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Selective access to dihydrophenanthridines and phenanthridinones *via* cyclisation of aryl amines onto *N*-tethered arynes†

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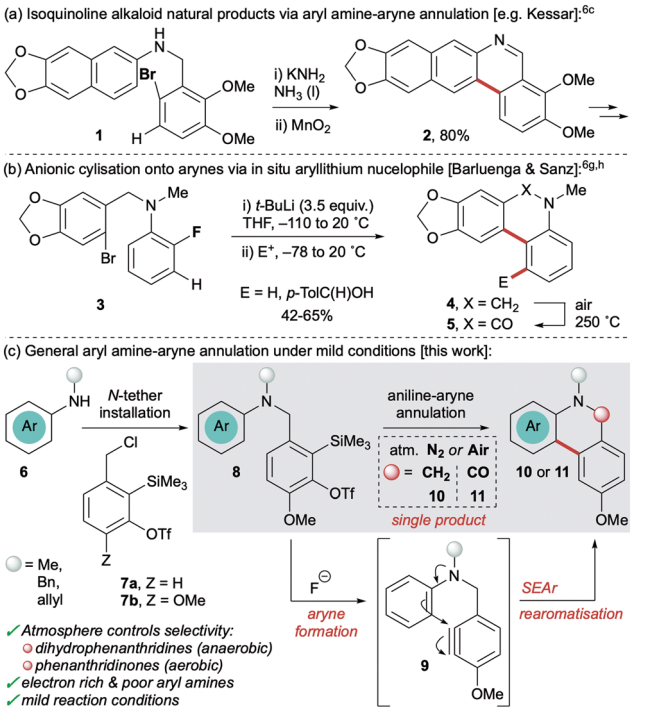
5,6-Dihydrophenanthridines are prepared from aryl amines *via* intramolecular addition to *N*-tethered arynes under mild conditions. A new *o*-silylaryl triflate precursor was developed to increase reactivity and enable electron-rich and electron-poor aryl amines to undergo cyclisation. A complete switch in product selectivity occurs when the reaction is conducted in air, affording the corresponding phenanthridin-6(5*H*)-one as the sole product under otherwise identical reaction conditions.

Phenanthridines and phenanthridinones are privileged heterocyclic scaffolds found in a range of natural products and therapeutically active compounds.[1] They possess broad biological properties, including anticancer,[2a] antitumour,[2b] antiviral,[2c] antimicrobial,[2d] antifungal[2e] and antimalarial[2f] activity. In addition, a high charge mobility renders these frameworks versatile building blocks for functional materials.[3] As a result, significant synthetic effort has been devoted to the synthesis of phenanthridines and their derivatives.[4] This includes the Bischler–Napieralski reaction,[5a] photochemical,[5b] radical[5c] and microwave-assisted[5d] cyclisations, transition metal free C–H arylation,[5e] aza-Wittig,[5f] anionic ring-closure,[5g] hypervalent iodine[5h] and metal catalysed approaches.[5i]

Arynes have also been utilised in the synthesis of phenanthridine derivatives and related alkaloid natural products.[6,7] These versatile reactive intermediates afford valuable benzenoid and heterocyclic frameworks[8] and have experienced a recent resurgence in interest due to the advent of aryne precursors that act under mild conditions, namely the *o*-trimethylsilylaryl triflates (*o*SATs)[9] and the hexadehydro-Diels–Alder reaction of polyalkynes.[10] Cyclisation onto a pendant aryne has proven a valuable method to furnish phenanthridine derivatives, most notably in the synthesis of natural products.[6a–e,g,h] However, these approaches all generate arynes using organometallic reagents or strong bases at low temperatures which restricts the functional group tolerance. Methods that operate *via* electrophilic aromatic substitution (SEAr) have also been limited to electron-rich aryl nucleophiles such as **1** (Scheme 1a),[6a–e] which although common in the natural products, precludes preparation of more diverse substrate analogues. Alternatively, Barluenga and Sanz utilised anionic cyclisation onto pendant arynes (accessed from **3**) to yield phenanthridine derivatives **4** and **5** by exploiting stronger *in situ*-formed aryllithium nucleophiles (Scheme 1b).[6g,h] However, this strategy also required organolithium reagents (in excess) to form both the aryne and the



Scheme 1 Cyclisation onto tethered arynes for the synthesis of phenanthridines and derivatives.

