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COMMUNICATION

Rapid access to polycyclic thiopyrylium compounds from unfunctionalized aromatics by thia-APEX reaction

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We developed a sulfur-embedding annulative π-extension (thia-APEX) reaction that could construct a sulfur-embedding cationic hexagonal aromatic ring, thiopyrylium, onto unfunctionalized aromatics in one step. The key of thia-APEX is the use of *S*-imidated *ortho*-arenoyl arenethiols, and a variety of π-extended thiopyryliums can easily be synthesized. The synthesized thiopyryliums showed diverse absorption and emission properties over the visible light to NIR region, depending on minor structural differences.

Thiopyrylium is a cationic organic skeleton which consists of sulfur-containing six-membered aromatic ring.[1] In recent years, polycyclic aromatic compounds containing thiopyrylium rings as well as other pyrylium rings[1h,1i] have gained attention and have been studied as candidate compounds for various functional materials because of their unique properties, such as long-wavelength absorption and emission, photoredox catalysis, and anion-sensing capability.[2] One of the classical methods for synthesizing thiopyryliums is the annulative condensation reaction of 1,5-dicarbonyl with H_2S in the form of Paal–Knorr synthesis.[1c,3] Thiopyrylium compounds can also be synthesized by reactions of arenethiols and 1,3-diketones or aminothioacrylamide derivatives with acids.[4] These methods are useful for constructing small π-conjugation systems such as thiopyrylium and benzothiopyrylium compounds. On the other hand, largely π-extended thiopyrylium compounds are accessible through inter/intramolecular Friedel–Crafts reactions of aromatic thioethers bearing an *ortho*-alkoxylcarbonyl group followed by 1,2-addition using aryl metal reagents and acid-mediated aromatization (Fig. 1A).[1b,2d] Although this method is useful, it requires prefunctionalization of the starting aromatics and multistep component-assembling reactions.

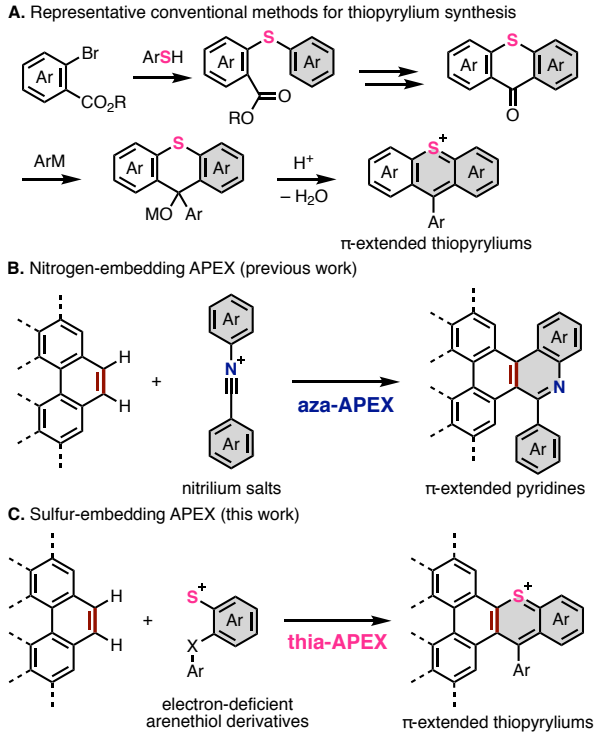

Fig. 1 (A) Representative conventional methods for thiopyrylium synthesis. (B, C) Heteroatom-embedding annulative π-extension (hetero-APEX) reactions: (B) Aza-APEX with nitrilium salts.[7a] (C) Thia-APEX with electron-deficient arenethiol derivatives.

