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Carbene-catalyzed enantioselective construction of a quasi-symmetrical spirocyclic hydroquinone with a minor chiral distinction†

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Constructing a nearly symmetrical chiral center with tiny chiral differences is a challenging task in asymmetric synthesis. The natural antibiotic fredericamycin A (FDM-A), a representative example, has a unique structure with a quasi-symmetrical spirocyclic hydroquinone and remains difficult to chemically synthesize. Herein we developed an *N*-heterocyclic carbene–catalyzed enantioselective hydroquinone formation reaction with desymmetrization of spirocyclic cyclopentene-1,3-diones to construct these challenging structures. Using our method, the asymmetric synthesis of FDM-A (previously requiring a 26-step or 32-step synthesis) was shortened to 11 steps. Several analogs of FDM-A were also readily made. Moreover, a more challenging all-carbon quaternary chiral center with minimal differences (H *vs.* D) in a remote position (6 atoms away from the chiral center) was also constructed to investigate the performance of the extremely weakly chiral small molecule.

Introduction

Fredericamycin A (FDM-A) was isolated from *Streptomyces griseus* (FCRC-48) by Pandey and co-workers in 1981 (Fig. 1a).[1a] It is a hexacyclic quinone-based natural product with a novel spiro [4.4] nonane ring, not previously observed in any antibiotic connected with naphthoquinone or isoquinoline aromatic moieties.[1b] The all-carbon quaternary chiral center in FDM-A is a unique symmetrical structure, whose chirality is enabled by a methoxy substituent in a remote position (6 atoms away from the chiral carbon center). The biosynthesis of natural FDM-A probably relies on an enzymatic asymmetric epoxidation of the highly symmetrical benastatin core and the following stereospecific transformations.[2] In comparison, the asymmetric chemical synthesis of this symmetrical chiral structure is much more challenging (Fig. 1b). Although several different strategies,[3a] including the aldol reaction,[3b,c] radical cyclization,[3d–g] Diels–Alder reaction,[3h,i] Tamura annulation[3j,k] and Hauser–

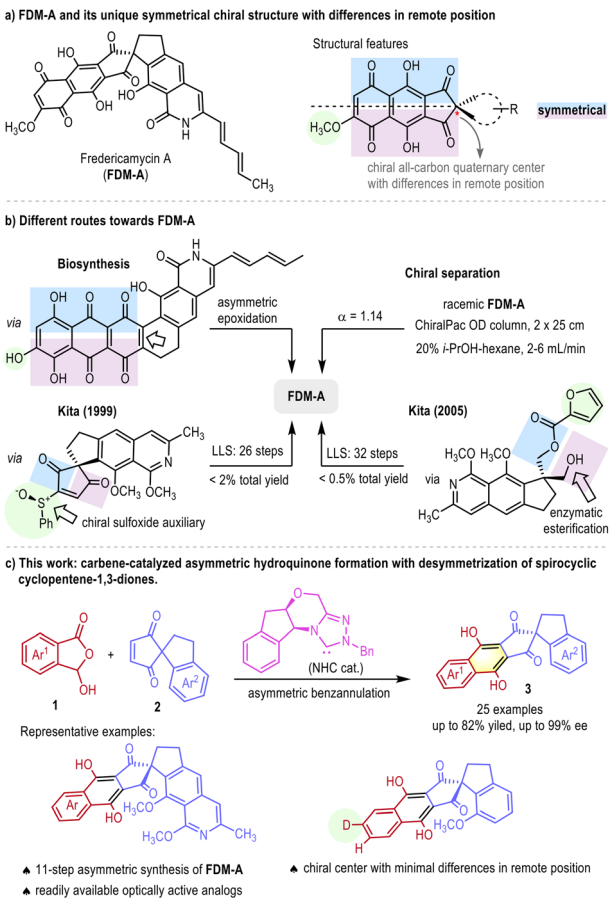

Fig. 1 Enantioselective construction of quasi-symmetrical spirocyclic hydroquinone with a minor chiral distinction.

