

Cite this: *Chem. Sci.*, 2023, 14, 6963

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 25th March 2023
Accepted 26th May 2023

DOI: 10.1039/d3sc01578e

rsc.li/chemical-science

An interrupted Corey–Chaykovsky reaction of designed azaarenium salts: synthesis of complex polycyclic spiro- and fused cyclopropanoids†

Bara Singh,‡ Arshad J. Ansari, ID ‡ Nirmal Malik and S. S. V. Ramasastry ID *

Simultaneous dearomatizing spirannulation of pyridinium salts is still in its infancy. Here, we present an organized skeletal remodeling of designed pyridinium salts by utilizing an interrupted Corey–Chaykovsky reaction to access unprecedented and structurally intriguing molecular architectures such as the vicinal bis-spirocyclic indanones and spirannulated benzocycloheptanones. This hybrid strategy rationally merges the nucleophilic features of sulfur ylides with the electrophilic pyridinium salts to achieve the regio- and stereoselective synthesis of new classes of cyclopropanoids. The plausible mechanistic pathways were derived from experimental results and control experiments.

Introduction

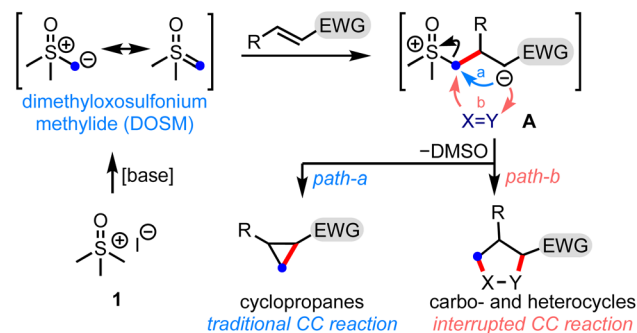
Small organic molecules with broad scaffold diversity have found relevance in several drug discovery programs.¹ The synthesis of privileged three-dimensional drug-like structures bears great potential for their ability to bind selectively to the desired target, and possess tunable physicochemical properties. Therefore, a synthetic challenge is to develop efficient methods to generate novel molecular architectures that can access untapped chemical space.

Sulfur ylide chemistry has been demonstrated to be one of the mainstay tools adapted in the step- and pot-economic synthesis of complex structural motifs.² In this context, it is worth mentioning the Corey–Chaykovsky (CC) reaction, which brings about the cyclopropanation of electron-deficient olefins by dimethyloxosulfonium methylide (DOSM), Scheme 1.³ The reaction involves displacing the dimethyl sulfoxide (DMSO) group from the zwitterionic intermediate **A** to generate cyclopropanes (path-a). In principle, **A** can be trapped by a suitable functionality (X = Y) to form various carbo- and heterocycles - the process we label as the interrupted CC reaction (path-b). This is the underlying theme of the present work.

Just as sulfur ylides, pyridinium salts have manifested profound synthetic applications in natural products chemistry, pharmaceuticals, and material science.⁴ The inherent

electrophilic nature of pyridinium salts facilitates nucleophilic additions at C-2/C-6 and C-4 positions, leading to the formation of dihydropyridines. During this process, the creation of an all-carbon quaternary center at C-4 can be envisioned, although sporadically pursued, Scheme 2a.⁵ In these lines, an *ipso*-nucleophilic addition of tethered nucleophiles at C-4 can be expected to create all-carbon spiro structures. But, the synthesis of spirocarbocyclic piperidines by this means is quite rarely accomplished.^{6,7} Interestingly, Eisch^{6a} and Fraenkel^{6c} achieved this synthetic feat through an intramolecular addition of hard nucleophiles such as organolithiums and Grignard reagents, although the C-4 position in pyridinium salts is soft. On the other hand, the synthetic utility of bis-enamine functionality of the so-formed dihydropyridines has also been underutilized.

With this background, we hypothesized an outline of the substrate design **B** as in Scheme 2b. We anticipated that rational incorporation of Nu¹-E tether (with dual electronic characters such as **A**) onto the pyridinium ring would trigger the



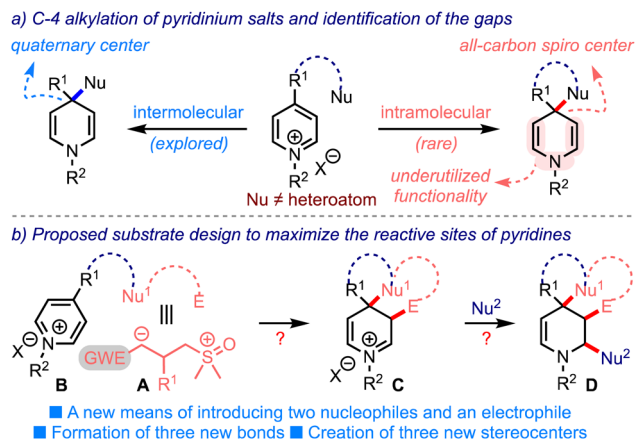
Scheme 1 General representation of the Corey–Chaykovsky cyclopropanation and realization of a potential opportunity to interrupt the process. EWG = electron-withdrawing group.

