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Desymmetric esterification catalysed by bifunctional chiral *N*-heterocyclic carbenes provides access to inherently chiral calix[4]arenes

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Calix[4]arenes display inherent chirality, with broad applications in synthetic and medicinal chemistry and in materials sciences. However, their use is hindered by their limited synthetic accessibility, primarily due to the lack of enantioselective methods for preparing chiral calix[4]arenes with an ABCC substitution pattern. Here, we address this challenge by presenting a simple, efficient, and metal-free protocol for organocatalytic desymmetrisation of prochiral diformylcalix[4]arenes. Through this highly effective and sustainable approach, we synthesize structurally unique products in gram-scale reactions. Accordingly, this method facilitates extensive post-functionalisations of the carbonyl groups, including for organocatalyst development. Furthermore, our experimental mechanistic studies demonstrate that desymmetrisation determines enantiocontrol in esterification reactions catalysed by *N*-heterocyclic carbenes. These findings underscore the broad potential of this method for providing versatile access to inherently chiral calix[4]arenes with an ABCC substitution pattern while offering a valuable platform for asymmetric molecular recognition and catalysis.

Chiral *N*-heterocyclic carbenes (NHCs)[1] have recently emerged as a transformative class of nucleophilic organocatalysts[2]. The success of NHCs stems from their broad spectrum of activation modes, which enable stereocontrolled transformations under mild reaction conditions with excellent selectivity[3,4]. As such, NHCs have prompted significant advancements in synthetic chemistry, including in asymmetric synthesis[5,6].

In asymmetric synthesis, NHC-mediated transformations have rapidly expanded into a major area of research thanks to the stability and accessibility of chiral carbene precursors. Case in point, NHC-catalysed desymmetrisation of prochiral or *meso*-compounds[7,8] stands out as a highly promising platform for enantioselective transformations (Fig. 1A)[9,10]. More specifically, NHC-catalysed stereoselective oxidative esterification of prochiral aldehydes offers a versatile pathway to various products with central chirality, including dihydropyridines[11], and non-carbon stereogenic centers[12–14]. In the last two years, though, research has increasingly focused on the development of axially chiral compounds[15–17]. In this context, carbene-catalysed desymmetric esterification has gained prominence as a key method for atroposelective synthesis, providing access to a wide range of biaryls[18] and related ethers[19–23]. Concurrently, our group has developed a versatile approach to synthesizing planar chiral [2.2]paracyclophanes over NHCs[24]. Despite these advances[25], to the best of our knowledge, NHC-mediated desymmetrisation has never been used to prepare inherently chiral products[26].

Among inherently chiral molecules, calix[4]arenes encompass the most studied class to date[27]. Their unique three-dimensional curved

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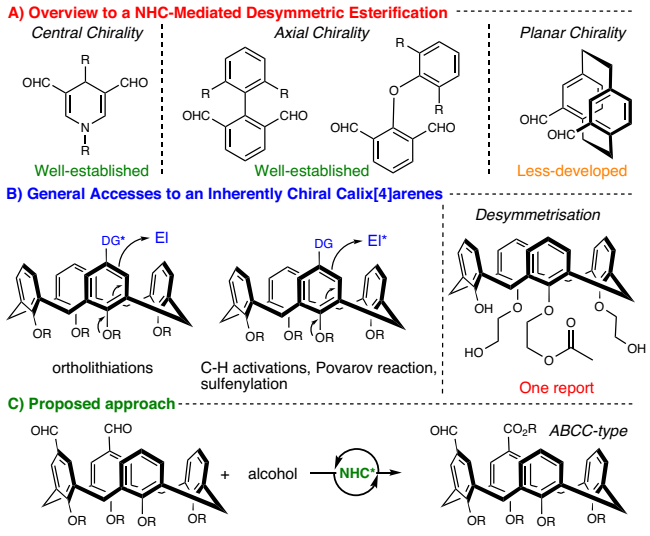

Fig. 1 | Selected desymmetric approaches to compounds possessing various chirality elements, the main approaches to inherently chiral calix[4]arenes. **A** Overview of NHC-mediated desymmetric esterification (highlighted in red). **B** Selected accesses to an inherently chiral calix[4]arenes (highlighted in blue). **C** Proposed approach (highlighted in green).

structure exemplifies a chiral macrocycle with a wide range of applications. For instance, calix[4]arenes enable chiral recognition as host-guest molecules, (bio)sensors[28], drug/gene delivery systems, enzymatic assays, and smart materials[29]. Beyond these applications, inherently chiral calix[4]arenes have been successfully employed as catalysts and ligands[30–33]. However, synthesizing inherently chiral calix[4]arenes remains a major challenge[34]. Most synthetic approaches rely on the separation of racemic mixtures by chiral HPLC or chemical resolution through diastereomeric intermediates with chiral auxiliaries[35,36]. These methods are limited by their maximum yield of enantiopure products, which is only 50%.