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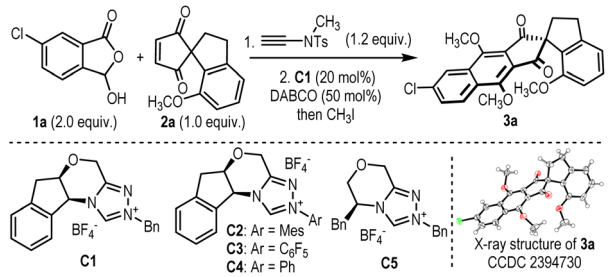
Kraus annulation[3l,m] have been applied in the total synthesis of FDM-A since the 1990s, few of them can achieve the desired enantioselective control. In 1995, Boger and coworkers obtained both enantiomers by conducting a chiral separation of racemic FDM-A, but with a low separation factor ($\alpha = 1.14$).[3c] The only two examples of asymmetric synthesis of FDM-A were reported by the Kita group, involving a 26-step (longest linear sequence, LLS) synthesis with a chiral sulfoxide auxiliary in 1999,[3j,k] and a 32-step (LLS) synthesis with enzymatic esterification and enantiospecific transformations in 2005.[3i] In comparison to the racemic synthesis, tedious steps (>15 steps) were required to achieve the enantioselective control. Our research group has continuous interest in building sophisticated aromatic cycles with asymmetric benzannulation.[4] Herein we developed a carbene-catalyzed asymmetric hydroquinone formation reaction to synthesize this symmetrical structure with small differences in a remote position by desymmetrization of spirocyclic dienophiles. An 11-step (LLS) synthesis of FDM-A as well as facile synthesis of FDM-A analogs were achieved. Moreover, we obtained a more challenging structure with only H/D differences in the remote position, which can hardly be identified even in the enzyme catalysis or chiral separation.

Results and discussion

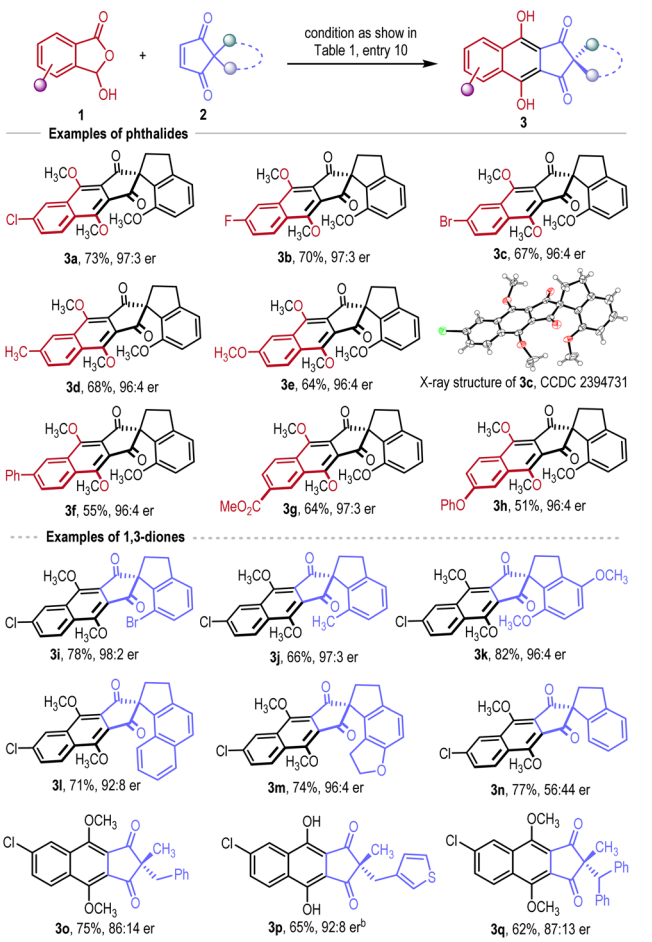
Our present study commenced with the 6-chloro phthalide **1a** and spirocyclic 1,3-cyclopentenedione **2a** (ref. 5) (spirocyclic core of FDM-A) used as model substrates (Table 1). With MYTsA (*N*-methylynetoluenesulfonamide)[6] as the coupling reagent, triazolium salt **C1** (ref. 4b) as the precatalyst, DABCO as the base and CH_3CN as the solvent, the reaction proceeded smoothly at room temperature and furnished the product **3a** in 65% yield with a 96 : 4 enantiomeric ratio (er) (Table 1, entry 1). Control tests showed that the absence of NHC catalyst or coupling reagent each totally deactivated the reaction (entry 2). Note the considerable difference between catalyst chosen in our reaction and the traditional examples for asymmetric NHC-organocatalysis.[7] *N*-Aryl-substituted triazolium salts such as **C2** (ref. 4a and 8) or **C3**,[9] which have been widely applied in asymmetric NHC-organocatalysis, were totally inactive in our reaction (entry 3). *N*-Phenyl triazolium catalyst **C4** (ref. 10) showed acceptable enantioselectivity but with only 8% yield (entry 4). *N*-Benzyl triazolium salts, while easily synthesized from S_N2 alkylation of triazole, were normally considered as unsuitable catalysts for asymmetric reactions[11] due to the lack of sufficient steric hindrance. Possibly due to the relatively crowded transition state with the phthalide-type Breslow intermediate, the reaction showed remarkable enantioselectivity when we used the *N*-benzyl triazolium catalyst. Another *N*-benzyl catalyst, namely **C5**, also gave the desired product in good yield but with lower er