Department of Chemical Sciences, Indian Institute of Science Education and Research (IISER) Mohali, Sector 81, Manauli PO, S. A. S. Nagar, Punjab 140306, India. E-mail: ramsastry@iisermohali.ac.in; ramsastrys@gmail.com; Web: <https://web.iisermohali.ac.in/faculty/sastry/>

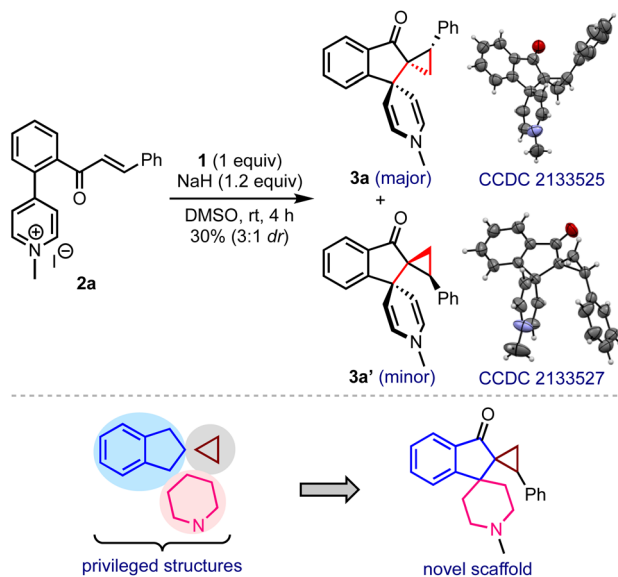
† Electronic supplementary information (ESI) available. CCDC 2133525 (3a), 2133527 (3a') and 2143316 (5a). For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc01578e>

‡ These authors contributed equally to this work.





Scheme 2 (a) The creation of an all-carbon quaternary/spiro center from pyridinium salts. (b) An outline of the proposed substrate design and an expected outcome. Nu = nucleophile. E = electrophile.



Scheme 3 Hypothesis-driven substrate design and a preliminary result providing unprecedented vicinal bis-spirocyclic indanones.

C-4 spirannulation. The resulting dienamine (not shown) could undergo an enamine-mediated alkylation, delivering the iminium species C. Subsequent intermolecular addition of an appropriate nucleophile (Nu^2) could then furnish spiro-fused tetrahydropiperidines D incorporated with at least three new bonds and three new stereogenic centers. Thus, the proposed design efficiently utilizes a minimum of three of the five reactive sites of pyridinium salts.⁸

Results and discussion

In line with the hypothesis presented in Scheme 2b, a model substrate **2a** was prepared by tethering the enone and pyridinium moieties *ortho* to each other on the arene backbone, Scheme 3. The reaction of **2a** with DOSM in DMSO delivered the

vicinal bis-spirocyclic indanones **3** as a 3 : 1 separable mixture of diastereomers, although in poor yield. The single-crystal X-ray diffraction analysis confirmed the structures, including the relative stereochemistry of **3a** and **3a'**.⁹ We were especially intrigued that a simple one-pot synthetic operation creates three new rings and three contiguous stereocenters, two of which are all-carbon vicinal spiro centers. As such, constructing a spiro structure is a synthetic challenge, even in the context of modern organic synthesis, and assembling vicinal spirocyclic systems is even more daunting.¹⁰ Considering the privileged status of indanes, cyclopropanes, and piperidines in drug discovery,¹¹ the hybrid structure **3** and its analogs embodying these elements may serve as new pharmacophores in drug discovery. The encouraging features mentioned above inspired us to optimize the reaction conditions.

The initial solvent screening revealed a significant improvement in the efficiency of the reaction in DMF (entries 1–3, Table 1). The desired product **3** was obtained in 86% yield in a short reaction time. Subsequently, we evaluated the effect of the temperature. The reaction of **2a** at 0 °C furnished **3** in moderate yield, whereas at 60 °C, the product was isolated in 75% yield (entries 4 and 5). Contrary to our expectation, we did not achieve a better result with the increased amounts of the base (entries 6 and 7). Our attempts to improve the yield by employing various inorganic or organic bases gave poor results (entries 8–12). Thus, a combination of NaH and DMF was suitable for an efficient outcome.

The optimized conditions were applied to a wide range of enone-tethered pyridinium salts **2**, and the results are compiled in Table 2. The electronic and steric roles of the substituents on the enone moiety (R^1), arene backbone (R^2), and pyridine core (R^3 and R^4) were thoroughly investigated.

