ARTICLES
https://doi.org/10.1038/s41557-021-00715-0
nature chemistry

Check for updates

Catalytic reductive desymmetrization of malonic esters

Pengwei Xu and Zhongxing Huang ✉

Desymmetrization of fully substituted carbons with a pair of enantiotopic functional groups is a practical strategy for the synthesis of quaternary stereocentres, as it divides the tasks of enantioselection and C–C bond formation. The use of disubstituted malonic esters as the substrate of desymmetrization is particularly attractive, given their easy and modular preparation, as well as the high synthetic values of the chiral monoester products. Here, we report that a dinuclear zinc complex with a tetradentate ligand can selectively hydrosilylate one of the carbonyls of malonic esters to give α-quaternary β-hydroxyesters, providing a promising alternative to the desymmetric hydrolysis using carboxylesterases. The asymmetric reduction features excellent enantiocontrol that can differentiate sterically similar substituents and high chemoselectivity towards the diester motif of substrates. Together with the versatile preparation of malonic ester substrates and post-reduction derivatization, the desymmetric reduction has enabled the synthesis of a diverse array of quaternary stereocentres with distinct structural features.

Enantioselective construction of quaternary stereocentres is an enduring challenge in organic synthesis[1–3], as these motifs are prevalent in bioactive molecules and add considerably to the degree of saturation and three-dimensionality of molecules, parameters that are increasingly recognized as crucial to drug effectiveness[4,5]. While the majority of existing approaches hinge on the enantiofacial selection of prochiral reactants[6,7] and cationic intermediates[8–10], a growing number of desymmetrization processes have emerged in recent years describing efforts to selectively transform one of the enantiotopic substituents on a preformed quaternary carbon (Fig. 1a). As the desymmetrization process splits up the demanding tasks of enantiocontrol and C–C bond formation, almost any type of enantioselective transformation could be employed in the paradigm to forge quaternary stereocentres using suitable prochiral substrates. While the desymmetric approach continues to find success in assorted substrates, such as 1,3-diketones, diols, dienes and small rings, accessibility of the prochiral reactants and versatility of the chiral products remain two of the ultimate touchstones for the synthetic value and practicality of desymmetrization[11,12]. In this Article, we consider α,α-disubstituted malonic esters as an ideal class of desymmetrization substrates owing to their straightforward preparation from diesters and monoesters, diverse substituents that can be introduced to the carbon centre and high synthetic values of the resulting chiral monoesters (Fig. 1b). Nonetheless, as the ester carbonyls are directly bonded to the congested quaternary carbon, it is non-trivial to devise a catalytic system that has both high reactivity and precise enantiocontrol while inhibiting the undesired overreaction to give achiral bis-functionalization products.

To date, desymmetrization of malonic esters is predominated by the catalytic hydrolysis using crude pig liver esterase (PLE, EC 3.1.1) to give α-quaternary carboxylic acids[13,14]. A widely recognized cubic model by Jones and co-workers (as illustrated in Fig. 1c) indicated that the excellent stereoselectivity of crude PLE originates from the organized orientation of substrate within two polar binding sites (P_{Front} and P_{Back}) and two hydrophobic pockets[15,16] (H_{Large} and H_{Small}). However, the limited size of the large hydrophobic pocket (H_{Large}) inhibits the reactivities of malonic esters with large substituents[16] (for example, biphenyl groups) and enantioselection between two small and sterically similar substituents, such as methyl and ethyl, is suboptimal[17]. The applicability of crude PLE is also weakened by its accessibility to only one of the enantiomers and undesired reversals of stereoselectivity were observed for substrates with similar structures[17]. Nevertheless, a recent advance in recombinant DNA technology has enabled the production of pure isoenzymes of PLE (ref. [18]) with distinct reactivities and opposite stereoselectivities[19], thus offering an additional source of catalysts for application.

In comparison, nonenzymatic approaches for the desymmetrization of malonic esters are largely elusive. While isolated cases of intramolecular desymmetrization have been reported[20–22], the more daunting challenge of creating acyclic quaternary stereocentres has not been addressed. We anticipated that a reductive desymmetrization would be a practical alternative to the enzymatic hydrolysis of malonic esters, as the resulting aldehyde or primary alcohol is highly versatile and differs considerably in reactivities from the unreacted ester (Fig. 1d). Thus, the ensuing chemoselective transformation of the pair of functional groups, together with the diversity of substituents that can be introduced during the substrate preparation, would facilitate the modular construction of a myriad of quaternary stereocentres with distinct structural features. We also hypothesized that silanes would be a prominent choice of reductant for the desymmetrization, as hydrosilylation has proven to be a mild and selective method for carbonyl reduction and can be enabled by a variety of catalysts[23–25]. The high enantioselectivities obtained in the reduction of ketones and imines are particularly encouraging[26], as we seek to devise chiral catalyst manifolds that can deliver the hydride selectively to one of the carbonyls of malonic esters. In addition, as a generally inert reductant in the absence of activating catalysts, silanes would not give background reduction that erodes the enantioselectivity of the desymmetrization.

Results and discussion

Zinc-catalysed asymmetric hydrosilylation of malonic esters. Considering that zinc complexes are one of the most widely used catalysts for carbonyl hydrosilylation[27–29] and have demonstrated great potential as alternatives to expensive noble metal catalysts[30–32], we initiated our search of desymmetrization catalysts by employing

State Key Laboratory of Synthetic Chemistry, Department of Chemistry, The University of Hong Kong, Hong Kong, China. ✉e-mail: huangzx@hku.hk