As part of our ongoing efforts to achieve streamlined and diversity-oriented synthesis of large π-conjugated systems, we have developed a series of one-step annulative π-extension reactions (APEX)[5] of polycyclic aromatic hydrocarbons (PAHs) and heteroaromatics. Region-selective APEX reactions allow access to unprecedented nanographenes that are difficult to

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synthesize using conventional coupling reactions.[6] In addition, we have developed the APEX reaction for constructing heteroaromatics (hetero-APEX reaction)[7] (Figs. 1B and 1C). For example, the nitrogen-embedding APEX (aza-APEX) reaction of unfunctionalized aromatics using highly electrophilic diaryl nitrilium salts rapidly constructed a new pyridine ring on unfunctionalized aromatics (Fig. 1B).[7a] Herein, we report a novel sulfur-embedding APEX (thia-APEX) reaction that furnishes π-extended thiopyrylium compounds from unfunctionalized aromatics using electron-deficient arenethiol derivatives as π-extending agents (Fig. 1C).

To achieve the thia-APEX reaction, we designed and adopted *S*-succinimidated *ortho*-arenoyl arenethiols as novel π-extending agents (Fig. 2). These thiols include two electrophilic reaction sites: the *S*-succinimide moiety for C–S bond formation and carbonyl group for C–C bond formation. Succinimide groups act as leaving groups in the presence of Brønsted/Lewis acids to electrophilic sulfur atoms.[8] This electrophilic sulfur atom can form diaryl thioethers or benzothiophenes by reacting with other benzene derivatives or alkynes. We envisioned that an adjacent *ortho*-arenoyl unit on the arenethiol would promote a sequence of C–S bond formation, intramolecular Friedel–Crafts addition, and dehydroxylative aromatization using acids.[9] With this concept, various new sulfur-embedding APEX agents were prepared utilizing the synthesis of benzophenonethiols from arylmetals and thiosalicylic acid or arylonitriles and arenethiols.[10] Subsequently, the succinimide groups were introduced through *S*-chlorination reaction with SO_2Cl_2 followed by reaction of succinimides with NEt_3 (See ESI for details).[8b]

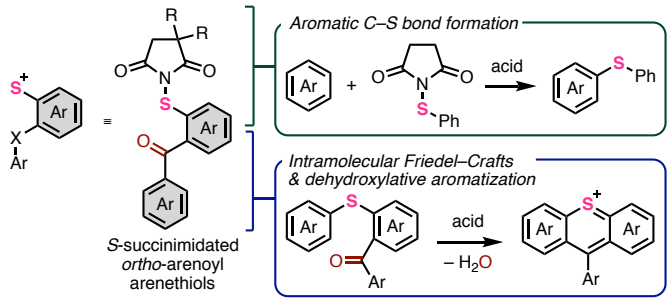


Fig. 2 Design of sulfur-embedding π-extending agents for thia-APEX reaction.

First, we optimized the conditions for the thia-APEX reaction of phenanthrene with the newly prepared sulfur-embedding APEX agents (see ESI for details). After screening the reaction parameters such as solvents, temperature, amounts of π-extending agents, and succinimide-moieties, we found that the π-extending agent **2** (1.1 equiv) was efficiently activated by TfOH (2.3 equiv) in 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP) (0.2 M of aromatic substrate **1** to HFIP) to react with unfunctionalized aromatics **1** (Fig. 3). After heating at 80 °C for 17 h, various fused thiopyrylium salts **3** were obtained. Because the obtained thiopyrylium salts were sensitive to excess amounts of water, working with water or purification by preparative thin-layer chromatography (PTLC) on silica gel resulted in the formation of thioxanthenol **3ha-OH** (see ESI for details). Therefore, we chose a purification method involving precipitation, filtration, and washing with diethyl ether, followed by recrystallization to remove succinimides and other impurities, which allowed us to obtain high-quality products. In some thia-APEX reactions, superior isolated yields were obtained using ethosuximide derivatives (**2-etho**) instead of succinimide derivatives (**2-succ**). This could be due to the higher solubility of **2-etho** than that of **2-succ**, which facilitated easy separation from the crude mixture by simple filtration and washing.