Table 1 Optimization of the conditions[a]



Entry	Variation of conditions	Yield[a,b] (%)	e.r[c]
1	None	65%	96 : 4
2	w/o MYTsA or NHC	0	—
3	**C2** or **C3** instead of **C1**	Trace	—
4	**C4** instead of **C1**	8%	96 : 4
5	**C5** instead of **C1**	62%	75 : 25
6	DBU instead of DABCO	58%	93 : 7
7	Cs_2CO_3 instead of DABCO	63%	95 : 5
8	CH_2Cl_2 instead of CH_3CN	54%	91 : 9
9	0 °C instead of 25 °C	64%	97 : 3
10[d]	with 100 mg 4 Å MS	73%	97 : 3

[a] Conditions: (1) **1a** (0.2 mmol), MYTsA (0.24 mmol), CH_2Cl_2 (1 mL), 25 °C, 0.5 h. (2) **2a** (0.1 mmol), **C1** (20 mol%), DABCO (50 mol%), CH_3CN (2 mL), 25 °C, 24 h. (3) CH_3I (0.24 mmol), K_2CO_3 (0.24 mmol), DMF (1 mL), 25 °C, 2 h. [b] Yield of isolated product. [c] Determined using chiral SFC analysis. [d] Reaction performed at 0 °C.

