



Catalytic enantioselective synthesis of chiral tetraarylmethanes

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While synthetic chemistry has experienced substantial development in the past century, challenges still remain to fully satisfy the needs in drug development. A bias in sampling linear and disc-shaped molecules in drug discovery over spherical ones has existed due to the lack of efficient access to the latter chemical space. Specifically, efficient strategies to synthesize tetraarylmethanes, a unique family of spherical molecules, has remained scarce. In particular, there has been essentially no efficient asymmetric synthesis of chiral tetraarylmethanes due to the overwhelming steric congestion and challenging stereocontrol encountered in assembly of the all-aryl-substituted quaternary stereocentre. Here we disclose an efficient catalytic synthesis of chiral tetraarylmethanes with high enantioselectivity via a stereoconvergent formal nucleophilic substitution reaction. Control experiments and density functional theory calculations provided strong support on hydrogen bonding interactions as the key elements to successful stereocontrol. The obtained enantioenriched products showed impressive preliminary anticancer activities.

Synthetic chemistry has greatly enabled discovery and innovation in pharmaceutical, materials and other industries^{1,2}. However, despite substantial development in the past century, modern synthetic chemistry is still not perfect or mature enough. For example, the lack of robust and straightforward synthetic methods has limited the thorough sampling of the chemical space in drug discovery efforts^{2,3}. A strong bias towards linear and disc-shaped molecules has been observed in drug molecules. By contrast, spherical molecules have been much less exploited due to the lack of efficient access (Fig. 1a)³.

The properties of a molecule can be influenced by its shape to some degree. Thus, enhancing the ability of synthetic chemistry to access the less explored spherical chemical space would have a strong impact on decoding the full potential of such a large family of molecules. Tetraarylmethanes represent such a unique family of spherical molecules. Their unusual geometry bestows them with special properties, allowing applications in different areas, such as optoelectronic devices, functional materials, drug delivery and protein translocation detection^{4–12}. Consequently, substantial efforts have been devoted to their synthesis, dating back to the 1930s (refs. 13–19). However, the general synthesis of these molecules remains elusive today^{20–24}. For instance, chiral tetraarylmethanes (CTAMs), which bear four different aryl groups with defined stereochemistry (Fig. 1b), remain a mystery due to the lack of efficient asymmetric synthesis.

The challenge in asymmetric synthesis of CTAMs lies in not only the high barrier in making the extremely congested C–C bond connecting the central carbon and the aryl rings by conventional strategies, but also the difficult stereodifferentiation between the existing and likely similar aryl rings when attaching a new aryl ring to the central carbon. Both are formidable tasks in organic synthesis, particularly in an acyclic intermolecular context^{25,26}. Consequently, there has been no direct strategy to construct the central C–C bond

in CTAMs with concomitant establishment of the quaternary stereogenic centre²⁷.

Herein we describe a catalytic asymmetric synthesis of tetraarylmethanes by chiral phosphoric catalysis. Starting from suitably tagged triarylmethanols, this protocol takes advantage of the hydrogen bonding interactions in the key *para*-quinone methide and extended iminium intermediates to build two libraries of enantioenriched CTAMs. Preliminary biological activity studies indicated that these spherical molecules are potential anticancer agents.

Results

Reaction development. Our general strategy to address the above problem is depicted in Fig. 1c. We hypothesized that a racemic triarylmethane **1** with a leaving group on the central carbon would be easily activated by a catalyst to generate the triarylmethyl cation intermediate. Next, an electron-rich arene **2** serves as the nucleophile to react to form the desired tetraarylmethane **3**. Furthermore, the leaving group and the chiral catalyst could be initially designed such that the remaining part of the catalyst serves as a chiral counter anion paired with the corresponding cation. Thus the critical asymmetric induction in the next bond formation would be expected to originate from the chiral counter anion. While the asymmetric ion-pairing catalysis concept has been well established^{28–30}, its practice in differentiating three aryl groups is unknown. In this context, we envisioned that other weak interactions, such as hydrogen bonding, might be employed to direct such subtle differentiation (Fig. 1d)³¹. Thus, two of the three aryl groups were differently tagged, one of which would be a hydrogen-bond donor group (for example, OH) and the other of which would be a hydrogen-bond acceptor (for example, an alkoxy group). These electron-donating groups could further restrict the rotation of the central C–C bonds via resonance, thereby benefiting stereocontrol. Indeed, when a hydroxy group is attached to one of the aryl groups, the chiral ion pair intermediate