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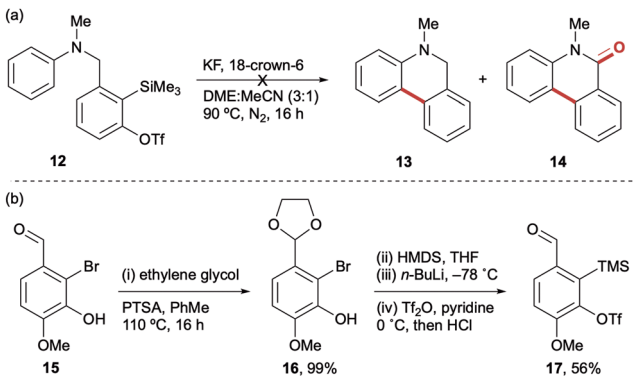
nucleophile, plus pre-functionalisation (*o*-bromination) of the pronucleophilic arene.

Given our interests in the chemistry of arynes,[11] we sought to develop a cyclisation approach to phenanthridine derivatives that exploited the benzylic *o*SAT precursor **7a** previously used in our group (Scheme 1c).[11b] Inspired by the strategy of both Kessar and Stermitz in their syntheses of alkaloid natural products,[6c,d] it was proposed that aryl amines bearing an *N*-tethered aryne precursor (**8**) would undergo SEAr, upon generation of the aryne **9**, to afford 5,6-dihydrophenanthridine derivatives **10**. Given the propensity for such frameworks to undergo oxidation there would also be potential to access the corresponding phenanthridinones **11**. Importantly, by using the *o*SAT precursor it removes the harsher reaction conditions of previous reports and should facilitate a wider range of aryl amine nucleophiles **6**, especially those containing useful functional handles. Furthermore, tethering the aryne at nitrogen enables more facile synthesis of the starting materials, compared to linking *via* C–C bonds,[6a,b] thereby expediting the preparation of structural analogues.

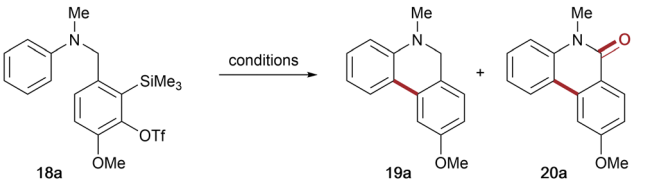
To test this cyclisation hypothesis, benzylic *o*SAT precursor **7a** was tethered to *N*-methyl aniline to afford precursor **12**, which was then subjected to our standard aryne-forming conditions previously used with this tether (Scheme 2a).[11b] Unfortunately, this afforded a mixture of compounds and no clear evidence of cyclisation to dihydrophenanthridine **13** nor phenanthridinone **14**. Intriguingly, a significant by-product was observed in the ^{1}H NMR spectrum of the crude reaction mixture that suggested intermolecular attack at the aryne was taking precedence over the desired intramolecular process (although we were unable to isolate a clean sample for characterisation).[12] With a goal to promote the cyclisation and suppress undesired intermolecular reactivity, a modified aryne precursor **17** was developed (Scheme 2b). It was rationalised that a *p*-methoxy substituent in **17** should increase reactivity by inductively polarising the aryne towards nucleophilic addition *ortho* to the tether – as supported by Garg and Houk's aryne distortion model[13] – in addition to providing increased stabilisation of the resulting aryl anion.[8a] To this end, the novel *p*-methoxybenzyl aryne precursor **17** was prepared in four steps from commercially available 2-bromo-isovanillin **15** with no purification of the intermediates required.