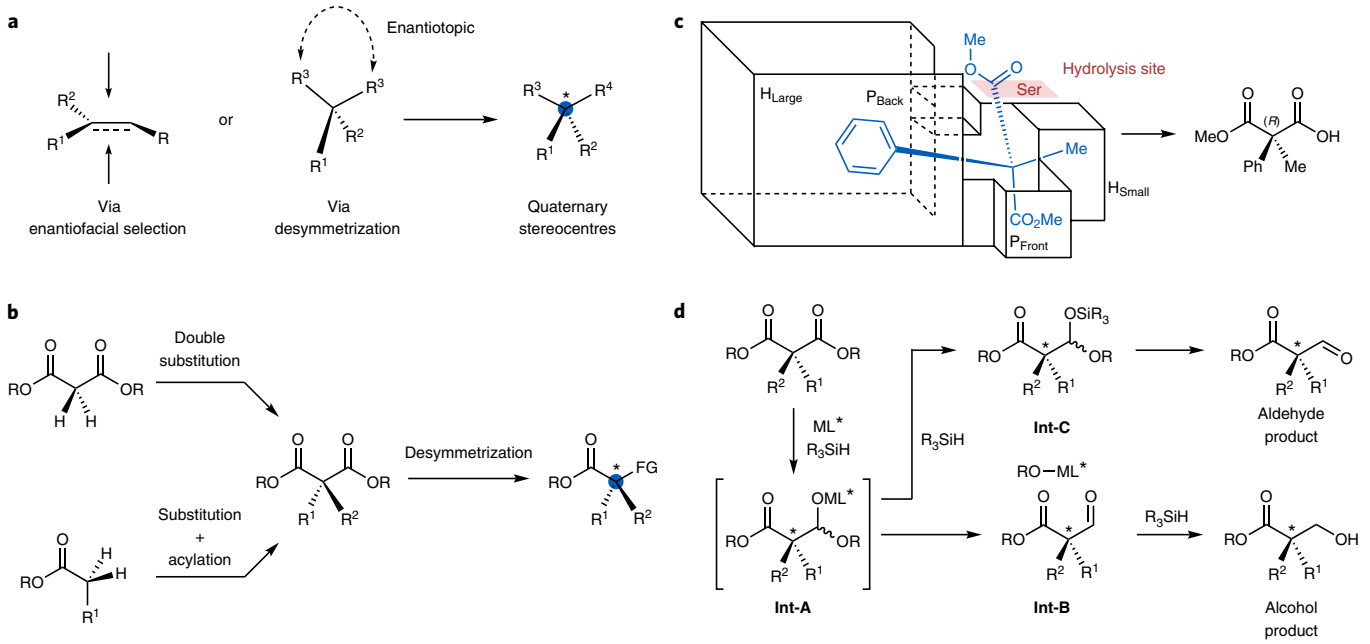
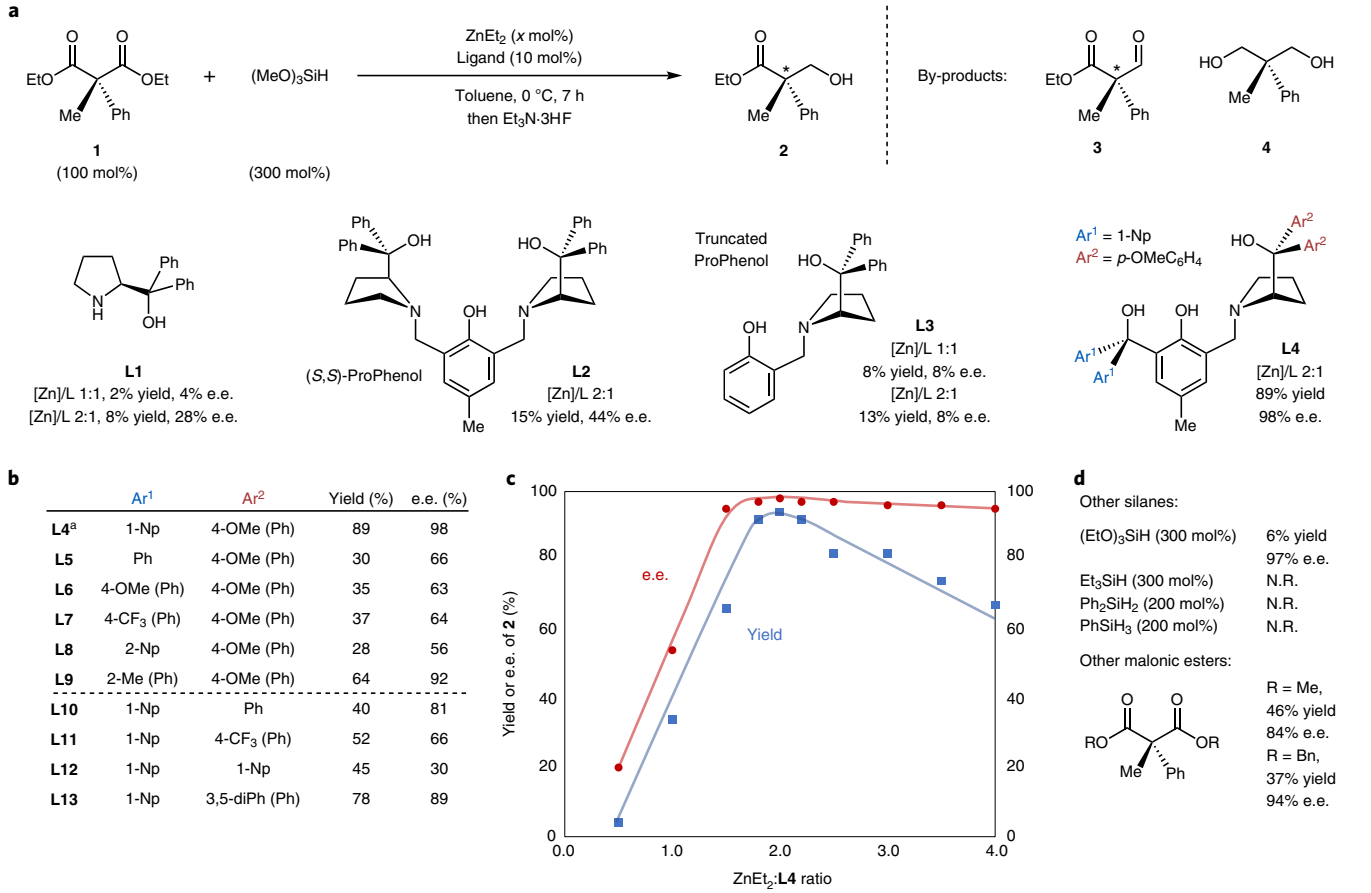


Fig. 1 | Quaternary stereocentres via desymmetrization of malonic esters. a, Quaternary stereocentres can be generated via two major approaches. They can be synthesized from an enantioselective C–C bond formation reaction of prochiral substrates or intermediates, such as alkenes and enolates. Alternatively, quaternary stereocentres can be accessed by desymmetrizing one of the enantiotopic functional groups on a preformed tetrasubstituted carbon. **b**, Synthesis and desymmetrization of malonic esters. Disubstituted malonic esters can be synthesized using two sequential substitution reactions from unsubstituted malonic esters. In addition, through a combination of acylation and substitution reactions, monoesters can also be used to access disubstituted malonic esters. The desymmetrization of disubstituted malonic esters will give chiral monoesters with a quaternary stereocentre. FG, functional group. **c**, Assisted by computational methods, Jones and co-workers proposed a cubic model for the active site of crude pig liver esterase. The model consists of two hydrophobic pockets (H_{Large} and H_{Small}) and two polar binding sites (P_{Front} and P_{Back}). Take dimethyl methyl(phenyl)malonate as an example, the phenyl and methyl substituents are proposed to fit into the large and small hydrophobic pockets, respectively. This orientation would place the Pro-(*S*) ester in proximity to the serine hydrolysis site and eventually gives the desymmetrization product with *R* configuration. **d**, Our proposed reductive desymmetrization initiates with the enantioselective hydrosilylation of the malonic ester to give **Int-A**. If **Int-A** undergoes an in situ elimination to **Int-B**, a further hydrosilylation of the resulting aldehyde would take place and the alcohol product will be generated after workup. Alternatively, the silylation of **Int-A** with silane would release **Int-C** from the catalyst which, after workup, gives the aldehyde product. ML, ligated metal complex.

diethylzinc with a variety of chiral alcohol- and amine-based ligands (Fig. 2a and Supplementary Fig. 1). To our delight, the monoreduction product (**2**) of malonic ester **1** was generated using simple (*S*)-α,α-diphenylprolinol (**L1**), albeit with marginal yield and enantioselectivity. More encouragingly, when diethylzinc and **L1** were applied in a 2:1 ratio instead of an equimolar manner, a higher enantioselectivity was observed, indicating a possible role of bimetallic zinc species as the reduction catalyst. Indeed, it was discovered that the use of Zn–ProPhenol complex[33,34], a prominent catalyst known for its well-defined dinuclear structure, resulted in an enhanced enantioselectivity. However, the yield of the desymmetrization remained low when (*S*,*S*)-ProPhenol (**L2**) or its closely related pseudo-C_2 symmetric derivatives (Supplementary Fig. 1) were employed. We envisioned that structural pruning of the ProPhenol skeleton would be beneficial, as the low reactivities may arise from the insufficient size of its pocket that struggles to host both the disubstituted malonic ester and silane reductant. Indeed, while the truncated ProPhenol (**L3**) with one sidechain removed was ineffective, improved reactivity and enantioselectivity were obtained when one of the prolinol motifs was replaced by a smaller and achiral triarylmethanol anchor. Further iterative optimization of the tetradentate scaffold led to **L4** as the optimal ligand and comparison among a series of derivatives (**L5**–**L13**) indicated that the steric bulkiness of 1-naphthyl groups on the achiral anchor (Ar^1) and the electron-rich 4-methoxyphenyl substituents of the prolinol (Ar^2) are both critical for the high reactivity and enantioselectivity (Fig. 2b). It is worth noting that, based on the variable-temperature NMR experiment (Supplementary Fig. 2), **L4** exists as a pair of inseparable diastereomers that differ in the helicity of the triarylmethanol group. Their high interconversion barrier also suggests that the helicity of the dinaphthyl motif has little effect on the enantioselectivity of the desymmetrization.

