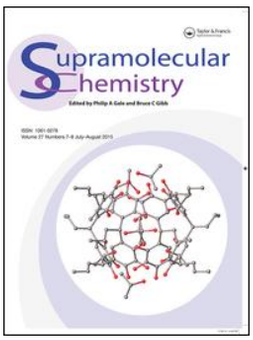

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Crown-ether-modified cyclic dipeptides as supramolecular chiral catalysts

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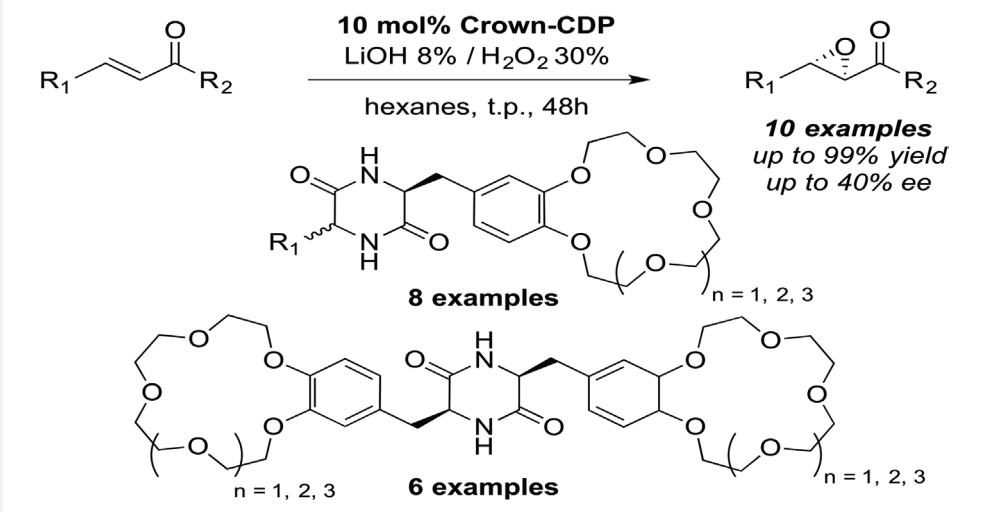
ABSTRACT

With the objective to develop supramolecular catalysts for useful chemical transformations, we report here a rapid and efficient solid-phase synthesis of novel cyclic dipeptides (crown-CDPs) with a diversity of L-DOPA derived crown ether substituents and stereochemistry. We prepared and characterized 14 crown-CDPs and evaluated their efficiency as supramolecular epoxidation catalysts in a water/hexanes biphasic system. Yields increase significantly in the presence of the crown-CDPs, though enantioselectivity depends on the nature of the substituents. The results reported constitute a useful approach for chiral epoxides of interest and further illustrate the potential of cyclic peptides as supramolecular catalysts.



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Artificial amino acids; crown ethers; cyclic dipeptide; chiral receptors; supramolecular catalysis

1. Introduction

Cyclic dipeptides (CDPs) are an excellent, easily accessible scaffold for producing supramolecular receptors and catalysts (*1–9*). CDPs have two chiral side chains on a flat cyclic dipeptide ring, which allows a rich diversity of substituents to be added with a preferential orientation. We recently reported an example of interfacial supramolecular catalysis, the asymmetric epoxidation of electron-deficient ketones catalysed by several CDPs in a water/hexanes media (*10,11*). Good enantioselectivities were obtained, though conversions were good to moderate after 48 h.

We also demonstrated that some structural features are required for efficient conversion and, more importantly, induction of chirality into the products. Very subtle changes in the CDPs can lead to significant drops in efficiency. Among all the CDPs prepared, the most efficient one was derived from L-Leucine, leading to 70% ee in the epoxidation process. Computational studies provided insight into the functional supramolecular interfacial complex between *cyclo*(L-Leu-L-Leu), the enone, a sodium cation and a hydroperoxide ion, which is required for good enantioselectivity, consistent with the experimental data (*11*).

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Thus, the well-defined supramolecular complex located at the interface with a cation inspired us to develop a second generation of CDP catalysts. We hypothesized that incorporating one or two crown ethers as cation ligands onto the cyclic dipeptide core could enhance both reaction rate and enantioselectivity, thus acting as supramolecular phase-transfer catalysts. Crown ethers are well known phase-transfer catalysts used efficiently in numerous processes (*12*). Interestingly, Bakó et al. reported the use of monoaza-[15]-crown-5 derived from monosaccharides as an asymmetric phase-transfer catalyst in the epoxidation of electron-deficient enones (*13–17*) and other further theoretical studies have been described (*18*). Also, chiral crown ethers have been examined for asymmetric phase-transfer epoxidation of olefins (*19,20*). Herein, we report our results on the efficiency of *mono*- and *bis*- L-DOPA derived crown ether cyclic dipeptides (crown-CDPs) using different oxidant systems.

Early examples of similar crown-CDPs were reported by Sonveaux et al. In their studies, five crown-CDPs were prepared in solution by the condensation of one *N*-Boc protected amino acid and a crown DOPA methyl ester (*21,22*). A further cyclization step of the linear dipeptide in solution led to *cis* (**1–2**), *trans* (**3–4**) and *bis* (**5**) crown-CDPs, as depicted in Figure 1. Also, Závada et al. synthesized three crown-CDPs (**6–8**) with a spiro-crown ether attached to the α-carbons (Figure 1) (*23*).

Our strategy to prepare crown-CDPs with one crown ether side chain involved using one proteogenic amino acid and one L-DOPA-derived crown ether. We use leucine, alanine and phenylalanine, based on our previous results (*11*). In addition, we investigated crown-CDPs with two crown ether side chains in an attempt to exploit a cooperative binding of metal cations, which in turn could facilitate the migration of the hydroperoxide anion at the interface. This could lead to an increase of the epoxidation reaction rate and enantioselectivity.