Introducing chiral-directing groups, typically to the upper rim of the calix[4]arene, has provided some diastereocontrol during subsequent functionalisation (Fig. 1B)[37–40]. More recently, innovative strategies, such as metal-catalysed annulation[41–45], Povarov reaction[46,47], and sulfenylation[48], have leveraged non-chiral directing groups that either interact with chiral reaction partners or generate active chiral species for enantioselective desymmetric functionalisation. But none of these methods yield calix[4]arenes derivatised at more than one phenolic unit. And while inherently chiral derivatives with two or more substituted phenolic units[49] have facilitated the enantioselective preparation of inherently chiral calix[4]arenes with an ABCC substitution pattern (Fig. 1B)[50], enzymatic desymmetrisation of prochiral alcohol resulted in less than 20% yield of the desired product. Therefore, no progress has been made in stereocontrolled access to calix[4]arenes with an ABCC aromatic ring substitution pattern since 1998[51].

In this work, we develop a method for synthesizing inherently chiral calix[4]arene derivatives through oxidative NHC catalysis (Fig. 1C). Through our highly efficient protocol using prochiral calix[4]arenes, we prepare valuable synthon products containing carbonyl groups suitable for further functionalisation and development.

Results and discussion

Optimisation of the model reaction

Building on insights from our previous study[24], we selected methanol as the initial substrate for esterification of the prochiral diformylcalix[4]arene **1a**. Mixing **1a** with excess methanol (Table 1, entry 1), an NHC precursor derived from L-valine (*pre*-**C1**), an oxidant (Kharasch reagent, 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone, DQ), and a base (cesium carbonate) resulted in an inseparable (by standard column chromatography) mixture of an inherently chiral monoester and an achiral diester. However, this process lacked enantiocontrol (59:41 *er*), as shown by chiral HPLC analysis. Despite these initial challenges, we identified the optimal alcohol substrate and found that 2-naphthol (entry 2) promoted the separation of the products **3a**/**4a**. Through this reaction, we obtained ester **3a** in 58% yield, albeit with low optical purity (52:48 *er*).

Based on these proof-of-concept experiments, we set out to improve the efficiency and stereochemical outcomes by varying reaction conditions for the model reaction. To this end, we tested several NHC precursors, solvents, oxidants, bases, and other parameters (for full details, please refer to the Supplementary Information (SI) file). However, none of the numerous NHC precursors tested in this study improved the stereocontrol over catalysts with enantiodiscrimination governed by steric hindrance from the chiral backbone. For instance, a camphor-derived NHC precursor (*pre*-**C2**) resulted in a product with a low enantiomeric ratio (64:36 *er*). Nevertheless, enantioselectivity was significantly improved when using bifunctional NHCs (*pre*-**C3,4**) combining an NHC moiety with hydrogen-bond-donating[52,53] (thio)urea functionality[54–60]. In both cases (entries 4 and 5), the corresponding ester **3a** was isolated in good yields and excellent optical purity (98:2 *er*). Upon further optimisation, the reaction became less tolerant to changes in base and solvent. For example, substituting cesium carbonate with rubidium carbonate or using DMSO or MTBE as solvents reduced the enantiocontrol and yield whilst increasing the proportion of the diester (entries 6-8). Similarly, most alternative oxidants proved unsuitable, especially MnO_2 (entry 9). With MnO_2, the yield was only 24%, and the optical purity was slightly reduced. However, decreasing the amount of catalyst precursor to 10 mol% (entry 10) and increasing the base loading to 200 mol% (entry 11) improved the overall yield. As a result, the product was obtained in a high yield (84%) with an excellent enantiomeric excess (97.5:2.5 *er*).

Reaction scope

After optimising the reaction conditions, we investigated the scope of the desymmetrisation reaction using various lower-ring-substituted diformylcalix[4]arenes and substituted 2-naphthols (Fig. 2). When performed with the opposite enantiomeric form of the chiral catalyst (*ent-pre*-**C3**), the reaction yielded 80% of the opposite enantiomeric product (*ent*-**3a**) with excellent enantiopurity (98.5:1.5 *er*). Subsequently, we examined the influence of alkyl-group substitution on the lower ring of diformylcalix[4]arenes, focusing on their impact on reaction rate and stereochemical outcomes (Fig. 2A). The desymmetrisation reaction was well-tolerated by various alkyl chain substitutions. For instance, the tetraethyl derivative produced the desired product **3b** in 73% yield, with excellent enantiomeric purity (97:3 *er*). These values matched the results of the less-polar tetraoctyl derivative. Then, we explored the scope of this method using various substituted naphthols (Fig. 2B). Naphthols bearing electron-donating groups (EDGs) at positions 7 or 8 slightly shortened the reaction times (typically ~10 min for EDG-substituted naphthols, in contrast to over 30 min for those with electron-withdrawing groups (EWGs)). Other than this difference in reaction time, no significant deviations were observed in yield (56–84%) or stereochemical outcomes (96:4-99:1 *er*). When we faced some difficulties in separating the major product **3** (usually for methoxy-substituted derivatives) from minor components (diester **4** or starting material **1a**), we directly subjected the reaction mixture to sodium borohydride reduction, thereby yielding pure alcohols **5**. Both 1-naphthol and its tetrahydro derivative produced the corresponding product in high yields and reasonable stereochemical outcomes. We also revisited the desymmetrisation of **1a** using methanol (Fig. 2C), noting a significant decrease in the reaction rate. Product **5 v** was isolated after reduction, albeit in moderate yield (44%, two steps) and with slightly lower optical purity (85:15 *er*).