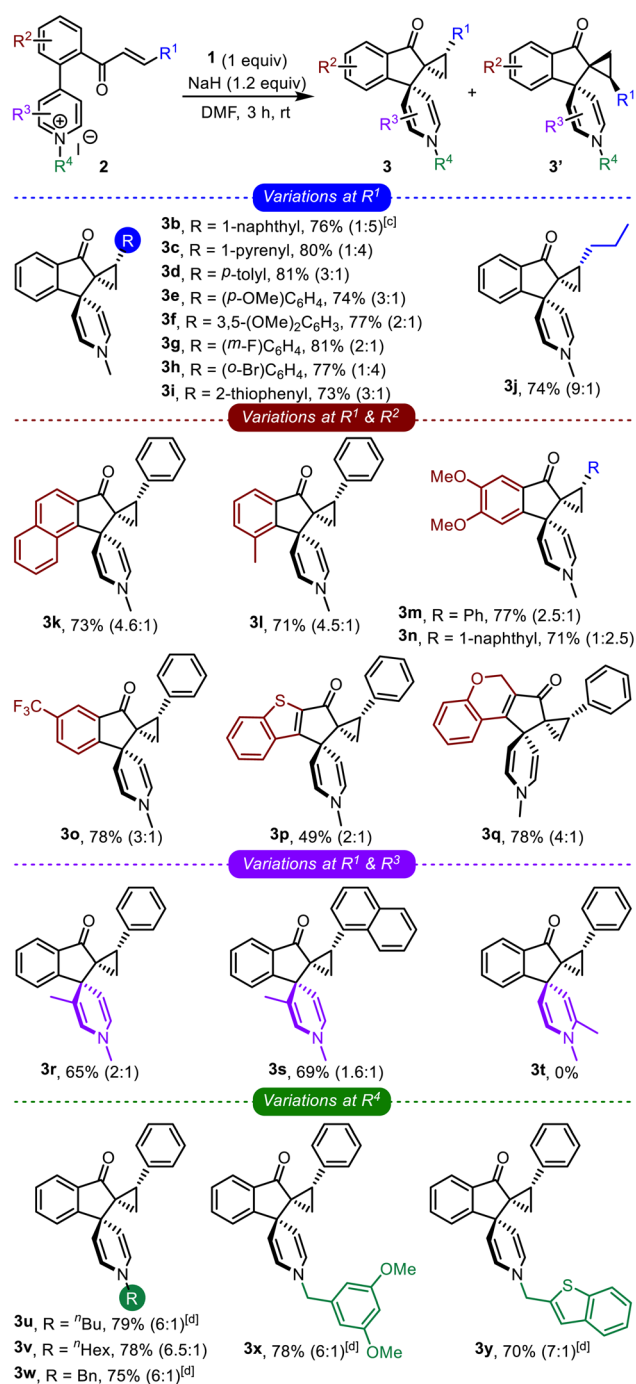
Different types of arenes possessing electron-donating as well as electron-withdrawing groups (**3b–3h**), heteroarenes (**3i**),

Table 1 Optimisation of reaction parameters^a

Entry	2a		1 (1 equiv), base (1.2 equiv)		3a + 3a'
	solvent, rt				
Entry	Base	Solvent	Time (h)	Yield of 3 ^b [%]	
1	NaH	Acetamide	24	23	
2	NaH	MeCN	24	30	
3 ^c	NaH	DMF	3	86	
4 ^d	NaH	DMF	12	39	
5 ^e	NaH	DMF	3	75	
6 ^f	NaH	DMF	24	79	
7 ^g	NaH	DMF	24	76	
8	KO ^t Bu	DMF	24	15	
9	CS ₂ CO ₃	DMF	24	—	
10	K ₂ CO ₃	DMF	24	—	
11	DBU	DMF	24	—	
12	Guanidine	DMF	24	—	

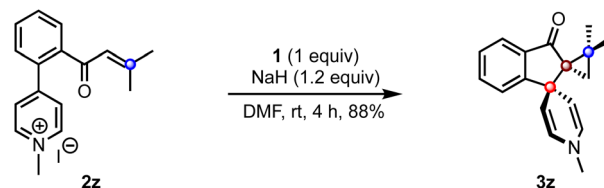
^a See the ESI for a detailed procedure. ^b Chromatographic yields. ^c Obtained in 3.5 : 1 diastereomeric ratio (dr). ^d At 0 °C. ^e At 60 °C. ^f In the presence of 1.5 equiv. of NaH. ^g In the presence of 2 equiv. of NaH.



Table 2 Substrate scope: vicinal bis-spirocyclic indanones^{a,b}

^a See the ESI for a detailed procedure. ^b Isolated yields after column chromatography. ^c The dr was estimated from the analysis of the crude ¹H-NMR data. ^d Bromide salts were used instead.

and even alkyl groups (3j) were well-tolerated on the enone functionality and generated the respective bis-spirocyclic indanones in good yields, Table 2. Next, the role of the substituents on the arene backbone was studied. To that extent, the reaction was found to be quite efficient with substrates bearing the naphthalene backbone (3k), electron-rich arenes (3l–3n), CF₃-

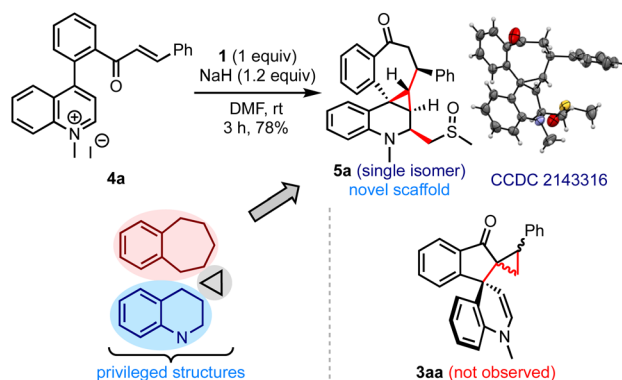
Scheme 4 The reaction of β,β -disubstituted enones to create three contiguous quaternary centers.

substituted arenes (3o), heteroarenes such as benzothiophene (3p), and also with a non-aromatic backbone (3q). Although we were apprehensive about the fate of the C-3 substituted pyridinium salts, the respective products were still obtained in good yields (3r and 3s). However, surprisingly, the reaction of C-2 substituted pyridinium salts did not generate the desired product (3t).