Recently, we reported a rapid and efficient parallel synthetic procedure toward optically pure CDPs, using enantiopure *N*-*t*-butyloxycarbonyl (*N*-Boc) protected amino acids (*11,24*). We used a Kaiser oxime resin with an *N*-Boc protection strategy to prepare linear dipeptides, which were cleaved from the resin by an intramolecular cyclization to yield highly pure CDPs. Using this synthetic strategy, we report herein the preparation of novel enantiopure crown-CDPs bearing one or two crown ether side chains and their utilization as asymmetric supramolecular catalysts in the epoxidation of electron-deficient ketones.

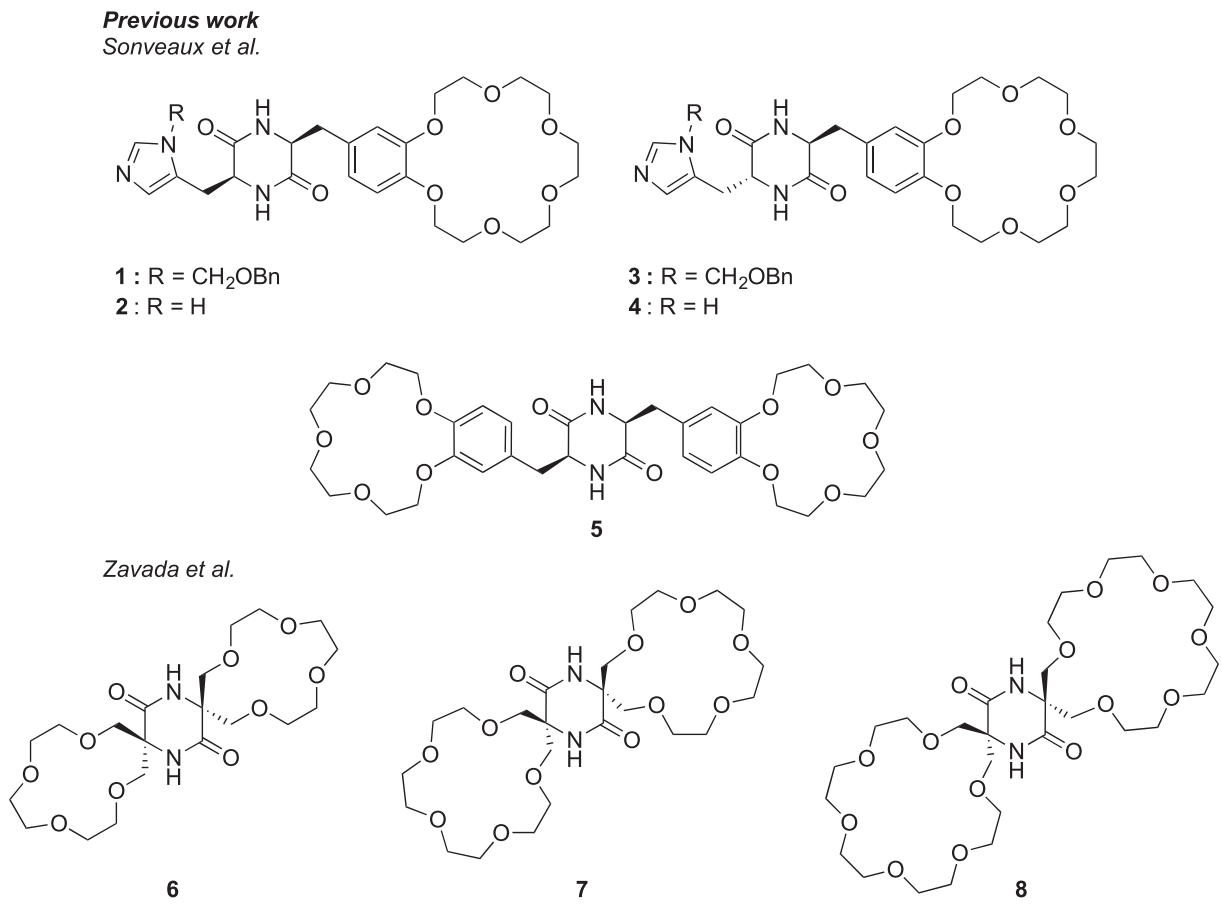


Figure 1. Previous work by Sonveaux and Závada.

2. Results and discussion

2.1. Crown ether amino acids synthesis

The binding selectivity of crown ethers depends on their size and on the number of oxygen atoms each contains. Hence, we devised a general synthetic strategy for enantiopure crown ether amino acids with different macrocycle sizes (*25*). The synthetic procedure starts with commercially available 3,4-dihydroxy-L-phenylalanine, L-DOPA (**9**). Taking advantage of the catechol function, macrocycles were formed in solution from fully protected L-DOPA **11** and dibromo-oligo(ethylene glycol) synthons **12–14,** leading to a variety of crown ether amino acids **15–17** (Figure 2). The acid function was then deprotected using NaOH in methanol to provide the desired *N*-Boc protected amino acids **18–20,** which were used in peptide synthesis. Overall, the *N*-Boc crown ether L-phenylalanines **18**, **19** and **20** were prepared in five steps with respectively 35, 42 and 53% isolated yields from L-DOPA. The crown ethers were optically pure, as established previously (*26*).