The desymmetrization turned out to be highly chemoselective—the aldehyde (**3**) and bis-reduction (**4**) products were generated only in trace amounts. On the other hand, the yield and enantioselectivity of the desymmetrization reached optimum when diethylzinc and **L4** were used in a 2:1 ratio, consistent with the proposed dinuclear mode of the catalyst (Fig. 2c). The use of trimethoxysilane as the reductant also proved critical, as bulkier triethoxysilane and other common primary, secondary and tertiary silanes showed minimal or no reactivity (Fig. 2d). In addition, dimethyl and dibenzyl malonic esters could both participate in the desymmetrization to give enantioenriched monoesters, notwithstanding the inferior reactivity compared with their ethyl counterpart.

Substrate scope of malonic esters. The reductive desymmetrization could be readily scaled up and a gram-scale synthesis of chiral hydroxy ester **2** was accomplished with a lowered catalyst loading (Table 1). Additionally, phenyl, aryl and heteroaryl groups (**16** and **17**) with different electronic properties (**5**–**11**) and substitution patterns (**12**–**15**) could all be accommodated to yield a diverse array of benzylic stereocentres in good yields and enantioselectivities. We also demonstrated that quaternary stereocentres could be rapidly forged from two nonsteroidal anti-inflammatory drugs,



b

	Ar[1]	Ar[2]	Yield (%)	e.e. (%)
L4[a]	1-Np	4-OMe (Ph)	89	98
L5	Ph	4-OMe (Ph)	30	66
L6	4-OMe (Ph)	4-OMe (Ph)	35	63
L7	4-CF_3 (Ph)	4-OMe (Ph)	37	64
L8	2-Np	4-OMe (Ph)	28	56
L9	2-Me (Ph)	4-OMe (Ph)	64	92
L10	1-Np	Ph	40	81
L11	1-Np	4-CF_3 (Ph)	52	66
L12	1-Np	1-Np	45	30
L13	1-Np	3,5-diPh (Ph)	78	89

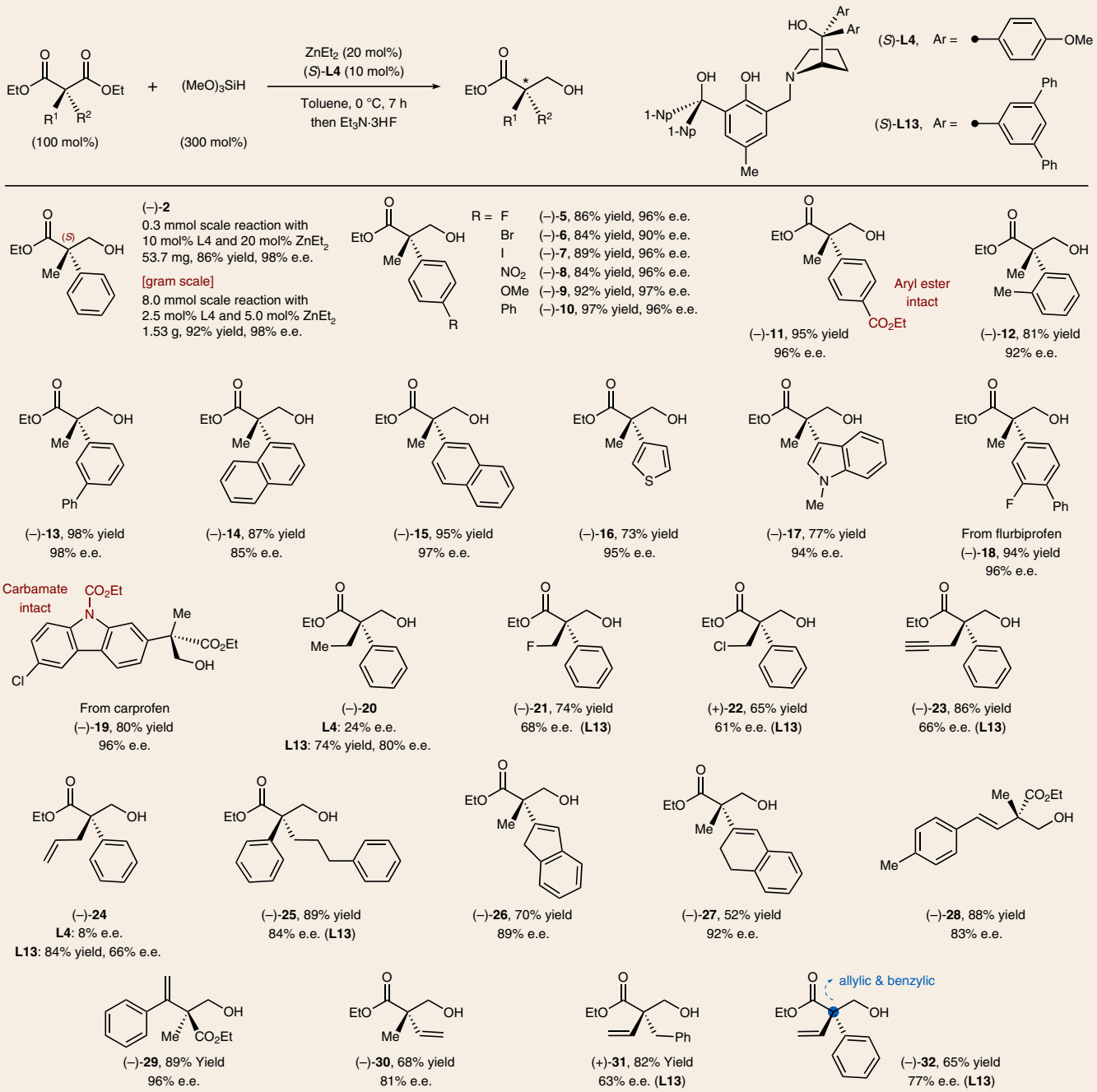
Fig. 2 | Zinc-catalysed desymmetric hydrosilylation of malonic esters. a, Discovery of a tetradentate ligand for dinuclear zinc complex. The ligand screening reactions were run with 0.1 mmol malonic ester, 300 mol% trimethoxysilane, 10 mol% ligand and 10 mol% diethylzinc when [Zn]/L = 1:1 or 20 mol% diethylzinc when [Zn]/L = 2:1 in toluene at 0 °C for 7 h. The yield and e.e. refer to the reduction product **2**. Aldehyde **3** and diol **4** were identified as the by-products. Compared with simple prolinol ligand **L1**, (*S*,*S*)-ProPhenol **L2** and truncated ProPhenol **L3**, desymmetrization with tetradentate ligand **L4** gives a significantly higher yield and enantioselectivity. Np, naphthyl. **b**, Results of the reaction in **a** when **L4** was replaced by its variants. Inferior performance in reactivity and enantioselectivity of **L5**–**L9** indicates that the fused ring structure and sterics of 1-naphthyl groups are critical for the desymmetrization, while results of **L10**–**L13** show that the electron-rich 4-methoxyphenyl substituents on the prolinol motif of **L4** are also indispensable. [a]The first reaction listed, using **L4**, gave <2% of **3** and <2% of **4**. **c**, Investigation of different diethylzinc/**L4** ratios on the reactivity and enantioselectivity of the desymmetrization reaction shown in **a**. These reactions were run with 10 mol% **L4** and varied amounts of diethylzinc ranging from 5 to 40 mol%. Both the yield and e.e. of the desymmetrization product **2** reached optimum when diethylzinc and **L4** were used in a 2:1 ratio, which indicated a possible dinuclear zinc complex as the catalyst. **d**, Control experiments using silanes other than trimethoxysilane or malonic esters with alkyl groups other than ethyl for the desymmetrization reaction shown in **a** with **L4**. The results of these reactions showed that bulkier triethoxysilane and other common primary, secondary and tertiary silanes are inferior reductants for the desymmetrization compared with trimethoxysilane. While dibenzyl and dimethyl malonate did give the monoester products, their yields and e.e. are lower than those of the diethyl malonate **1**. N.R., no reaction; Bn, benzyl.

