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[2.2]Paracyclophane-substituted quinolines by skeletal editing strategies†

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The synthesis of 2- and 3-substituted [2.2]paracyclophanyl quinolines using two distinct skeletal editing strategies is described. The first approach relies on indole ring expansion and furnishes 3-aryl quinolines with the paracyclophanyl substituent in the 2-position. In contrast, the second uses a paracyclophane-derived carbene precursor and delivers the complementary 3-[2.2]paracyclophanyl quinolines, highlighting skeletal editing as a powerful tool for advancing the synthetic chemistry of [2.2]paracyclophanes.

Introduction

[2.2]Paracyclophane (PCP) **1** ranks among the most versatile organic scaffolds, owing to its unique electronic properties and the inherent planar chirality of monosubstituted derivatives.[1–4] While incorporating heteroaromatic residues into the PCP scaffold has traditionally been challenging due to its unusual chemical reactivity, heterocyclic [2.2]paracyclophanes have been known since the 1960s.[5–7] Today, a broad spectrum of these derivatives is synthetically accessible, encompassing compounds where the heterocycle is directly attached to the PCP core or fused to the aromatic rings or aliphatic bridges.[8] The motivation for this research arises from the potential to introduce planar chirality to the heterocycles, as this feature has been repeatedly shown to impart a diverse array of biological activities. For instance, indoloparacyclophanes demonstrated highly selective aryl bioisosteric activity as D4 receptor ligands, while [2.2]paracyclophanyl thiazole conjugates exhibit promising anticancer properties.[9–13] Moreover, such compounds are frequently employed as chiral ligands in stereoselective synthesis.[14–16] As a result, there is substantial ongoing interest in developing novel synthetic methodologies for heterocyclic [2.2]paracyclophanes.[17,18]

Skeletal editing is the precise manipulation of the molecular framework, achieved through the insertion, deletion, or replacement of single atoms *via* highly selective transformations.[19–21] Although still an emerging field, it could significantly impact organic synthesis by streamlining synthetic pathways and enabling the rapid diversification of core structures, all while circumventing the need for costly and labor-intensive *de novo* synthesis. Among the available techniques, the development of the Ciamician-Dennsted chemistry for the synthesis of quinolines through indolocyclopropane rearrangement has recently undergone substantial advancements in substrate compatibility, rendering it a very powerful synthetic tool. The current state of the indole ring-expansion involves the use of various types of carbene precursors, such as chloroform, arylchlorodiazirines, α-halodiazoacetates, dibromofluoromethanes, and hydrazone-derived diazo compounds with reactions proceeding either catalyzed or uncatalyzed.[22–28]

A review of existing heterocyclic [2.2]paracyclophane compounds highlights the lack of straightforward synthetic routes to PCP-substituted quinolines. To our knowledge, only Minuti *et al.* have described the synthesis of a furoquinoline and quinolinyl cyclophane *via* a complex synthetic approach, while Kryvenko *et al.* have reported the formation of a 4-[2.2]paracyclophanyl benzoquinoline as a by-product obtained in very low yield.[29,30] Inspired by the advances in skeletal editing methodology, we explored these strategies for the synthesis of novel [2.2]paracyclophane quinoline derivatives. We hypothesized that the newly developed indole ring-expansion techniques could provide a convenient route to 2- and 3-paracyclophane-substituted quinolines and enable the rapid diversification of the target structures (Scheme 1).

Results and discussion

Our approach toward the synthesis of (*rac*)-2-[2.2]paracyclophanylquinolines relied on a three-step synthetic sequence comprising the synthesis of the paracyclophane indoles **4a–4d**
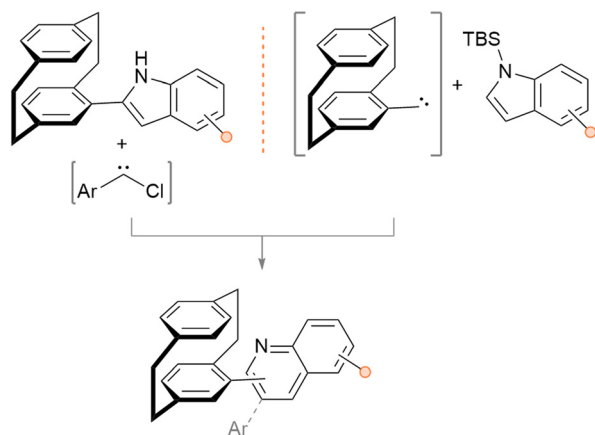
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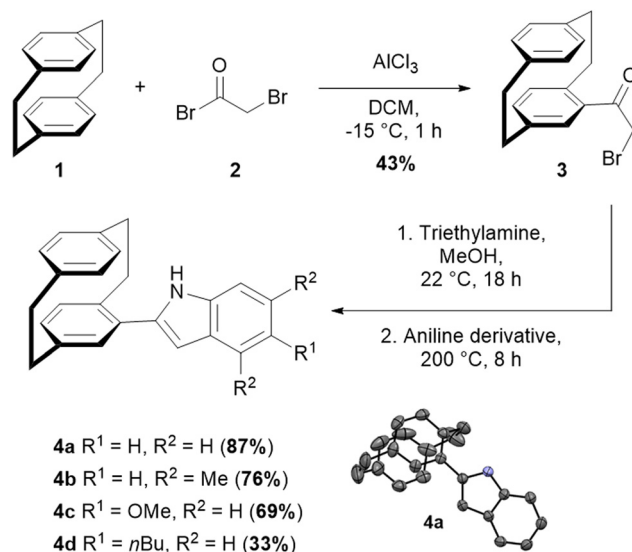
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Scheme 1 PCP-quinoline synthesis *via* two distinct skeletal editing strategies.