2.2. Cyclic dipeptide synthesis

Fourteen new crown-CDPs were prepared by solid-phase synthesis using Kaiser oxime resin (*27,28*). Taking advantage of the availability of natural and unnatural chiral amino acids as chiral synthons, the crown-CDPs were synthesized with a variety of substituents and stereochemistry. The key step of this rapid method is the concomitant cyclization and cleavage of a linear dipeptide from the oxime ester linkage from resin, as previously reported (*10,11,24,29,30*). The first amino acid was coupled for three hours using diisopropylcarbodiimide (DIC) as a coupling reagent. The *N*-Boc protecting group was removed using a mixture of 1:1 trifluoroacetic acid (TFA)/dichloromethane, while the second amino acid was activated with 6-Chloro-1-hydroxybenzotriazole (6-Cl-HOBt) and *O*-(6-Chlorobenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HCTU). After deprotection, the linear dipeptide was treated with diisopropylethylamine (DIEA; 2.5 equiv.)

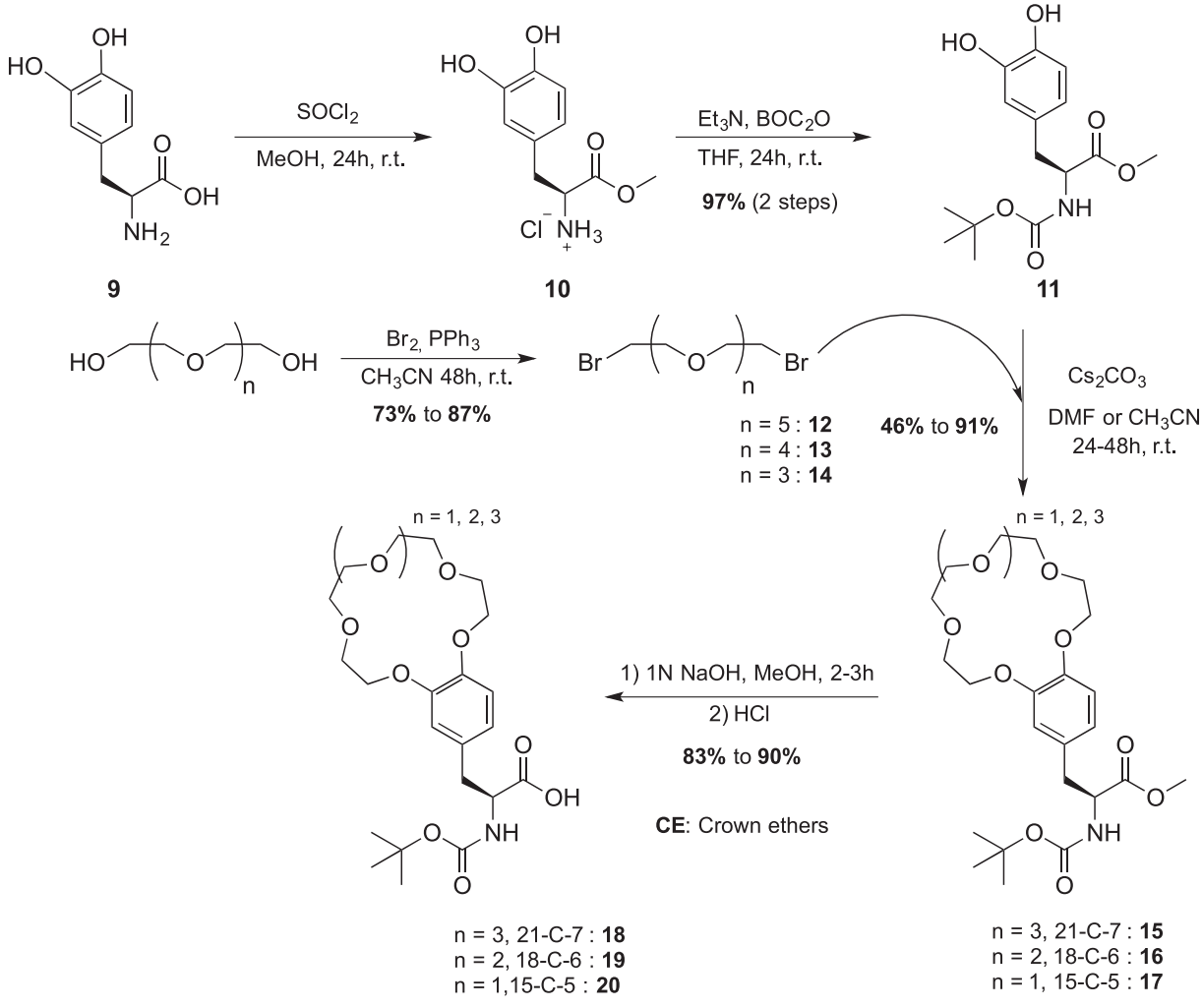


Figure 2. Synthetic procedure for crowned DOPA amino acid derivatives **18–20.**

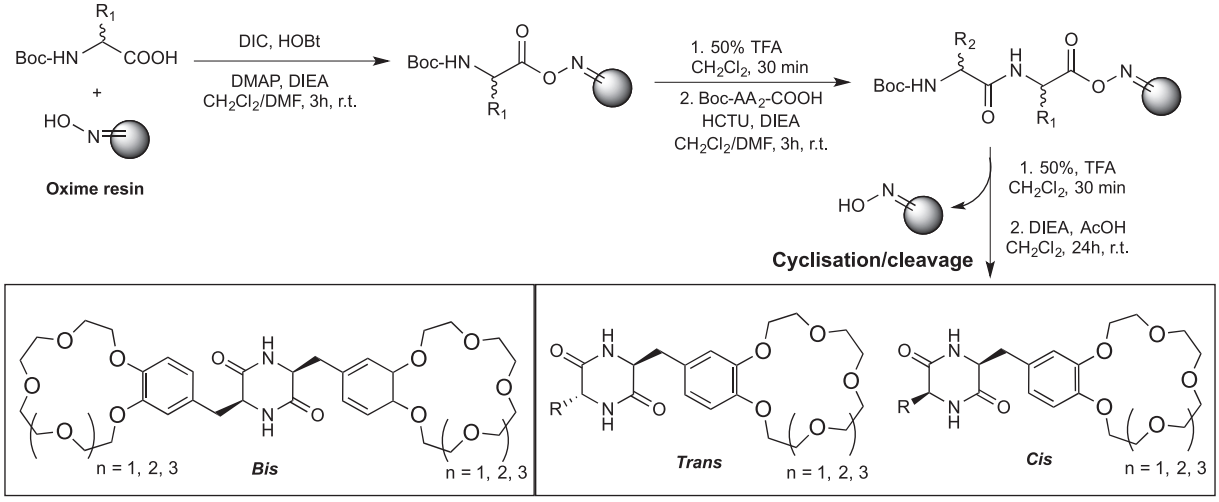
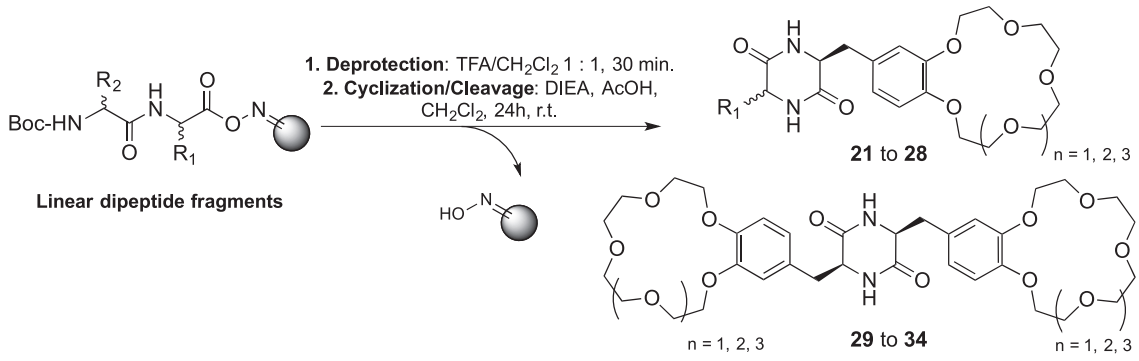


Figure 3. Synthetic procedure for crown-CDPs.

Table 1. Novel synthesized crown-CDPs.



Entry	R_1	R_2	Crown-CDPs	Yield (%)
1	(*S*)-$CH_2CH(CH_3)_2$	(*S*)-DOPA(18-C-6)	**21**	65
2	(*R*)-$CH_2CH(CH_3)_2$	(*S*)-DOPA(18-C-6)	**22**	43
3	(*S*)-$CH_2CH(CH_3)_2$	(*S*)-DOPA(21-C-7)	**23**	72
4	(*R*)-$CH_2CH(CH_3)_2$	(*S*)-DOPA(21-C-7)	**24**	67
5	(*S*)-$CH_2CH(CH_3)_2$	(*S*)-DOPA(15-C-5)	**25**	81
6	(*R*)-$CH_2CH(CH_3)_2$	(*S*)-DOPA(15-C-5)	**26**	74
7	(*S*)-CH_3	(*S*)-DOPA(18-C-6)	**27**	40
8	(*S*)-CH_2Ph	(*S*)-DOPA(18-C-6)	**28**	67
9	(*S*)-DOPA(15-C-5)	(*S*)-DOPA(15-C-5)	**29**	72
10	(*S*)-DOPA(15-C-5)	(*S*)-DOPA(18-C-6)	**30**	59