Subsequently, we also investigated the role of *N*-substituents on the course of the reaction, Table 2. Various linear and branched alkyl systems were well-tolerated, giving the respective products in good yields (3u–3y). We observed that the diastereoselectivity improved (to 7:1) with the longer alkyl substituents. Next, the role of the counter anion (bromide instead of iodide) was also verified (3u and 3w–3y) and realized to be insignificant. Overall, the comprehensive study of the impact of R¹, R², R³, and R⁴ revealed that the transformation is quite robust, broad in scope, and capable of accommodating substituents with distinct electronic and steric characters.

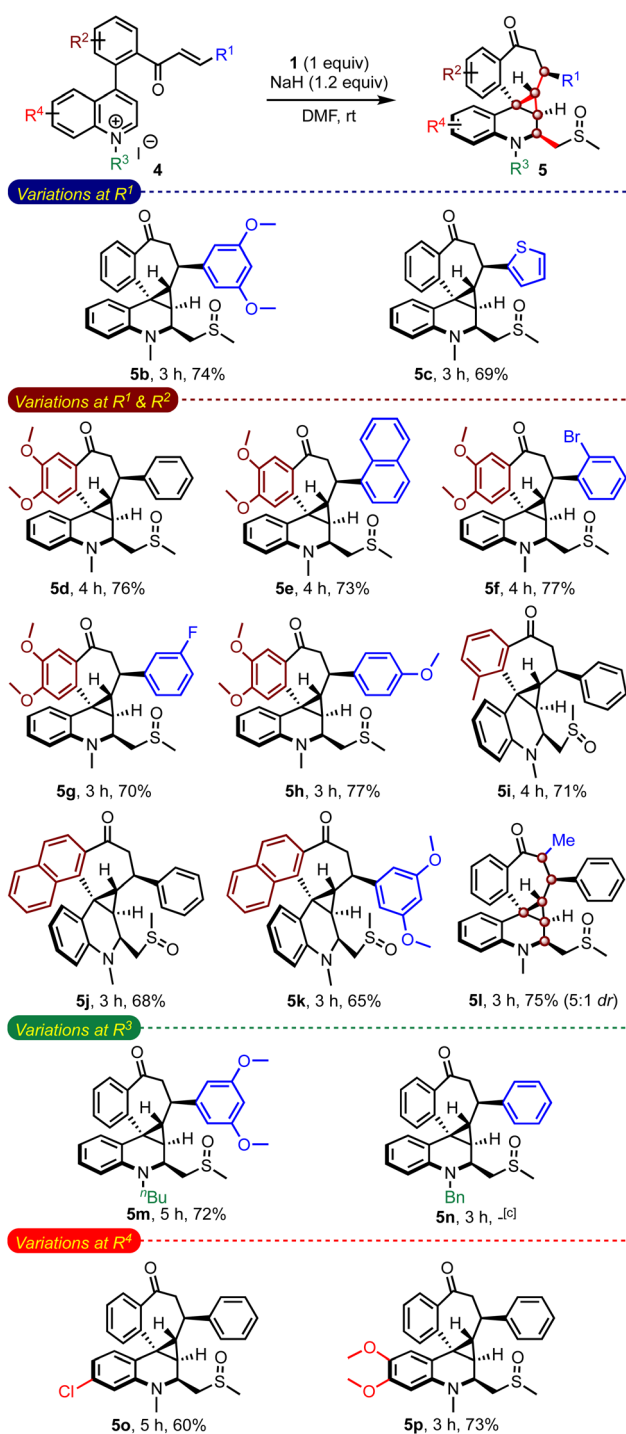
To extend the scope of the method, we attempted the reaction of the biaryl pyridinium salt possessing the β,β -disubstituted enone system (2z), Scheme 4. To our delight, the expected indanone 3z was isolated in good yield despite the steric encumbrance at the β -position. This result demonstrates the feasibility of creating three contiguous quaternary carbons, two of which are spiro centers.

While evaluating the substrate scope, we questioned whether the enone-tethered quinolinium salts such as 4a could be tolerated under the reaction conditions and generate the expected product 3aa, Scheme 5. Interestingly, the reaction of 4a



Scheme 5 An unexpected result obtained with enone-tethered quinolinium salts: access to a new class of polycyclic benzocycloheptanones.