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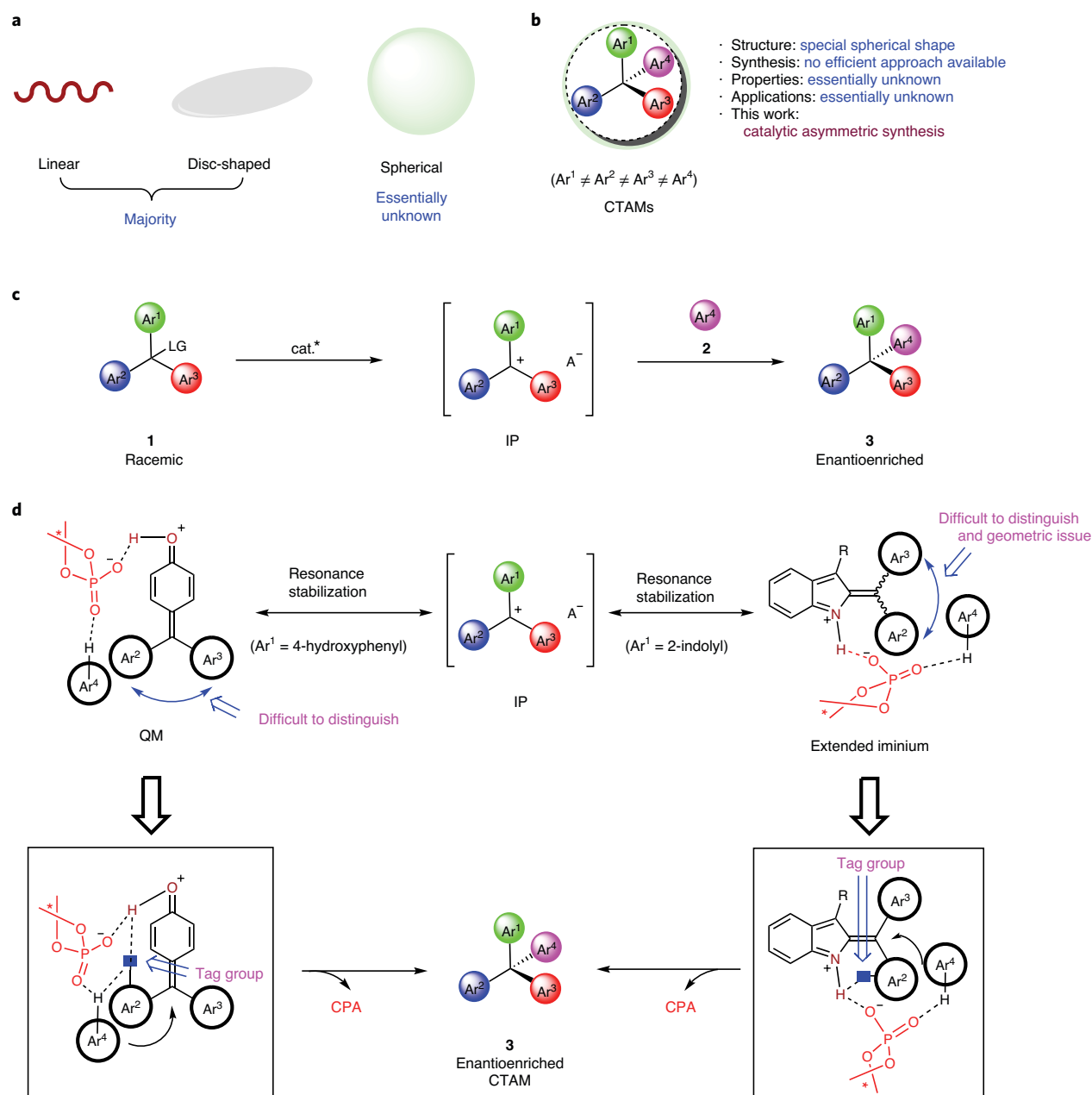
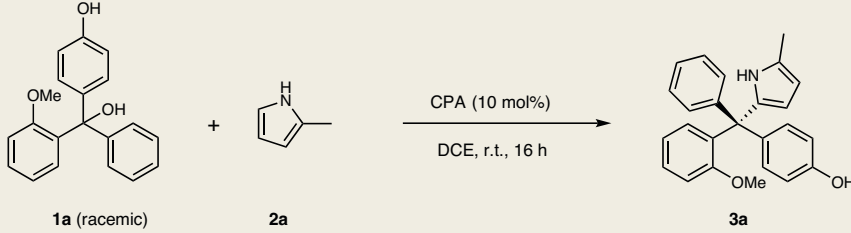


Fig. 1 | Catalytic enantioselective synthesis of CTAMs. a, Introduction to molecular space in drug discovery. **b**, Introduction to CTAMs. **c**, Initial reaction design for CTAM synthesis. LG, leaving group; IP, ion pair; cat., catalyst. **d**, The designed tagging strategy for the differentiation of aryl groups.

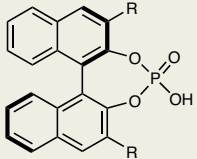
could be further stabilized as a hydrogen-bonded quinone methide (QM)^{32–41}. The other tag then provides a secondary hydrogen-bond interaction to provide the key differentiation (Fig. 1d). Another scenario we could envision is to employ an extended iminium as the intermediate⁴², which could potentially react in a similar manner (Fig. 1d). If successful, this process could be extended to CTAMs containing an indole motif, an important heterocycle widely present in numerous pharmaceuticals and natural products^{43,44}. However, compared with the above *para*-QM intermediate, two possible geometric isomers (*Z* and *E*) could be possible in this extended iminium intermediate. This might lead to additional complication in asymmetric induction.

Condition optimization. To test our hypothesis, we chose the readily available triarylmethanol **1a** as the model substrate. As designed,

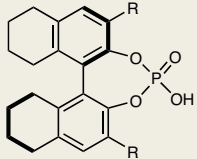
a *para*-hydroxy group and an *ortho*-methoxy group were used as tags in two of the three phenyl groups. We used 2-methylpyrrole **2a** as a model nucleophile (Table 1). In the presence of 10 mol% of acid (*R*)-**A1** (refs. 45,46), the reaction proceeded cleanly at room temperature to form the desired tetraarylmethane **3a** in quantitative yield, albeit with low enantioselectivity (entry 1). Further screening other analogous catalysts identified that (*R*)-**A3** could catalyse this process with both excellent efficiency (97% yield) and enantioselectivity (93% e.e., entry 3). The use of other chiral backbones did not further improve the reaction outcome (entries 5–9). Optimization on other reaction parameters, such as solvent, concentration, temperature and catalyst loading, finally concluded that the best result (97% yield, 96% e.e.) could be obtained when the reaction was run at 0 °C with 7.5 mol% of catalyst (*R*)-**A3** in 1,2-dichloroethane (DCE; entry 10; Supplementary Tables 1–4 for more details).