11	(*S*)-DOPA(15-C-5)	(*S*)-DOPA(21-C-7)	**31**	64
12	(*S*)-DOPA(18-C-6)	(*S*)-DOPA(18-C-6)	**32**	40
13	(*S*)-DOPA(18-C-6)	(*S*)-DOPA(21-C-7)	**33**	63
14	(*S*)-DOPA(21-C-7)	(*S*)-DOPA(21-C-7)	**34**	50

and acetic acid (AcOH; 5 equiv.) in dichloromethane to cause simultaneous cyclization and cleavage from the resin, leading to high-purity crown-CDPs **21–34** (Table 1) with control over substitution patterns and the stereochemistry.

In this way, we successfully synthesized *cis* and *trans* analogues of crown-CDPs with a variety of crown ether side chains. We also prepared all possible combinations of crown-CDPs bearing two crown ether side chains using *N*-Boc amino acids **18–20**. Overall, 14 crown-CDPs were prepared in good yields (40–81%) with between 80 and 92% purity by a simple treatment of the crude cyclization products with Amberlite IR-120 and trituration with ether. The purity of all crown-CDPs was sufficient to be used as-is in the epoxidation reactions. It is worth mentioning that the overall synthesis proceeds with very low racemization (5% or less), as measured by NMR signals of the diastereomeric crown-CDPs (*24*).

2.3. Use of crown-CDPs in the epoxidation of electron-deficient enones

2.3.1. Optimization of reaction conditions

With a series of diverse enantiopure crown-CDPs in hand, we investigated their efficacy in the asymmetric epoxidation of a model substrate, the *trans*-chalcone **35,** producing the epoxychalcone **36a**. At first, we investigated the epoxidation using *cis* crown-CDP **21,** which has a benzo-18-crown-6 side chain and an isobutyl side chain. The epoxidation of **35** was carried out in a liquid-liquid toluene/water biphasic system employing aqueous sodium hydroxide in 30% hydrogen peroxide as a reagent, with 10 mol% of catalyst **21** (Table 2, entries 1–2).