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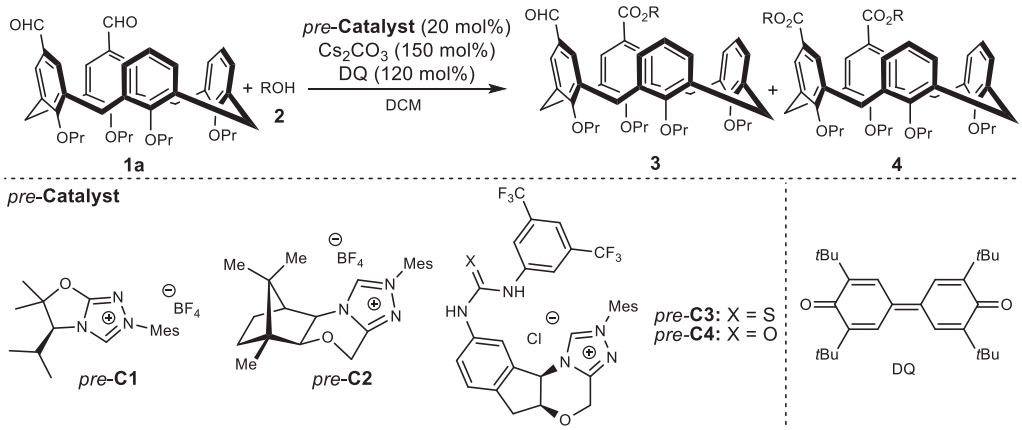
Table 1 | Optimisation of the model reaction



Entry[a]	Alcohol	*pre*-Catalyst	Time (h)	Yield[b] (3, %)	Yield[b] (4, %)	*Er*[c] (3)
1[d]	MeOH	*pre*-**C1**	48	n.d.	n.d.	59:41
2	2-naphthol	*pre*-**C1**	15	58	11	52:48
3	2-naphthol	*pre*-**C2**	15	51	13	64:36
4	2-naphthol	*pre*-**C3**	1	61	15	98:2
5	2-naphthol	*pre*-**C4**	1	63	13	98:2
6[e]	2-naphthol	*pre*-**C3**	30	37	5	57:43
7[f]	2-naphthol	*pre*-**C3**	1	62	13	60:40
8[g]	2-naphthol	*pre*-**C3**	1	61	27	83:17
9[h]	2-naphthol	*pre*-**C3**	72	24	–	81:19
10[i]	2-naphthol	*pre*-**C3**	1	68	10	98:2
11[i,j]	2-naphthol	*pre*-**C3**	1	84	8	98:2

Er enantiomeric ratio.
[a]Reactions performed with **1a** (0.06 mmol), corresponding alcohol **2** (0.05 mmol), Cs_2CO_3 (0.075 mmol), DQ (0.06 mmol), and precatalyst (20 mol%) in DCM (1.0 ml) at room temperature.
[b]Isolated yield after column chromatography.
[c]Determined by chiral HPLC analysis.
[d]Reaction performed with **1a** (0.05 mmol) and methanol (0.25 mmol).
[e]Using Rb_2CO_3 as a base.
[f]Using DMSO as a solvent.
[g]Using MTBE as a solvent.
[h]Using MnO_2 as an oxidant.
[i]With 10 mol% of *pre*-**C3**.
[j]Using 0.10 mmol Cs_2CO_3.

Despite our best efforts, though, we failed to extend this method to other nucleophiles, such as amines, ureas, and azides, with significant conversion of the starting material. So to comprehensively explore the potential of our method, we introduced various phenols as examples of typical aromatic alcohols (Fig. 3). The desymmetrisation of phenol yielded the expected product **6a** with the highest level of enantiopurity among all examples discussed so far (99.5:0.5 *er*). Furthermore, introducing both EDGs and EWGs at the para position of phenol (Fig. 3A) generated the corresponding products **6b-i** in high-to-excellent (57-86%) yields whilst maintaining exceptional enantiocontrol (94:6-99.5:0.5 *er*). The position of the bromine as a substituent had no significant effect on the reaction efficiency or stereochemical outcomes. Given this functional group tolerance, we tested this method for late-stage modification of structurally diverse alcohols derived from natural and bioactive molecules (Fig. 3B). These desymmetrisation reactions proceeded in good-to-high (55-86%) yields, consistently producing esters with high levels of enantiopurity, except for *ortho*-substituted phenols with bulky substituents. The propofol-derived product **6o** was obtained in a significantly lower reaction rate (without full conversion within 24 hrs) in a virtually racemic form. Broadly speaking, low-soluble (in DCM) starting phenols slightly lengthened the reaction. For instance, the ester derived from estrone (**6r**) was isolated in excellent (84%) yield as a single diastereomer (20:1 *dr*). With ezetimibe, which contains secondary alcohol, we demonstrated the chemoselectivity of our method to phenols. With ezetimibe, we exclusively isolated ester **6s** in high (86%) yield, virtually matching the yield of the *O*-protected derivative (**5t**).

