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Deaminative ring contraction for the synthesis of polycyclic heteroaromatics: a concise total synthesis of toddaquinoline†

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A concise strategy to prepare polycyclic heteroaromatics involving a deaminative contraction cascade is detailed. The efficient deaminative ring contraction involves the *in situ* methylation of a biaryl-linked dihydroazepine to form a cyclic ammonium cation that undergoes a base-induced [1,2]-Stevens rearrangement/dehydroamination sequence. The presence of pseudosymmetry guides the retrosynthetic analysis of pyridyl-containing polycyclic heteroaromatics, enabling their construction by the reductive cyclization and deaminative contraction of tertiary amine precursors.

Introduction

Polycyclic aromatic natural products exhibit a host of exciting biological properties,[1,2] and their highly varied arene substitution patterns have motivated creative strategies[3] for their assembly. Dehydrojuncusol **1**,[4] litebamine **2**,[5] toddaquinoline **3**,[6] and santiagonamine **4**,[7] serve to emphasize the diverse substitution patterns displayed by biologically active secondary plant metabolites that share the 'phenanthrene skeleton' (Fig. 1a). Biosynthetic rearrangements of the embedded tertiary amine lead to scaffold diversification, as exemplified by the dehydroaminative conversion of the aporphine alkaloid boldine **5**, into phenanthrene alkaloids secoboldine **6** and litebamine **2** (Fig. 1b).[8] The experimental replication of this biogenic pathway[8c] reveals the potential of dehydroamination toward family-level access to these phenanthrenes from tertiary amine precursors,[8,9] and highlights the utility of amine-derived molecular rearrangements[10,11] for the convergent synthesis of densely substituted polycyclic aromatics.

Classic approaches[12] to build phenanthrenes from stilbene precursors include the Pschorr,[13] and Mallory reactions,[14,15] which have seen impressive procedural updates.[16,17] Unsurprisingly, the advent of transition metal-catalyzed cross-coupling reactions makes construction of the biaryl bond a natural entry point to these scaffolds.[18] Recent approaches toward polycyclic aromatics have relied on these methods, using transition metal-,[19] oxidation-,[20] Lewis acid-,[21,22] and base-promoted[23] alkene-forming reactions. With some exceptions,

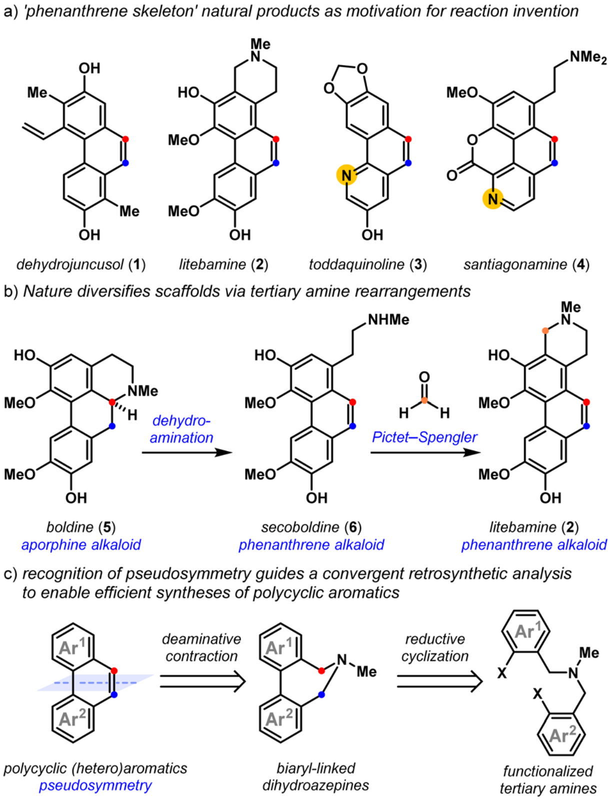

Fig. 1 Polycyclic aromatic natural products as motivation for reaction invention: (a) 'phenanthrene skeleton' natural products as motivation for reaction invention; (b) nature diversifies scaffolds *via* tertiary amine rearrangements; (c) recognition of pseudosymmetry guides a convergent retrosynthetic analysis.

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these methods demonstrate limited access to polycyclic heteroaromatics containing important pyridyl motifs[24] and while useful, Friedländer annulation strategies[25] are less convergent. Recently, Lambert and coworkers elegantly addressed this through the development of a hydrazine-catalyzed ring-closing carbonyl–olefin metathesis reaction that is compatible with Lewis basic functionality.[26] We drew inspiration from strategies that are also tolerant of Lewis basic arenes that use a *Z*-selective Wittig olefination to build the alkene, followed by a transition-metal catalyzed cyclization to forge the biaryl bond.[27] The recognition of pseudosymmetry and knowing that tertiary amines can react to form alkenes guided our retrosynthetic analyses,[11,28] leading to the development of a convergent approach to polycyclic (hetero)aromatics by the reductive cyclization and deaminative contraction of appropriately halogenated tertiary amine precursors (Fig. 1c).