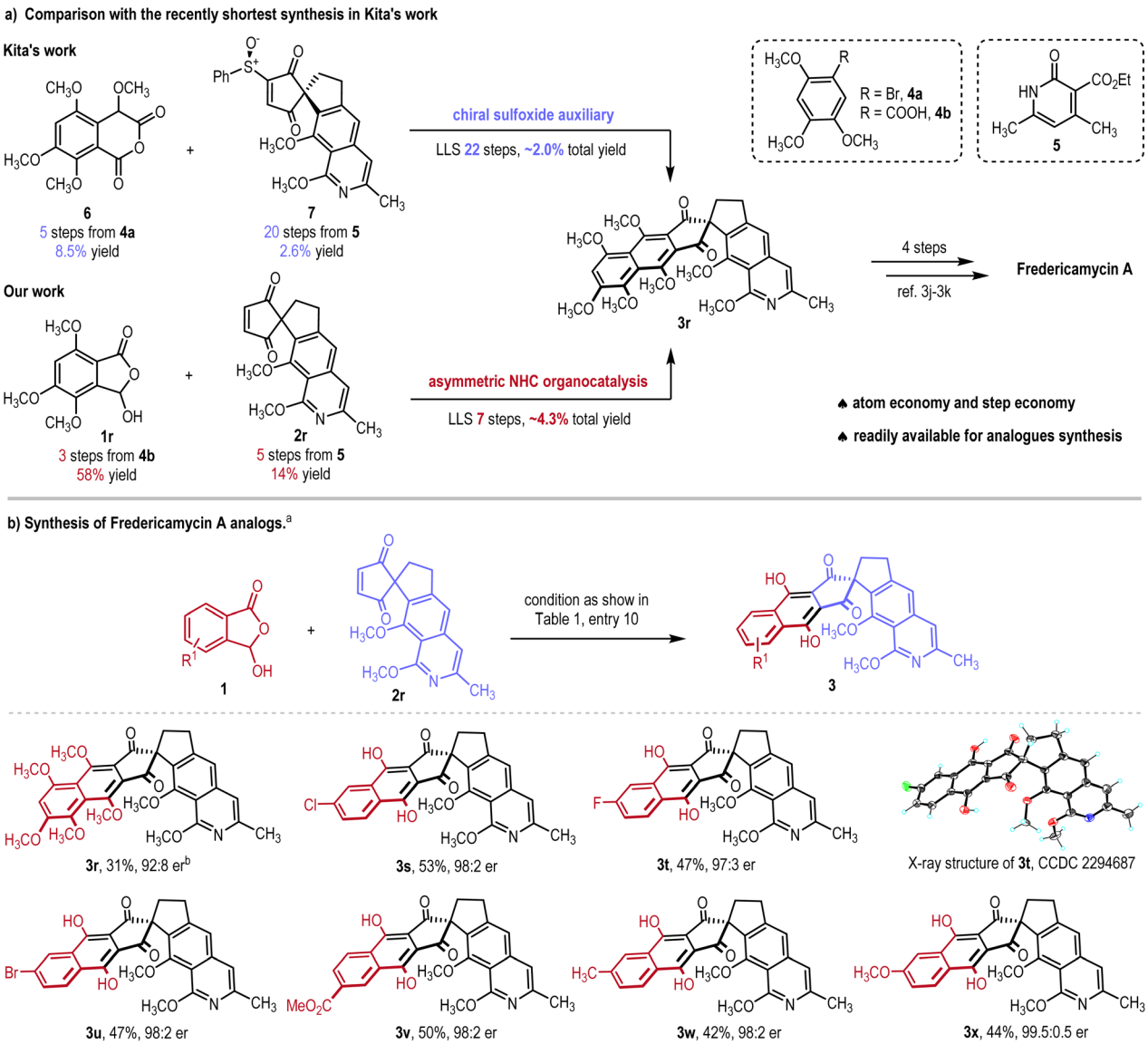


Scheme 1 Substrates scope [a]All yields are isolated yields and the er values were determined from the results of chiral SFC analysis. [b]Without methylation.

(entry 5). Reactions with other bases such as DBU (entry 6) or Cs_2CO_3 (entry 7) showed slightly lower yields and enantioselectivities. Other solvents such as CH_2Cl_2 gave inferior results (entry 8, see the ESI† for details). Performing the reaction at 0 °C instead of 25 °C resulted in a slight enhancement of enantioselectivity (entry 9). Finally, the use of 4 Å molecular sieves to maintain a more anhydrous environment gave the optimized results, affording **3a** in a 73% yield with a 97 : 3 er (entry 10).

With the optimized conditions in hand, we next turned our attention to examine the scope of the reaction (Scheme 1). First, we evaluated the scope of 3-hydroxyl phthalides by using **2a** as a model substrate. Halogenation (products **3a–3c**), methylation (product **3d**), methoxylation (product **3e**), and phenylation (product **3f**) in the 6-position of phthalides were all well tolerated, affording the desired products **3a–3f** in moderate to good yields (55–73%) with excellent enantioselectivities (96 : 4–97 : 3 er). The absolute configurations of **3a** and **3c** were unambiguously confirmed from the results of single-crystal X-ray diffraction analysis. 5-Substituted phthalides with the electron-withdrawing carbonyl group (product **3g**) or electron-donating phenyloxy group (product **3h**) were also applicable substrates in our reaction, giving similar good results in both yields and enantioselectivities (51–64% yield, 96 : 4–97 : 3 er).

Using **1a** as a model phthalide substrate, the scope of the 1,3-cyclopentenediones was also evaluated. Replacing the methoxy group of **2a** with a bigger bromo group led to a slightly enhanced enantioselectivity (product **3i**, 98 : 2 er), while replacement with a methyl group gave product **3j** in 66% yield with 97 : 3 er. Introducing a *para*-methoxy substitution in **2a** gave product **3k** in 82% yield with 96 : 4 er. Replacing the phenyl ring of **2a** with a naphthyl unit (product **3l**) and dihydrobenzofuranyl unit (product **3m**) also afforded the desired



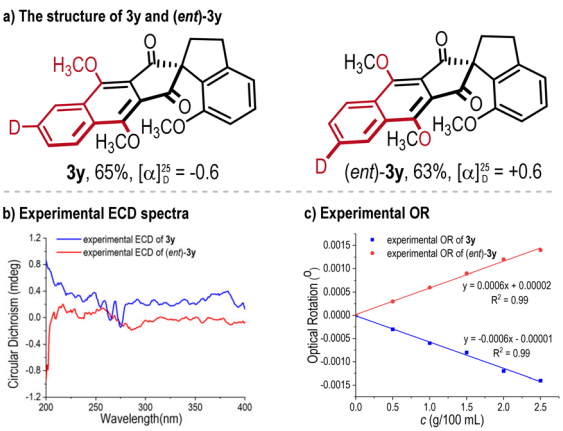
Scheme 2 Asymmetric synthesis of fredericamycin A and its analogs. [a]Unless otherwise specified, all the reactions were conducted without methylation. [b]See the ESI† for details.

products with good results (71–74%, 92 : 8–96 : 4 er). The rigid spirocyclic structure and substitution maintaining the enantiofacial differences are very important for the enantioselectivity of our reaction. Removing the methoxy group in **2a** led to a sharp decline in enantioselectivity (product **3n**, 56 : 44 er). The more flexible 2,2-dialkyl 1,3-cyclopentenediones all gave products with reduced enantioselectivities (products **3o–3q**, 86 : 14–92 : 8 er).