Reaction mechanism

We investigated the reaction mechanism and the origin of stereocontrol by combining experimental observations with DFT calculations. In line with several literature reports[61], we proposed a possible catalytic pathway (Fig. 4). Briefly, carbene **I** is formed by base deprotonation of the corresponding azolium salt (*pre*-**C3**). Then, the nucleophilic carbene attacks (step A) the aldehyde carbon, yielding a tetrahedral intermediate **II**, which is proposed to be non-covalently stabilized by hydrogen bond formation with thiourea unit of carbene. This intermediate undergoes a 1,2-C-to-O proton shift (step B), generating a Breslow intermediate (**III**). In the presence of an oxidant (DQ), the Breslow intermediate is irreversibly oxidized (step C) into an acyl azolium intermediate (**IV**). The resulting acyl azolium is electrophilic at the carbonyl carbon and thus undergoes acyl substitution (step D) with alcohol **2** (or alkoxide). The final acyl substitution regenerates the carbene back to the catalytic cycle, yielding ester **3** or **6**.

Focusing more on the formation of the Breslow intermediate (**III**), which we proposed to be crucial for enantiodiscrimination, we performed mechanistic and computational studies (Fig. 5). At the outset,

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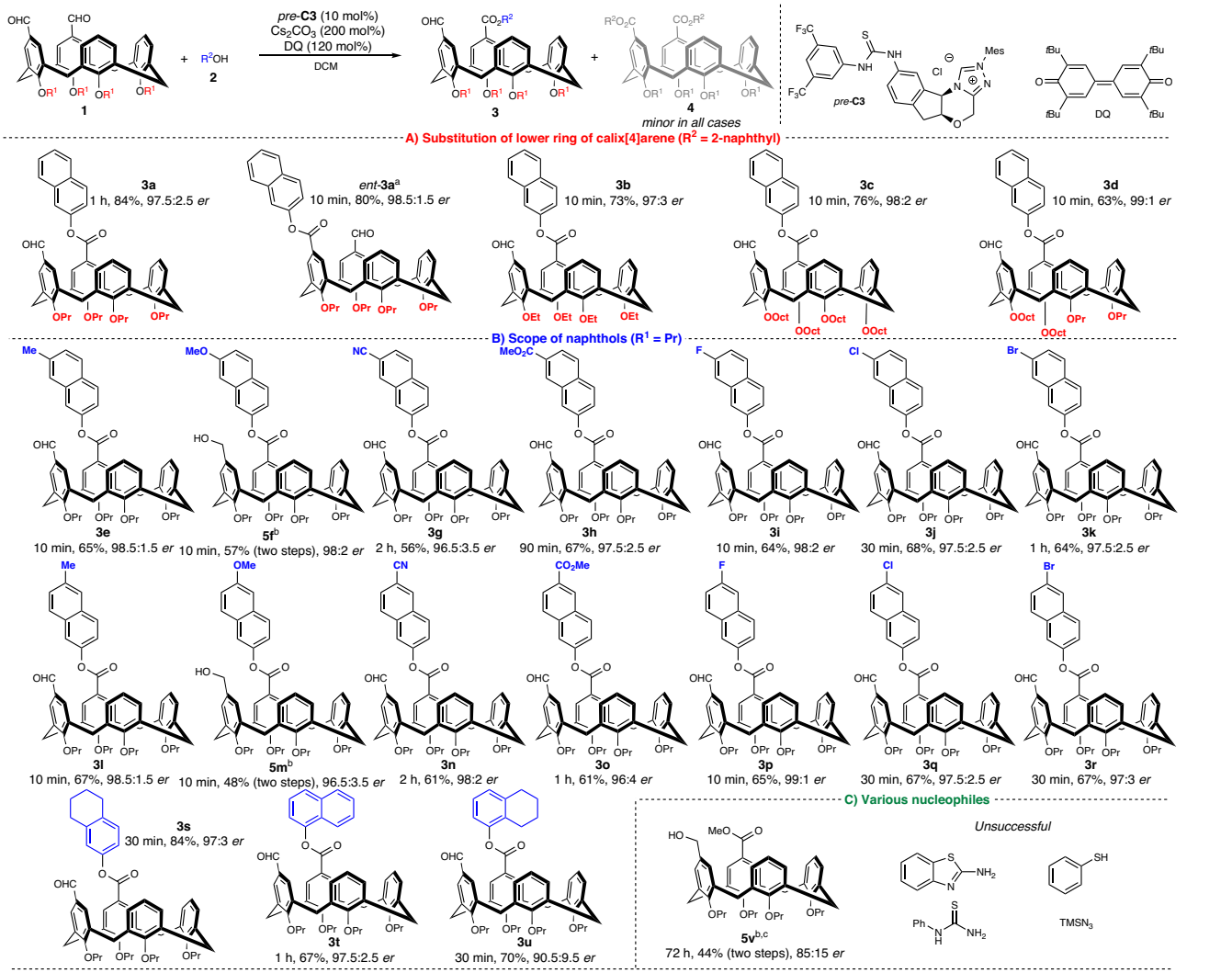

[a] *Ent-pre*-**C3** was used. [b] Product **3** was isolated as an inseparable mixture with **1a**. The mixture was directly subjected to sodium borohydride reduction. The reaction time refers to the esterification reaction. [c] Reaction was conducted with **1a** (0.05 mmol) and methanol (0.25 mmol). Full consumption of calixarene was not observed.