With the second generation aryne tether **17** in hand, the corresponding *N*-methyl aniline precursor **18a** was then subjected to the conditions used for attempted cyclisation of **12**. Gratifyingly, the new aryne tether promoted significant intramolecular reaction, affording dihydrophenanthridine **19a** in 50% yield and the corresponding phenanthridinone **20a** in 23% yield, with a marked decrease in deleterious *N*-arylation (8% by-product) (entry 1, Table 1). Having addressed the issue of overall reactivity, attention turned to optimising the reaction conditions to avoid mixtures of cyclisation products (see Table 1 for selected optimisation experiments). Evaluation of some common *o*-SAT activators (entries 2–5) identified CsF in acetonitrile and KF/18-crown-6 in THF as promoting cyclisation to the dihydrophenanthridine **19a** in good yields, albeit with phenanthridinone and by-product still present. Encouragingly, replacing THF with DME led to an excellent yield of the desired dihydrophenanthridine **19a**, with only trace amounts of the phenanthridinone **20a** and no evidence of the competing intermolecular by-product (entries 5 & 6). Further investigations found that lowering the reaction temperature and concentration both decreased the overall yield (entries 7 and 8). Finally, increasing concentration led to more of the competing



Scheme 2 Investigating cyclisation of aryl amine onto *N*-tethered aryne, (a) unsuccessful preliminary attempt to form 5,6-dihydrophenanthridine **13** or phenanthridinone **14**. Reaction conditions: aryl amine (1.0 equiv.), KF (2.0 equiv.), 18-crown-6 (2.0 equiv.), DME : MeCN (3 : 1 by volume, 0.01 M), 90 °C, 24 h, N_2 atmosphere. (b) Synthesis of a new *p*-methoxy benzylic aryne precursor **17**. Reaction conditions: (i) ethylene glycol (5.0 equiv.), pyridinium *p*-toluenesulfonate (0.12 equiv.), PhMe, 110 °C, (ii) hexamethyldisilazane (0.8 equiv.), THF, 66 °C, 2 h, (iii) *n*-BuLi, THF, −78 °C, 30 min, (iv) trifluoromethanesulfonic anhydride (1.3 equiv.), pyridine (3.0 equiv.), CH_2Cl_2, 0 °C, 3 h, then HCl (4 M aq.), 16 h. Yields of isolated products throughout.

Table 1 Selected optimization studies for the preparation of dihydrophenanthridines[a]