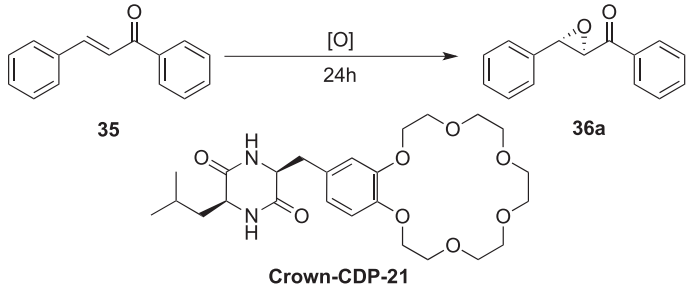
These experiments revealed that a higher concentration of sodium hydroperoxide increases the reaction rate. The use of dichloromethane instead of toluene led to a lower yield and provided racemic epoxychalcone **36a** (Table 2, entry 3). Both diethyl ether and hexanes led to high yields, though only hexanes yielded enantio-enriched **36a,** albeit with a low 9% ee (Table 2, entries 4–5). Overall, hexanes were found to be the most adequate organic solvent in terms of rate and enantioselectivity (Table 2, entry 5).

Further investigations were done with different oxidation reagents such as *tert*-butyl hydroperoxide (TBHP) and sodium hypochlorite (NaOCl), keeping hexanes as the organic solvent and 10 mol% of **21** as the catalyst loading (Table 2, entries 6 and 7). In both cases, racemic epoxychalcone was obtained, pointing to the importance of sodium peroxide and the formation of a supramolecular complex.

We then explored the impact of counter cations on the process. Lithium, potassium and cesium ions were investigated (Table 2, entries 8–12). The lithium cation was more efficient than other cations in providing epoxychalcone with higher enantioselectivity (37% ee), which replicates a phenomena observed by others (*31,32*). Interestingly, we observed a higher reaction rate at a lower base concentration using lithium hydroxide. This could be due to the ability of the benzo-18-crown-6 to more efficiently bind sodium and potassium ions, hence possibly decreasing the stability of the supramolecular complex necessary for catalysis. In fact, the nature of the counter cation significantly impacts the chemical yield and the enantioselectivity at lower concentrations.

An attempt to enhance the enantioselectivity by lowering the reaction temperature to zero degrees led to a slightly increased enantioselectivity, from 37% to 39% ee of epoxychalcone **36a** (Table 2, entry 13). Finally, using 5 mol% of catalyst loading (crown-CDP-**21)** led to comparable epoxidation results, with 31% conversion and 36% ee (Table 2, entry 14).

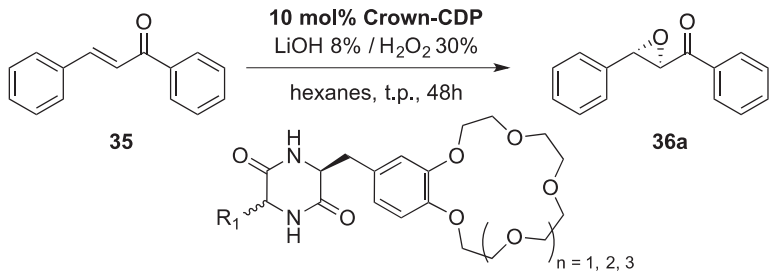
Table 2. Optimization of epoxidation conditions[a].



Entry	Crown-CDP-**21** (mol%)	Oxidant system	Solvent	Yield (%)[b]	ee (%)[b]
1	10	8% NaOH/30% H_2O_2	PhMe	16	0
2	10	20% NaOH/30% H_2O_2	PhMe	70	0
3	10	20% NaOH/30% H_2O_2	DCM	13	0
4	10	20% NaOH/30% H_2O_2	Et_2O	93	0
5	10	20% NaOH/30% H_2O_2	Hexanes	98	9
6	10	20% NaOH/70% TBHP	Hexanes	98	0
7	10	13% NaOCl[c]	Hexanes	6	0
8	10	8% LiOH/30% H_2O_2	Hexanes	46	37
9	10	8% KOH/30% H_2O_2	Hexanes	25	0
10	10	20% KOH/30% H_2O_2	Hexanes	98	5
11	10	20% K_2CO_3/30% H_2O_2	Hexanes	25	0
12	10	20% Cs_2CO_3/30% H_2O_2	Hexanes	25	0
13[d]	10	8% LiOH/30% H_2O_2	Hexanes	27	39
14	5	8% LiOH/30% H_2O_2	Hexanes	31	36

[a]Unless otherwise noted, the reaction was performed as a biphasic system using **35** (0.1 mmol) and **21** (0.01 mmol) in solvent (0.3 ml) and a solution (0.2 ml) b of base in 30% H_2O_2 for 24 h.
[b]Determined by chiral HPLC.
[c]0.5 mL was used.
[d]Reaction performed at 0 °C.

Table 3. Evaluation of crown-CDPs synthesized in the optimized asymmetric reaction conditions[a].