Fig. 2 | Substrate scope of various calix[4]arenes and naphthols. A Substitution of lower ring of calix[4]arene (highlighted in red). **B** Scope of naphthols (highlighted in blue). **C** Various nucleophiles (highlighted in green).

we conducted desymmetrisation reactions of diformylcalix[4]arene **1a** using deuterated 2-naphthols (d_1 or d_8) under optimised conditions (Fig. 5A). In both cases, deuterium was not incorporated into the aldehydic group of the products, as shown by ^{2}H NMR. Although the reversible formation of the Breslow intermediate should induce aldehyde deuteration[62]. On the other hand, we accept the limitations of this experiment, such as the use of a lower amount of naphthol in comparison to diformyl derivative **1**. So, we also investigated the kinetic isotope effect[63,64] (KIE) of the desymmetrization reaction by introducing two parallel reactions (for more information, please refer to SI) and by performing an intremolecular competition reaction (Fig. 5B) with **1a**-d_2 or **1a** as starting materials. In both experiments, we assessed secondary kinetic isotope effects (KIE ~ 1.5), which could be caused by rehybridization during 1,2-C-to-O proton shift. This finding indicates that proton shift (step B) is most likely the product-determining step.

Supporting our experimental mechanistic study, computational analysis provided insights into the initial enantiodiscrimination step. First, density functional theory (DFT) calculations revealed that the most stable conformer of the catalyst adopts a *syn-anti* conformation of the thiourea unit. In line with a previously reported conformational analysis[65], we corroborated our DFT calculations with ROESY NMR experiments of *pre*-**C3**. These experiments revealed distinct conformations of the precursors in non-polar (dichloromethane (DCM)) and polar (DMSO) solvents, with a significant drop in enantioselectivity when performing desymmetrization in DMSO (Table 1, entry 7), highlighting carbene conformation as one of the potential determinants of enantiocontrol. We also proposed that the nucleophilic attack of carbene (process A) was the enantiodiscrimination step, so we further elucidated this step by calculating the energy of carbene-aldehyde adducts and energies of their transition states. Briefly, computations revealed only minor energetic preference (Fig. 5C) and low energetical barriers, suggesting a reversible initial nucleophilic attack by the carbene (for more details, please refer to the Supplementary Data 1).

Subsequently, we experimentally examined the origin of stereocontrol (Fig. 5D). Conducted with a reduced amount of oxidant (50 mol%), the model reaction yielded **3a** with excellent enantiocontrol (98:2 *er*). This result indicated that desymmetrisation determines stereocontrol, as confirmed by kinetically resolving *rac*-**3a**, which yielded enantioenriched **3a** (91:9 *er*), albeit with a low selectivity factor (2.9). Based on these findings, not only dialdehydes but also those calix[4]arenes, emerge as excellent candidates for further elaboration in desymmetrization processes.

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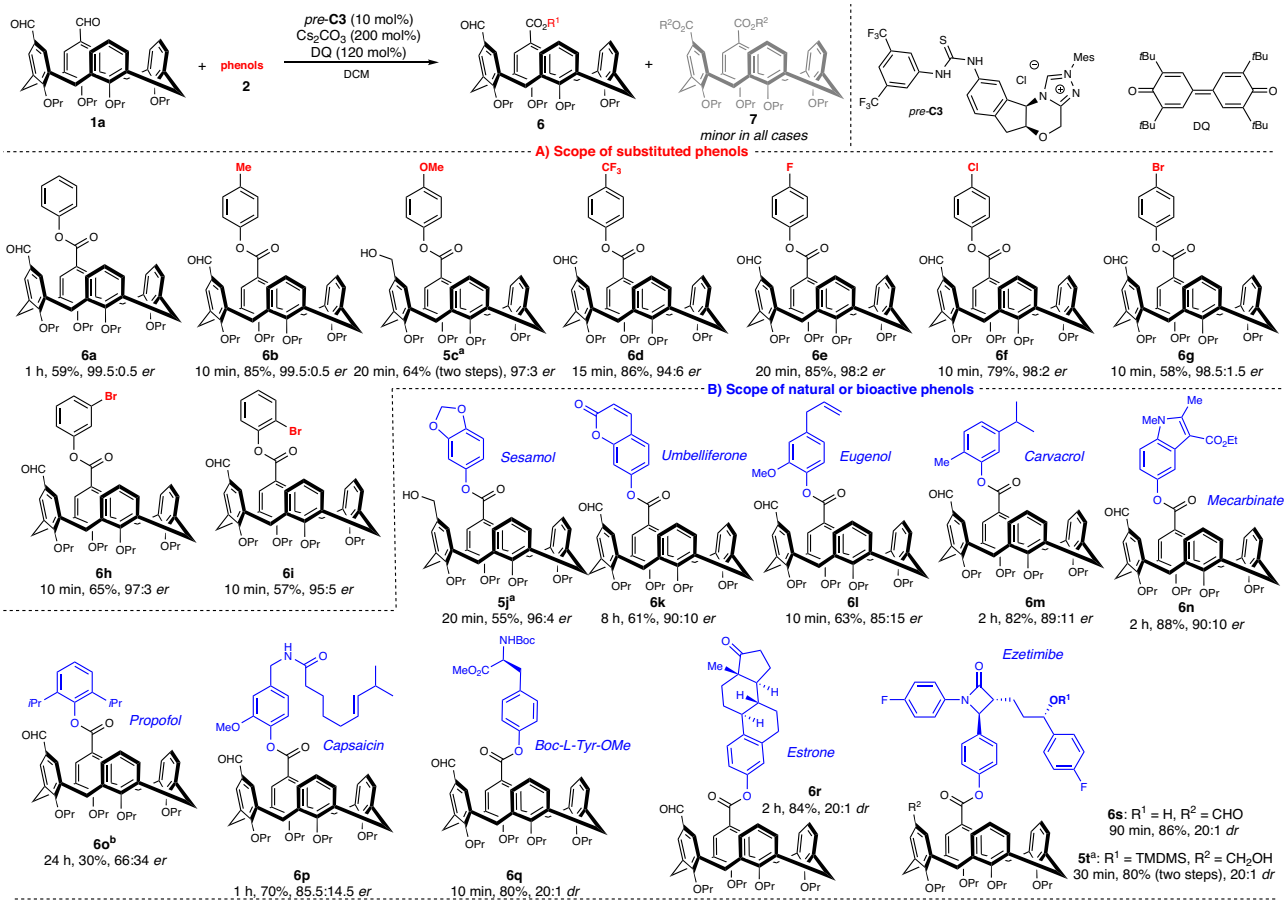