Table 1 | Initial investigation of the conditions for enantioselective synthesis of CTAM^a


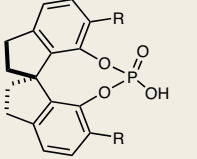
Entry	Catalyst	Conv. (%)	Yield (%) ^b	e.e. (%)
1	(<i>R</i>)- A1	100	>99	11
2	(<i>R</i>)- A2	100	>99	77
3	(<i>R</i>)- A3	98	97	93
4	(<i>R</i>)- A4	100	>99	92
5	(<i>R</i>)- B1	98	94	93
6	(<i>R</i>)- B2	100	99	68
7	(<i>R</i>)- B3	75	75	93
8	(<i>R</i>)- C1	68	64	–24
9	(<i>R</i>)- C2	100	>99	–75
10 ^c	(<i>R</i>)- A3	100	97	96



(*R*)-**A1**: R = H
 (*R*)-**A2**: R = 9-anthryl
 (*R*)-**A3**: R = 2,4,6-(Cy)₃C₆H₂
 (*R*)-**A4**: R = 2,4,6-(ⁱPr)₃C₆H₂



(*R*)-**B1**: R = 2,4,6-(ⁱPr)₃C₆H₂
 (*R*)-**B2**: R = 9-phenanthryl
 (*R*)-**B3**: R = 2,4,6-(Cy)₃C₆H₂



(*R*)-**C1**: R = 2,4,6-(ⁱPr)₃C₆H₂
 (*R*)-**C2**: R = 9-phenanthryl

^aReaction conditions: **1a** (0.025 mmol), **2a** (2 equiv.), catalyst (10 mol%), DCE (0.5 ml). CPA, chiral phosphoric acid; DCE, 1,2-dichloroethane; Conv., conversion; r.t., room temperature. ^bYield is based on analysis of the ¹H NMR spectroscopy of the crude reaction mixture using 1,3,5-triisopropylbenzene as an internal standard; e.e. is determined by HPLC with a chiral stationary phase. ^cRun at 0 °C for 48 h with 7.5 mol% of catalyst.

Substrates scope exploration. With this protocol, a wide range of enantioenriched tetraarylmethanes could be successfully generated with excellent efficiency and enantioselectivity under mild conditions (Table 2). In addition to alkoxy groups, other groups (for example, sulfonamide, thioether, fluorine and even free hydroxy group) present in the *ortho*- position also worked well as the stereo-directing tag. From the enantioselectivities, we may also conclude that the *ortho*-alkoxy groups are stronger directing tags than sulfonamide, fluorine and acetal groups. Another important observation is that the remaining untagged aryl ring could also be substituted with various groups (**3p–3y**) as long as these substituents do not outcompete the *ortho*-methoxy group on the other aryl ring. For example, as a strong tagging group, the methoxy group could also be present in the untagged ring, but only at the *para*- and *meta*- positions (**3q**, **3r** and **3t**). However, weaker tags, such as fluorine and acetal, can be present at any position without much compromise in stereocontrol (for example, **3p**, **3v** and **3w**). These interesting observations indicated that the excellent stereocontrol is based on weak interactions, and the subtle difference in interaction is sufficient to provide extraordinary control, which is remarkable in this delicate system. Moreover, substitution on the

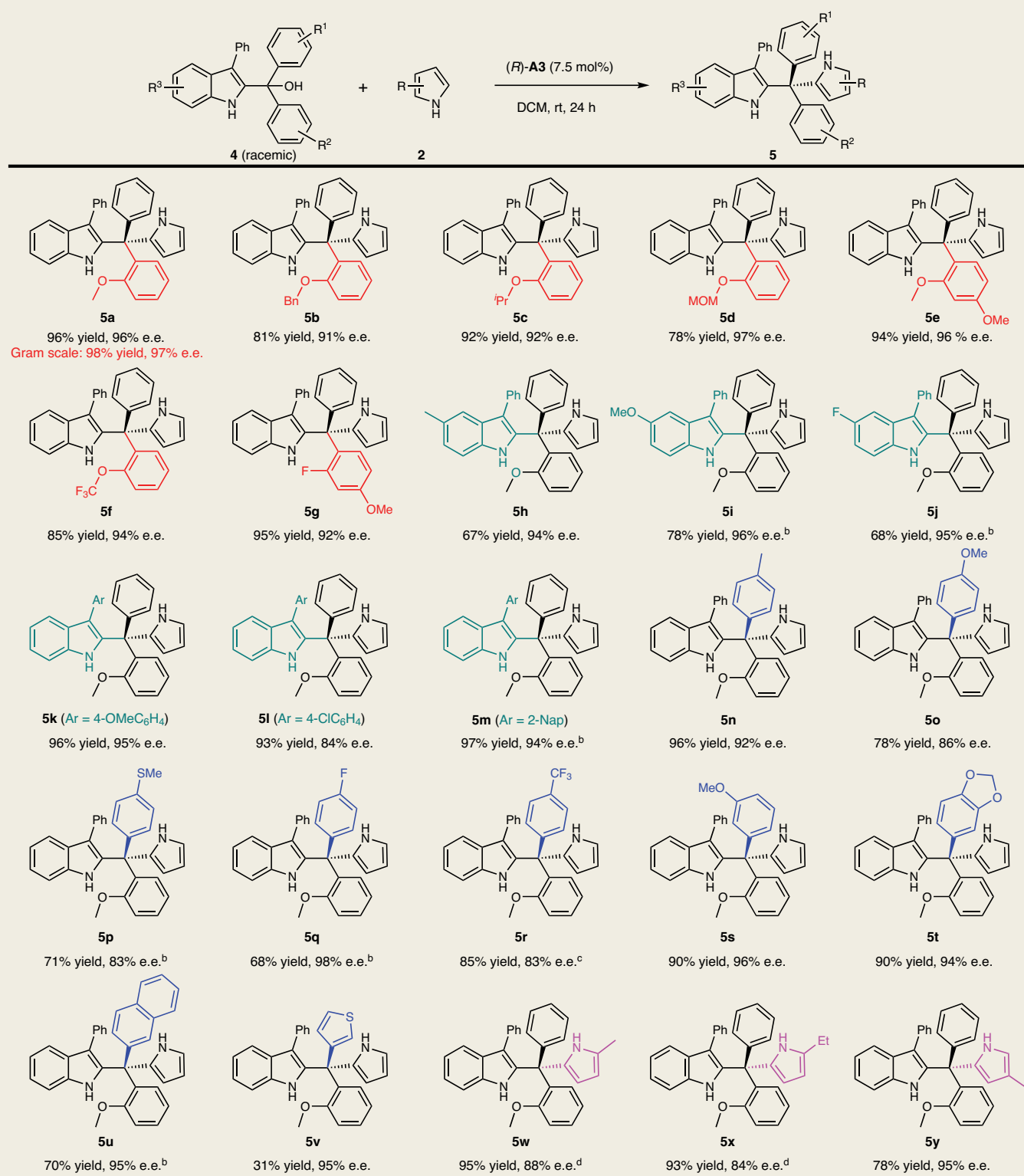
arene with a *para*-hydroxy group led to a lower rate, thus requiring a higher temperature and/or a higher catalyst loading (**3z** and **3aa**). A range of other substituted pyrroles were also suitable nucleophiles (**3ab–3af**). Finally, product **3ag** resulting from 4,7-dihydroindole could be easily oxidized to indole-substituted compound **3af**, thus leading to another type of CTAM structure.