4a R^1 = H, R^2 = H (**87%**)
4b R^1 = H, R^2 = Me (**76%**)
4c R^1 = OMe, R^2 = H (**69%**)
4d R^1 = nBu, R^2 = H (**33%**)

Scheme 2 Synthesis of PCP-indoles **4a–4d** through Bischler–Möhlau reaction.

through Bischler–Möhlau reaction, as reported by Kryvenko *et al.* and Thennakoon *et al.*, followed by indole ring-expansion using arylchlorodiazirines as carbene precursors.[29,31] Among the numerous protocols for indole ring expansion, the method developed by the Levin group was deemed particularly promising due to its mild thermolytic conditions, requiring only simple heating at 50 °C for carbene generation, which was assumed to be compatible with the challenging [2.2]paracyclophane substrates as well as the tolerance for the 2-indole substitution motif (see ESI for mechanistic rationale†).

Using this approach, 4-bromoacetyl [2.2]paracyclophane (**3**) was obtained in varying yields, with a maximum of 72% on a 400 mg scale. However, on a gram scale, moderate yields of around 40% were consistently achieved, with unreacted [2.2] paracyclophane constituting the remainder of the material. Subsequently, electron-rich indoles **4a–4d** were synthesized in good to moderate yields, whereas attempts to prepare an electron-deficient PCP-indole using 4-(trifluoromethyl)aniline were unsuccessful. Single crystals of indole **4a** suitable for X-ray diffraction analysis were obtained through slow evaporation of a chloroform solution, unambiguously confirming the target structure. Thus, several examples of electron-rich substrates with varying steric profiles and substitution patterns were available (Scheme 2). With these compounds in hand, we proceeded to evaluate the ring expansion of PCP-indoles using arylchlorodiazirines as carbene precursors. To our delight, the desired [2.2]paracyclophanyl quinoline product **5a** was obtained in 51% yield under initial testing conditions, employing acetonitrile as a solvent and sodium carbonate as a base. However, further optimization of reaction conditions consistently resulted in diminished yields (see ESI†). Single-crystal X-ray analysis of product **5a** unequivocally confirmed its molecular structure (Scheme 3).