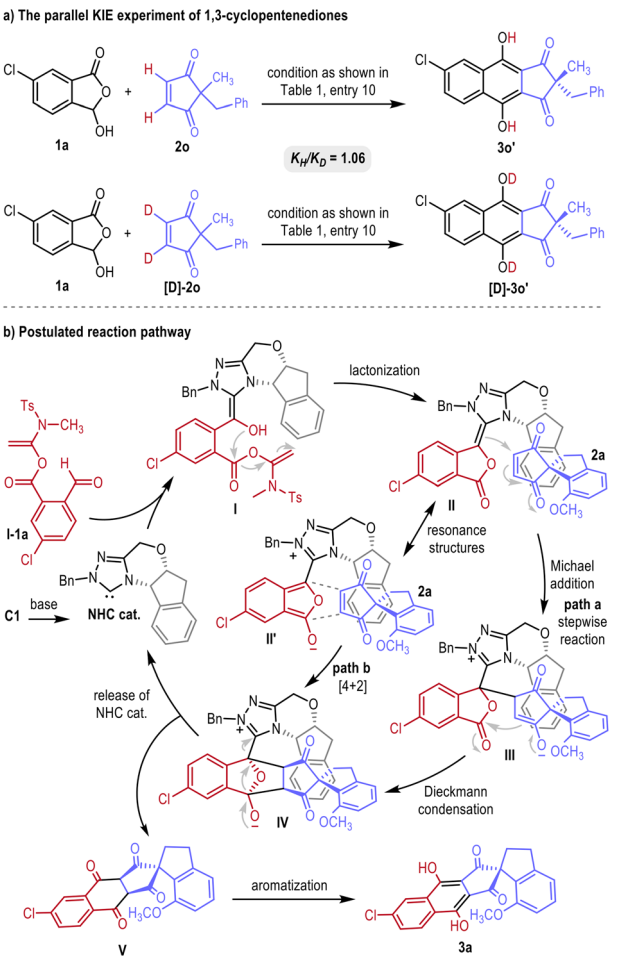
Encouraged by the general good performance of our method as shown in Scheme 1, we turned our attention to the total synthesis of FDM-A. As shown in Scheme 2, the previously shortest synthesis of FDM-A, reported by Kita, relied on a Tamura annulation of the anhydride **6** and the chiral sulfoxide-auxiliary–attached dienophile **7**. The anhydride **6** required a 5-step synthesis from **4a** (8.5% yield), and the dienophile **7** required a 20-step synthesis from **5** (2.6% total yield).[3j,k] In our synthesis, phthalide **1r** can be obtained with a 3-step synthesis from **4b** and the yield was found to be nearly 7 times higher than that of the synthesis of **6** (58% total yield). In comparison to the synthesis of dienophile **7**, from the same starting material **5**, our synthesis of dienophile **2r** only required one-fourth of the synthetic steps (5 steps) and gave more than 5 times the yield (14% yield). Overall, the key intermediate **3r** was successfully obtained in 7 LLS steps with 4.3% total yield, that is fewer than one-third of the synthetic steps and more than twice the yield than those in the synthesis by Kita. The key intermediate **3r** for the synthesis of FDM-A was also reported in the 4-step synthesis in the work by Kita.[3j,k] Notably, with dienophile **2r** as a model substrate, a variety of FDM-A analogs (**3s–3x**) were afforded in moderate yields (42–53%) with excellent enantioselectivities (97 : 3–99.5 : 0.5 er). The absolute configuration of **3t** was unambiguously confirmed from the results of single-crystal X-ray diffraction analysis.