flurbiprofen (**18**) and carprofen (**19**), via malonic ester synthesis and subsequent desymmetrization. It is worth noting that the carbamate motifs in the carprofen derivative (**19**) and the aryl ester in **11** were both found intact after the hydrosilylation, showcasing the high chemoselectivity of the dinuclear zinc catalyst. Meanwhile, the enantioselectivity of the desymmetrization diminished significantly when methyl was replaced with larger groups (**20**–**24**), presumably due to the smaller difference in size between the pair of substituents on the quaternary carbon. Nevertheless, we were delighted to find that the enantioselection improved when a ligand equipped with a bulkier prolinol sidearm (**L13**) was employed and the enhancement enabled us to synthesize enantioenriched esters with various C1–C3 units, including halomethyl (**21** and **22**), propargyl (**23**) and allyl groups (**24**). Moreover, a good enantioselectivity was also obtained when malonic ester was substituted with a 3-phenylpropyl group (**25**), probably owing to its large size that considerably outcompetes phenyl.

In addition to aryl groups, alkenyl sp^2 substituents on the malonic esters were well tolerated to yield allylic quaternary stereocentres with assorted olefins, including cyclic (**26** and **27**), 1,2- or 1,1-disubstituted (**28** and **29**) and α-olefins (**30** and **31**). Malonic ester with both a vinyl and a phenyl group also proceeded smoothly (**32**). The olefin moieties in these chiral synthons add greatly to the synthetic value of the reduction products, as they can serve as an additional handle for further modification.

Di-C(sp^3)-substituted malonic esters with various steric/electronic properties and pendant functional groups are another important class of substrates (Table 2). Gratifyingly, a simple malonic ester with a methyl and a benzyl group (**33**) was successfully desymmetrized and equally excellent yields and enantioselectivities were obtained for its higher homologues (**34** and **35**). We were also delighted to find that oxygen-containing functional groups, such as ethers (**36**) and alcohols with different types of protecting group (**37**–**39**), were compatible with the reduction to give chiral

Table 1 | Substrate scope of aryl- or alkenyl-substituted malonic esters[a]

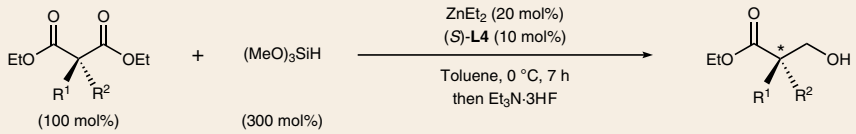


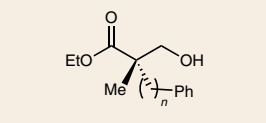
[a]Unless otherwise noted, desymmetrization reactions were run with 20 mol% $ZnEt_2$, 10 mol% tetradentate ligand **L4**, 0.3 mmol malonic ester and 300 mol% trimethoxysilane in toluene at 0 °C for 7 h (see Supplementary Information Section 6 for full details). [b]The absolute configuration of **2** was determined through the oxidation of the primary alcohol to acid and comparison with reported literature data.

and chemically differentiated 1,3- and 1,4-diols. The zinc catalyst could also deliver the desymmetrization product that contains a thioether motif (**40**) efficiently and enantioselectively without being affected by its high Lewis basicity. We were particularly interested to discover that the substrate containing a phthalimide unit could undergo the desymmetrization chemoselectively with the strained imide intact and the multi-functional product (**41**) could be viewed as a chiral 1,3-amino alcohol or β-amino ester. A successful attempt was also made to fashion a quaternary stereocentre with moderate enantioselectivity on the alkyl chain of oxaprozin that consists of an oxazole moiety (**42**).

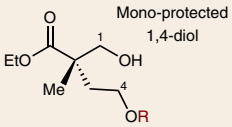
Dialkyl-substituted malonic esters with unsaturated groups, such as allyl (**43**), cinnamyl (**44**), geranyl (**45**) and propargyl (**46**) motifs, reacted smoothly to give homoallylic/homopropargylic stereocentres[35]. It is worth noting that when a β-pinene-derived substrate with pre-existing stereocentres was used, a match–mismatch effect was observed: while (*S*)-**L4** gave excellent reactivity and enantioselection (**47**), its enantiomer led to both lower diastereoselectivity and reduction rate (**48**). Considering that the construction of stereocentres containing a pair of small and marginally differentiated substituents is a notoriously challenging task for both enzymatic and chemical catalysis[36,37], we were most excited

Table 2 | Substrate scope of alkyl-substituted and cyclic malonic esters[a]

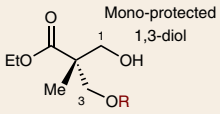




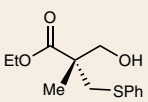
n = 1 (–)-**33**, 85% yield, 95% e.e.[b]
n = 2 (+)-**34**, 95% yield, 96% e.e.
n = 3 (+)-**35**, 96% yield, 96% e.e.



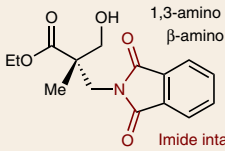
Mono-protected 1,4-diol
R = Ph, (+)-**36**
97% yield, 94% e.e.
R = Cbz, (+)-**37**
88% yield, 86% e.e.



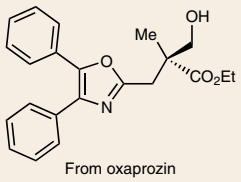
Mono-protected 1,3-diol
R = Bn, (–)-**38**
83% yield, 91% e.e.
R = Bz, (+)-**39**
88% yield, 87% e.e.



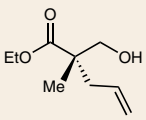
(–)-**40**, 94% yield
90% e.e.



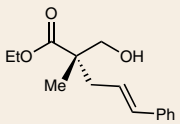
1,3-amino alcohol/ β-amino ester
Imide intact
(+)-**41**, 80% yield
97% e.e.



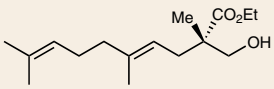
From oxaprozin
(–)-**42**, 74% yield,
67% e.e.



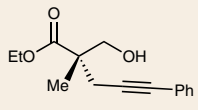
(–)-**43**, 73% yield
92% e.e.



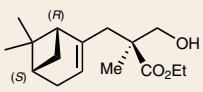
(–)-**44**, 91% Yield
92% e.e.



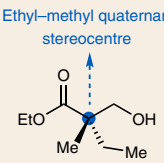
From geranyl bromide
(–)-**45**, 85% yield
94% e.e.



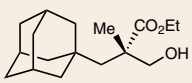
(+)-**46**, 88% yield
69% e.e.



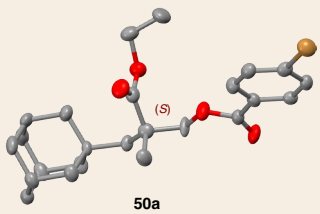
From (–)-β-pinene
(*S*)-**L4**: (–)-**47**, 61% yield, d.r. > 20:1 (7 h)
(*R*)-**L4**: (–)-**48**, 30% yield, d.r. 1:10 (7 h)
89% yield, d.r. 1:10 (24 h)



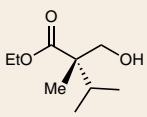
Ethyl–methyl quaternary stereocentre
(–)-**49**, 93% yield, 95% e.e.
5.0 mmol scale reaction with
2.5 mol% L4 and 5.0 mol% $ZnEt_2$



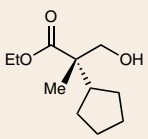
(+)-**50**, 91% yield
92% e.e.[c]



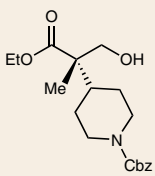
50a
p-bromobenzoyl ester of **50**



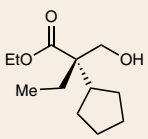
(+)-**51**, 83% yield
98% e.e.