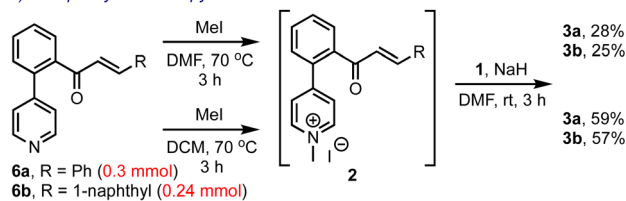


Table 3 Substrate scope: polycyclic benzocycloheptanones^{a,b}

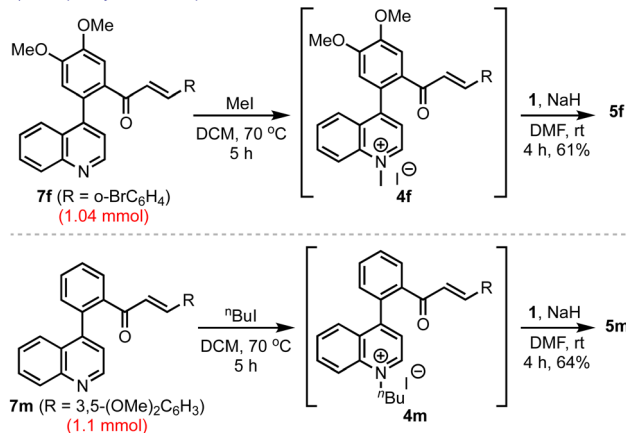
^a See the ESI for a detailed procedure. ^b Isolated yields after column chromatography. ^c The desired product was not observed.

and **1** under the optimized conditions delivered an unexpected product **5a** in 78% yield as a single isomer. The structure and the relative stereochemistry of **5a** were confirmed from the single-crystal X-ray diffraction analysis.¹² We were surprised by the formation of three new rings with an unusual 6-3-7 fusion,

a) One-pot synthesis of pyridinium salts and their reaction with DOSM



b) One-pot synthesis of quinolinium salts and their reaction with DOSM



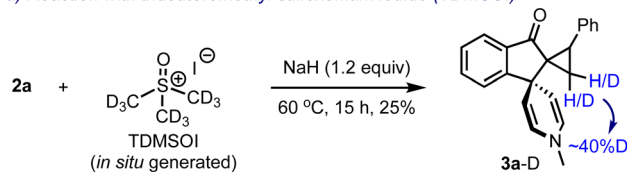
Scheme 6 One-pot synthesis of bis-spirocyclic indanones and spiro-fused benzocycloheptanones.

four new C-C bonds, five contiguous stereocenters, and a fully-substituted quinoline core incorporated with a methylene sulfoxide moiety in a simple one-step operation. The unprecedented pentacyclic scaffold **5** can be envisioned as a combination of (benzo)cycloheptanes, (tetrahydro)quinolines, and cyclopropanes, which are commonly encountered in several natural products and drug candidates.¹³ With the belief that this hybrid motif finds applications in devising novel classes of bioactive molecules and becomes a new template in drug discovery, we examined the generality of the method.

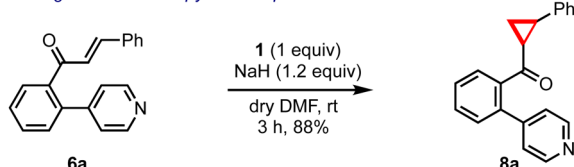
An evaluation of the substrate scope with an array of enone-tethered quinolinium salts **4** revealed the generality of the method in assembling a range of complex spiro-fused benzocycloheptanones **5b–5n**, Table 3.¹⁴ The role of the substituents on the enone moiety (R¹) and the arene backbone (R²), and *N*-substituents (R³) was studied in detail. For example, an arene ring with electron-donating methoxy groups at R¹ gave the expected product **5b** in good yield, although unfavourable for the initial Michael addition of the sulfur ylide. Even heteroarene moieties were also tolerated at R¹ (**5c**). We also evaluated the substrates with methoxy and methyl groups on the arene backbones (R²) while varying substituents at R¹ (**5d–5i**). All of them fared consistently well under the reaction conditions. Natural product-like hexacyclic benzocycloheptanone derivatives such as **5j** and **5k** could also be efficiently synthesized. Of particular interest, the reaction of α,β -substituted enone-quinolinium salt **4l** resulted in forming **5l** with six contiguous stereocenters. On the other hand, the reaction of the *n*-butyl quinolinium salt delivered the respective product **5m** in good yield, but the *N*-benzyl salt did not generate the expected



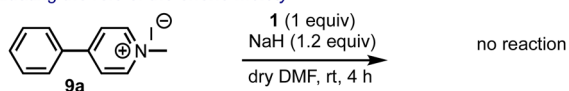
a) Reaction with trideuteromethyl sulfoxonium iodide (TDMSOI)



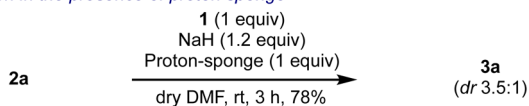
b) Evaluating the role of the pyridinium portion



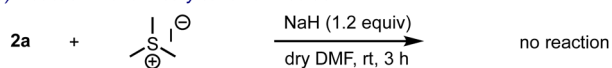
c) Evaluating the role of the enone moiety



d) Reaction in the presence of proton sponge



e) Reaction with trimethylsulfonium iodide



Scheme 7 Control experiments performed to gain mechanistic insights.