Recognizing tiny differences between prochiral substrates for the construction of symmetrical chiral centers is a challenging task in asymmetric organic synthesis.[12] To achieve an extremely symmetrical chiral structure with minimal differences, the chloro group of **1a** was replaced with a deuterium atom in our reaction, giving the interesting product **3y** in 65% yield. As shown in Scheme 3a, the only difference to ensure the all-carbon quaternary chiral center was the difference between hydrogen and deuterium 6 atoms away from the chiral center. Using different enantiomers of the NHC catalyst, both enantiomers of **3y** were obtained with similar enantioselectivities. Based on substitutions in compound **1** only slightly influencing the enantioselectivity (Scheme 1, products **3a–3h**, 92%∼94% ee), **3y** should be obtained in about 92% ee. However, the exact ee of **3y** was not confirmed as no chiral-stationary column can separate the two enantiomers. No obvious signal was observed in the ECD spectra of the two enantiomers (Scheme 3b). Only optical rotation provided evidence to recognize the chirality of **3y**. The optical rotations of **3y** and its enantiomer each at various concentrations were measured, and good linear relationships were found (R^2 > 0.99), showing a reliable specific rotation of 0.6 (Scheme 3c). Our method thus can readily provide both enantiomers of the extremely weakly chiral compounds with minimal differences in remote position as challenging examples in chiral separation and chirality measurement.

To better understand the mechanism of the carbene-catalyzed hydroquinone formation reaction, a kinetic isotope effect (KIE) experiment was conducted and the result is shown



Scheme 3 Quasi-symmetrical spirocyclic structure with minor chiral distinction.



Scheme 4 Proposed mechanism.

in Scheme 4a. The parallel KIE experiment revealed a secondary KIE ($k_H/k_D = 1.06$), showing the breaking of the C–H bond to not be the rate-determining step (but probably a fast step). The postulated pathway of carbene-catalyzed hydroquinone formation reaction is illustrated in Scheme 4b. Briefly, the reaction starts with the formation of Breslow intermediate **I** *via* nucleophilic addition of the carbene catalyst to the aldehyde group. The following lactonization step forms the phthalide-type Breslow intermediate **II** (see ESI† for details of the phthalide-type Breslow intermediate),[13] which has a resonance structure **II′**. The annulation may carry on *via* a stepwise Michael addition and Dieckmann condensation from intermediate **II** to intermediate **IV** (path a, Scheme 4b),[14] or *via* a concerted [4 + 2] annulation from intermediate **II′** to **IV** (path b, Scheme 4b).[15] During the annulation process, the chiral indane moiety favors the less steric hindered part and realizes the enantioselective control. The release of carbene catalyst from intermediate **IV** gives intermediate **V** and finally a rapid aromatization process with rapid C–H bond breaking gives the hydroquinone product **3a**.

Conclusions

We have developed an NHC organocatalytic strategy for the enantioselective construction of spirocyclic hydroquinones bearing an all-carbon quaternary chiral center with small differences in a remote position. 3-Hydroxy phthalides were used as easily accessible starting materials and reacted with the prochiral spirocyclic dienophiles to afford the desired hydroquinone products in moderate to good yields with excellent enantioselectivities. Unlike the normal NHC organocatalytic model involving the Breslow intermediate, the annulation described in this manuscript involving the phthalide-type Breslow intermediate was found to favor the *N*-benzyl triazolium salts rather than the *N*-aryl ones. The *N*-benzyl triazolium salts were found to be easier to synthesize *via* simple alkylation of triazole, facilitating the building of a catalyst library for future investigations. With the help of this powerful method, the facile synthesis of FDM-A was achieved, shortening the synthetic route from 26 steps to 11 steps. Several analogs of FDM-A were readily synthesized as well. A more challenging quasi-symmetrical spirocyclic structure with only differences of hydrogen and deuterium was also successfully synthesized to investigate the special performance of "weak" chirality.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data [for compounds **3a**, **3c** and **3t**] have been deposited at the CCDC [under CCDC 2294687 and 2394730–2394731] and can be obtained from **https://www.ccdc.cam.ac.uk**.

Author contributions

P. Ren conducted most of the experiments. Q. Zhao prepared the substrates for the synthesis of fredericamycin A. Additionally, Y. R. Chi and T. Zhu conceptualized and directed the project, and drafted the manuscript with the assistance of all co-authors. All authors contributed to discussions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) R. C. Pandey, M. W. Toussaint, R. M. Stroshane, C. C. Kalita, A. A. Aszalos, A. L. Garretson, T. T. Wei, K. M. Byrne, R. F. Geoghegan and R. J. White, *J. Antibiot.*, 1981, **34**, 1389–1401; (*b*) D. J. Warnick-Pickle, K. M. Byrne, R. C. Pandey and R. J. White, *J. Antibiot.*, 1981, **34**, 1402–1407.