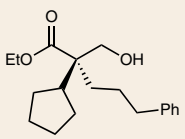
(–)-**52**, 99% yield
99% e.e.



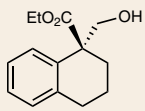
(–)-**53**, 73% yield
99% e.e.



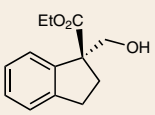
(+)-**54**, 88% yield
74% e.e. (**L13**)



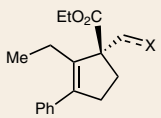
(+)-**55**, 73% yield
62% e.e. (**L13**)



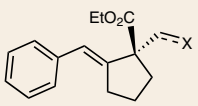
(–)-**56**, 71% yield, 88% e.e.
(aldehyde:alcohol 1:6.6)



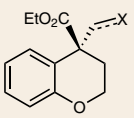
(+)-**57**, 66% yield, 96% e.e.
(aldehyde:alcohol 1:3.3)



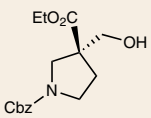
X = O or OH
(–)-**58**,[d] 81% yield, 97% e.e.
(aldehyde:alcohol 1:2.0)



X = O or OH
(–)-**59**,[d] 90% yield, 94% e.e.
(aldehyde:alcohol 1:1.3)



X = O or OH
(–)-**60**,[d] 95% yield, 98% e.e.
(aldehyde:alcohol 1.6:1)



(+)-**61**, 61% yield
56% e.e.

[a]Unless otherwise noted, desymmetrization reactions were run with 20 mol% $ZnEt_2$, 10 mol% tetradentate ligand **L4**, 0.3 mmol malonic ester and 300 mol% trimethoxysilane in toluene at 0 °C for 7 h (see Supplementary Information Section 6 for full details). [b]The absolute configuration of **33** was determined through the hydrolysis of the ethyl ester to acid and comparison with reported literature data. [c]The absolute configuration of **50** was determined by X-ray crystallography after derivatization to its *p*-bromobenzoyl ester **50a**. [d]These optical rotation signs refer to the alcohol products. Cbz, benzyloxycarbonyl; Bn, benzyl; Bz, benzoyl.

to find that an ethyl–methyl quaternary stereocentre (**49**) could be efficiently formed in higher enantioselectivity than in the conventional PLE-catalysed hydrolysis[17]. Compared with crude PLE, the dinuclear zinc catalyst also has a better tolerance for substituents of large sizes. Notably, while malonic ester-containing large biphenyl (**13**) and adamantylmethyl (**50**) groups reacted efficiently in the reduction, they were used as 'borderline substrates' to define the size of Jones and co-workers' PLE model, as their hydrolysis took days to complete or reach only marginal conversion, respectively[16]. Malonic esters with a tertiary alkyl substituent were also reduced efficiently. While the enantiodifferentiation between tertiary alkyl and methyl groups is excellent (**51**–**53**), decreased enantioselectivity was observed for substrates with both a tertiary and secondary alkyl substituent (**54** and **55**).

The reductive desymmetrization can also provide an expeditious route towards chiral carbocycles (**56**–**59**) and heterocycles (**60** and **61**) with quaternary stereocentres by using cyclic malonic esters that are readily accessible from mono-substituted malonic esters via various transformations, such as oxidative coupling, Conia-ene reaction and [3+2] cycloaddition. However, the enantioselection of a

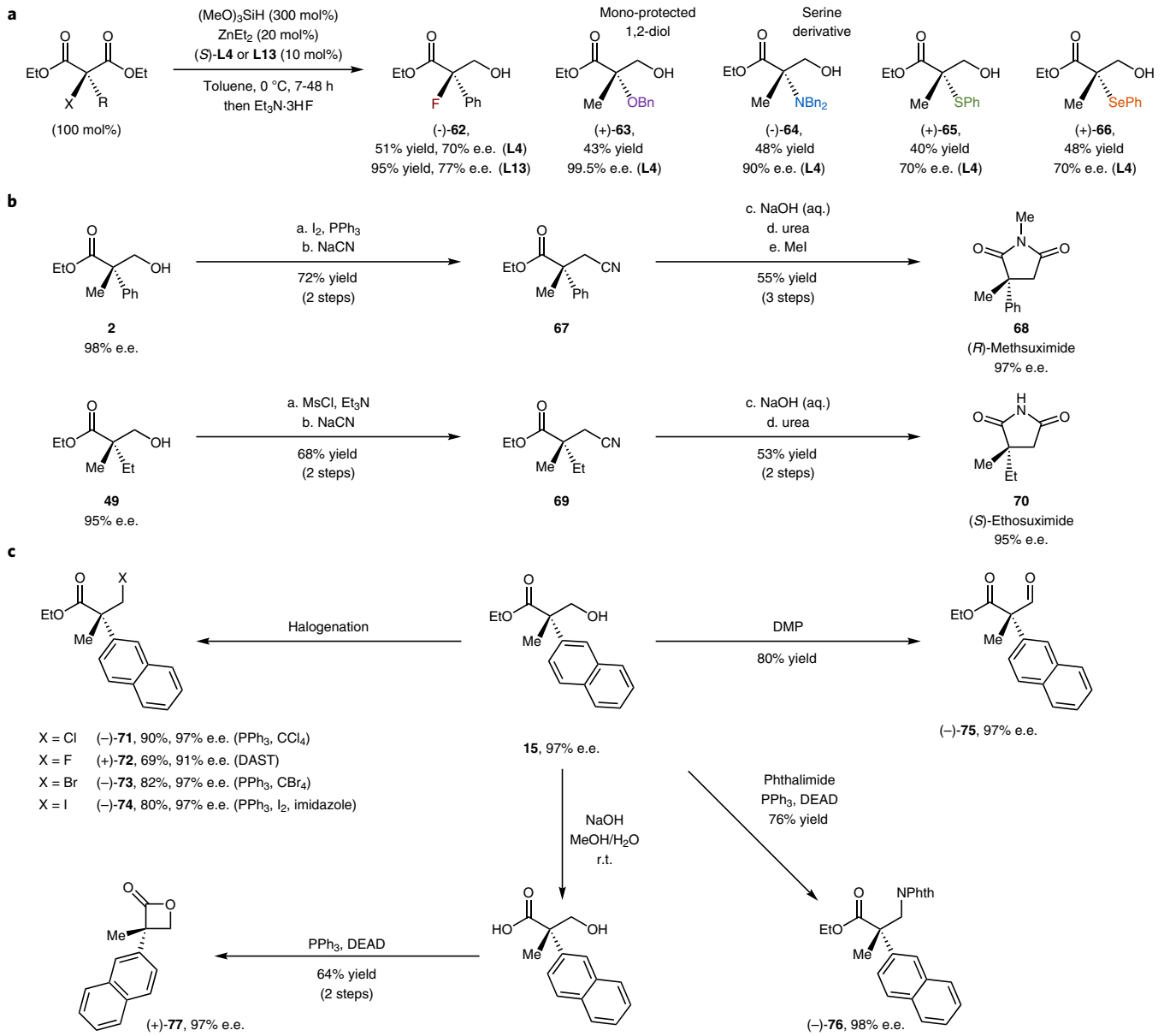


Fig. 3 | Application of the reductive desymmetrization. a, Reductive desymmetrization of heteroatom-substituted malonic esters (see Supplementary Information Section 6 for full details). The compatibility of the desymmetrization with substituents of various electronic and steric properties showcases the potential of the method in the synthesis of structurally diverse tetrasubstituted stereocentres. **b**, Desymmetrization products **2** and **49** can proceed through a sequence of cyanation and succinimide formation to access chiral anti-absence drugs methsuximide and ethosuximide, respectively (see Supplementary Information Section 7 for full details). Ms, methanesulfonyl. **c**, Chiral hydroxy ester **15** can be readily halogenated to give β-chloro, -fluoro, -bromo and -iodo esters with a quaternary stereocentre. The oxidation using DMP (Dess–Martin periodinane) and amination under Mitsunobu conditions both proceeded smoothly to give corresponding aldehyde (**75**) and β-amino ester derivative (**76**), respectively. Through sequential ester hydrolysis and intramolecular esterification, **15** was converted into lactone **77** in a good yield (see Supplementary Information Section 7 for full details). DAST, diethylaminosulfur trifluoride; NPhth, phthalimidyl; DEAD, diethyl azodicarboxylate; r.t., room temperature. See Fig. 2 caption for other definitions.