In the reactions of 1,2-dimethoxybenzene (**1a**) with *S*-succinimides having simple benzophenone structures (**2a-succ** and **2a-etho**) and phenyl substituents (**2b-succ**), thiopyrylium salts **3aa** and **3ab** were obtained in 86–91% isolated yields. Compounds **3ba** and **3ca** were also obtained from 1,3-dimethoxybenzene (**1b**) and 1,4-dimethoxybenzene (**1c**) in 64–66% and 81% yields, respectively. We consider that the electron-rich dimethoxy benzenes **1a**–**1b** possess comparably high reactivities, and the difference in yield is derived from the ease/difficulty of solidification of the products; thiopyrylium **3aa** and **3ca** are more easily solidified than **3ba**. Interestingly, no other regioisomers were obtained or isolated in the case of **3aa**, **3ab**, and **3ba**. 1,2,3,4-Tetramethylbenzene (**1d**) afforded thiopyrylium **3da** in a 67% yield. In addition, the use of ethosuximide **2a-etho** afforded thiopyrylium **3da** with better yield and reproducibility. The PAH-type substrates 2,7-di-*tert*-butylphenanthrene (**1e**), 2,7-di-*tert*-butylpyrene (**1f**), and pristine pyrene (**1g**) were used. From substrate **1e**, thiopyryliums **3ea**–**3ec** were obtained in 57–86% yields. The use of **2a-etho** increased the yield of thiopyrylium **3ea** from 58% (with **2a-succ**) to 75%. Thiopyrylium **3ec** was more difficult to solidify in crude oil, which seemed to cause a decrease in the yield. Substrate **1f** afforded not only the desired product **3fa** but also a small amount of double thia-APEX that was not isolated, but detected by ESI-MS analysis. However, multiple recrystallizations of crude **3fa** afforded pure **3fa** in 59% yield. Interestingly, pyrene was regioselectively transformed into thiopyrylium **3ga** in up to 58% yield, whereas pyrene possessed multiple reaction sites. Furthermore, the reaction monitoring by ^{1}H NMR spectra indicates that the C–S bond formation proceeded at the C1 position on pyrene, which is a general reactive site for electrophilic aromatic substitutions, such as bromination and acylation.[11] However, when pristine phenanthrene was employed under the standard thia-APEX conditions, the first C–S bond formation seemed to proceed preferentially at the C9 position (*K*-region), but the reaction gave a complex mixture including regioisomeric mixtures which were difficult to be isolated (see ESI for details).

Because synthesized π-extended thiopyrylium salts displayed diverse colors in CH_2Cl_2, we first measured the UV-Vis-NIR absorption spectra of the π-extended thiopyrylium salts **3aa**–**3ca** (Fig. 4). The reported spectroscopic data for 9-phenylthioxanthylium triflate (**3a**)[12] are also described for comparison. The dimethoxy-substituted thiopyryliums **3aa**–**3ca** showed weak longest wavelength absorption maxima in the visible light region, and their wavelengths at each peak were dramatically red-shifted in the order **3aa** < **3ba** < **3ca**.