[a] Product **6** was isolated as an inseparable mixture with **1a**. The mixture was directly subjected to sodium borohydride reduction. The reaction time refers to the esterification reaction. [b] Full consumption of alcohol **2** was not observed.

Fig. 3 | Substrate scope of various phenols. A Scope of substituted phenols (highlighted in red). **B** Scope of natural or bioactive phenols (highlighted in blue).

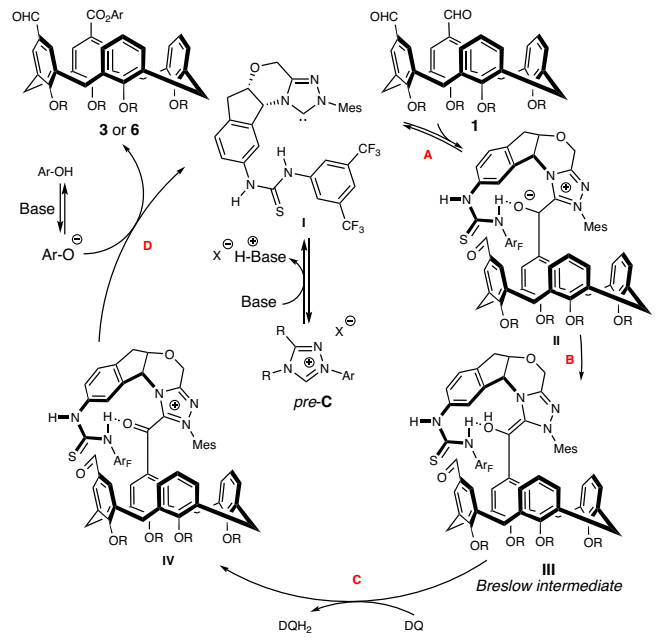

Fig. 4 | Proposed reaction mechanism. Catalytic cycle including the generation of NHC, formation of the Breslow intermediate, and following oxidative esterification.

Synthetic utilisation of the chiral product

To evaluate the practicality of our desymmetrisation method and synthetic utility of chiral product **3a**, we conducted a gram-scale reaction of **1a** under optimised conditions (Fig. 6A). In this gram-scale reaction, we isolated the inherently chiral product **3a** in 79% yield, with an excellent stereochemical outcome (99:1 *er*). Post-functionalisation increased molecular complexity through modifications of the aldehydic and ester group (Fig. 5B). As expected, Wittig olefination produced *α,β*-unsaturated ester **8** in high yield (86%), retaining optical purity from aldehyde **3a**. Unsurprisingly, NHC-mediated oxidative esterification with excess methanol afforded diester product **9** in high yield without changing optical purity. Similar outcomes were observed in borohydride reduction, and oxidative condition also led to the expected products with high yields and preserved stereochemical integrity, but Bayer-Viliger oxidation produced formate **10** in a slightly lower yield (43%). By Pinnick oxidation, the corresponding carboxylic acid **11** was formed in 83% yield with retained optical purity. Lastly, the ester group of derivative **3a** was hydrolysed under excess of lithium hydroxide, producing acid **12** in high yield. This compound was suitable for X-ray crystallographic analysis, enabling us to confirm its structure and absolute configuration.