diester embedded on a pyrrolidine skeleton (**61**) was only moderate, as the steric bulk of the carbamate unit is relatively far away from the stereocentre. It should be noted that, unlike acyclic malonic esters that gave alcohols as the reduction product in high chemoselectivity, the reactions with cyclic substrates often resulted in a mixture of aldehyde and alcohol. We propose that the different product selectivity results from the rigidness and steric congestion of the intermediates (see above, Fig. 1d, **Int-A**) from cyclic substrates that may disfavour the in situ elimination to aldehyde (**Int-B**) and further hydrosilylation to silyl ether. Instead, the direct silylation of **Int-A** would release silyl acetal **Int-C** that only yields the aldehyde product during the workup.

Application and mechanistic investigation of the catalytic reductive desymmetrization. We sought to apply the reductive desymmetrization to the synthesis of heteroatom-substituted tertiary stereocentres (Fig. 3a). Our preliminary results demonstrated that tertiary alkyl fluoride **62** could be accessed in moderate enantioselectivity from the corresponding fluorinated malonic ester. On the other hand, the reductive desymmetrization of malonic esters with

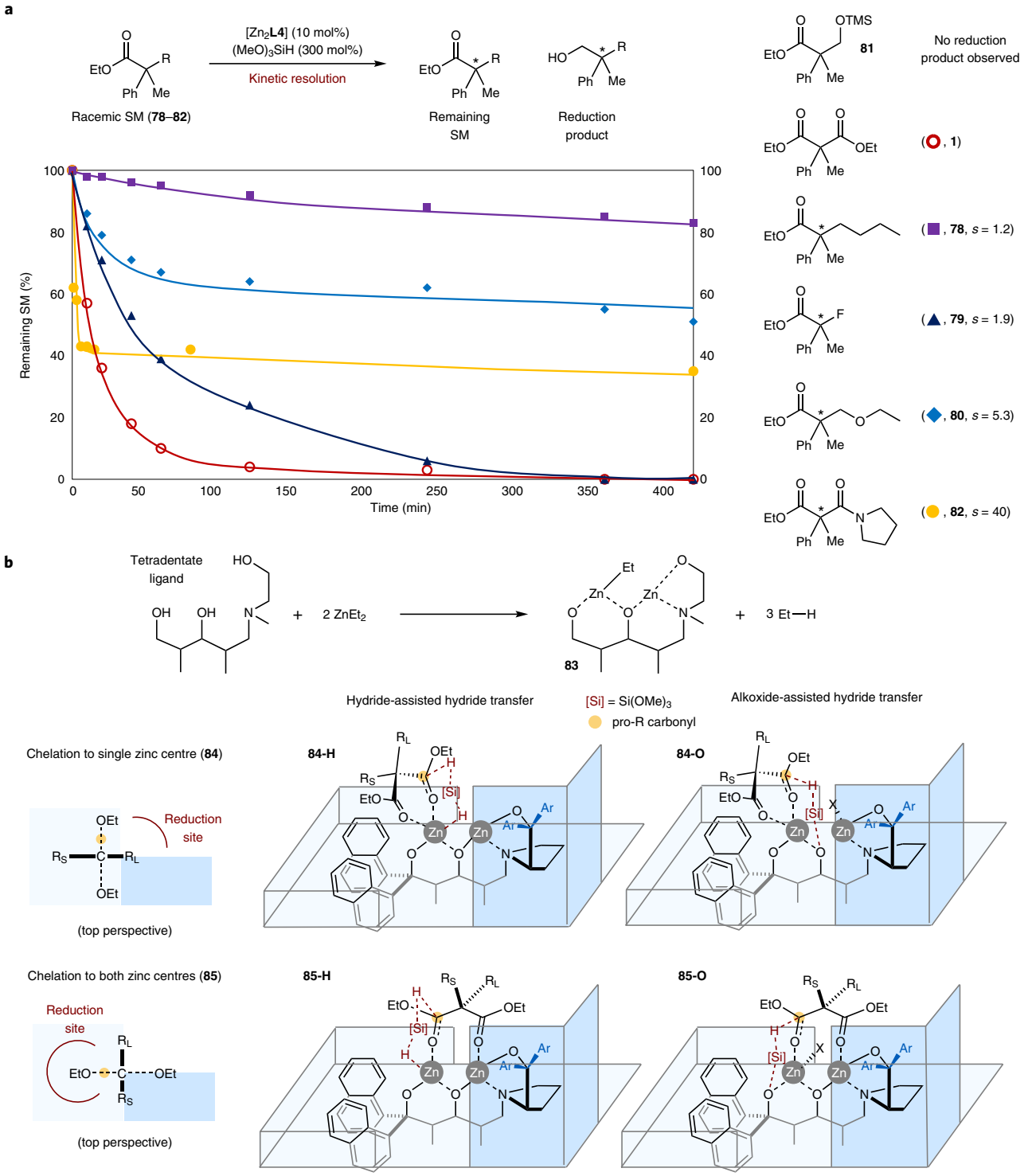


Fig. 4 | Kinetic study and proposed hydride transfer transition states. a, Kinetic resolution of structurally similar monoesters (see Supplementary Information Section 8 for full details). The asymmetric hydrosilylation of several monoesters with a similar structure to malonic ester **1** was run and monitored. The comparison among these monoesters and malonic ester **1** indicated that the presence of a second coordinating functional group in addition to the ester, such as the ether in **80** and amide in **82**, is important for a high level of enantiocontrol. SM, starting material; TMS, trimethylsilyl. **b**, The dinuclear zinc manifold **83** is proposed to be generated via the reaction of the tetradentate ligand and diethylzinc. It is also hypothesized that, during the hydride transfer, the two carbonyls of the malonic ester can chelate to the less sterically hindered zinc centre with the larger substituent (R_L) pointing to the inner and upper space of the catalyst framework (**84**), or each coordinate to one of the zinc centres with the larger group pointing to the opposite side of the diarylprolinol (**85**). In both orientations, the hydride transfer can proceed via either of the possible six-membered transition states assisted by zinc alkoxide (**84-O** and **85-O**) or zinc hydride (**84-H** and **85-H**). R_S, smaller substituent.

a benzyl-protected alcohol (**63**) or amine (**64**) gave good enantioselectivities and offered an expeditious access to chiral 1,2-diol and serine derivatives. Additionally, enantioenriched thioether (**65**) and selenoether (**66**) were successfully obtained from malonic ester substrates with highly Lewis-basic chalcogen atoms directly attached.

Next, the versatility of the desymmetrization product was demonstrated through a rapid succinimide formation that brought the quaternary stereocentres along to two anti-absence drugs, methsuximide (**68**) and ethosuximide (**70**), in their enantioenriched forms (Fig. 3b). Meanwhile, chiral and disubstituted β-lactone **77** was readily constructed from the chiral product **15** via hydrolysis and Mitsunobu reaction (Fig. 3c). Additionally, the common hydroxy ester core of the desymmetrization product could also be converted into other valuable and acyclic chiral synthons, such as β-halo esters (**71**–**74**), α-formyl esters (**75**) and β-amino esters (**76**) in a straightforward manner.