Indole-containing triarylmethanols **4** could also serve as the starting materials (Table 3). After slight modification of the reaction conditions (Supplementary Tables 5–10 for details), the same catalyst (*R*)-**A3** was able to catalyse these reactions to form the corresponding indole-containing tetraarylmethanes **5** with excellent efficiency and enantioselectivity. The structure and absolute configuration of **5a** were confirmed by X-ray crystallography. Again, the presence of an *ortho*- tag (for example, alkoxy group) in one of the phenyl groups proved critical to selectivity control. It is likely that a weak hydrogen-bond interaction with the tag not only facilitates asymmetric control, but also stabilizes one of the *Z/E* isomers in the iminium intermediate and the transition state. Finally, we note that this synthetic protocol is equally robust for gram-scale synthesis with no erosion of yield or enantioselectivity even at reduced catalyst loading (for example, **3ae** and **5a**).

Table 2 | Substrate scope of enantioselective synthesis of CTAMs based on QM intermediate^a

 3a , R = Me, 97% yield, 96% e.e. 3b , R = ^t Bu, 93% yield, 95% e.e. 3c , R = ⁱ Pr, 91% yield, 92% e.e. 3d , R = Bn, 97% yield, 86% e.e. 3e , R = Allyl, 92% yield, 96% e.e.	 3f 94% yield, 93% e.e.
 3g 98% yield, 91% e.e. ^b	 3h 93% yield, 94% e.e.
 3i 94% yield, 78% e.e. ^c	 3j 94% yield, 88% e.e. ^d
 3k 44% yield, 83% e.e. ^e	 3l 65% yield, 89% e.e. ^e
 3m (R = ⁿ PrSO ₂) 85% yield, 95% e.e. ^e	
 3n 90% yield, 81% e.e. ^f	 3o 93% yield, 91% e.e.
 3p 93% yield, 92% e.e.	 3q 94% yield, 83% e.e. ^f
 3r 99% yield, 95% e.e. ^g	
 3s 98% yield, 81% e.e. ^{b,h}	 3t 96% yield, 91% e.e.
 3u 98% yield, 91% e.e.	 3v 93% yield, 84% e.e.
 3w 97% yield, 80% e.e. ^g	
 3x 92% yield, 93% e.e.	 3y 87% yield, 87% e.e. ⁱ
 3z 91% yield, 72% e.e. ^f	 3aa 63% yield, 83% e.e. ^j
 3ab 98% yield, 91% e.e.	
 3ac 92% yield, 83% e.e.	 3ad 98% yield, 81% e.e.
 3ae 94% yield, >99% e.e.	 3af 86% yield, 86% e.e.
 3ag (from 3af) ^k 81% yield, 86% e.e.	
Gram scale: 98% yield, >99% e.e. ^k	

^aReaction conditions: all reactions were performed with **1a** (0.20 mmol, c = 0.05 M), **2a** (0.40 mmol) and (R)-**A3** (0.015 mmol) in DCE (4.0 ml) at 0 °C for 48 h unless otherwise noted. Isolated yields are provided. c, concentration; r.t., room temperature; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. ^bRun at r.t., c = 0.1 M. ^cRun with (R)-**B3** as catalyst. ^dRun at –20 °C. ^eRun in DCM at 40 °C with 20 mol% of catalyst. ^fRun at r.t. ^gc = 0.1 M. ^h10 mol% of catalyst. Run at 40 °C. ⁱRun at 40 °C with 20 mol% of catalyst. ^j5 mol% of catalyst. ^kMeI, K₂CO₃; DDQ, DCM.

Table 3 | Scope of enantioselective synthesis of indole-containing CTAMs^a

^aReaction conditions: all reactions were carried out with **4** (0.20 mmol, *c* = 0.2 M), **2** (0.40 mmol) and (*R*)-**A3** (0.015 mmol) in DCM (1.0 ml) at room temperature for 24 h unless otherwise noted. Isolated yields are provided. ^b*c* = 0.05 M, 36 h. ^c40 °C, 36 h. ^d*c* = 0.05 M.