In an earlier effort,[28] we demonstrated that functionalized tertiary amines can be converted into substituted benzo[*h*]quinolines following reductive cyclization[29–33] and deaminative contraction reactions (Fig. 2a). We were able to show that the deaminative contraction of **7** comprises a cascade reaction sequence wherein amine methylation, a [1,2]-Stevens rearrangement of the resultant ammonium cation, and a dehydroamination of the rearranged tertiary amine ensued to yield **8**. Yet, the multievent transformation suffered from low efficiency and system-dependent side reactions. Herein, we detail our use of these mechanistic insights to develop a general and high yielding reductive cyclization/deaminative contraction strategy to prepare a diverse array of these polycyclic heteroaromatics. We show that appropriately halogenated tertiary amines[28] are simple to prepare and cyclize. Readily accessed biaryl-linked dihydroazepines undergo efficient deaminative contraction, providing substituted polycyclic (hetero)aromatic products as highlighted by a concise total synthesis of toddaquinoline **3**.

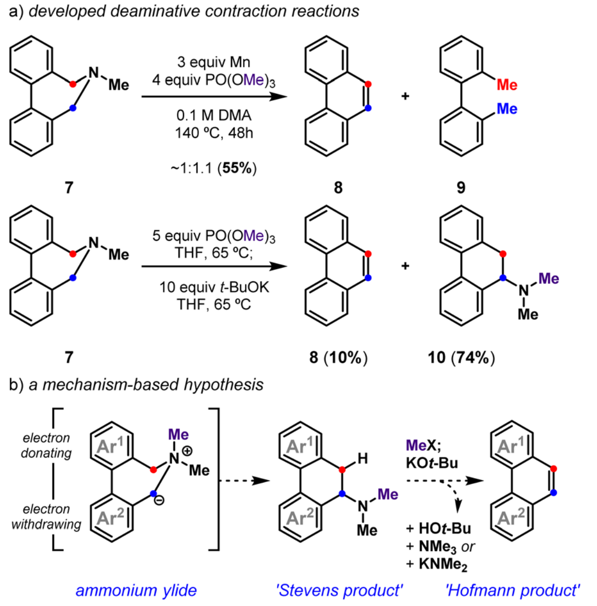


Fig. 2 Deaminative contraction for the synthesis of polycyclic (hetero)aromatics: (a) developed deaminative contraction reactions; (b) a mechanism-based hypothesis.

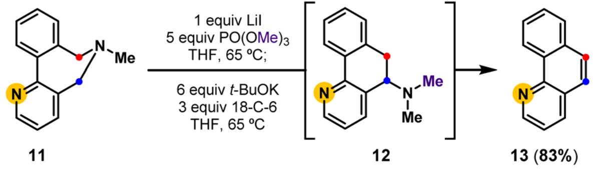
Results and discussion

We previously demonstrated that biaryl-linked dihydroazepine **7** can form phenanthrene **8** and 2,2′-dimethylbiaryl **9** upon treatment with Mn and trimethyl phosphate, $PO(OMe)_3$ (Fig. 2).[28] The Mn additive served no obvious mechanistic role, but its presence improved the yield for some benzo[*h*]quinoline-forming examples. Excess Mn led to reductive deamination without contraction to favor 2,2′-dimethylbiaryls (*e.g.*, **9**), especially when the substrate lacked a pyridyl motif. With a better mechanistic level understanding of this cascade reaction,[28] we developed one-pot conditions that leverage $PO(OMe)_3$ as an amine-methylating reagent[34] and *t*-BuOK as a Brønsted base. Here we presume Stevens product **10** forms en route to phenanthrene **8**, as **10** can be resubjected to the reaction conditions to exclusively form **8**. Závada and coworkers previously noted that biaryl-linked dihydroazepinium salts are susceptible to a [1,2]-Stevens rearrangement/Hofmann elimination process upon treatment with excess base (3.1 equiv *n*-BuLi).[35] They noted that binaphthyl dihydroazepeniums undergo the [1,2]-Stevens rearrangement more efficiently than the corresponding biphenyl derivatives by several orders of magnitude.[35,36] We reasoned the net deaminative ring contraction process involving amine methylation, [1,2]-Stevens rearrangement, and Hofmann elimination events could be made general by improving the methylation and base-catalyzed events. We proposed that *in situ* formed biaryl-linked azepeniums would undergo more efficient [1,2]-Stevens rearrangement and Hofmann elimination events. These hypotheses, and our interest in pyridyl-containing natural products such as **3** and **4**, directed us to develop a general deaminative reaction for access to substituted and pyridyl-containing polycyclic heteroaromatics (Fig. 3).

Deaminative contraction for the convergent synthesis of substituted benzo[*h*]quinolines and other polycyclic aromatics

Optimization revealed that the reagent combination of LiI and $PO(OMe)_3$ facilitates tertiary amine methylation,[37] while subsequently added *t*-BuOK[38] and 18-crown-6 (18-C-6) affects [1,2]-Stevens rearrangement and concomitant Hofmann elimination events to convert biaryl-linked dihydroazepine **11**, *via* Stevens product **12**, into benzo[*h*]quinoline **13** in 83% isolated yield (Fig. 3). Toward substituted benzo[*h*]quinolines, the Stevens product is only observed in reactions that are stopped prematurely. Mechanistic studies have shown the combination of LiI and $PO(OMe)_3$ to be useful for the metered generation of MeI, especially when substrates harbor Lewis basic sites (*e.g.*, pyridines) that are susceptible to methylation (entry 2).[37] Other deviations from the optimal conditions such as less *t*-BuOK (entry 3), the omission of LiI (entry 4), and the omission of 18-C-6 (entry 5), result in diminished yields. Finally, a control