The synthetic utility of the inherently chiral calix[4]arene synthon was further demonstrated through the development of an organocatalyst that combines the inherent chirality of calix[4]arene with a centrally chiral catalyst to enhance its properties (Fig. 6B). In this context, catalysts incorporating a centrally chiral secondary amine with calix[4]arene can

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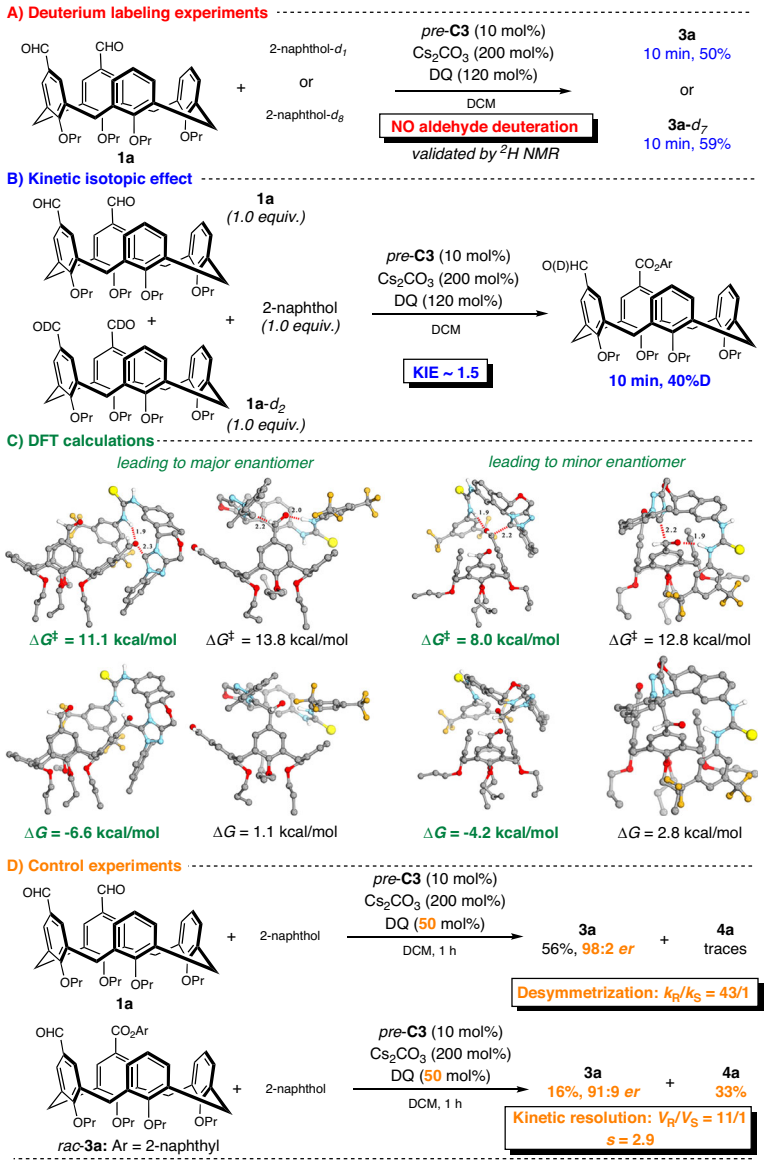

Fig. 5 | Mechanistic studies. A Deuterium labeling experiments (highlighted in red). **B** Kinetic isotopic effect (highlighted in blue). **C** DFT calculations (highlighted in green). **D** Control experiments (highlighted in orange).

promote reactions in water. It is hypothesized that a hydrophobic and a hydrophilic region are generated through the formation of hydrogen bonds between the functionalized calix[4]arene catalyst and interfacial water molecules[66]. To develop these catalysts, we modified a secondary amine-based chiral catalyst by introducing a carboxylic function to the upper ring of calix[4]arene (Fig. 6C). This additional carboxylic unit could facilitate aldol-type reactions, where carboxylic acids are often used as additives. As the starting chiral synthon, carboxylic acid **12** was converted by EDCI-mediated amine coupling to the desired product **13** in high yield (76%). But to avoid having to purify polar intermediates, such as free acid, we prepared **14** via NHC-mediated oxidative esterification in high yield. After deprotection, the proposed organocatalyst **15** was isolated and tested in an aldol reaction conducted in water, yielding a highly enantioenriched aldol product (**18**).

Additionally, we highlighted the synthetic potential of our desymmetrization method by applying this approach to chiral recognition studies. Firstly, we applied a chiral carboxylic acid **12** as a key chiral synthon in the synthesis of compound **24** (Fig. 6D), which was introduced as a chiral solvating agent for mandelic acid[67]. By adapting this follow-up transformation (EDCI-mediated coupling followed by Baeyer-Villiger oxidation), we obtained formate **23** in high yields in both steps (68 and 72%). In the final step, the reduction of both amide and formate groups provided versatile access to target compound **24**. Additionally, we tested and confirmed aldehydes **3a** and **12** as potential chiral solvating agents for amino alcohols via imine formation (for more details, please refer to the Supporting Information file).

In summary, our straightforward method for enantioselective desymmetrisation of diformylcalix[4]arenes provides versatile access to unique, inherently chiral calix[4]arenes with ABCC substitution patterns[68]. This operationally simple and highly effective strategy shows excellent functional group tolerance, enabling post-functionalisation of natural and bioactive compounds. Furthermore, the feasibility of gram-scale desymmetrisation, the utility of the resulting valuable synthon, and its broad synthetic applications underscore the significance of this method. Complemented by DFT calculations, comprehensive experimental mechanistic studies demonstrate that desymmetrisation determines enantiocontrol in esterification reactions catalysed by *N*-heterocyclic carbenes, reinforcing the potential of diformyl derivatives as valuable starting materials for further elaboration. Moving forward, ongoing research in our