Mechanistic studies and synthetic applications. Next, we carried out a series of experiments to understand the reaction mechanism. First, substrate **1ab** did not show any reactivity under the

standard conditions, which is consistent with the formation of a *para*-quinone methide (Fig. 2a). Indeed, when substrate **1j** was treated with the acid catalyst in the absence of a nucleophile,

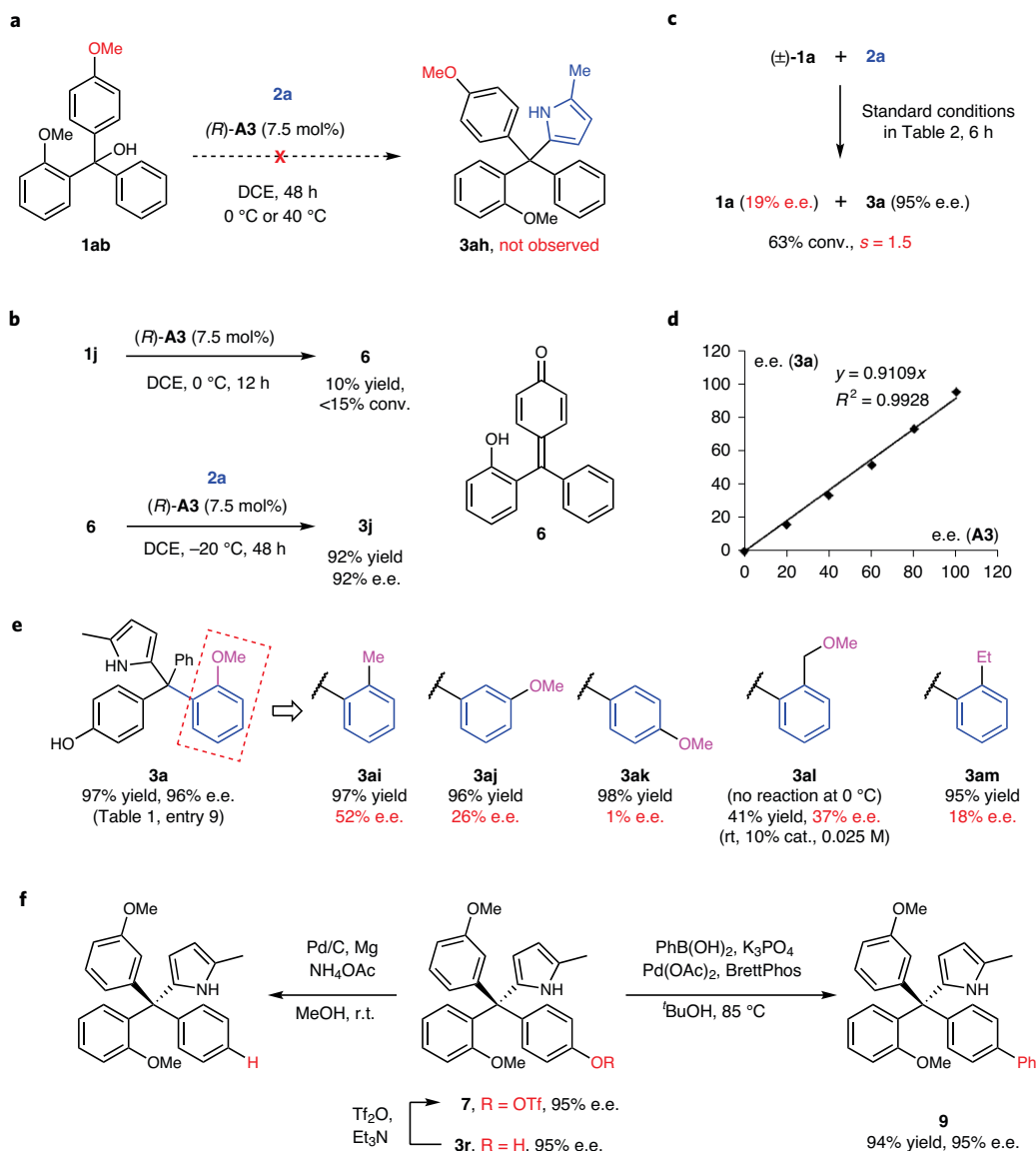


Fig. 2 | Control experiments and derivatizations. a, Reaction of **1ab**. **b**, Isolation and reaction of the QM intermediate **6**. **c**, Observation of kinetic resolution. s , selectivity factor. **d**, Absence of non-linear effects. **e**, Comparison of other tag groups in the substrates. **f**, Conversion and removal of the *p*-hydroxy group. BrettPhos, 2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl.

para-QM **6** could be isolated and fully characterized. Next, the standard reaction of **6** with nucleophile **2a** proceeded efficiently to form the corresponding product **3j** with excellent enantioselectivity (Fig. 2b). This result clearly demonstrated the chemical competence of the *para*-QM intermediate. Furthermore, carefully monitoring the standard reaction between **1a** and **2a** indicated kinetic resolution of **1a** with a selectivity factor of 1.5 (Fig. 2c). The product enantioselectivity remained constant (~95% e.e.) during the whole reaction progress, consistent with its stereoconvergent nature involving an achiral *p*-QM intermediate. Moreover, the product e.e. showed a linear correlation to that of the catalyst (Fig. 2d), suggesting that only one catalyst molecule is likely involved in the enantiodetermining transition state. Then, the *ortho*-methoxy group in the model substrate **1a** was modified to probe its role in stereocontrol (Fig. 2e). Replacing it with *o*-Me, *m*-OMe, *p*-OMe, *o*-CH₂OMe or *o*-Et resulted in a uniformly dramatic decrease in enantioselectivity, suggesting that this *o*-OMe group mainly functions as a hydrogen-bond donor. The *ortho*-position of this tag is also crucial to the excellent

stereocontrol. Finally, with compound **3r** as an example, we demonstrated that the *p*-hydroxy group could be easily removed (**8**) or converted by cross-coupling reactions (**9**) without erosion in enantiopurity via triflate **7**. Similar transformations were also expected for the *ortho*-tags (Fig. 2f).