a) *deaminative contraction optimization*



entry	deviation from optimal conditions	% of 13
1	none	83
2	MeI instead of $PO(OMe)_3$	78
3	3 equiv of *t*-BuOK	47
4	LiI omitted	46
5	18-C-6 omitted	20
6	*t*-BuOK and 18-C-6 omitted	nd
7	4 equiv Mn, 20 equiv $PO(OMe)_3$	12-40

b) *accessible polycyclic aromatics*

c) *evaluation of access to electronically perturbed benzo[h]quinolines*

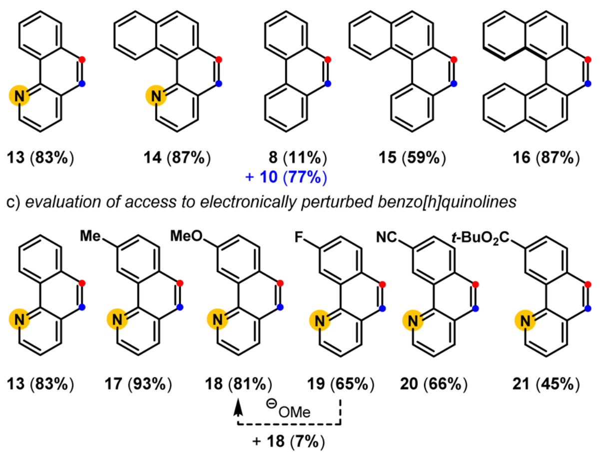


Fig. 3 Deaminative contractions for the convergent synthesis of polycyclic aromatics and substituted benzo[*h*]quinolines: (a) deaminative contraction optimization; (b) accessible polycyclic aromatics; (c) evaluation of electronically perturbed benzo[*h*]quinolines. nd = not detected.

reaction (entry 6) indirectly shows that lithium dimethyl phosphate is an ineffective base at 65 °C, suggesting that base-promoted rearrangements, and eliminations do not occur until *t*-BuOK and 18-C-6 are added. Relative to previously developed conditions (entry 7), this deaminative contraction method showed general applicability toward polycyclic aromatics. Readily accessible biaryl-linked dihydroazepines undergo deaminative contraction to afford **14**, **8**, **15**, and **16** in good yields (Fig. 3b). Interestingly, Stevens product **10** is halted en route to phenanthrene **8**, supporting the prior observation made by Závada and coworkers.[35] Our interest in pyridyl-containing polycyclic aromatic natural products directed us to further evaluate the impact of system electronics. Electron-rich (**17**, **18**) and electron-deficient (**19–21**) benzo[*h*]quinolines are all accessed in good yields (Fig. 3c). Notably, during the preparation of **19** (65%), we observed the formation of a minor amount of **18** (7%). We speculate that methoxide is a potential byproduct of the one-pot conditions and may convert **19** into **18** *via* nucleophilic aromatic substitution (S_NAr).[39] While unoptimized, this observation suggests that other benzo[*h*]quinoline substitution patterns could be accessible *via* S_NAr of an appropriately halogenated precursor. Due to the preliminary efficiency of this deaminative contraction method and its potential

a) *general strategy to prepare polycyclic heteroaromatics*

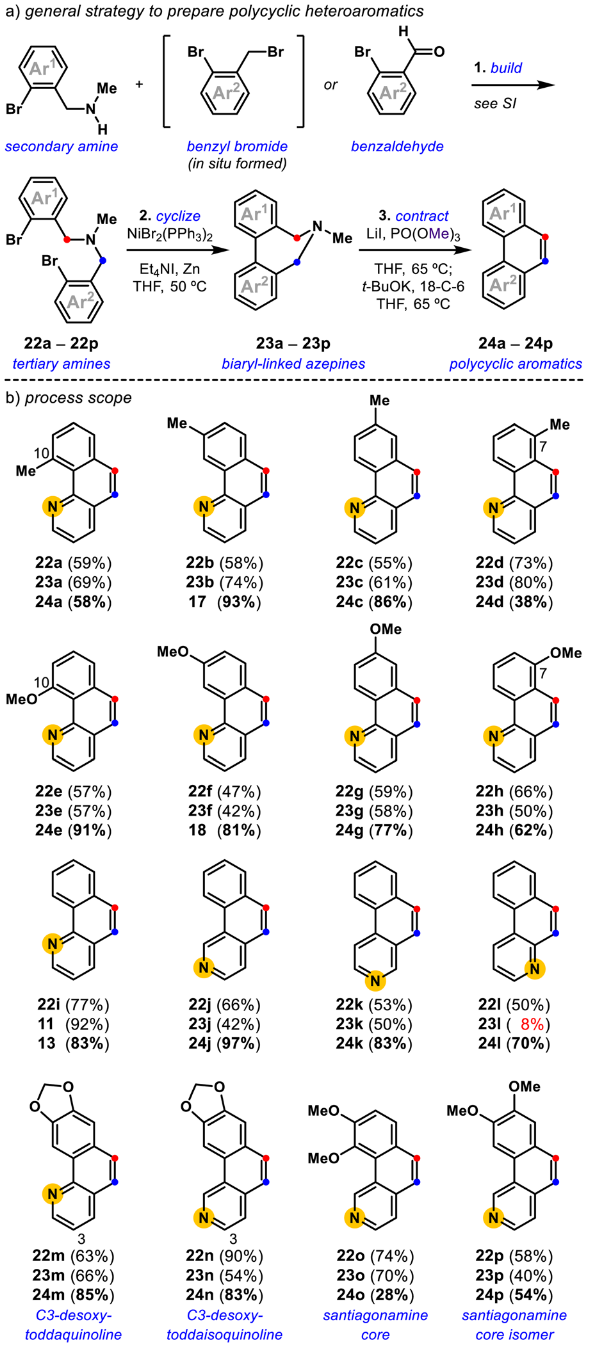


Fig. 4 Synthesis of polycyclic aromatics (a) a general strategy to prepare polycyclic heteroaromatics; (b) process scope: the final polycyclic heteroaromatics are shown for each three-step synthesis, the yields for each step are shown in order: build (step 1)-cyclize (step 2)-contract (step 3).