2 (*a*) K. M. Byrne, B. D. Hilton, R. J. White, R. Misra and R. C. Pandey, *Biochemistry*, 1985, **24**, 478–486; (*b*) E. Wendt-Pienkowski, Y. Huang, J. Zhang, B. Li, H. Jiang, H. Kwon, C. R. Hutchinson and B. Shen, *J. Am. Chem. Soc.*, 2005, **127**, 16442–16452; (*c*) Y. Chen, Y. Luo, J. Ju, E. Wendt-Pienkowski, E. S. R. Rajski and B. Shen, *J. Nat. Prod.*, 2008, **71**, 431–437; (*d*) Y. Chen, E. Wendt-Pienkowski and B. Shen, *J. Bacteriol.*, 2008, **190**, 5587–5596; (*e*) A. Das, P. H. Szu, J. T. Fitzgerald and C. Khosla, *J. Am. Chem. Soc.*, 2010, **132**, 8831–8833; (*f*) P. H. Szu, S. Govindarajan, M. J. Meehan, A. Das, D. D. Nguyen, P. C. Dorrestein, J. Minshull and C. Khosla, *Chem. Biol.*, 2011, **18**, 1021–1031; (*g*) B. Tsakem, G. Li and R. B. Teponno, *Bioorg. Chem.*, 2024, **150**, 107572.

3 Several different strategies in the total synthesis of FDM-A, see: (*a*) S. Kotha and A. Fatma, *Asian J. Org. Chem.*, 2021, **10**, 129–148; (*b*) T. R. Kelly, S. H. Bell, N. Ohashi and R. J. Armstrong-Chong, *J. Am. Chem. Soc.*, 1988, **110**, 6471–6480; (*c*) D. L. Boger, O. Hueter, K. Mbiya and M. Zhang, *J. Am. Chem. Soc.*, 1995, **117**, 11839–11849; (*d*) D. L. J. Clive, Y. Tao, A. Khodabocus, Y. Wu, A. G. Angoh, S. M. Bennett, C. N. Boddy, L. Bordeleau, D. Kellner, G. Kleiner, D. S. Middleton, C. J. Nichols, S. R. Richardson and P. G. Vernon, *J. Chem. Soc. Chem. Commun.*, 1992, 1489–1490; (*e*) D. L. J. Clive, Y. Tao, N. Khodabocus, Y. Wu, A. G. Angoh, S. M. Bennett, C. N. Boddy, L. Bordeleau, D. Kellner, G. Kleiner, D. S. Middleton, C. J. Nichols, S. R. Richardson and P. G. Vernon, *J. Am. Chem. Soc.*, 1994,

116, 11275–11286; (*f*) A. V. R. Rao, A. K. Singh, B. V. Rao and K. M. Reddy, *Tetrahedron Lett.*, 1993, **34**, 2665–2668; (*g*) A. V. R. Rao, A. K. Singh, B. V. Rao and K. M. Reddy, *Heterocycles*, 1994, **37**, 1893–1912; (*h*) Y. Kita, K. Lio, K. Kawaguchi, N. Fukuda, Y. Takeda, H. Ueno, R. Okunaka, K. Higuchi, T. Tsujino, H. Fujioka and S. Akai, *Chem.–Eur. J.*, 2000, **6**, 3897–3905; (*i*) S. Akai, T. Tsujino, N. Fukuda, K. Iio, Y. Takeda, K. Kawaguchi, T. Naka, K. Higuchi, E. Akiyama, H. Fujioka and Y. Kita, *Chem.–Eur. J.*, 2005, **11**, 6286–6297; (*j*) Y. Kita, K. Higuchi, Y. Yoshida, K. Iio, S. Kitagaki, S. Akai and H. Fujioka, *Angew. Chem., Int. Ed.*, 1999, **38**, 683–686; (*k*) Y. Kita, K. Higuchi, Y. Yoshida, K. Iio, S. Kitagaki, K. Ueda, S. Akai and H. Fujioka, *J. Am. Chem. Soc.*, 2001, **123**, 3214–3222; (*l*) J. A. Wendt, P. J. Gauvreau and R. D. Bach, *J. Am. Chem. Soc.*, 1994, **116**, 9921–9926; (*m*) F. X. Wang, J. L. Yan, Z. Liu, T. Zhu, Y. Liu, S. C. Ren, W. X. Lv, Z. Jin and Y. R. Chi, *Chem. Sci.*, 2021, **12**, 10259–10265.

4 (*a*) K. Xu, W. Li, S. Zhu and T. Zhu, *Angew. Chem., Int. Ed.*, 2019, **58**, 17625–17630; (*b*) P. Ren, Q. Zhao, K. Xu and T. Zhu, *ACS Catal.*, 2024, **14**, 13195–13201.