Intrigued by the high chemoselectivity and enantioselectivity of the dinuclear zinc catalyst towards malonic esters, we envisioned that structurally similar monoesters with different electronic, steric and/or coordination properties (**78**–**82**) could serve as an informative probe for the catalyst–substrate interaction, considering that the kinetic resolution of these α-quaternary monoesters should proceed through similar chiral recognition as the desymmetrization of diesters[38] (Fig. 4a). Compared with standard malonic ester substrate **1**, the replacement of one ester with a plain *n*-butyl group resulted in a much lower reduction rate (**78**) and only slight enantioselection with a negligible *s*-factor (the ratio of the rate constants for the hydrosilylation of the two enantiomers of the monoester reactant). While a monoester with a small fluorine substituent as an electron-withdrawing surrogate for an ester (**79**) reacted considerably faster in comparison, the enantioselectivity remained marginal. On the other hand, the presence of a Lewis-basic ether motif (**80**) as a potential second coordination site (besides the ester) was shown to enhance the enantioselection. The effect of chelation was further supported by the inhibited reactivity of hydroxy ester **81** where the oxygen is shielded by a trimethylsilyl group. The inactivity also explains the high mono-/di- selectivity observed in the desymmetrization (low yield of **4**, Fig. 2b, see above), as the lack of chelation in the silylated monoreduction product should prevent hydrosilylation of the remaining ester group to give diols. The indispensable role of chelation was further evidenced by the superior resolution rate and selectivity of an amide-substituted monoester (**82**) that closely resembles the malonic ester substrate. Together, results from the structure–reactivity/selectivity study of these monoesters provided indirect evidence for chelation as a major contributing factor to the high reactivity and enantioselectivity of the desymmetrization of malonic esters.

Therefore, we postulated that there are two interaction modes between the malonic ester substrate and possible dinuclear zinc catalyst (for example, **83**) derived from the deprotonation of the ligand with diethylzinc (Fig. 4b). In a classic chelation mode **84**, both carbonyls of the malonic esters are coordinated to the less sterically hindered zinc centre, with the larger substituent (R_L) pointing towards the inner and upper space of the catalyst framework to avoid clashing with the naphthlenes. On the other hand, a 'two-point chelation' (**85**) could also give the correct enantioselectivity. In this mode, each carbonyl is coordinated to one of the zinc atoms and R_L would point to the opposite side of the large diarylprolinol due to repulsion. Under either substrate–catalyst interaction mode, the key hydride transfer step could proceed through possible zinc hydride intermediates, originally proposed by Mimoun et al.[27] in the hydrosilylation of ketones. As well as the direct transfer via a four-membered transition state between zinc hydride and carbonyl (not shown), a pentavalent hydridosilicate could assemble in a relatively open space inside the catalyst pocket (**84**-**H**) or above the *gem*-dinaphthyl unit (**85**-**H**) to enable the transfer in a six-membered transition state. Alternatively, without the involvement of zinc hydrides, alkoxide ligands of the zinc complex could also participate in the hydride transfer (**84**-**O** and **85**-**O**) to give zinc hemiacetalates and a silyl exchange in the later stage would regenerate the zinc-bonded alkoxide[39].

In summary, the desymmetric reduction reported here significantly enhances the potential of easily available malonic esters to access valuable chiral synthons containing quaternary stereocentres. By alternating the oxidation state of one of the enantiotopic esters, the asymmetric reduction offers a practical alternative to the esterase-catalysed desymmetric hydrolysis by creating abundant capacity for product derivatization. The dinuclear zinc catalyst developed here is capable of exerting exceptional enantiocontrol and reducing malonic esters with high chemoselectivity, possibly through a chelating mode of substrate–catalyst interaction. By connecting the well-established malonic ester synthesis with the versatile derivatization of the β-hydroxyester product, the reductive desymmetrization here is expected to provide expeditious routes towards a plethora of chiral synthons with quaternary stereocentres.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41557-021-00715-0.

Received: 4 November 2020; Accepted: 27 April 2021;
Published online: 10 June 2021

References

1. Quasdorf, K. W. & Overman, L. E. Catalytic enantioselective synthesis of quaternary carbon stereocentres. *Nature* **516**, 181–191 (2014).
2. Trost, B. M. & Jiang, C. Catalytic enantioselective construction of all-carbon quaternary stereocenters. *Synthesis* 369-396 (2006).
3. Corey, E. J. & Guzman-Perez, A. The catalytic enantioselective construction of molecules with quaternary carbon stereocenters. *Angew. Chem. Int. Ed.* **37**, 388–401 (1998).
4. Lovering, F., Bikker, J. & Humblet, C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **52**, 6752–6756 (2009).
5. Lovering, F. Escape from flatland 2: complexity and promiscuity. *MedChemComm* **4**, 515–519 (2013).
6. Das, J. P. & Marek, I. Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems. *Chem. Commun.* **47**, 4593–4623 (2011).
7. Feng, J., Holmes, M. & Krische, M. J. Acyclic quaternary carbon stereocenters via enantioselective transition metal catalysis. *Chem. Rev.* **117**, 12564–12580 (2017).
8. Wendlandt, A. E., Vangal, P. & Jacobsen, E. N. Quaternary stereocentres via an enantioconvergent catalytic S_N1 reaction. *Nature* **556**, 447–451 (2018).
9. Braun, M. & Kotter, W. Titanium(IV)-catalyzed dynamic kinetic asymmetric transformation of alcohols, silyl ethers, and acetals under carbon allylation. *Angew. Chem. Int. Ed.* **43**, 514–517 (2004).
10. Zhao, W., Wang, Z., Chu, B. & Sun, J. Enantioselective formation of all-carbon quaternary stereocenters from indoles and tertiary alcohols bearing a directing group. *Angew. Chem. Int. Ed.* **54**, 1910–1913 (2015).
11. Zeng, X.-P., Cao, Z.-Y., Wang, Y.-H., Zhou, F. & Zhou, J. Catalytic enantioselective desymmetrization reactions to all-carbon quaternary stereocenters. *Chem. Rev.* **116**, 7330–7396 (2016).
12. Petersen, K. S. Nonenzymatic enantioselective synthesis of all-carbon quaternary centers through desymmetrization. *Tetrahedron Lett.* **56**, 6523–6535 (2015).
13. de María, P. D., García-Burgos, C. A., Bargeman, G. & van Gemert, R. W. Pig liver esterase (PLE) as biocatalyst in organic synthesis: from nature to cloning and to practical applications. *Synthesis* 1439-1452 (2007).
14. García-Urdiales, E., Alfonso, I. & Gotor, V. Enantioselective enzymatic desymmetrizations in organic synthesis. *Chem. Rev.* **105**, 313–354 (2005).
15. Toone, E. J., Werth, M. J. & Jones, J. B. Enzymes in organic synthesis. 47. Active-site model for interpreting and predicting the specificity of pig liver esterase. *J. Am. Chem. Soc.* **112**, 4946–4952 (1990).
16. Provencher, L. & Jones, J. B. A concluding specification of the dimensions of the active site model of pig liver esterase. *J. Org. Chem.* **59**, 2729–2732 (1994).