The diversification of the quinoline target compounds was readily achieved by varying the combinations of arylchlorodiazirines and PCP-based indoles, enabling the synthesis of a library comprising 25 novel PCP-quinoline candidates. When exploring the scope of the transformation, it was observed that
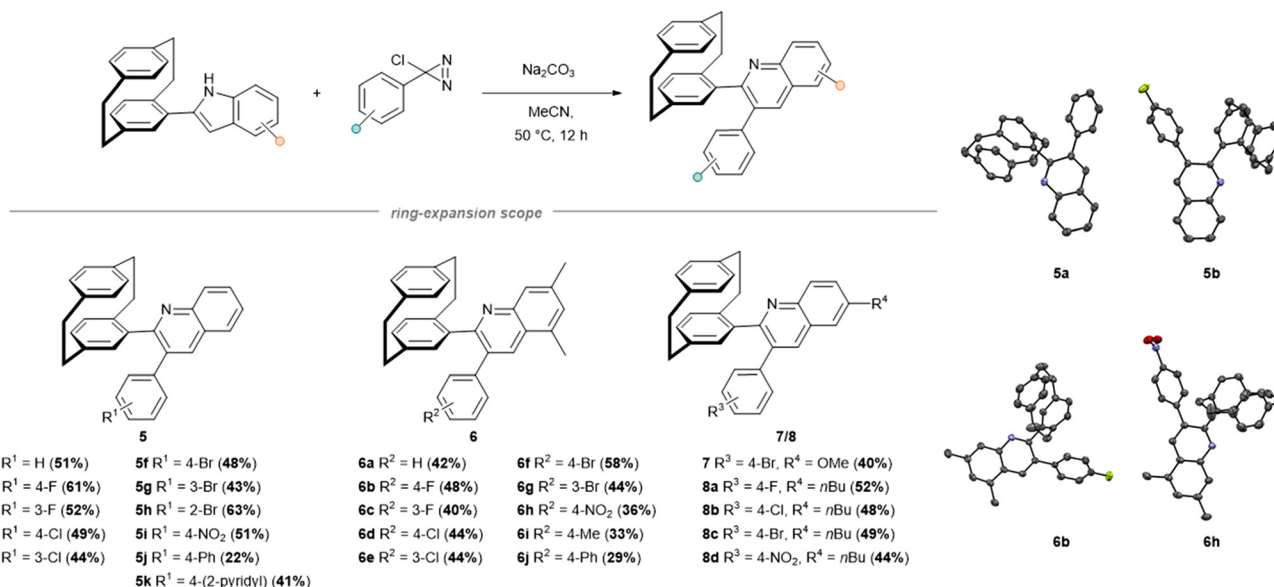
the sterically more demanding indole substrates **4b–4d** consistently produced lower yields than the unsubstituted derivative **4a**. Similarly, and consistent with earlier reports,[23,24] the electronic properties of the arylchlorodiazirines played a significant role. Strongly electron-deficient and electron-rich diazirines, as in the cases of quinolines **6h** and **6i**, resulted in lower yields. In contrast, haloquinolines **5b–5h**, **6b–6g**, and **8a–8c** were obtained in relatively good yields around 50%. Highly electron-rich 4-methoxyphenylchlorodiazirine failed to yield any product, underscoring the need for a careful balance of electronic effects in diazirine selection. Different substitution patterns on the diazirine were generally well tolerated. *para-* and *meta*-Substitution produced reasonable yields between 40% and 52%, though *meta*-substitution often resulted in slightly reduced yields possibly due to increased steric hindrance. For *ortho*-substituted quinoline **5h**, a diastereomeric mixture of rotamers in a 5 : 4 ratio was isolated in 63% yield, confirmed through high-temperature NMR analysis (see ESI†). The incorporation of heteroaryl diazirines proved more challenging. Only 2-pyridyl diazirine produced its corresponding quinoline **5k**, but five equivalents were required instead of the standard three. To evlauate the influence of the paracyclophanyl substituent, we performed the ring expansion of 2-(*o*-tolyl)-1*H*-indole with 4-bromo-1*H*-chlorodiazirine. The corresponding quinoline product was obtained in a comparable 51% yield, indicating that the transformation generally achieves moderate yields with *ortho*-substituted 2-aryl indoles. The structures of the products were elucidated by spectral analysis, including NMR spectroscopy and mass spectrometry. Additionally, well-defined crystals of quinolines **5b**, **6b**, and **6h** were obtained through layering techniques, allowing for definitive structural characterization through single-crystal X-ray analysis (Scheme 3).

Having established a convenient access to 2-paracyclophane-substituted quinolines, we envisioned that a comp-
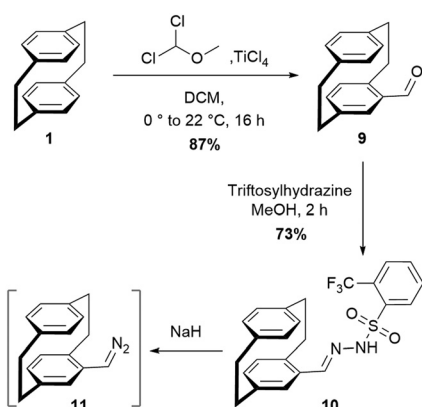
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Scheme 3 Scope of 2-[2.2]paracyclophanyl-3-arylquinolines.

lementary strategy using a PCP-based carbene species could provide a straightforward route to the 3-substitution motif. However, aside from the PCP-diazo compound **11**,[31] no suitable PCP-carbene precursor candidates are available in the literature. Moreover, due to the inherent instability of donor-diazo compounds, attempts to directly employ PCP-diazo **11** in synthetic transformations were unsuccessful. However, the well-established strategy of *in situ* generation of diazo compounds from a suitable diazo surrogate appeared promising for addressing this issue.[28,32–35]