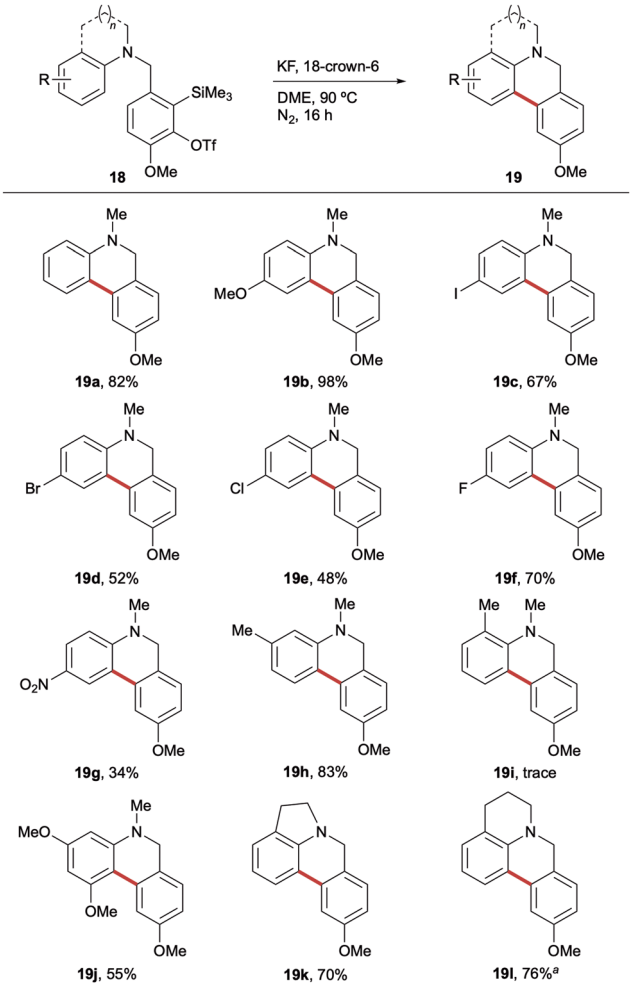


Entry	Activator	Solvent	T (°C)	Yield[b] (%) 19a	20a	By-product
1	KF 18-crown-6	DME : MeCN (3 : 1)	90	50	23	8
2	CsF	MeCN	90	69	2	7
3	CsF	PhMe : MeCN	90	64	10	11
4	TBAF[c]	THF	90	36	—	—
5	KF 18-crown-6	THF	90	69	10	5
6	KF 18-crown-6	DME	90	84(82)	2	—
7	KF 18-crown-6	DME	70	69	2	5
8	KF 18-crown-6	DME[d]	90	69	—	9
9	KF 18-crown-6	DME[e]	90	46	—	35

[a] Reaction conditions: aryl amine (1.0 equiv.), activator (2.0 equiv.), additive (2.0 equiv.), solvent [0.01 M], 16 h, N_2 atmosphere. [b] ^{1}H NMR yield *vs.* dibromomethane internal standard, isolated yield in parentheses, all reactions proceeded to full conversion after 16 h. [c] 1.0 M in THF. [d] 0.002 M. [e] 0.05 M.

intermolecular *N*-arylation and subsequent erosion of the dihydrophenanthridine yield (entry 9).

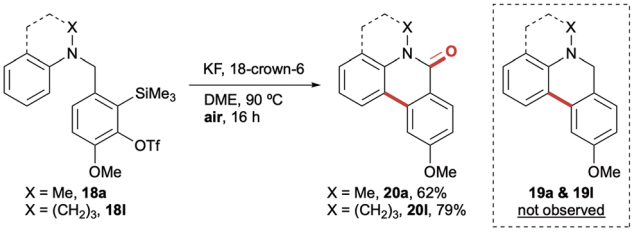
Having optimised the reaction conditions, attention turned to investigating substrate scope. Pleasingly, a range of substituted aniline derivatives were found to undergo cyclisation in generally good to excellent yields (Scheme 3). 4-Substituted anilines were evaluated first, with the electron-rich 4-methoxy derivative affording the corresponding dihydrophenanthridine **19b** in 98% yield. The halogenated series showed an interesting trend, with the 4-iodo and 4-fluoro precursors undergoing efficient cyclisation to **19c** (67%) and **19f** (70%), respectively, however, the 4-bromo and 4-chloro derivatives furnished **19d** and **19e** in more moderate yields (52% and 48%). With the electron deficient 4-fluoro analogue proving highly amenable to the cyclisation, it was encouraging to observe that the 4-nitroaniline precursor also underwent the transformation to generate the corresponding electron-poor dihydrophenanthridine **19g** in 34% yield. These are particularly noteworthy as most reports of intramolecular SEAr with arynes rely on markedly electron rich aromatic systems. A comparison of the propensity for cyclisation of the 3-methyl (**18h**) and 2-methylaniline (**18i**) precursors revealed a key role played by sterics. 3-Methylaniline **18h** afforded the corresponding dihydrophenanthridine **19h** in an excellent 83% yield, whereas only a trace of the 2-methyl analogue was observed. This suggested that **19i** experiences significant 1,5-strain in the transition state required for cyclisation; instead favouring a mixture of the *N*-arylation by-product and an intramolecular dearomative aryne Diels–Alder cycloaddition.[14] Interestingly, the more conformationally rigid indoline (**18k**) and tetrahydroquinoline (**18l**) precursors underwent efficient SEAr to furnish the corresponding tetracyclic products, **19k** and **19l**, respectively. It was noted that the THQ-derived framework afforded **19l** in 76% yield by ^{1}H NMR spectroscopic analysis; however, during attempted purification it proved susceptible to oxidation, leading to an isolated mixture (1 : 1.2) of **19l** and the corresponding phenanthridinone.