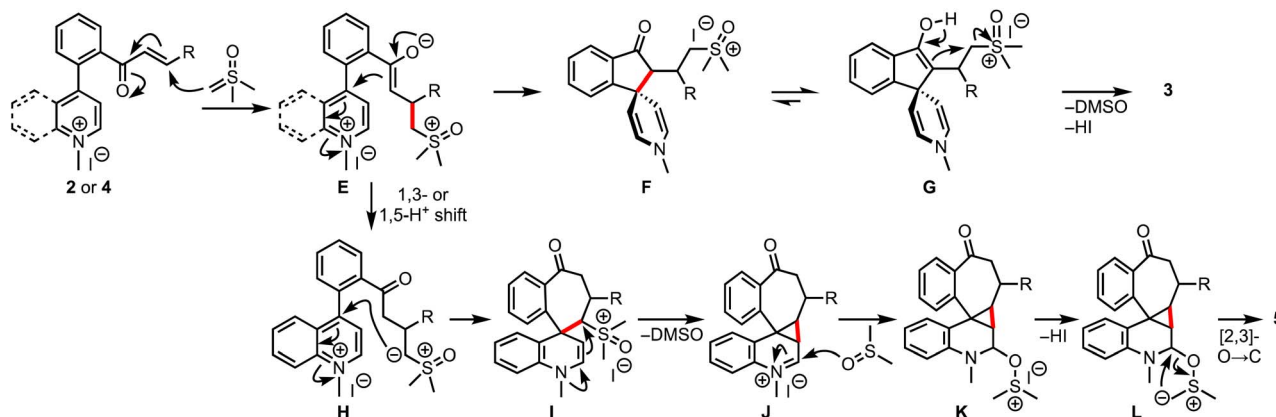
product **5n**. We also evaluated the role of substituents on the quinoline portion (R^4). Accordingly, we prepared complex pentacyclic structures with chloro (**5o**) and dimethoxy (**5p**) groups. A narrow yield range (60–77%) across a wide range of substrates is indicative of the robustness of the method.

Next, we intended to develop a one-pot synthesis of bis-spirocyclic indanones **3** starting from biaryl pyridine-enones **6**, avoiding the pre-formation of the salts **2**, Scheme 6. Accordingly, **6a** and **6b** were treated with methyl iodide in DMF. After ensuring their conversion to the respective pyridinium salts, **2a** and **2b**, they were treated with DOSM and obtained **3a** and **3b**, in

28% and 25% yields, respectively. However, when the salt-making step was performed in DCM, the overall yields improved significantly (to 59% and 57%, respectively). This was attributed to the high solubility of the pyridinium salts **2** in DCM. Subsequently, we extended this strategy to synthesizing spiro-fused benzocycloheptanones **5** in one-pot, starting from the respective biaryl quinolines **7**. Thus, **5f** and **5m** were obtained in 61% and 64% yields from **7f** and **7m**, respectively, even when performed on 1 mmol scales.

Prior to arriving at the plausible mechanistic pathways leading to the product formation, we conducted a few control experiments, Scheme 7. The reaction of **2a** was performed with an *in situ* generated trideuteromethyl sulfoxonium iodide (TDMSOI)¹⁵ and obtained the respective product **3a-D** with ~40% deuterium incorporation at the methylene group of the cyclopropane moiety, Scheme 7a. The simple biaryl pyridine-enone **6a**, when treated with DOSM, gave only the cyclopropylketone **8a**, Scheme 7b. Interestingly, the pyridinium salt **9a** lacking the enone portion remained as such under the reaction conditions, Scheme 7c. The reaction of **2a** was conducted in the presence of DOSM, and the proton sponge still generated **3a** in 78% yield, indicating that the reaction generated no acid and it was not responsible for facilitating any transformation, Scheme 7d. Finally, we also evaluated the reaction of **2a** with trimethylsulfonium iodide and sodium hydride, but surprisingly, it did not yield any product, Scheme 7e.

Based on the experimental results and control experiments, a plausible mechanism is proposed in Scheme 8. The reaction commences with the Michael addition of DOSM to **2** or **4**, leading to the formation of enolates **E**, which, in the case of pyridinium salts, react in an aldol fashion from the C-4 position to generate spiroindanones **F**.¹⁶ Eventually, the bis-spirocyclic indanones **3** are produced *via* enol-assisted displacement of the DMSO. On the other hand, in the case of quinolinium salts, a 1,3-/1,5-proton shift of **E** provides ylides **H**, which undergo C-4 addition to generate the key intermediate **I**. An enamine-assisted displacement of the DMSO follows the entrapment of iminium ions **J** with sulfoxide to form **K**. Subsequent [2,3]-O-to-C rearrangement of ylides **L** provides **5**.¹⁷

Scheme 8 Plausible mechanism for the formation of **3** and **5**.