Density functional theory (DFT) studies. To gain further insights into the mechanism and origins of selectivity, we performed DFT calculations on the reaction of **1a** and **2a** with phosphoric acid (R) -**A3** as catalyst using Gaussian 16 (ref. 47). The structures were fully optimized at the B3LYP-D3BJ/6-31G(d)-SMD(dichloroethane) level of theory^{48–50}, and single-point energies were obtained with M06-2X/6-311+G(d,p)-SMD(dichloroethane)^{51,52}. On the basis of previous experimental observations, the proposed catalytic cycle for the model reaction is shown in Fig. 3a. In the initiation step, the chiral phosphoric acid (R) -**A3** forms a hydrogen bond with the substrate to generate two relatively stable complexes **I-R** and **I-S**. These intermediates **I** then undergo dehydration via **TS1-R** and **TS1-S**

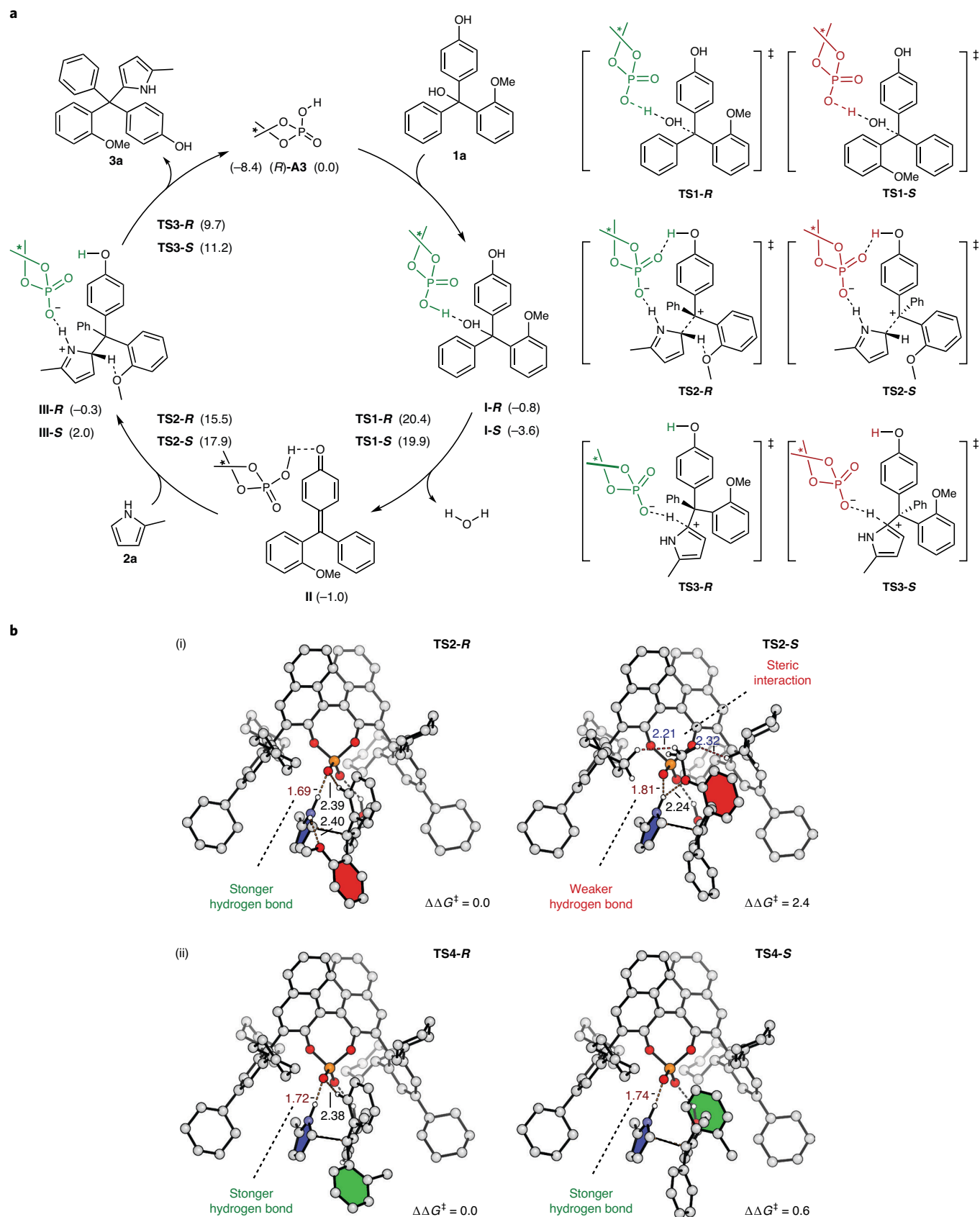


Fig. 3 | DFT calculations for the formation of CTAM 3a. a, The proposed catalytic cycle for the model reaction. **b**, (i) DFT-optimized enantiodetermining transition states for **3a**. (ii) DFT-optimized enantiodetermining transition states for **3ai**. $\Delta\Delta G^\ddagger$, relative activation energies. Numbers in parentheses are DFT-calculated free energies. Coloured rings: red, 2-methoxyphenyl; blue, 2-methylpyrrole; green, 2-methylphenyl. The values of the geometry information are given in Ångström. Energy differences are given in kcal mol⁻¹.