orthogonality to recent oxidative deaminative ring contraction methods,[40,41] we set out to develop a general build-cyclize-contract strategy to prepare polycyclic heteroaromatics (Fig. 4).

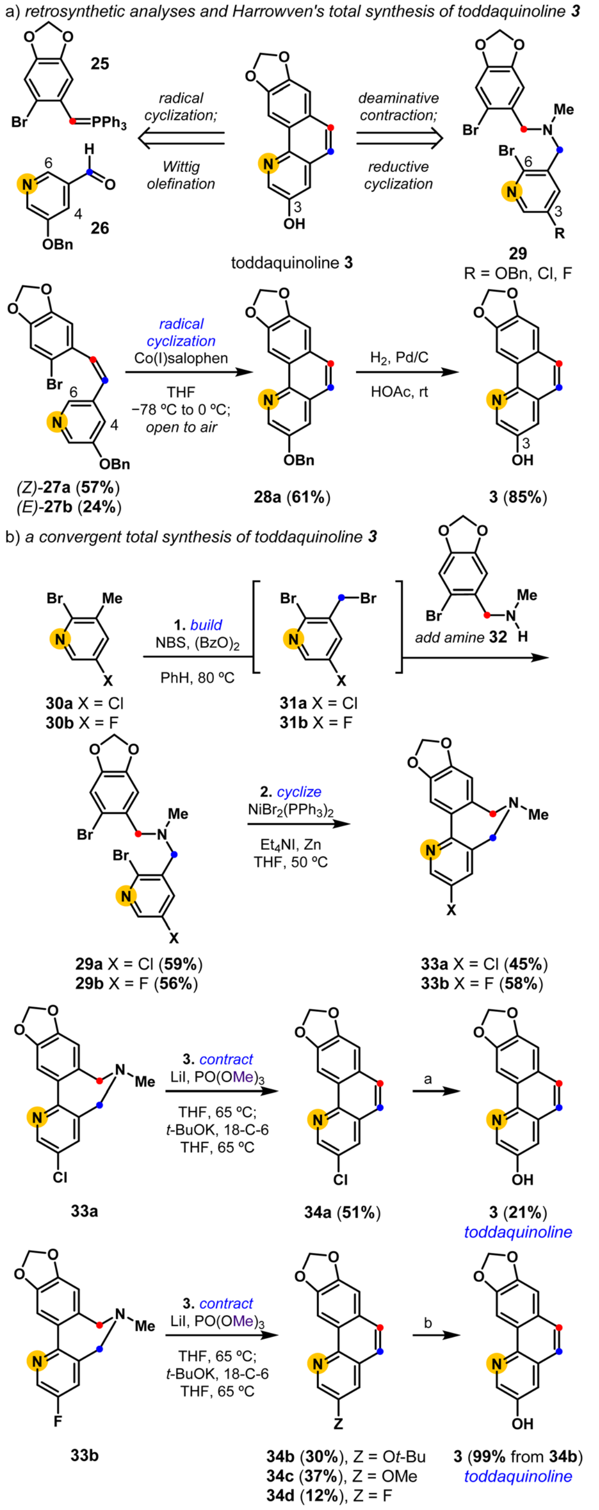
A general strategy to prepare polycyclic heteroaromatics

In the build step, synthetic secondary amines are advanced to tertiary amines using either radical halogenation/alkylation or reductive amination procedures, dependent on the availability of the respective methyl aryl and benzaldehyde derivatives (Fig. 4a, see the ESI†). Tertiary amines synthesized by the one-pot radical halogenation/alkylation method proceeded with a yield range of 23–74% for the 18 examples (Fig. 4b, see the ESI†). Tertiary amines prepared by reductive amination are accessible with a yield range of 53–90% for the six examples (Fig. 4b, see the ESI†). Following the build step, synthetic tertiary amines were cyclized using a Ni-promoted reaction[28,30,32,33] to access the corresponding biaryl-linked dihydroazepines in moderate to good yields. Notably, the biaryl bond-forming cyclization is tolerant of *ortho*-substitution (**23a**, **23e**, and **23o**) and allows access to all possible pyridyl isomers (**11**, **23j**, **23k**, and **23l**).[42] In some cases, the Ni-mediated reaction conditions give lower conversion, which we attribute to the chelating 1,2-diamine nature of certain tertiary amine substrates.[40d] This was most evident for the conversion of pyridyl variant **22l** into **23l** (8%).