Conclusions

We demonstrated an interrupted Corey–Chaykovsky reaction of designed enone-tethered azaarenium salts to access complex spiro- and fused cyclopropanoids, which are difficult to access *via* conventional synthetic transformations. This method also provided rapid and efficient access to structurally and electronically diverse unprecedented scaffolds such as vicinal bis-spirocyclic indanones **3** and spirannulated polycyclic benzocycloheptanones **5**. We also addressed several important questions surrounding the mechanism of the divergent pathways from detailed experimental studies. Some other salient features of this study are: (i) it represents the first stereoselective transformation of sulfoxonium ylides and pyridinium salts, and (ii) it establishes a new substrate-based folding pathway. The synthetic methods described herein hold great potential and will stimulate further research in synthesizing novel carbo- and heterocycles from easily accessible pyridine derivatives. Efforts to extend the concepts to new substrate classes are in progress, and the details will be communicated in due course.

Data availability

Data supporting this article have been uploaded as ESI.†

Author contributions

B. S. and A. J. A. conducted the investigation under S. S. V. R.'s supervision. B. S., A. J. A. and S. S. V. R. wrote the manuscript. B. S., A. J. A. and N. M. prepared the ESI.† All authors contributed to the editing and revision of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank IISER Mohali for the NMR, mass spectrometry, and X-ray facilities. S. S. V. R. thanks SERB for the Swarnajayanti fellowship (DST/SJF/CSA-01/2017–18) and IISER Mohali for funding. B. S. thanks UGC for a research fellowship and N. M. thanks the Ministry of Education for the Prime Minister's Research Fellowship (PMRF). A. J. A. thanks IISER Mohali for a postdoctoral fellowship.

Notes and references

- (a) B. R. Stockwell, *Nature*, 2004, **432**, 846–854; (b) M.-Q. Zhang and B. Wilkinson, *Curr. Opin. Biotechnol.*, 2007, **18**, 478–488; (c) S. L. Schreiber, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6699–6702; (d) Y. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673–3682; (e) S. E. Dalton and S. Campos, *ChemBioChem*, 2020, **21**, 1080–1100.
- (a) A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341–2372; (b) D. Kaiser, I. Klose, R. Oost, J. Neuhaus and N. Maulide, *Chem. Rev.*, 2019, **119**, 8701–8780; (c) P. Li, *Synlett*, 2021, **32**, 1275–1280.
- (a) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353; (b) Y. G. Gololobov, A. N. Nesmeyanov, V. P. Lysenko and I. E. Boldeskul, *Tetrahedron*, 1987, **43**, 2609–2615; (c) M. M. Heravi, S. Asadi, N. Nazari and B. M. Lashkariani, *Curr. Org. Synth.*, 2016, **13**, 308–333.
- Selected reviews: (a) S. Sowmiah, J. M. S. S. Esperança, L. P. N. Rebelo and C. A. M. Afonso, *Org. Chem. Front.*, 2018, **5**, 453–493; (b) F.-S. He, S. Ye and J. Wu, *ACS Catal.*, 2019, **9**, 8943–8960; (c) S. L. Rossler, B. J. Jelier, E. Magnier, G. Dagousset, E. M. Carreirs and A. Togni, *Angew. Chem., Int. Ed.*, 2020, **59**, 9264–9280.
- (a) M. W. Gribble, S. Guo and S. L. Buchwald, *J. Am. Chem. Soc.*, 2018, **140**, 5057–5060; (b) Y. Yang, C.-H. Xu, Z.-Q. Xiong and J.-H. Li, *Chem. Commun.*, 2020, **56**, 9549–9552; (c) C.-H. Xu, J.-H. Li, J.-N. Xiang and W. Deng, *Org. Lett.*, 2021, **23**, 3696–3700.
- For pyridine C4-carbospirannulations, see: (a) J. J. Eisch, C. A. Kovacs, P. Chobe and M. P. Boleslawski, *J. Org. Chem.*, 1987, **52**, 4427–4437; (b) T. Muramatsu, A. Toyota and M. Suzuki, *J. Am. Chem. Soc.*, 2005, **127**, 4572–4573; (c) G. Fraenkel, A. Chow, Y. Liang, J. Song and J. A. Gallucci, *Helv. Chim. Acta*, 2012, **95**, 2063–2071; (d) R.-J. Yan, B.-X. Xiao, Q. Ouyang, H.-P. Liang, W. Du and Y.-C. Chen, *Org. Lett.*, 2018, **20**, 8000–8003; (e) J. C. Abell, C. P. Bold, L. Vicens, T. Jentsch, N. Velasco, J. L. Tyler, R. N. Straker, A. Noble and V. K. Aggarwal, *Org. Lett.*, 2023, **25**, 400–404.
- For pyridine C4-heterospirannulations, see: (a) D. D. Weller, G. R. Luellen and D. L. Weller, *J. Org. Chem.*, 1983, **48**, 3061–3067; (b) J. Clayden, S. D. Hamilton and R. T. Mohammed, *Org. Lett.*, 2005, **7**, 3673–3676; (c) G. Arnott, H. Brice, J. Clayden and E. Blaney, *Org. Lett.*, 2008, **10**, 3089–3092; (d) S. G. Parameswarappa and F. C. Pigge, *Org. Lett.*, 2010, **12**, 3434–3437.
- Some interesting strategies to functionalize pyridinium salts, see: (a) J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642–2713; (b) O. G. Mancheno, S. Asmus, M. Zurro and T. Fischer, *Angew. Chem., Int. Ed.*, 2015, **54**, 8823–8827; (c) G. Bertuzzi, A. Sinisi, L. Caruana, A. Mazzanti, M. Fochi and L. Bernardi, *ACS Catal.*, 2016, **6**, 6473–6477; (d) G. Bertuzzi, L. Bernardi and M. Fochi, *Catalysts*, 2018, **8**, 632; (e) J. Lee, D. Ko, H. Park and E. J. Yoo, *Chem. Sci.*, 2020, **11**, 1672–1676; (f) H.-J. Miao, L.-L. Wang, H.-B. Han, Y.-D. Zhao, Q.-L. Wang and Z.-W. Bu, *Chem. Sci.*, 2020, **11**, 1418–1424; (g) X.-G. Bai, H.-J. Miao, Y. Zhao, Q.-L. Wang and Z.-W. Bu, *Org. Lett.*, 2020, **22**, 5068–5073; (h) X. Song, R.-J. Yan, W. Du and Y.-C. Chen, *Org. Lett.*, 2020, **22**, 7617–7621; (i) D. J. Robinson, S. P. Spurlin, J. D. Gordon and R. R. Karimov, *ACS Catal.*, 2020, **10**, 51–55; (j) T.-T. Li, Y. You, T.-J. Sun, Y.-P. Zhang, J.-Q. Zhao, Z.-H. Wang and W.-C. Yuan, *Org. Lett.*, 2022, **24**, 5120–5125; (k) L.-J. Gu, H.-B. Han, Z.-W. Bu and Q.-L. Wang, *Org. Lett.*, 2022, **24**, 2008–2013.
- X-ray crystallographic data of compounds **3a** and **3a'** are provided in the ESI. CCDC 2133525 (**3a**) and 2133527 (**3a'**).†