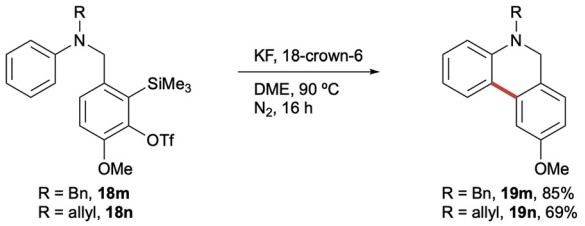
Scheme 3 Synthesis of 5,6-dihydrophenanthridine derivatives **15**. Reaction conditions: aryl amine (1.0 equiv.), KF (2.0 equiv.), 18-crown-6 (2.0 equiv.), DME (0.01 M), 90 °C, 16 h, N_2 atmosphere. Yields of isolated products throughout. [a] ^{1}H NMR yield *vs.* dibromomethane internal standard, note: **19l** partially oxidised upon purification to give isolated 1 : 1.2 mixture of **19l** and corresponding phenanthridinone **20l**.

Having established the formation of dihydrophenanthridines from a range of electron rich and electron deficient aryl amines, we next investigated whether the product selectivity could be reversed to instead access phenanthridinones. During the initial optimisation studies, dihydrophenathridine **19a** had been found to be susceptible to partial oxidation upon exposure to air, whilst **19l** had part-oxidised during purification. This afforded mixtures of the dihydrophenanthridines and phenanthridinones; however a discrete second oxidative step was always required to effect complete conversion. With a view to accessing the phenanthridinone derivatives in a single step from the analogous aryl amine precursors **18**, the reaction was performed in the presence of a range of oxidants, with most attempts affording mixtures of the two cyclisation products. However, it was extremely pleasing to observe that when **18a** and **18l** were exposed to the previously optimised cyclisation conditions, only in air rather than under an inert atmosphere, it resulted in a complete switch of selectivity to exclusively afford the corresponding phenanthridin-6(5*H*)-ones **20a** and **20l** in 62% and 79% yields respectively (Scheme 4).[15]

Finally, *N*-benzyl (**18m**) and *N*-allyl (**18n**) aniline precursors were also found to be amenable to cyclisation (Scheme 5). Given the increased potential for subsequent protecting group cleavage, the comparable yields obtained for the analogous



Scheme 4 Cyclisation in air exclusively affords phenanthridinones **20a** and **20l**. Reaction conditions: aryl amine (1.0 equiv.), KF (2.0 equiv.), 18-crown-6 (2.0 equiv.), DME (0.01 M), 90 °C, 16 h, air. Yields of isolated products throughout.



R = Bn, **18m**
R = allyl, **18n**

R = Bn, **19m**, 85%
R = allyl, **19n**, 69%

Scheme 5 5,6-Dihydrophenanthridines bearing alternative *N*-protecting groups. Reaction conditions are as shown in Scheme 3. Yields of isolated products throughout.

N-benzyl (**19m**, 85%), *N*-allyl (**19n**, 69%) and *N*-Me (**19a**, 82%) dihydrophenanthridines were particularly encouraging for the synthetic utility of the method.

In conclusion, the cyclisation of aryl amines onto *N*-tethered arynes has been developed under mild reaction conditions using a novel silylaryl triflate precursor. This enabled the new biaryl linkage to be generated by SEAr using both electron rich and poor aryl amines and furnished a range of phenanthridine derivatives with handles for subsequent functionalisation. Selective access to dihydrophenanthridines or the corresponding phenanthridinones is dependent upon a simple switch between anaerobic and aerobic reaction environments.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) F. Viladomat, J. Bastida, G. Tribo, C. Codina and M. Rubiralta, *Phytochemistry*, 1990, **29**, 1307; (*b*) R. B. Macgregor, R. M. Clegg and T. M. Jovin, *Biochemistry*, 1987, **26**, 4008; (*c*) Z. Jin, *Nat. Prod. Rep.*, 2009, **26**, 363.

2 (*a*) V. Holl, D. Coelho, D. Weltin, P. Dufour and P. Bischoff, *Anticancer Res.*, 2000, **20**, 3233; (*b*) T. C. Johnstone, S. M. Alexander, W. Lin and S. J. Lippard, *J. Am. Chem. Soc.*, 2014, **136**, 116; (*c*) G. T. Tan, M. J. Pezzuto and A. D. Kinghorn, *J. Nat. Prod.*, 1991, **54**, 143; (*d*) G. Y. Zuo, F. Y. Meng, X. Y. Hao, Y. L. Zhang, G. C. Wang and G. L. Xu, *J. Pharm. Pharm. Sci.*, 2008, **11**, 90; (*e*) X. J. Yang, F. Miao, Y. Yao, F. J. Cao, R. Yang, Y. N. Ma, B. Q. Qin and L. Zhou, *Molecules*, 2012, **17**, 13026; (*f*) M. Rivaud, A. Mendoza, M. Sauvain, A. Valentin and V. Jullian, *Bioorg. Med. Chem.*, 2012, **20**, 4856.