Table 4 | The cytotoxicity of the synthetic compounds in various human cell lines

Compound	IC ₅₀ value (μM) ^a					
	HeLa	A2780	MCF-7	HCT116	A549	MRC-5
3s	7.1 ± 1.8	10.1 ± 0.7	21.1 ± 1.0	38.8 ± 3.3	13.0 ± 0.6	59.7 ± 5.5
3t	5.4 ± 1.2	14.6 ± 2.6	32.8 ± 0.7	45.6 ± 3.6	12.9 ± 0.3	106.8 ± 6.4
5a	3.2 ± 0.5	7.2 ± 0.6	8.0 ± 0.9	4.8 ± 0.3	14.2 ± 1.2	19.8 ± 2.1
5g	3.7 ± 0.2	11.1 ± 0.9	7.4 ± 0.6	6.4 ± 0.7	9.7 ± 0.8	18.1 ± 1.2
5s	1.5 ± 0.1	9.6 ± 0.7	4.8 ± 0.5	16.7 ± 2.3	8.3 ± 0.8	22.6 ± 1.9
Doxorubicin	1.7 ± 0.3	0.38 ± 0.09	0.42 ± 0.07	1.2 ± 0.3	0.19 ± 0.03	0.77 ± 0.1

^aThe half maximal inhibitory concentration (IC₅₀) was determined by MTT assay in 72 h. Data were calculated from three independent experiments using OriginLab 2019 software. The error bars were calculated as the standard deviation from the mean value.

to afford an identical *p*-QM intermediate **II**, requiring an activation free energy of 21.2 and 23.5 kcal mol⁻¹, respectively. Next, the nucleophile pyrrole **2a** attacks the *p*-QM intermediate via **TS2-R** and **TS2-S** to obtain **III-R** and **III-S**. The energy difference between **TS2-S** and **TS2-R** is 2.4 kcal mol⁻¹, in good accord with the 96% e.e. obtained experimentally. The subsequent intermolecular proton shift process via **TS3-R** and **TS3-S** is facile with barriers of only 10.0 and 9.2 kcal mol⁻¹, respectively. Therefore, the enantiodetermining step for this reaction is the nucleophilic attack of pyrrole on the *p*-QM intermediate, **TS2**. However, the turnover-limiting step is the dehydration from **I** to **II**, which is consistent with the kinetic resolution observed in Fig. 2c.

We next investigated the origins of enantioselectivity. The geometries of transition states **TS2-R** and **TS2-S** were explored. As shown in Fig. 3b(i), obvious hydrogen-bonding interactions are detected between the 2-methoxyphenyl oxygen atom and the 2-methylpyrrole hydrogen atom in transition states **TS2-R** and **TS2-S**. However, in the minor **TS2-S**, the methoxy group is oriented towards the cyclohexyl groups in the catalyst, and H...H distances of 2.21 Å and 2.32 Å are observed, indicating steric interaction between the methoxy and cyclohexyl groups. However, there are no such steric repulsions in **TS2-R**. Further investigations revealed that this steric clash in **TS2-S** resulted in a longer O–H hydrogen-bond distance (1.81 Å) and thus weaker hydrogen-bonding interaction than that in **TS2-R** (1.69 Å). This is the key contribution to the 2.4 kcal mol⁻¹ preference for the formation of the major product. To better understand the pivotal importance of the hydrogen-bonding interactions, the methoxy group was replaced by a methyl group in the stereodetermining step as in **3ai** (Fig. 3b(ii)). In the absence of the *ortho*-hydrogen bonding in **TS4**, the methyl group rotates away from the cyclohexyl substituents, which leads to a shorter O–H hydrogen-bond distance in **TS4-S** (1.74 Å) than that in **TS2-S** (1.81 Å). The stronger hydrogen bond and weaker steric repulsion in **TS4-S** make the energy difference between transition states **TS4-S** and **TS4-R** as low as only 0.6 kcal mol⁻¹, which agrees with the low enantioselectivity observed for **3ai** (52% e.e.). These results further support the dominant role of the *ortho*-hydrogen-bonding tag in achieving high enantioselectivity.

To further verify the accuracy of our computational results, the predicted enantioselectivities were compared with the experimentally observed values (Supplementary Table 11). A plot of the experimental and theoretical data on ten different products indicated a good correlation between the corresponding energy values derived from the experimentally observed e.e. and the calculated activation free energy difference ($R^2 = 0.81$, Supplementary Fig. 1). Meanwhile, single-point energies were also evaluated within the SMD model using the B3LYP-D3BJ, ωB97X-D, PBE0-D3BJ and MN15 functionals to compare the stereoselectivities computed using different methods (Supplementary Table 12). The predicted enantioselectivities are consistent with each of five density

functional methods. These results indicate that the calculated enantiodetermining transition state is likely correct, and not an artefact of a specific computational method.

Biological activity study. Finally, we were intrigued by the potential biological activities of these spherical enantioenriched tetraarylmethanes. Thus, five randomly selected products were evaluated for their preliminary cytotoxicity by MTT assay (MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). We first screened their cytotoxicity in human cervical adenocarcinoma (HeLa) cells with the widely used anticancer drug doxorubicin as a control. As shown in Table 4, all of them were cytotoxic to HeLa cells with half maximal inhibitory concentration (IC₅₀) values in the low micromolar range. We further examined their anticancer potency in other human cancer cells, including A2780 ovarian carcinoma cells, MCF-7 breast adenocarcinoma cells, HCT116 colorectal carcinoma cells and A549 lung carcinoma cells. These compounds also exhibited impressive preliminary cytotoxicity, with IC₅₀ values in the range of 1.5 to 45.6 μM. HeLa cells were found to respond the most, followed by A2780 and A549 cells. For comparison, we also tested their cytotoxicity in human normal lung fibroblasts (MRC-5). Notably, all of them were less cytotoxic towards these normal cells (versus cancer cells, or versus the drug molecule doxorubicin). These preliminary results indicate that the unusual spherical tetraarylmethanes show great potential for further development into anticancer agents.

