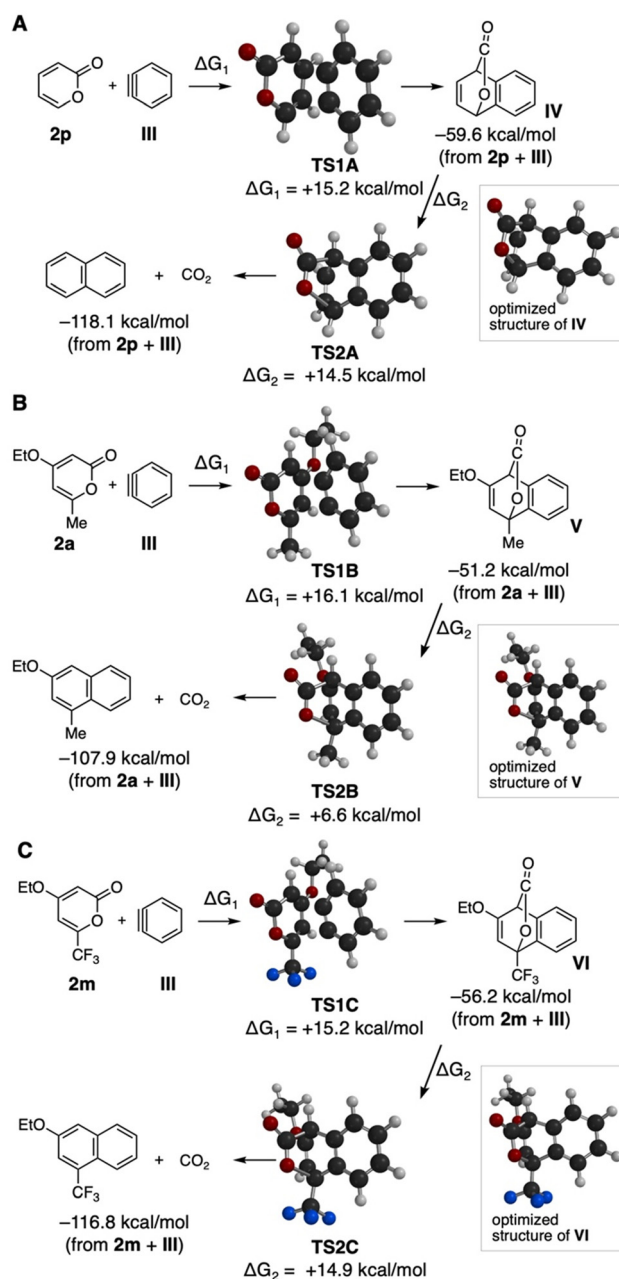


Fig. 7 (A) Calculated reaction pathways of the reaction between **2p** and **III**. (B) Calculated reaction pathways of the reaction between **2a** and **III**. (C) Calculated reaction pathways of the reaction between **2m** and **III**. Atoms in **TS1A–C** and **TS2A–C**: black = C; grey = H; red =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

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.

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