3 (*a*) N. Stevens, N. O'Connor, H. Vishwasrao, D. Samaroo, E. R. Kandel, D. L. Atkins, C. M. Drain and N. J. Turro, *J. Am. Chem. Soc.*, 2008, **130**, 7182; (*b*) Y.-L. Chen, F.-H. Li and Z.-S. Bo, *Macromolecules*, 2010, **43**, 1349; (*c*) P. Pang, X. Miao, L. Ying, G. Kong, C. Che and W. Deng, *J. Phys. Chem. C*, 2020, **124**, 5665.

4 Selected reviews: (*a*) F. Rafiee, *Appl. Organomet. Chem.*, 2017, **31**, 12; (*b*) N. Kshirsager, R. Sonawane, S. Pathan, G. Kamble and G. P. Singh, *Lett. Org. Chem.*, 2021, **19**, 434; (*c*) R. R. Aleti, A. A. Festa, L. G. Voskressensky and E. V. Van der Eycken, *Molecules*, 2021, **26**, 5560.

5 (*a*) B. A. Lorsbach and M. Kurth, *J. Chem. Rev.*, 1999, **99**, 1549; (*b*) R. Alonso, P. J. Campos, B. Garcia and M. A. Rodriguez, *Org. Lett.*, 2006, **8**, 3521; (*c*) M. Tobisu, K. Koh, T. Furukawa and N. Chatani, *Angew. Chem., Int. Ed.*, 2012, **51**, 11363; (*d*) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *J. Org. Chem.*, 2008, **73**, 5558; (*e*) C. Tang, Y. Yuan and N. Jiao, *Org. Lett.*, 2015, **17**, 2206; (*f*) S. P. Marsden, A. E. McGonagle and D. McKeever-Abbas, *Org. Lett.*, 2008, **10**, 2589; (*g*) M. Lysén, J. L. Kristensen, P. Vedsø and M. Begtrup, *Org. Lett.*, 2002, **4**, 257; (*h*) Q. Wang, X. Dong, T. Xiao and L. Zhou, *Org. Lett.*, 2013, **15**, 4846; (*i*) H. A. McManus, M. J. Fleming and M. Lautens, *Angew. Chem., Int. Ed.*, 2007, **46**, 433.

6 (*a*) T. Kametani and K. Ogasawara, *J. Chem. Soc. C*, 1967, 2208; (*b*) S. V. Kessar, N. Parkash and G. S. Joshi, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1158; (*c*) S. V. Kessar, M. Singh and P. Balakrishnan, *Indian J. Chem.*, 1974, **12**, 323; (*d*) J. P. Gillespie, L. G. Amoros and F. R. Stermitz, *J. Org. Chem.*, 1974, **39**, 3239; (*e*) T. Nakanishi and M. Suzuki, *Org. Lett.*, 1999, **1**, 985; (*f*) J. Pawlas and M. Begtrup, *Org. Lett.*, 2002, **4**, 2687; (*g*) J. Barluenga, F. J. Fananas, R. Sanz and Y. Fernandez, *Chem. – Eur. J.*, 2002, **8**, 2034; (*h*) R. Sanz, Y. Fernandez, M. P. Castroviejo, A. Perez and F. J. Fananas, *Eur. J. Org. Chem.*, 2007, 62; (*i*) R. S. Reddy, C. Lagishetti, S. Chen, I. N. Chaithanya Kiran and Y. He, *Org. Lett.*, 2016, **18**, 4586.