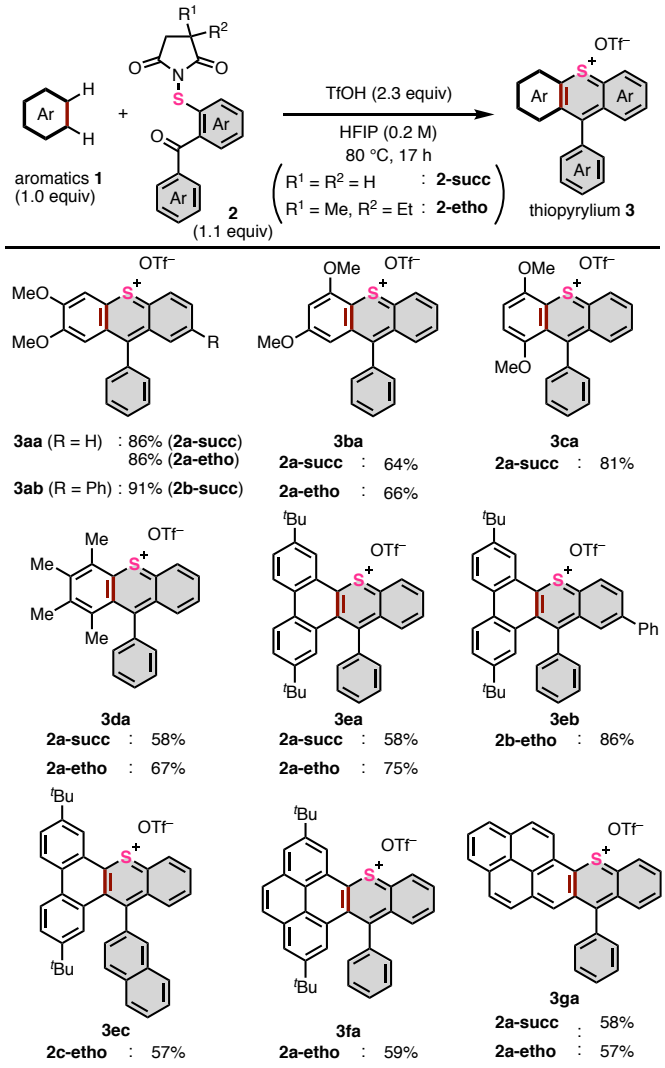
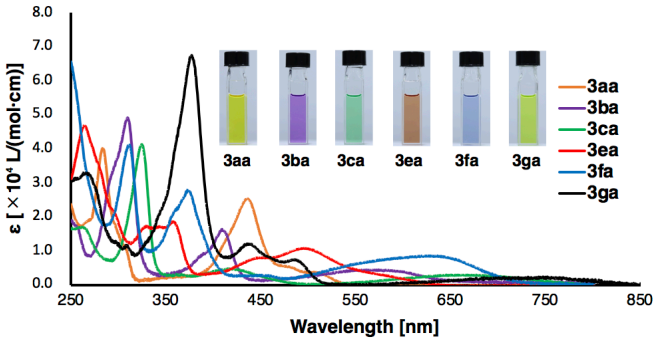


Fig. 3 Optimized reaction conditions and substrate scope of thia-APEX reaction.

Interestingly, the subtle difference in substitution patterns dramatically altered the photophysical properties (see ESI for detailed discussions). Next, we measured the absorption spectra of the thiopyryliums **3ea**, **3fa**, and **3ga** (Fig. 4). Red shifts of the absorption maxima in the longest wavelength region were found as their π-conjugation lengths were extended, and the absorptions were observed at 540–640 nm (**3ea**), 636 nm (**3fa**), and 744 nm (**3fa**) (Fig. 4). By comparing the TD-DFT calculation results for the corresponding cations **3ea'**, **3fa',** and **3ga'**, the lowest excitations were estimated to be originated from HOMO to LUMO excitations (See ESI for details).

In addition, thiopyryliums **3aa**–**3ca** and **3ea**–**3ga** exhibited weak emissions, as shown in Fig. 5. The emission maxima of **3aa**, **3ba**, and **3ca** were found at 551, 653, and 696 nm, and the Stokes shifts were 33, 79, and 50 nm, respectively. Similar to the absorption properties, the difference in the methoxylated sites induced a red shift in the emission wavelengths. The peak of **3ea** was observed at approximately 700 nm. Pyrene-fused thiopyryliums **3fa** and **3ga** exhibited NIR emission. The maximum peak tops of **3fa** and **3ga** were observed at 783 and 817 nm, respectively. Larger Stokes shifts (147 and 73 nm) were