5 (*a*) S. M. Bennett and D. L. J. Clive, *J. Chem. Soc. Chem. Commun.*, 1986, **11**, 878–880; (*b*) C. Wu, Z. Chang, C. Peng, C. Bai, J. Xing and X. Dou, *Chem. Sci.*, 2023, **14**, 7980–7987.

6 (*a*) L. Hu, S. Xu, Z. Zhao, Y. Yang, Z. Peng, M. Yang, C. Wang and J. Zhao, *J. Am. Chem. Soc.*, 2016, **138**, 13135–13138; (*b*) S. Xu, D. Jiang, Z. Peng, L. Hu, T. Liu, L. Zhao and J. Zhao, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212247; (*c*) L. Hu and J. Zhao, *Acc. Chem. Res.*, 2024, **57**, 855–869.

7 For selected reviews on NHC catalysis, see:(*a*) M. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485–496; (*b*) D. M. Flanigan, F. Romanov-Michailidis, N. A. White and T. Rovis, *Chem. Rev.*, 2015, **115**, 9307–9387; (*c*) R. S. Menon, A. T. Biju and V. Nair, *Chem. Soc. Rev.*, 2015, **44**, 5040–5052; (*d*) K. J. R. Murauski, A. A. Jaworskia and K. A. Scheidt, *Chem. Soc. Rev.*, 2018, **47**, 1773–1782; (*e*) A. T. Biju, in *N-Heterocyclic Carbenes in Organocatalysis.*,ed. A. T. Biju, Wiley-VCH Verlag GmbH & Co. KGaA, 2019; (*f*) X. Chen, H. Wang, Z. Jin and Y. R. Chi, *Chin. J. Chem.*, 2020, **38**, 1167–1202; (*g*) X. Chen, Z. Gao and S. Ye, *Acc. Chem. Res.*, 2020, **53**, 690–702; (*h*) P. Bellotti, M. Koy, M. N. Hopkinson and F. Glorius, *Nat. Rev. Chem*, 2021, **5**, 711–725; (*i*) R. Song, Y. Xie, Z. Jin and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2021, **60**, 26026–26037; (*j*) A. Ghosh and A. T. Biju, *Angew. Chem., Int. Ed.*, 2021, **60**, 13712–13724; (*k*) B. Zhang, G. Yang, D. Guo and J. Wang, *Org. Chem. Front.*, 2022, **9**, 5016–5040; (*l*) Y. Nakano, J. T. Maddigan-Wyatt and D. W. Lupton, *Acc. Chem. Res.*, 2023, **56**, 1190–1203.

8 M. He, J. R. Struble and J. W. Bode, *J. Am. Chem. Soc.*, 2006, **128**, 8418–8420.

9 (*a*) M. S. Kerr and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 8876–8877; (*b*) X. Yang, L. Wei, Y. Wu, L. Zhou, X. Zhang and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2022, e202211977.

10 (*a*) M. S. Kerr, J. R. Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 10298–10299; (*b*) T. Jian, L. He, C. Tang and S. Ye, *Angew. Chem., Int. Ed.*, 2011, **50**, 9104–9107; (*c*) Q. Wang, S. Wu, J. Zou, X. Liang, C. Mou, P. Zheng and Y. R. Chi, *Nat. Commun.*, 2023, **14**, 4878.

11 (*a*) D. Enders, J. Han and A. Henseler, *Chem. Commun.*, 2008, 3989–3991; (*b*) D. Enders and J. Han, *Synthesis*, 2008, **23**, 3864–3868; (*c*) P. Shao, X. Chen and S. Ye, *Angew. Chem., Int. Ed.*, 2010, **49**, 8412–8416; (*d*) L. Sun, Z. Liang, W. Jia and S. Ye, *Angew. Chem., Int. Ed.*, 2013, **52**, 5803–5806.

12 (*a*) H. Zhou, Y. Zhou, H. Y. Bae, M. Leutzsch, Y. Li, C. K. De, G. Cheng and B. List, *Nature*, 2022, **605**, 84–89; (*b*) M. Wang, S. Liu, H. Liu, Y. Wang, Y. Lan and Q. Liu, *Nature*, 2024, **631**, 556–562.

13 M. Sharique and U. K. Tambar, *Chem. Sci.*, 2020, **11**, 7239–7243.

14 (*a*) F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, 1978, **43**, 178–180; (*b*) G. A. Kraus and H. Sugimoto, *Tetrahedron Lett.*, 1978, **19**, 2263–2266.

15 J. C. Evans, R. C. Klix and R. D. Bach, *J. Org. Chem.*, 1988, **53**, 5519–5527.