- 10 (a) W.-L. Chan, X. Tang, F. Zhang, G. Quek, G.-J. Mei and Y. Lu, *Angew. Chem., Int. Ed.*, 2019, **58**, 6260–6264; (b) J. Zhang, W.-L. Chan, L. Chen, N. Ullah and Y. Lu, *Org. Chem. Front.*, 2019, **6**, 2210–2214; (c) C. Wang, D. Wen, H. Chen, Y. Deng, X. Liu, X. Liu, L. Wang, F. Gao, Y. Guo, M. Sun, K. Wang and W. Yan, *Org. Biomol. Chem.*, 2019, **17**, 5514–5519; (d) W. Luo, B. Shao, J. Li, X. Xiao, D. Song, F. Ling and W. Zhong, *Org. Chem. Front.*, 2020, **7**, 1016–1021.
- 11 (a) M. Vilums, J. Heuberger, L. H. Heitman and A. P. Ijzerman, *Med. Res. Rev.*, 2015, **35**, 1097–1126; (b) T. T. Talele, *J. Med. Chem.*, 2016, **59**, 8712–8756; (c) A. Peneau, P. Retailleau, C. Guillou and L. Chabaud, *J. Org. Chem.*, 2018, **83**, 2324–2340; (d) M. M. Abdelshaheed, I. M. Fawzy, H. I. El-Subbagh and K. M. Youssef, *Future J. Pharm. Sci.*, 2021, **7**, 188–198.
- 12 X-ray crystallographic data of compounds **5a** is provided in the ESI. CCDC 2143316 (**5a**).†
- 13 (a) K. Kaur, M. Jain, R. P. Reddy and R. Jain, *Eur. J. Med. Chem.*, 2010, **45**, 3245–3264; (b) R. Musiol, K. Malarz and J. Mularski, *Curr. Org. Chem.*, 2017, **21**, 1896–1906; (c) J.-H. Fan, Y.-J. Hu, L.-X. Li, J.-J. Wang, S.-P. Li, J. Zhao and C.-C. Li, *Nat. Prod. Rep.*, 2021, **38**, 1821–1851; (d) A. Mondal, Shivangi, P. Tung, S. V. Wagulde and S. S. V. Ramasastry, *Chem. Commun.*, 2021, **57**, 9260–9263.
- 14 The lifetime of the products was found to be short (of the range of 5–8 days) even when refrigerated.
- 15 (a) Z. Shen, S. Zhang, H. Geng, J. Wang, X. Zhang, A. Zhou, C. Yao, X. Chen and W. Wang, *Org. Lett.*, 2019, **21**, 448–452; (b) M.-H. Zhu, C.-L. Yu, Y.-L. Feng, M. Usman, D. Zhong, X. Wang, N. Nesnas and W.-B. Liu, *Org. Lett.*, 2019, **21**, 7073–7077.
- 16 Owing to design considerations, the reaction at C-2/C-6 position is highly unlikely.
- 17 A. Kobayashi, T. Matsuzawa, T. Hosoya and S. Yoshida, *Chem. Commun.*, 2020, **56**, 5429–5432.