With various biaryl-linked dihydroazepines in hand, we evaluated their conversion into polycyclic heteroaromatics by deaminative contraction (Fig. 4). We find that methyl-substituted benzo[*h*]quinolines, **24a** (58%), **17** (93%), **24c** (86%), and **24d** (38%), are all accessible, with a trend toward slightly diminished conversion for 10-methyl (**24a**) and 7-methyl (**24d**) variants. Toward **24a**, we attribute the lower yield to the 10-methyl substituent-induced torsional strain,[36] likely rendering the [1,2]-Stevens rearrangement difficult. Toward **24d**, we attribute the overall lower conversion to the steric encumbrance induced by the amine-neighboring C7-methyl substituent that may preclude the requisite methylation and [1,2]-Stevens rearrangement events. In this case, the Stevens product can be observed. A similar, albeit less pronounced trend is noted for the corresponding methoxy-substituted benzo[*h*]quinolines, **24e** (91%), **18** (81%), **24g** (77%), and **24h** (62%). The comparatively better yields for **24e** (C10-OMe) *vs.* **24a** (C10-Me) and **24h** (C7-OMe) *vs.* **24d** (C7-Me) are consistent with the smaller *B*-value steric measure for methoxy ($B = 5.6$ kcal mol^{-1}) *vs.* methyl ($B = 7.4$ kcal mol^{-1}) substituents,[43] but cannot be decoupled from differences due to electronic effects. Intriguingly, we find that isomers of the parent benzo[*h*]quinoline system **13** (83%), **24j** (97%), **24k** (83%), and **24l** (70%) are accessible in comparable yields, with **24j** produced in exceptional yield. Consistent with our initial substrate polarization hypothesis, we reason that resonance-stabilized ammonium ylide intermediates, undergo more efficient [1,2]-Stevens rearrangement and Hofmann elimination events en route to their corresponding polycyclic heteroaromatics. The ability to access several pyridyl variations of the polycyclic aromatic core enables general access to the benzo[*h*]quinoline core of toddaquinoline **3** (ref. 6) and the benzo[*h*]isoquinoline core of santiagonamine **4** (ref. 7) (Fig. 1a). To highlight the efficiency and flexibility of the developed strategy, both natural and isomeric variations are straightforward to access. The build-cyclize-contract strategy provides efficient access to C3-desoxy-toddaquinoline **24m** (85%),[28,44] C3-desoxy-toddaisoquinoline **24n** (83%),[26] santiagonamine core **24o** (28%),[7] and an isomeric santiagonamine core **24p** (54%). This general efficiency prompted us to evaluate the build-cyclize-contract strategy to realize a concise total synthesis of toddaquinoline **3**.

Total synthesis of toddaquinoline

Harrowven and coworkers completed the first and only total synthesis of toddaquinoline **3** in three steps from accessible



Scheme 1 A build-cyclize-contract total synthesis of toddaquinoline 3. (a) 3 equiv. KOH, 10 mol% Pd_2dba_3, 40 mol% Me_4t-BuXPhos, 1,4-dioxane/H_2O, 100 °C; (b) CF_3CO_2H, CH_2Cl_2, rt. dba = dibenzylideneacetone.

precursors, **25** and **26** (Scheme 1).[45,46] Their concise assembly of the oxygenated benzo[*h*]quinoline natural product leveraged a partly *Z*-selective Wittig olefination ((*Z*)-**27a** and (*E*)-**27b**, 2.4 : 1), followed by a cobalt(I) salophen-mediated C6-regiocontrolled radical cyclization of the pendent pyridine. While olefination followed by cyclization sequences have since become a reliable means to build polycyclic aromatics,[27,47] these strategies can suffer from alkene isomer selectivity and cyclization regiocontrol issues. We set out to develop an alternative total synthesis of toddaquinoline **3** from the reductive cyclization and deaminative contraction of a functionalized tertiary amine. The efficient synthesis of **29** (R = OBn) proved difficult as the electron-rich *O*-benzylated pyridyl derivative is prone to over-halogenation (see the ESI†). We therefore pursued an alternative strategy to complete the total synthesis of **3**, leveraging a one-pot radical halogenation/alkylation procedure from halopyridines **30a** (X = Cl) and **30b** (X = F) to access respective tertiary amines **29a** and **29b**. Both tertiary amines (**29**) undergo chemoselective reductive cyclizations to provide biaryl-linked dihydroazepines (**33**). Their subsequent deaminative contractions provide intriguingly varied results, with both biaryl-linked dihydroazepines enabling access to toddaquinoline **3**. The deaminative contraction of 3-Cl dihydroazepine (**33a**) provides a 3-Cl derivative of toddaquinoline (**34a**) which is readily converted into **3** (21%) using an unoptimized Pd-catalyzed hydroxylation reaction.[48] Alternatively, the deaminative contraction of 3-F dihydroazepine (**33b**) provides a separable mixture of three ring-contracted products, **34b** (Z = O*t*-Bu), **34c** (Z = OMe), and **34d** (Z = F), where we presume S_NAr reactivity[39] gives rise to substituted variants **34b** and **34c**. The *tert*-butyl ether variant (**34b**) is quantitatively converted into toddaquinoline **3** (99%) using acidolysis conditions.[49] Overall, each three-step process yields a polysubstituted benzo[*h*]quinoline core (**34**) while completely avoiding alkene isomer and cyclization regiocontrol challenges.