Entry	Crown-CDPs	Yield (%)[b]	ee (%)[b]
1	*cyclo*[L-Leu-L-DOPA(18-C-6)] **21**	93	34
2	*cyclo*[D-Leu-L-DOPA(18-C-6)] **22**	85	7
3	*cyclo*[L-Leu-L-DOPA(21-C-7)] **23**	99	11
4	*cyclo*[D-Leu-L-DOPA(21-C-7)] **24**	88	8
5	*cyclo*[L-Leu-L-DOPA(15-C-5)] **25**	67	0
6	*cyclo*[D-Leu-L-DOPA(15-C-5)] **26**	88	0
7	*cyclo*[L-Ala-L-DOPA(18-C-6)] **27**	99	9
8	*cyclo*[L-Phe-L-DOPA(18-C-6)] **28**	92	5
9	*cyclo-bis*[L-DOPA(15-C-5)] **29**	91	6
10	*cyclo*[L-DOPA(15-C-5)-L-DOPA(18-C-6)] **30**	53	8
11	*cyclo*[L-DOPA(15-C-5)-L-DOPA(21-C-7)] **31**	76	4
12	*cyclo-bis*[L-DOPA(18-C-6)] **32**	93	0
13	*cyclo*[L-DOPA(18-C-6)-L-DOPA(21-C-7)] **33**	86	4
14	*cyclo-bis*[L-DOPA(21-C-7)] **34**	93	4

[a]Unless otherwise noted, the reaction was performed as a triphasic system using **35** (0.1 mmol) and catalyst in hexanes (0.3 mL) using a solution (0.2 mL) of 8% LiOH in 30% H_2O_2 for 48 h.
[b]Determined by chiral HPLC.

2.3.2. Investigation of the efficacy of crown-CDPs prepared

Using the optimized conditions, we investigated the supramolecular catalytic ability of all the crown-CDPs prepared. First, *cis* crown-CDP-**21,** bearing isobutyl and benzo-18-crown-6 side chains, provided a higher enantioselectivity of (*2R,3S*)-epoxychalcone **36a** (34%) than the *trans* diastereoisomer crown-CDP-**22** (7%) (Table 3, entries 1–2). Using crown-CDPs with a benzo-21-crown-7 (**23–24**) or a benzo-15-crown-5 (**25–26**), high yields of epoxide **36a** were obtained, though lower enantioselectivities were observed (0–11% ee), especially using *trans* crown-CDPs.

In order to verify the steric impact of side chains in the epoxidation process, further investigations were performed with crown-CDPs bearing a methyl (**27**) or a benzyl (**28**) side chain and both having a benzo-18-crown-6 side chain. Using crown-CDPs with methyl or benzyl moieties gave lower enantioselectivities as compared to an isobutyl group (Table 3, entries 7–8). We also investigated crown-CDPs bearing two different crown ethers. In all cases, regardless of the combination of crown ether side chains, crown-CDP **29–34** yielded epoxychalcone **36a** with low enantiomeric excesses (up to 8%).

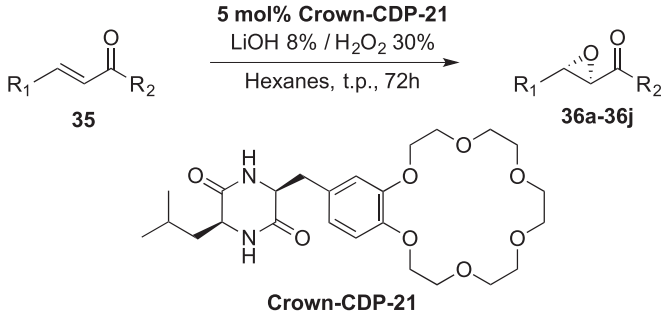
In general, as reported previously (*11*), *cis* crown-CDPs provided better asymmetric induction than *trans* crown-CDPs. Moreover, crown-CDPs with only one crown ether side chain were more efficient in asymmetric induction than crown-CDPs bearing two crown ethers in the epoxidation process. These results point to the importance of having a higher dissymmetry in the supramolecular catalyst to induce higher enantioselectivity.

2.3.3. Reaction scope using crown-CDP 21

We next investigated the substrate scope of the crown-CDP catalyzed epoxidation under optimal conditions, but using only 5 mol% of CDP-**21** for 72 h. Under those conditions, epoxidation of *trans*-chalcone **35** provided a high yield (93%) and 34% ee of (*2R,3S*)-epoxide **36a** (Table 4, entry 1). Epoxidation of chalcone with electron-withdrawing chloro group on the β-phenyl moiety led to moderate yield (32%) and 27% ee of (*2R,3S*)-epoxide **36b** (Table 4, entry 2).

We also verified the effect of a *para*-fluoro substitution on the α-phenyl moiety of the chalcone. Reaction with this substrate led to 31% yield and 30% ee of (*2R,3S*)-epoxide **36c** (Table 4, entry 3). A higher reaction rate was obtained

Table 4. Reaction scope in the epoxidation process[a] catalyzed by **21**.



Entry	R_1	R_2	No	Yield (%)	ee (%)[b]
1	Ph	Ph	**36a**	93	34
2	*p*-Cl-Ph	Ph	**36b**	32	27
3	*p*-F-Ph	Ph	**36c**	31	30
4	Ph	*p*-F-Ph	**36d**	67	18
5	*p*-F-Ph	*p*-CH_3-Ph	**36e**	54	40
6	*p*-NO_2-Ph	Ph	**36f**	81	21
7	*m*-NO_2-Ph	Ph	**36g**	54	15
8	*o*-NO_2-Ph	Ph	**36h**	43	6
9	*p*-OMe-Ph	Ph	**36i**	10	13
10	2-naphtyl	Ph	**36j**	45	19

[a]Unless otherwise noted, the reaction was performed as a biphasic system using a chalcone (0.1 mmol) and **21** (0.005 mmol) in hexanes (0.3 mL) using a solution (0.2 mL) of 8% LiOH in 30% H_2O_2 for 72 h.
[b]Determined by chiral HPLC.

with chalcone having a *para*-fluoro substitution on the β-phenyl moiety, leading to a good yield (67%). However, a decrease of enantioselectivity to 18% of (*2R,3S*)-epoxide **36d** is observed (Table 4, entry 4) in that case. Epoxidation of the *bi*-substituted chalcone **36e** led to a good yield (54%) and to the highest enantioselectivity observed in this study, 40% ee of (*2R,3S*)-epoxide **36e** (Table 4, entry 5).