17. Björkling, F. et al. Enzyme catalysed hydrolysis of dialkylated propanedioic acid diesters, chain length dependent reversal of enantioselectivity. *Tetrahedron* **41**, 1347–1352 (1985).
18. Musidlowska, A., Lange, S. & Bornscheuer, U. T. By overexpression in the yeast *Pichia pastoris* to enhanced enantioselectivity: new aspects in the application of pig liver esterase. *Angew. Chem. Int. Ed.* **40**, 2851–2853 (2001).
19. Smith, M. E. et al. Investigation of the cosolvent effect on six isoenzymes of PLE in the enantioselective hydrolysis of selected α,α-disubstituted malonate esters. *ChemCatChem* **4**, 472–475 (2012).
20. Wilent, J. & Petersen, K. S. Enantioselective desymmetrization of diesters. *J. Org. Chem.* **79**, 2303–2307 (2014).
21. Karad, S. N., Panchal, H., Clarke, C., Lewis, W. & Lam, H. W. Enantioselective synthesis of chiral cyclopent-2-enones by nickel-catalyzed desymmetrization of malonate esters. *Angew. Chem. Int. Ed.* **57**, 9122–9125 (2018).
22. Selmani, A. & Darses, S. Enantioenriched 1-tetralones via rhodium-catalyzed arylative cascade desymmetrization/acylation of alkynylmalonates. *Org. Lett.* **21**, 8122–8126 (2019).
23. Marciniec, B. (ed.) *Hydrosilylation: A Comprehensive Review on Recent Advances* (Springer, 2009).
24. Rendler, S. & Oestreich, M. in *Modern Reduction Methods* (eds Andersson, P. G. & Munslow, I. J.) 183–207 (Wiley, 2008).
25. Díez-González, S. & Nolan, S. P. Transition metal-catalyzed hydrosilylation of carbonyl compounds and imines. A review. *Org. Prep. Proced. Int.* **39**, 523–559 (2007).
26. Uvarov, V. M. & de Vekki, D. A. Recent progress in the development of catalytic systems for homogenous asymmetric hydrosilylation of ketones. *J. Organomet. Chem.* **923**, 121415 (2020).
27. Mimoun, H., de Saint Laumer, J. Y., Giannini, L., Scopelliti, R. & Floriani, C. Enantioselective reduction of ketones by polymethylhydrosiloxane in the presence of chiral zinc catalysts. *J. Am. Chem. Soc.* **121**, 6158–6166 (1999).
28. Mimoun, H. Selective reduction of carbonyl compounds by polymethylhydrosiloxane in the presence of metal hydride catalysts. *J. Org. Chem.* **64**, 2582–2589 (1999).
29. Das, S., Möller, K., Junge, K. & Beller, M. Zinc-catalyzed chemoselective reduction of esters to alcohols. *Chem. Eur. J.* **17**, 7414–7417 (2011).
30. Enthaler, S. & Wu, X.-F. (eds) *Zinc Catalysis: Applications in Organic Synthesis* (Wiley, 2015).
31. Enthaler, S. Rise of the zinc age in homogeneous catalysis? *ACS Catal.* **3**, 150–158 (2013).
32. Wu, X. & Neumann, H. Zinc-catalyzed organic synthesis: C–C, C–N, C–O bond formation reactions. *Adv. Synth. Catal.* **354**, 3141–3160 (2012).
33. Trost, B. M., Hung, C.-I. & Mata, G. Dinuclear metal-prophenol catalysts: development and synthetic applications. *Angew. Chem. Int. Ed.* **59**, 4240–4261 (2020).
34. Trost, B. M. & Mino, T. Desymmetrization of meso 1,3- and 1,4-diols with a dinuclear zinc asymmetric catalyst. *J. Am. Chem. Soc.* **125**, 2410–2411 (2003).
35. Liu, Y., Han, S.-J., Liu, W.-B. & Stoltz, B. M. Catalytic enantioselective construction of quaternary stereocenters: assembly of key building blocks for the synthesis of biologically active molecules. *Acc. Chem. Res.* **48**, 740–751 (2015).
36. Yang, Y., Cho, I., Qi, X., Liu, P. & Arnold, F. H. An enzymatic platform for the asymmetric amination of primary, secondary and tertiary C(sp^3)–H bonds. *Nat. Chem.* **11**, 987–993 (2019).
37. Zhang, F.-H., Zhang, F.-J., Li, M.-L., Xie, J.-H. & Zhou, Q.-L. Enantioselective hydrogenation of dialkyl ketones. *Nat. Catal.* **3**, 621–627 (2020).
38. Walsh, P. J. & Kozlowski, M. C. in *Fundamentals of Asymmetric Catalysis* 297–329 (University Science Books, 2009).
39. Ushio, H. & Mikami, K. Asymmetric reduction of *ortho*-multisubstituted benzophenones catalyzed by diamine–Zn–diol complexes. *Tetrahedron Lett.* **46**, 2903–2906 (2005).

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

© The Author(s), under exclusive licence to Springer Nature Limited 2021

Methods

Caution–safety when working with diethylzinc. Diethylzinc is a highly pyrophoric chemical and can be dangerous when not handled properly. Diethylzinc solution should be stored under an inert atmosphere and kept away from oxidants, water and heat. Diethylzinc solution can be handled inside a glovebox filled with inert gas (such as nitrogen or argon). When used in a fumehood, be sure to lower the sash down to the lowest operable height and remove all inflammable materials from the hood. In addition, transfer of diethylzinc solution using a syringe should be performed with the diethylzinc container and receiving tube both under an inert atmosphere (that is connected to a Schlenk line or using a balloon). The residual diethylzinc solution in the syringe should be diluted in a flask with hexane and consequently quenched with dropwise addition of isopropanol.

General procedure for catalytic reductive desymmetrization. To an oven-dried 10 ml round-bottom flask was added **L4** (71.5 mg, 0.1 mmol) or **L13** (96.0 mg, 0.1 mmol). The flask was sealed with a rubber septum and evacuated/refilled three times with nitrogen. Then, 2 ml of freshly distilled toluene was added to the flask using a syringe in the presence of a nitrogen balloon and the mixture was stirred at room temperature for 5 min. Subsequently, diethylzinc (200 µl, 1.0 M solution in hexane, 0.2 mmol) was added to the flask slowly using a syringe. The resulting catalyst solution was stirred at room temperature for 30 min before use.

A separate oven-dried 25 ml Schlenk tube was sealed with a rubber septum and evacuated/refilled 3 times with nitrogen. Under a nitrogen atmosphere, 3 ml of freshly distilled toluene, malonic ester (0.3 mmol, 100 mol%) and trimethoxysilane (110 mg, 0.9 mmol, 300 mol%) were added using a syringe. The mixture was stirred and cooled to 0 °C using a cooling bath and 0.6 ml of the aforementioned catalyst solution was added using a syringe to initiate the reduction. The reaction mixture was stirred at 0 °C for 7 or 24 h and 0.5 ml triethylamine trihydrofluoride was then added to quench the reaction. The mixture was diluted with 2 ml diethyl ether, allowed to warm to room temperature and stirred for 1 h. Subsequently, the reaction mixture was passed through a small plug of silica gel, eluted with diethyl ether (proceed with care as the remaining triethylamine trihydrofluoride reacts with silica gel and releases heat). The filtrate was concentrated under reduced pressure and submitted to flash column chromatography (hexanes/ethyl acetate) to yield the desymmetrization product.

Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information. Crystallographic data for **50a** reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition number CCDC 2025159. Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/. Source data are provided with this paper.

Acknowledgements

We thank the University of Hong Kong for a start-up fund. We acknowledge funding support from the Laboratory for Synthetic Chemistry and Chemical Biology under the Health@InnoHK Program launched by the Innovation and Technology Commission, the Government of HKSAR. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. C.-M. Che and P. Chiu are acknowledged for their kind support and sharing of chemicals. K.-H. Low, J. Yip and B. Yan are acknowledged for X-ray crystallography, mass spectroscopy and NMR spectroscopy, respectively. We also thank L. Wu for helpful discussion.

Author contributions

Z.H. conceived and designed the project. P.X. and Z.H. carried out the experiments, analysed the data and wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41557-021-00715-0.

Correspondence and requests for materials should be addressed to Z.H.

Peer review information *Nature Chemistry* thanks Marcin Kwit and the other, anonymous, reviewers(s) for their contribution to the peer review of this work.

Reprints and permissions information is available at www.nature.com/reprints.