An iterative strategy to access aminated benzo[*h*]quinolines and aza[*n*]helicenes

The C9-methyl substituent in benzo[*h*]quinoline **17** provides an additional opportunity to controllably extend the aromatic system to access aminated benzo[*h*]quinolines and aza[5]helicenes (Fig. 5).[47] A proof-of-concept experiment demonstrates that aminated derivatives are directly available from **17** following the developed one-pot radical halogenation/alkylation procedure to access pyrrolidine derivative **36** *via* benzyl bromide intermediate **35**. Using Sanford's C–H functionalization protocol,[50] the same 9-methyl benzo[*h*]quinoline (**17**) can be regioselectively brominated (C10) and subsequently converted into a pyridyl-containing dihydroazepine derivative **39** following radical halogenation/alkylation, and reductive cyclization. Finally, biaryl-linked dihydroazepine **39** undergoes deaminative contraction to access aza-pentahelicene **40** (phenanthro[3,4-*h*]quinoline), demonstrating a modular strategy to access pentahelicenes[35,50] that may enable the precision-controlled introduction of substituents by the strategic addition of aromatic rings.

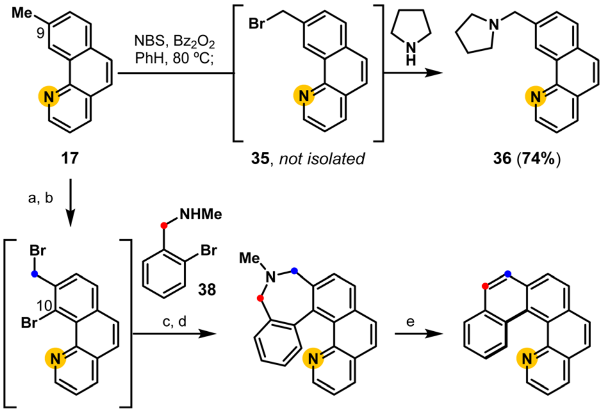


Fig. 5 Functionalization of methyl-substituted benzo[*h*]quinolines to access aminated benzo[*h*]quinolines and aza-helicenes: (a) $Pd(OAc)_2$, NBS, CH_3CN; (b) NBS, Bz_2O_2, PhH, 80 °C; (c) add **38** in THF; (d) $NiBr_2(PPh_3)_2$, Et_4NI, Zn, THF, 50 °C; (e) LiI, $PO(OMe)_3$, THF, 65 °C; *t*-BuOK, 18-C-6, THF, 65 °C.

Conclusions

We developed a build-cyclize-contract strategy to access polycyclic (hetero)aromatics. The key developed deaminative ring contraction involves a proposed *in situ* methylation followed by base induced [1,2]-Stevens rearrangement/dehydroamination cascade reaction. We report 25 examples of reductive cyclization and deaminative contraction (28–97% yields) processes to yield polycyclic (hetero)aromatics, culminating in a four-step total synthesis of toddaquinoline. Given the simple starting materials, this strategy can be readily applied to prepare substituted polycyclic (hetero)aromatics with utility as the diversifiable cores of many bioactive polycyclic natural products,[3,28] ligands for catalysis,[25] and the organic components for the discovery of novel materials.[26,51]

Data availability

The data supporting this article has been uploaded as part of the ESI.†

Author contributions

The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 For selected reviews, see: (*a*) A. Kovács, A. Vasas and J. Hohmann, *Phytochemistry*, 2008, **69**, 1084–1110; (*b*) Z.-X. Qing, P. Yang, Q. Tang, P. Cheng, X.-B. Liu, Y. Zheng, Y.-S. Liu and J.-G. Zeng, *Curr. Org. Chem.*, 2017, **21**, 1920–1934; (*c*) M. D. Douka and K. E. Litinas, *Molecules*, 2022, **27**, 7256.

2 For selected recent examples, see: (*a*) M.-E. Sahuc, R. Sahli, C. Rivière, V. Pène, M. Lavie, A. Vandeputte, P. Brodin, A. R. Rosenberg, J. Dubuisson, R. Ksouri, Y. Rouillé, S. Sahpaz and K. Séron, *J. Virol.*, 2019, **93**, e02009–e02018; (*b*) P. Patra and S. Patra, *Heterocycles*, 2023, **106**, 241.

3 For representative total syntheses of substituted polycyclic aromatics including natural products, see: (*a*) A. S. Kende and D. P. Curran, *J. Am. Chem. Soc.*, 1979, **101**, 1857–1864; (*b*) X. Wang and V. Snieckus, *Tetrahedron Lett.*, 1991, **32**, 4879–4882; (*c*) X. Wang and V. Snieckus, *Tetrahedron Lett.*, 1991, **32**, 4883–4884; (*d*) C. Hoarau, A. Couture, H. Cornet, E. Deniau and P. Grandclaudon, *J. Org. Chem.*, 2001, **66**, 8064–8069; (*e*) S. B. Jones, L. He and S. L. Castle, *Org. Lett.*, 2006, **8**, 3757–3760; (*f*) M. D. Markey, Y. Fu and T. R. Kelly, *Org. Lett.*, 2007, **9**, 3255–3257; (*g*) F. Gosselin, S. Lau, C. Nadeau, T. Trinh, P. D. O'Shea and I. W. Davies, *J. Org. Chem.*, 2009, **74**, 7790–7797.