	λ_{abs} [nm] (log ε)				$\lambda_{TD\text{-}DFT}$ (f)
3a[12]	494[12] (3.62)	384[12] (4.11)		281[12] (4.73)	487 (0.1016)
3aa	518 (3.47)	487 (3.65)	436 (4.40)	283 (4.60)	488 (0.0709)
3ba	574 (3.65)	409 (4.21)		310 (4.69)	637 (0.0520)
3ca	646 (3.44)	416 (3.67)		325 (4.61)	667 (0.0681)
3ea	540–640	495 (4.03)		357 (4.27)	586 (0.0511)
3fa	636 (3.92)	458 (3.43)		373 (4.44)	655 (0.1390)
3ga	744 (3.39)	499 (3.70)		378 (4.83)	774 (0.0314)

Fig. 4 UV-Vis-NIR absorption spectra of **3aa**–**3ca** and **3ea**–**3ga** in CH_2Cl_2, summary table of observed representative absorption peaks **3a**[12], **3aa**–**3ca** and **3ea**–**3ga**, and calculated excitation wavelengths ($\lambda_{TD\text{-}DFT}$) and oscillator strengths (f) of corresponding cations **3a'**, **3aa'**–**3ca'** and **3ea'**–**3ga'** (B3LYP/6-311++G(2d,p)//B3LYP/6-311+G(2d,p)). Concentrations: **3aa** = 6.0×10^{-6} M, **3ba** = 4.6×10^{-6} M, **3ca** = 7.6×10^{-6} M, **3ea** = 9.0×10^{-6} M, **3fa** = 4.9×10^{-6} M, **3ga** = 4.0×10^{-6} M. The pictures were taken using the concentrated solutions of each compound.

observed in these compounds, which can be rationalized by the existence of structural relaxation owing to intramolecular CT in each excited state. Furthermore, only thiopyryliums **3aa** and **3ba** showed sufficient emission intensities for measurements of their quantum yields (1% and 0.8%, respectively) and fluorescence lifetimes (0.32 and 0.93 ns, respectively) (See ESI).

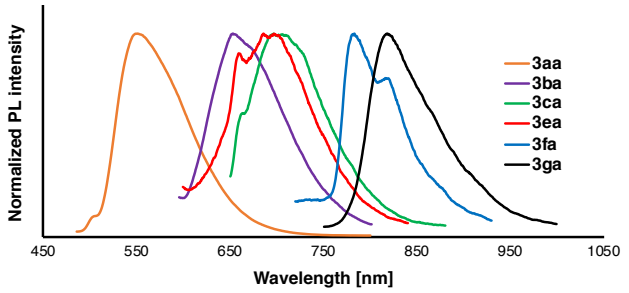


Fig. 5 Emission spectra of π-extended thiopyryliums **3aa**–**3ca** and **3ea**–**3ga** in CH_2Cl_2. Excitation wavelengths for each compound: **3aa** (436 nm), **3ba** (545 nm), **3ca** (600 nm), **3ea** (550 nm), **3fa** (636 nm), and **3ga** (564 nm).

In summary, we developed a thia-APEX reaction, a new synthetic method for polycyclic thiopyrylium compounds from unfunctionalized aromatics. Using *S*-succinimide/*S*–ethosuximide-containing *ortho*-arenonylarenethiols and TfOH, thia-APEX reactions took place to afforded 12 π-extended thiopyrylium salts in one-step. Furthermore, each product exhibited characteristic photophysical properties and dramatic changes depending on the substitution pattern and core aromatic structures; some of them showed NIR absorption and emission. We expect that thia-APEX reactions will contribute to the rapid and efficient creation of functional aromatics.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (a) D. M. Mckinnon, *Can. J. Chem.*, 1970, **48**, 3388; (b) S. Berényi, M. Tóth, S. Gyulai and L. Szilágyi, *Heterocycles*, 2002, **57**, 135; (c) W.D. Rudorf, *Sci. Synth.*, 2003, **14**, 649; (d) M.Z. Kassaee, N. Jalalimanesh, and S. M. Musavi, *J. Mol. Struct.: THEOCHEM*, 2007, **816**, 153; (e) R. V. Seller, P. V. Reshetov and A. P. Kriven'ko, *Chem. Heterocycl. Compd.*, 2001, **37**, 797; (f) V. G. Kharchenko, S. N. Chalaya, and T. M. Konovalova, *Chem. Heterocycl. Compd.*, 1975, **11**, 125; (g) G., Doddi, and G. Ercolani, *Adv. Heterocycl. Chem.*, 1994, **60**, 65. (h) M. Stępień, E. Gońka, M. Żyła and N. Sprutta, *Chem. Rev.* 2017, **117**, 3479. (i) A. Borissov, Y. K. Maurya, L. Moshniaha, W.-S. Wong, M. Żyła-Karwowska and M. Stępień, *Chem. Rev.* 2022, **122**, 565.