Substitutions at different positions on the β-phenyl moiety with the strong electron-withdrawing nitro group led to variable results (Table 4, entries 6–8). The yield (81%) and enantioselectivity (21%) are highest in the case of the *para*-nitro substitution of (*2R,3S*)-epoxide-**36f** (Table 4, entry 6). Yields and enantioselectivities decrease with *meta* and *ortho* substitutions leading to 15% and 6% respectively of (*2R,3S*)-epoxide **36g** and (*2R,3S*)-epoxide **36h**. In this case, both electronic and steric effects explain the significant decrease of reactivity. Lower electrophilicity of the enone with a *para* methoxy electron-donating group on the β-phenyl moiety afforded (*2R,3S*)-epoxide **36i** with a low yield (10%) and enantioselectivity (13%) (Table 4, entry 9). On the other hand, using a 2-napthyl substitution on the enone led to a good yield (45%) and low enantiomeric excess (19%) of (*2R,3S*)-epoxide **36j** (Table 4, entry 10).

In summary, studies with different substrates strongly suggest that both the steric hindrance and electronic factors of chalcones play a crucial role in the outcomes of the process. The level of enantioselectivity observed is highly variable, and seems to rely on many parameters. In all cases, the supramolecular catalysis of crown-CDPs led to (*2R,3S*)-epoxides, which shows that the same type of supramolecular complex is involved in the catalysis. Though multiple orientations of the substrate are possible, it has been previously demonstrated that in phase-transfer epoxidations, the chiral crown ethers complex the cation, which in turn brings the hydroperoxide anion to the interface for a nucleophilic 1,4-addition on the enone (*33*). In this study, we demonstrated that incorporating crown-DOPA derivatives into cyclic dipeptides does not improve the efficiency of the supramolecular catalytic epoxidation of electron-deficient enones. The results illustrate the difficulties in designing highly efficient supramolecular catalysts, at least for epoxidation processes.

3. Conclusion

In summary, we have prepared 14 new *cis*, *trans* crown-CDPs by taking advantage of solid-phase peptide synthesis and of the chemical reactivity of the Kaiser oxime resin. Crown-CDPs were obtained with good yields and high purities. We demonstrated the versatility of the methodology by preparing several crown-CDPs bearing various sizes of crown ethers and covering both of the substitution patterns that are possible with crown-CDPs. In a model epoxidation reaction, we showed that a catalytic amount (5 mol%) of crown-CDP can significantly enhance conversion yields (up to 99%) and introduce chirality in the process (up to 40%). Though the enantiomeric excesses obtained so far are low to moderate, the results reported illustrate the potential of this approach to prepare useful

supramolecular phase-transfer catalysts by combining the advantages of chiral crown ethers and of cyclic dipeptides. We are currently exploring the use of the crown-CDPs in other important chemical transformations.

4. Experimental section

4.1. General information

Oxime resin (1.12 mmol/g), coupling reagents, and *N*-Boc-protected amino acids were purchased from Matrix Innovation (Québec City, QC, Canada). Unless otherwise indicated, other starting materials were purchased from commercial sources (Sigma-Aldrich and VWR) and used without further purification. The reagents and the solvents were dried and purified before use by the usual procedures and kept under argon. All reagents were assembled under an inert atmosphere. ^{1}H and ^{13}C-NMR spectra were recorded on an Agilent DD2 500 MHz spectrometer and Varian Inova 400 MHz. The coupling constants are reported in hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), brs (broad singlet), ddt (doublet of doublet of triplets), and m (multiplet). Melting points were taken using a Stanford Research Systems OptiMelt MPA 100 instrument. Mass spectra were obtained on an Agilent 6210 LC Time of Flight Mass Spectrometer in direct injection mode. IR spectra were recorded on Thermo Scientific Nicolet 380 FT-IR using ZnSe crystal. HPLC purities data were measured on Agilent 1260 Infinity instrument with a C18 column (GraceVydac) and a DAD detector ($\lambda = 280$ nm). Retention time is in minutes, followed by the percentage integration of the total chromatogram. All solvents were degassed, using a gradient of (100% H_2O) to (46.4% H_2O/54.4% CH_3CN) in 35 min followed by 100% H_2O between 35 and 42 min. Optical rotations were measured at ambient temperature on a Jasco DIP-360 digital polarimeter using a sodium lamp. Crown amino acids were prepared following reported procedures (*25*). Their synthesis and characterization are reported in the SI.

4.2. Preparation of crown-CDPs

4.2.1. Coupling of the first N-Boc protected α-amino acid on oxime resin

A desired quantity of oxime resin (1.12 mmol/g) was added to a peptide synthesis vessel. The resin was treated three times with CH_2Cl_2. Amino acid (3.0 equiv.) and 6-Cl-HOBt (3.0 equiv.) were dissolved in DMF in a 100 mL flask and the mixture was stirred for few minutes at 0 °C. DIC (3.0 equiv.), DIEA (3.0 equiv.) and DMAP (0.1 equiv.) were added, and the mixture was introduced into the peptide synthesis vessel and stirred mechanically for 3 h. The mixture was filtered under vacuum and the resin was washed [DMF (3 × 15 mL), MeOH (3 × 15 mL), DMF (3 × 15 mL), MeOH (3 × 15 mL)] and dried under reduced pressure.