4 H. Sarkar, M. Zerezghi and J. Bhattacharyya, *Phytochemistry*, 1988, **27**, 3006–3008.

5 Y.-C. Wu, J.-Y. Liou, C.-Y. Duh, S.-S. Lee and S.-T. Lu, *Tetrahedron Lett.*, 1991, **32**, 4169–4170.

6 I.-S. Chen, I.-L. Tsai, S.-J. Wu, W.-S. Sheen, T. Ishikawa and H. Ishii, *Phytochemistry*, 1993, **34**, 1449–1451.

7 E. Valencia, A. Patra, A. J. Freyer, M. Shamma and V. Fajardo, *Tetrahedron Lett.*, 1984, **25**, 3163–3166.

8 (*a*) J. B. Bremner and K. N. Winzenberg, *Aust. J. Chem.*, 1978, **31**, 313–320; (*b*) S.-T. Lu and I.-L. Tsai, *Heterocycles*, 1988, **27**, 751; (*c*) S.-S. Lee, Y.-J. Lin, M.-Z. Chen, Y.-C. Wu and C.-H. Chen, *Tetrahedron Lett.*, 1992, **33**, 6309–6310; (*d*) S.-S. Lee, C.-M. Chiou, H.-Y. Lin and C.-H. Chen, *Tetrahedron Lett.*, 1995, **36**, 1531–1532; (*e*) Y. Masahide, H. Takamitsu, A. Yasuhiro and S. Kensuke, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 1451–1455.

9 S. V. Kini and M. M. V. Ramana, *Tetrahedron Lett.*, 2004, **45**, 4171–4173.

10 J. A. Vanecko, H. Wan and F. G. West, *Tetrahedron*, 2006, **62**, 1043–1062.

11 Z. Schwartz, C. Valiton, M. Lovasz and A. G. Roberts, *Synthesis*, 2023, **55**, DOI: 10.1055/s-0042-1751446.

12 A. J. Floyd, S. F. Dyke and S. E. Ward, *Chem. Rev.*, 1976, **76**, 509–562.

13 D. F. DeTar, in *Org. React.*, John Wiley & Sons, Ltd, 2011, pp. 409–462.

14 (*a*) F. B. Mallory and C. W. Mallory, in *Org. React.*, John Wiley & Sons, Ltd, 2005, pp. 1–456; (*b*) K. B. Jørgensen, *Molecules*, 2010, **15**, 4334–4358; (*c*) A. G. Lvov, *J. Org. Chem.*, 2020, **85**, 8749–8759.

15 For a pertinent review on photoelectrocyclization reactions and their applications in total synthesis, see: X. Zhao and J. D. Rainier, *Synthesis*, 2021, **53**, 1200–1212.

16 L. Liu, B. Yang, T. J. Katz and M. K. Poindexter, *J. Org. Chem.*, 1991, **56**, 3769–3775.

17 Y. Li, D. E. Wise, J. K. Mitchell and M. Parasram, *J. Org. Chem.*, 2023, **88**, 717–721.

18 For pertinent discussions, see: (*a*) N. Miyaura, in *Adv. Met.-Org. Chem.*, ed. L.S. Liebeskind, JAI, 1998, pp. 187–243; (*b*) X. Cai, S. Brown, P. Hodson and V. Snieckus, *Can. J. Chem.*, 2004, **82**, 195–205.

19 (*a*) R. C. Larock, M. J. Doty, Q. Tian and J. M. Zenner, *J. Org. Chem.*, 1997, **62**, 7536–7537; (*b*) A.-E. Gies and M. Pfeffer, *J. Org. Chem.*, 1999, **64**, 3650–3654; (*c*) V. Mamane, P. Hannen and A. Fürstner, *Chem. - Eur. J.*, 2004, **10**, 4556–4575; (*d*) A. Iuliano, P. Piccioli and D. Fabbri, *Org. Lett.*, 2004, **6**, 3711–3714; (*e*) T. J. Donohoe, A. J. Orr and M. Bingham, *Angew. Chem., Int. Ed.*, 2006, **45**, 2664–2670; (*f*) W. A. L. van Otterlo and C. B. de Koning, *Chem. Rev.*, 2009, **109**, 3743–3782; (*g*) C. Wang, S. Rakshit and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 14006–14008; (*h*) Y. Xia, Z. Liu, Q. Xiao, P. Qu, R. Ge, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 5714–5717; (*i*) W. C. Fu, Z. Wang, W. T. K. Chan, Z. Lin and F. Y. Kwong, *Angew. Chem., Int. Ed.*, 2017, **56**, 7166–7170.

20 Z. Zhao, L. H. Britt and G. K. Murphy, *Chem. - Eur. J.*, 2018, **24**, 17002–17005.

21 (*a*) M. Murai, N. Hosokawa, D. Roy and K. Takai, *Org. Lett.*, 2014, **16**, 4134–4137; (*b*) C. C. McAtee, P. S. Riehl and C. S. Schindler, *J. Am. Chem. Soc.*, 2017, **139**, 2960–2963.

22 H. Albright, A. J. Davis, J. L. Gomez-Lopez, H. L. Vonesh, P. K. Quach, T. H. Lambert and C. S. Schindler, *Chem. Rev.*, 2021, **121**, 9359–9406.

23 V. Mamane, F. Louërat, J. Iehl, M. Abboud and Y. Fort, *Tetrahedron*, 2008, **64**, 10699–10705.

24 Nitrogen-containing Heterocycles are present in 59% of U.S. FDA approved small-molecule drugs: (*a*) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; For a pertinent example of a benzo[h] quinoline in drug discovery, see: (*b*) N. Atatreh, C. Stojkoski, P. Smith, G. W. Booker, C. Dive, A. D. Frenkel, S. Freeman and R. A. Bryce, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1217–1222.