Conclusions

We have developed a catalytic enantioselective synthesis of CTAMs, a family of spherical molecules without previous direct access. In spite of the substantial challenges in steric demand and stereocontrol when establishing the all-aryl quaternary stereocentre, a delicate system created by utilizing well-positioned removable directing tags proved successful and effective. Mechanistically, the in-situ-generated *para*-quinone methides or extended iminium intermediates as well as the multiple weak hydrogen-bonding interactions with well-designed tags constitute the key elements to success. DFT calculations also provided strong support for the mechanism. With this process, two libraries of structurally distinct CTAMs were efficiently synthesized with high enantioselectivity. Preliminary biological activity studies indicate that these spherical molecules are highly promising anticancer agents. This study is expected to stimulate a more systematic exploration of this important chemical space.

Methods

General procedure for the synthesis of enantioenriched CTAM 3. At 0 °C, a solution of catalyst (*R*)-**A3** (14.9 mg, 0.015 mmol, 7.5 mol%) in DCE (0.4 ml) was slowly added to an oven-dried 10 ml vial charged with a solution of the tertiary alcohol **1** (0.2 mmol) and pyrrole **2** (0.4 mmol) in DCE (3.6 ml). The reaction mixture was stirred at the same temperature for 48 h. Next, Na₂CO₃ (212 mg,

2.0 mmol) was added. The mixture was stirred for 10 min and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography to afford the desired product.

General procedure for the synthesis of enantioenriched CTAM 5. At room temperature, a solution of catalyst (*R*)-A3 (14.9 mg, 0.015 mmol, 7.5 mol%) in dichloromethane (DCM, 0.2 ml) was slowly added to an oven-dried 4 ml vial charged with a solution of tertiary alcohol 4 (0.2 mmol) and pyrrole 2 (0.4 mmol) in DCM (0.8 ml). The reaction mixture was stirred at the same temperature for 24 h. Next, Na₂CO₃ (212 mg, 2.0 mmol) was added. The mixture was stirred for 10 min and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford the desired product.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All data generated and analysed during this study are included in this Article and its Supplementary Information. They are also available from the authors upon reasonable request. The X-ray crystallographic coordinates for the structures of 3ae' (derivative of 3ae) and 5a have been deposited at the Cambridge Crystallographic Data Centre under deposition numbers CCDC 1935077 and CCDC 1935078, respectively, and can be obtained free of charge from the CCDC via http://www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

X.L. conceived the project, performed the experiments and wrote the paper. M.D. and Q.S. performed DFT calculations. K.N.H. directed the DFT calculations and mechanism analysis. Z.D. performed the cytotoxicity experiments. G.Z. directed the cytotoxicity study. J.S. conceived and directed the project and wrote the paper. All the authors discussed the results and commented on the manuscript.

Competing interests

J.S. and X.L. are inventors on US patent application no. 62/918,404 submitted by the Hong Kong University of Science and Technology, which covers the catalytic system and its application in synthetic transformations. Other authors declare no competing interests.

Additional information

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No software was used

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We used Origin2019 (<https://www.originlab.com/2019>) for IC50 calculation and statistical analysis. All DFT calculations were performed using Gaussian 16 (<http://gaussian.com/gaussian16/>).

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Sample size	For the in vitro cytotoxicity test, the cell number of each cell line to seed is determined by cell titration assay. Firstly, cells (80,000 cells per well) were seeded in the 1st roll of 96-wells plate. Then, a 2-fold dilution was made for the rest 7 rolls. Thus, 80,000, 40,000, 20,000, 10,000, 5000, 2500, 1250, and 625 cells were contained in the each well of 1st, 2nd, 3rd, 4th, 5th, 6th, 7th, and 8th roll of the 96-wells plate, respectively. 4 plates were prepared in total. For the 1st plate, cells were cultured for 6 h to make sure all cells were attached on the culture plate. Then the culture medium was removed, 200 uL medium containing 1mg/mL MTT was added to each well. Cells were cultured for another 2 h, the medium was removed, 150 uL DMSO was added to each well. The plate was placed on a shaker (50 rpm) for 10 min, the OD value of each well at 570 nm was recorded to represent the cell number of day 0. After 24 h, the 2nd plate was taken out, and the above procedure was repeated to obtained the OD value to represent the cell number of day 1. After another 24h, the OD value of the 3rd plate was recorded to represent the cell number of day 2. At day 3, the OD value of the 4th plate was obtained accordingly. Based on these data, we calculated the proper cell number that fall in exponential phase from day 0 to day 3. Consequently, the seed number of cancer cells and normal cells was found to be 2,000, and 7,000, respectively.
Data exclusions	No data were excluded
Replication	In vitro cytotoxicity in triplicate (with untreated as the negative control and doxorubicin treatment as the positive control). All attempts at replication are successful.
Randomization	No randomization was used for in vitro experiments. In this study, randomization is not relevant as we did not use any animal models.
Blinding	No blinding was used for in vitro experiments. Blinding is not applicable, since our experiments are based on cell culture.

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Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Eukaryotic cell lines

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Cell line source(s)	HeLa (ATCC® CCL-2™), MCF7 (ATCC® HTB-22™), HCT116 (ATCC® CCL-247), A549 (ATCC® CCL-185™), and MRC-5 (ATCC® CCL-171) were obtained from American Type Culture Collection (ATCC). A2780 cell line (originally purchased from ATCC) is a kind gift from Prof. ANG Wee Han of the Department of Chemistry, National University of Singapore, Singapore.
Authentication	Cell lines were stored in liquid nitrogen, and were only used within passage 20. None of the cell lines used were authenticated.
Mycoplasma contamination	All the cell lines used were negative for mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	No cell lines used in this manuscript were misidentified.