Therefore, we aimed to synthesize the PCP-triftosyl hydrazone **10**, which can release the corresponding PCP-diazo compound **10** upon reaction with sodium hydride base. The triftosyl group is easily introduced to unsubstituted PCP **1** *via* a two-step synthetic route, including formylation followed by condensation with triftosyl hydrazine, performed on a gram scale without chromatographic purification (Scheme 4).
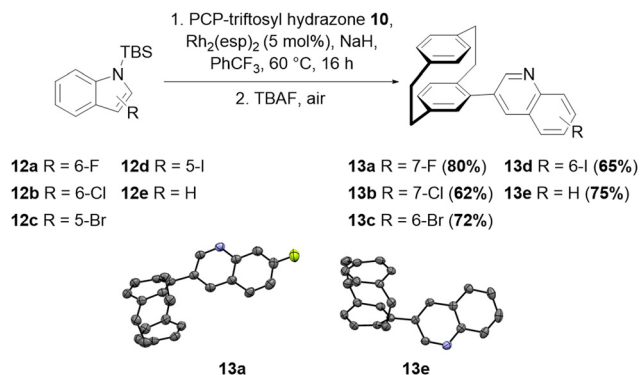
Subjecting the PCP-triftosyl hydrazone **10** to initial testing conditions employing silver(I) triflate as a catalyst, sodium hydride base, and TBS-protected indole **12a** resulted in the desired 3-quinoline **13a**, but only in 12% isolated yield. Through optimization of the reaction conditions, moderate to good yields were achieved. Notably, the key to the successful

Table 1 Optimization of the Ciamician-Dennstedt reaction employing a PCP-derived carbene[a]

	Catalyst/solvent	Yield of **13a**[c] (%)
1	AgOTf	18(12)
2	AgTp(CF$_3$)$_2$(THF)	18
3	Rh(OAc)$_2$	15
4	Rh$_2$(esp)$_2$	84(80)
5	Rh$_2$(S-DOSP)$_4$	70
6	Rh$_2$(S-PTAD)$_4$	66
7	Rh$_2$(S-TCPTAD)$_4$	92
8	Rh$_2$(S-BTPCP)$_4$	4
9	Dirhodium(II) tetrakis(caprolactam)	n.d.
10	Rh(III)Cl$_2$Cp*	n.d.
11	FeTPPCl	n.d.
12	DCM[b]	76
13	DCE[b]	70
14	THF[b]	10
15	Dioxane[b]	52

[a] Reaction conditions: **10** (0.06 mmol) and **12a** (2.00 equiv.) with silver catalyst (20 mol%) or rhodium catalyst (5 mol%), NaH (2.00 equiv.) and PhCF$_3$ or specified solvent (1 mL) at 60 °C for 16 h. [b] With Rh$_2$(esp)$_2$ catalyst at reflux temperature. [c] ^{19}F NMR yield. Isolated yield in parentheses.

Scheme 4 Synthesis of PCP-triftosyl hydrazone **10**.

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Scheme 5 Ciamician-Dennstedt reaction employing a PCP-derived carbene.

transformation was the switch from the silver-catalyzed system to rhodium catalysis. With the optimized conditions, quinoline **13a** was obtained in 80% yield, and X-ray diffraction distinctly confirmed the molecular structure. Furthermore, a concise scope of haloquinolines **13b–13h** and quinoline **13e** was synthesized, achieving moderate to high yields ranging from 62% to 80%. Although not explored in this work, enantiomerically pure 3-[2.2]paracyclophanyl quinolines could, in principle, be accessed through chiral resolution of the PCP-aldehyde **9**. Importantly, to our knowledge, this work represents the first reported application of a PCP-derived carbene species in an intermolecular transformation (Table 1, Scheme 5 and see ESI for mechanistic ratio†).

Conclusions

In conclusion, we achieved the facile synthesis of 2- and 3-substituted [2.2]paracyclophanyl quinolines using two distinct skeletal editing strategies. This work highlights the potential of skeletal editing in [2.2]paracyclophane chemistry, enabling broader functional diversification and unlocking access to novel compound classes that hold promise for applications in materials science, catalysis, and, due to their biological activity, in medicinal research. Additionally, the PCP-triftosyl hydrazone **10** exhibits broad synthetic utility, which is currently under investigation.

Data availability

The data that support the findings of this publication are available in the repository Chemotion (**https://www.chemotion-repository.net**). All DOIs minted for the data are linked to the specific experiments in this section and a summary of all new data obtained in this publication can be gained with the collection **https://doi.org/10.14272/collection/TIK_2024-02-02**.[36] The data supporting this article have been also included as part of the ESI.†

Crystallographic data for compounds **4**, **4a**, **4b**, **5b**, **5h**, **13a**, and **13e** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as ESI no. CCDC 2422599–2422605.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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