25 E. C. Riesgo, X. Jin and R. P. Thummel, *J. Org. Chem.*, 1996, **61**, 3017–3022.

26 E. K. Cho, P. K. Quach, Y. Zhang, J. H. Sim and T. H. Lambert, *Chem. Sci.*, 2022, **13**, 2418–2422.

27 (*a*) D. C. Harrowven, I. L. Guy and L. Nanson, *Angew. Chem., Int. Ed.*, 2006, **45**, 2242–2245; (*b*) G. Chelucci, D. Addis and S. Baldino, *Tetrahedron Lett.*, 2007, **48**, 3359–3362.

28 T. P. McFadden, C. I. Nwachukwu and A. G. Roberts, *Org. Biomol. Chem.*, 2022, **20**, 1379–1385.

29 T. Ross Kelly, Q. Li and V. Bhushan, *Tetrahedron Lett.*, 1990, **31**, 161–164.

30 M. Iyoda, H. Otsuka, K. Sato, N. Nisato and M. Oda, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 80–87.

31 S. Zhang, D. Zhang and L. S. Liebeskind, *J. Org. Chem.*, 1997, **62**, 2312–2313.

32 S. Leleu, C. Papamicaël, F. Marsais, G. Dupas and V. Levacher, *Tetrahedron: Asymmetry*, 2004, **15**, 3919–3928.

33 W. Xue, H. Xu, Z. Liang, Q. Qian and H. Gong, *Org. Lett.*, 2014, **16**, 4984–4987.

34 C. I. Nwachukwu, T. P. McFadden and A. G. Roberts, *J. Org. Chem.*, 2020, **85**, 9979–9992.

35 I. G. Stara, I. Stary, M. Tichy, J. Zavada and V. Hanus, *J. Am. Chem. Soc.*, 1994, **116**, 5084–5088.

36 H. Joshua, R. Gans and K. Mislow, *J. Am. Chem. Soc.*, 1968, **90**, 4884–4892.

37 Z.-T. He, H. Li, A. M. Haydl, G. T. Whiteker and J. F. Hartwig, *J. Am. Chem. Soc.*, 2018, **140**, 17197–17202.

38 S. Hanessian and M. Mauduit, *Angew. Chem., Int. Ed.*, 2001, **40**, 3810–3813.

39 A. S. Abel, A. Yu Mitrofanov, A. A. Yakushev, I. S. Zenkov, G. V. Morozkov, A. D. Averin, I. P. Beletskaya, J. Michalak, S. Brandès and A. Bessmertnykh-Lemeune, *Asian J. Org. Chem.*, 2019, **8**, 2128–2142.

40 For the oxidative deaminative ring contraction of secondary amines, see: (*a*) S. H. Kennedy, B. D. Dherange, K. J. Berger and M. D. Levin, *Nature*, 2021, **593**, 223–227; (*b*) H. Qin, W. Cai, S. Wang, T. Guo, G. Li and H. Lu, *Angew. Chem., Int. Ed.*, 2021, **60**, 20678–20683; (*c*) C. Hui, L. Brieger, C. Strohmann and A. P. Antonchick, *J. Am. Chem. Soc.*, 2021, **143**, 18864–18870; (*d*) H. Na and L. M. Mirica, *Nat. Commun.*, 2022, **13**, 1313; (*e*) B. A. Wright, A. Matviitsuk, M. J. Black, P. García-Reynaga, L. E. Hanna, A. T. Herrmann, M. K. Ameriks, R. Sarpong and T. P. Lebold, *J. Am. Chem. Soc.*, 2023, **145**, 10960–10966.

41 J. Jurczyk, J. Woo, S. F. Kim, B. D. Dherange, R. Sarpong and M. D. Levin, *Nat. Synth.*, 2022, **1**, 352–364.

42 M. W. Danneman, K. B. Hong and J. N. Johnston, *Org. Lett.*, 2015, **17**, 3806–3809.

43 R. Ruzziconi, S. Spizzichino, L. Lunazzi, A. Mazzanti and M. Schlosser, *Chem. - Eur. J.*, 2009, **15**, 2645–2652.

44 H. Abe, G. Serban, Y. Shigeta, H. Nishioka, Y. Takeuchi and T. Harayama, *Heterocycles*, 2007, **71**, 1623.

45 D. C. Harrowven, M. I. T. Nunn, N. J. Blumire and D. R. Fenwick, *Tetrahedron Lett.*, 2000, **41**, 6681–6683.

46 D. C. Harrowven, M. I. T. Nunn, N. J. Blumire and D. R. Fenwick, *Tetrahedron*, 2001, **57**, 4447–4454.

47 N. Takenaka, R. S. Sarangthem and B. Captain, *Angew. Chem., Int. Ed.*, 2008, **47**, 9708–9710.

48 K. W. Anderson, T. Ikawa, R. E. Tundel and S. L. Buchwald, *J. Am. Chem. Soc.*, 2006, **128**, 10694–10695.

49 H. S. Tae, J. Hines, A. R. Schneekloth and C. M. Crews, *Org. Lett.*, 2010, **12**, 4308–4311.

50 A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300–2301.

51 (*a*) M. Stępień, E. Gońka, M. Żyła and N. Sprutta, *Chem. Rev.*, 2017, **117**, 3479–3716; (*b*) X. Feng, Y. Bai, M. Liu, Y. Li, H. Yang, X. Wang and C. Wu, *Energy Environ. Sci.*, 2021, **14**, 2036–2089.