2 (a) A. Scarpaci, A. Nantalaksakul, J. M. Hales, J. D. Matichak, S. Barlow, M. Rumi, J. W. Perry and S. R. Marder, *Chem. Mater.*, 2012, **24**, 1606; (b) S. J. Wagner, A. Skripchenko, L. Cincotta, D. Thompson-Montgomery and H. Awatefe, *Transfusion*, 2005, **45**, 752; (c) D. Wu, W. Pisula, M. C. Haberecht, X. Feng and K. Müllen, *Org. Lett.*, 2009, **11**, 5686; (d) N. Nagahora, T. Kushida, K. Shioji and K. Okuma, *Organometallics*, 2019, **38**, 1800; (e) N. Nagahora, K. Kitahara, Y. Mizuhata, N. Tokitoh, K. Shioji and K. Okuma, *J. Org. Chem.*, 2020, **85**, 7748; (f) N. Nagahora, R. Tanaka, T. Tada, A. Yasuda, Y. Yamada, K. Shioji and K. Okuma, *Org. Lett.*, 2020, **22**, 6192; (g) K. Tanaka, M. Kishimoto, M. Sukekawa, Y. Hoshino and K. Honda, *Tetrahedron Lett.*, 2018, **59**, 3361; (h) K. Tanaka, Y. Iwama, M. Kishimoto, N. Ohtsuka, Y. Hoshino and K. Honda, *Org. Lett.*, 2020, **22**, 5207; (i) H. Zhou, X. Zeng, A. Li, W. Zhou, L. Tang, W. Hu, Q. Fan, X. Meng, H. Deng, L. Duan, Y. Li, Z. Deng, X. Hong and Y. Xiao, *Nat. Commun.*, 2020, **11**, 6183. (j) W. R. Browne, M. M. Pollard, B. d. Lange, A. Meetsma and B. L. Feringa, *J. Am. Chem. Soc.*, 2006, **128**, 12412; (k) H. Kearns, S. Sengupta, I. R. Sasselli, L. Bromley III, K. Faulds, T. Tuttle, M. A. Bedics, M. R. Detty, L. Velarde, D. Graham and W. E. Smith, *Chem. Sci.*, 2016, **7**, 5160.

3 V. G. Kharchenko, V. I. Kleimenova, and A. R. Yakoreva, *Chem. Heterocycl. Compd.*, 1970, **6**, 834.

4 (a) J. Liebscher, B. Abegaz, and A. Knoll, *Phosphorus Sulfur Silicon Relat. Elem.*, 1988, **35**, 5; (b) J. Fabian and H. Hartmann, *Tetrahedron Lett.*, 1969, **10**, 239.

5 Reviews on APEX reaction: (a) H. Ito, K. Ozaki, and K. Itami, *Angew. Chem. Int. Ed.,* 2017, **56**, 11144; (b) H. Ito, Y. Segawa, K. Murakami, and K. Itami, *J. Am. Chem. Soc.*, 2019, **141**, 3.

6 (a) K. Ozaki, K. Kawasumi, M. Shibata, H. Ito, and K. Itami, *Nat. Commun.*, 2015, **6**, 6251; (b) W. Matsuoka, H. Ito, and K. Itami, *Angew. Chem. Int. Ed.*, 2017, **56**, 12224; (c) W. Matsuoka, H. Ito, D. Sarlah, and K. Itami, *Nat. Commun.*, 2021, **12**, 3940.