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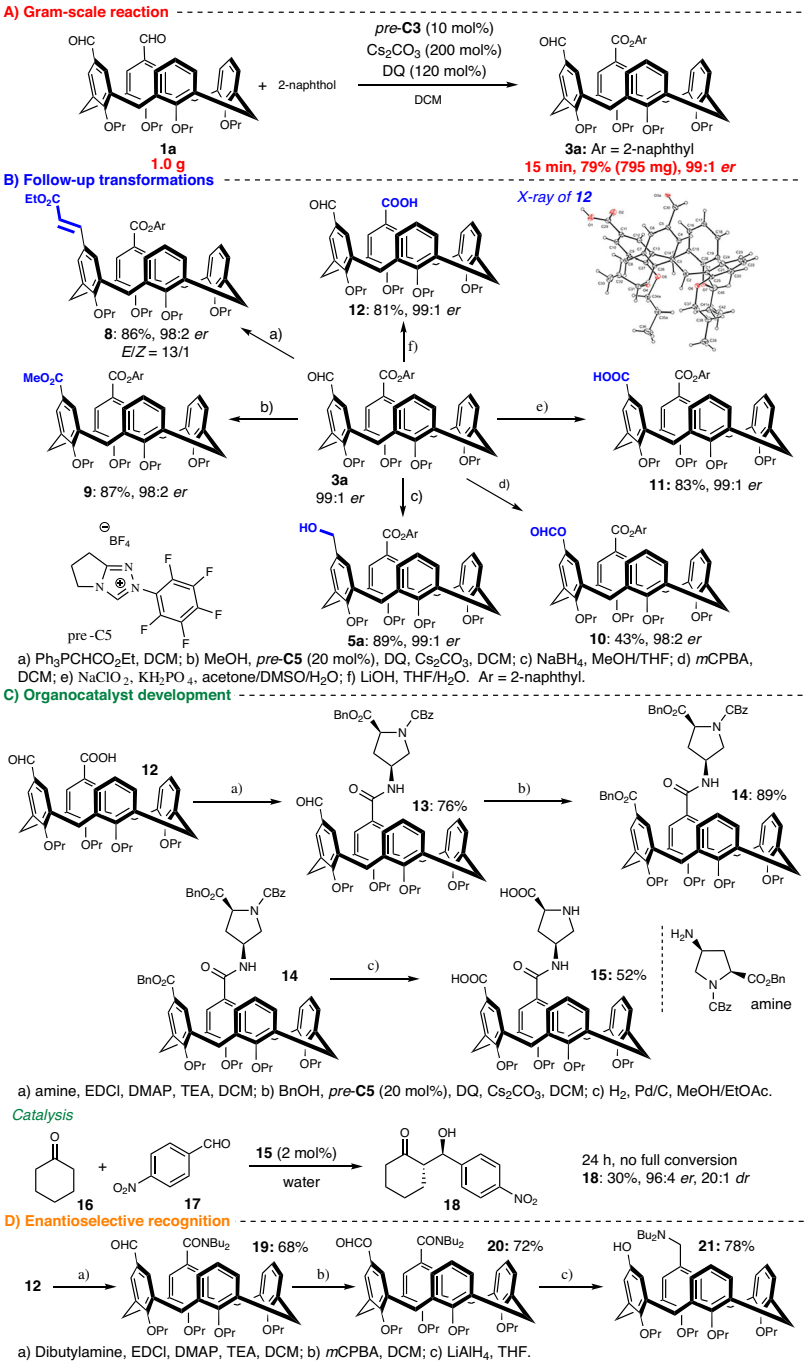

Fig. 6 | Gram-scale desymmetrisation and synthetic utility demonstration. A Gram-scale reaction (highlighted in red). **B** Follow-up transformations (highlighted in blue). **C** Organocatalyst development (highlighted in green). **D** Enantioselective recognition (highlighted in orange).

laboratories will focus on the synthesis of inherently chiral molecules via organocatalytic reactions and their diverse applications.

Methods

Representative procedure

The vial (4 ml) was charged with calix[4]arene **1** (0.06 mmol, 1.2 equiv.), *pre*-**C3** (3.3 mg, 0.005 mmol, 0.1 equiv.), DQ (24.5 mg, 0.06 mmol, 1.2 equiv.), Cs_2CO_3 (32.6 mg, 0.10 mmol, 2.0 equiv.), and the corresponding alcohol **2** (0.05 mmol, 1.0 equiv.) and dissolved in DCM (1.0 ml) at room temperature (~20 °C). At this temperature, the reaction mixture was stirred for the indicated time. Once the alcohol **2** was no longer detected by thin-layer chromatography (TLC), the reaction mixture was directly loaded to the silica gel column chromatography, and the product was eluted by hexane/EtOAc mixtures.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information file. Data supporting the findings of this manuscript are also available from the corresponding author upon request. The primary NMR data generated in this study have been deposited in the Figshare repository under accession code (https://doi.org/10.6084/m9.figshare.28105094)[69]. Cartesian coordinates are available as Supplementary Data 1. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic

Data Centre (CCDC), under deposition number CCDC 2404192. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif, or by emailing da-ta_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author contributions

V.D. designed the project conceived the study, and performed the synthesis. L.L. performed the synthesis. A.K. performed DFT calculations. I.C. performed X-ray analysis. J.V. supervised the project. V.D. and J.V. wrote the manuscript. All authors have approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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