7 Selected examples: (*a*) C. Lu, A. V. Dubrovskiy and R. C. Larock, *J. Org. Chem.*, 2012, **77**, 8648; (*b*) Y. Yang, H. Huang, L. Wu and Y. Liang, *Org. Biomol. Chem.*, 2014, **12**, 5351; (*c*) X. Peng, W. Wang, C. Jiang, D. Sun, Z. Xu and C.-H. Tung, *Org. Lett.*, 2014, **16**, 5354; (*d*) S. Pimparkar and M. Jeganmohan, *Chem. Commun.*, 2014, **50**, 12116; (*e*) M. Feng, B. Tang, N. Wang, H.-X. Xu and X. Jiang, *Angew. Chem., Int. Ed.*, 2015, **54**, 14960; (*f*) C. Zhu and T. R. Hoye, *J. Am. Chem. Soc.*, 2022, **144**, 7750; (*g*) R. Fang, S. Liu, Q. Yan, Y. Wei, J. Wang, Y. Lan and J. Tan, *Chem. Sci.*, 2023, **14**, 4278.

8 Selected reviews: (*a*) R. Sanz, *Org. Prep. Proced. Int.*, 2008, **40**, 215; (*b*) P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550; (*c*) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, 2013, **11**, 191; (*d*) R. W. Hoffmann and K. Suzuki, *Angew. Chem., Int. Ed.*, 2013, **52**, 2655; (*e*) D. Pérez, D. Peña and E. Guitían, *Eur. J. Org. Chem.*, 2013, 5981; (*f*) J.-A. Garcia-Lopez and M. F. Greaney, *Chem. Soc. Rev.*, 2016, **45**, 6766; (*g*) O. J. Diamond and T. J. Marder, *Org. Chem. Front.*, 2017, **4**, 891; (*h*) F. I. M. Idiris and C. R. Jones, *Org. Biomol. Chem.*, 2017, **15**, 9044; (*i*) J. Shi, L. Li and Y. Li, *Chem. Rev.*, 2021, **121**, 3892.

9 Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.*, 1983, 1211.

10 T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby and B. P. Woods, *Nature*, 2012, **490**, 208.

11 (*a*) P. Trinchera, W. Sun, J. E. Smith, D. Palomas, R. Crespo-Otero and C. R. Jones, *Org. Lett.*, 2017, **19**, 4644; (*b*) F. I. M. Idiris, C. E. Majesté, G. B. Craven and C. R. Jones, *Chem. Sci.*, 2018, **9**, 2873; (*c*) W. Sun, P. Trinchera, N. Kurdi, D. Palomas, R. Crespo-Otero, S. Afshinjavid, F. Javid and C. R. Jones, *Synthesis*, 2018, 4591; (*d*) Y. Yang, Y. Xu and C. R. Jones, *Eur. J. Org. Chem.*, 2019, 5196; (*e*) E. A. Neal, A. Y. R. Werling and C. R. Jones, *Chem. Commun.*, 2021, **57**, 1663; (*f*) Y. Xu, R. Xie, Q. Li, J. Feng, H. Luo, Q. Ye, Z. Guo, Y. Cao, M. Palma, G. Chai, M.-M. Titirici and C. R. Jones, *Small*, 2023, 2302795.

12 Unable to isolate pure sample of by-product. 1H NMR spectroscopic and mass spectrometric analyses of reaction mixture supported tentative assignment: postulated attack of aniline nitrogen onto second molecule of aryne affords quaternary ammonium species that could undergo cleavage of labile N-benzyl bond.

13 J. M. Medina, J. L. Mackey, N. K. Garg and K. N. Houk, *J. Am. Chem. Soc.*, 2014, **136**, 15798.

14 H. Takikawa, A. Nishii, H. Takiguchi, H. Yagashita, M. Tanaka, K. Hirano, M. Uchiyama, K. Ohmori and K. Suzuki, *Angew. Chem., Int. Ed.*, 2020, **59**, 12440.

15 H. Wang, Z. Wang, H. Huang, J. Tan and K. Xu, 18-Crown-6 ether was found to promote oxidation. No reduction in phenanthridinone yield when reaction conducted in the presence of TEMPO (1.3 equivalents) and no substrate-TEMPO adducts observed, *Org. Lett.*, 2016, **18**, 5680.