7 Hetero-APEX reactions: (a) K. P. Kawahara, W. Matsuoka, H. Ito, and K. Itami, *Angew. Chem. Int. Ed.*, 2020, **59**, 6383; (b) J. Yan, A. P. Pulis, G. J. P. Perry and D. J. Procter, *Angew. Chem. Int. Ed.*, 2019, **58**, 15675; (c) E. Schendera, L.-N. Unkel, P. P. H. Quyen, G. Salkewitz, F. Hoffmann, A. Villinger and M. Brasholz, *Chem. Eur. J.*, 2020, **26**, 269; (d) Z. Yu, Y. Zhang, J. Tang, L. Zhang, Q. Liu, Q. Li, G. Gao and J. You, *ACS Catal.*, 2020, **10**, 203; (e) S. Tokita, K. Hiruta, K. Kitahara, and H. Nishi, *Synthesis*, 1982, **3**, 229; (f) S. Maiti, T. K. Achar, and P. Mal, *Org. Lett.*, 2017, **19**, 2006; (g) R. Regar, R. Mishra, P. K. Mondal, and J. Sankar, *J. Org. Chem.*, 2018, **83**, 9547; (h) Y. Tokimaru, S. Ito, and K. Nozaki, *Angew. Chem. Int. Ed.*, 2017, **56**, 15560; (i) A. Qarah, M. Gasonoo, D. Do, and D. A. Klumpp, *Tetrahedron Lett.*, 2016, **57**, 3711; (j) C. Chen, Y. Wang, X. Shi, W. Sun, J. Zhao, Y.-P. Zhu, L. Liu, and B. Zhu, *Org. Lett.*, 2020, **22**, 4097; (k) M. Wang, L. Kong, F. Wang, and X. Lia, *Adv. Synth. Catal.*, 2017, **359**, 4411

8 (a) E. Ramesh, M. Shankar, S. Dana, and A. K. Sahoo, *Org. Chem. Front.*, 2016, **3**, 1126; (b) X. Wang, T. Gensch, and F. Glorius, *Org. Chem. Front.*, 2016, **3**, 1619; (c) E. Ramesh, T. Guntreddi, and A. K. Sahoo, *Eur. J. Org. Chem.*, 2017, 4405; (d) P. Saravanan, and P. Anbarasan, *Org. Lett.*, 2014, **16**, 848; (e) T. Hostier, V. Ferey, G. Ricci, D. G. Pardo, and J. Cossy, *Org. Lett.*, 2015, **17**, 3898.

9 (a) X. Ye, B. Xu, J. Sun, L. Dai, Y. Shao, Y. Zhang, and J. Chen, *J. Org. Chem.*, 2020, **85**, 13004; (b) X. Pang, Z. Lou, M. Li, L. Wen, and C. Chen, *Eur. J. Org. Chem.*, 2015, 3361.

10 (a) L. W. Souza, R. A. Squitieri, C. A. Dimirjian, B. M. Hodur, L. A. Nickerson, C. N. Penrod, J. Cordova, J. C. Fettinger, and J. T. Shaw, *Angew. Chem. Int. Ed.*, 2018, **57**, 15213; (b) A. R. Katritzky, K. Kirichenko, Y. Ji, and I. Prakash, *Chem. Heterocycl. Compd.*, 2002, **38**, 156.

11 Representative reports on C1-selective S_EAr reactions of pristine pyrene: (a) M. Liu, X. Gong, C. Zheng, and D. Gao, *Asian J. Org. Chem.*, 2017, **6**, 1903; (b) W. H. Gumprecht, *Org. Synth.*, 1968, **48**, 30; (c) D. Zych, *Molecules*, 2019, **24**, 2551.

12 D. T. Hogan, and T. C. Sutherland, *J. Phys. Chem. Lett.*, 2018, **9**, 2825.