4.2.2. Acetylation of unreacted sites on oxime resin

The resin was treated three times with DMF (3 × 20 mL). A solution of 50% v/v DMF/acetic anhydride (15 mL) and DIEA (1.5 mL) were added to the peptide synthesis vessel and shaken for 1 h. Then, the mixture was filtered under vacuum and the resin was washed [DMF (3 × 15 mL), MeOH (3 × 15 mL), DMF (3 × 15 mL), MeOH (3 × 15 mL)] and dried under reduced pressure.

4.2.3. Removal of the N-Boc protecting group

The resin was treated three times with CH_2Cl_2 (15 mL). A 50% v/v solution of trifluoroacetic acid (TFA) in CH_2Cl_2 was added to the peptide synthesis vessel and shaken for 30 min. Then, the mixture was filtered under vacuum and the resin was washed with DMF (3 × 15 mL), MeOH (3 × 15 mL), DMF (3 × 15 mL), MeOH (3 × 15 mL) and with a solution of 10% v/v DIEA in CH_2Cl_2 (15 mL).

4.2.4. Coupling of the second N-Boc protected α-amino acid

The amino acid (3.0 equiv.) was dissolved in DMF in a 100 mL flask. The solution was cooled to 0 °C, then HCTU (3.0 equiv.) and HOBt (3.0 equiv.) were added. The mixture was poured into the peptide synthesis vessel, in which the resin was previously treated with CH_2Cl_2. DIEA (6.0 equiv.) was also added to the vessel and the mixture was shaken for 3 h. After filtration under vacuum, the resin was washed [DMF (3 x 15 mL), MeOH (3 × 15 mL), DMF (3 × 15 mL) and MeOH (3 × 15 mL)] and dried under reduced pressure. The Kaiser ninhydrin test was performed to monitor the efficiency of the coupling, and the coupling procedure was repeated as needed.

4.2.5. Cyclization/cleavage from the resin

First, the *N*-Boc group was removed using the procedure described in (4.2.3), but without the 10% v/v DIEA/CH_2Cl_2 washing step. After drying, CH_2Cl_2 and DIEA (2.5 equiv.) were added to the peptide synthesis vessel and the mixture was shaken for 2 min. Acetic acid (5.0 equiv.) was added and the contents were shaken for 24 h. Then the filtrate was collected and the resin was rinsed several times with CH_2Cl_2 and MeOH. All the filtrates were combined and evaporated, and the resulting solid was dissolved in CH_2Cl_2. Amberlite IR-120 was introduced to the solution to remove the remaining traces of DIEA. The mixture was stirred for a few minutes and filtered. The filtrate was evaporated to give compounds **21**–**34**. Trituration in a minimum of cold ether was performed and led to the desired compounds with satisfying purity.

4.2.5.1. cyclo[L-Leu-L-DOPA(18-C-6)](21). Yellow powder, 65% yield. **mp** 150 °C. $[\alpha]_D^{22}$ + 27.8° (c 0.1 in MeOH). **ATR** (ZnSe) 3102, 3052, 2870, 1663, 1513, 1457, 1265, 1123, 799 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.08 (d, *J* = 2.3 Hz, 1H), 8.06 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 1.8 Hz, 1H), 6.63 (dd, *J* = 8.2, 1.8 Hz, 1H), 4.10 (brt, 1H), 4.06–3.95 (m, 5H), 3.76–3.69 (m, 4H), 3.62–3.57 (m, 4H), 3.56–3.50 (m, 8H), 3.03 (dd, *J* = 13.5, 3.8 Hz, 1H), 2.75 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.49–1.41 (m, 1H), 1.30–1.22 (m, 2H), 0.65 (d, *J* = 6.6 Hz, 3H), 0.62 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 167.8, 166.8, 148.3, 147.9, 128.9, 123.1, 116.3, 113.4, 70.3, 69.2, 69.1, 68.8, 68.7, 56.0, 52.8, 44.2, 38.5, 23.4, 23.2, 21.9. **HRMS** (ESI) m/z calcd for $C_{25}H_{42}N_3O_8$ $(M + NH_4)^+$: 512.2955, found 512.2971. **HPLC** (Retention time, purity): 20.74 min, 87%.

4.2.5.2. cyclo[D-Leu-L-DOPA(18-C-6)] (22). Pale yellow powder, 43% yield. **mp** 164 °C. $[\alpha]_D^{22}$ + 42.6° (c 0.1 in MeOH). **ATR** (ZnSe) 3183, 3054, 2921, 2867, 1668, 1514, 1455, 1263, 1124 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6). δ 7.99 (s, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 1.7 Hz, 1H), 6.69 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.09 (brt, 1H), 4.02–3.99 (m, 5H), 3.75–3.72 (m, 4H), 3.61–3.58 (m, 4H), 3.55–3.52 (m, 8H), 3.03 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.97 (t, *J* = 6.1 Hz, 1H), 2.80 (dd, *J* = 13.6, 4.7 Hz, 1H), 1.75–1.67 (m, 1H), 1.48–1.43 (m, 1H), 1.40–1.34 (m, 1H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.9, 167.9, 148.1, 147.6, 128.9, 122.9, 116.0, 113.3, 70.3, 70.2, 69.2, 69.1, 68.6, 55.8, 52.4, 41.9, 38.1, 23.9, 23.2, 22.4. **HRMS** (ESI) m/z calcd for $C_{25}H_{42}N_3O_8$ $(M + NH_4)^+$: 512.2966, found 512.2948. **HPLC** (Retention time, purity): 19.68 min, 92%.

4.2.5.3. cyclo[L-Leu-L-DOPA(21-C-7)] (23). Pale orange powder, 72% yield. **mp** 140 °C. $[\alpha]_D^{22}$ + 10.2° (c 0.1 in MeOH). **ATR** (ZnSe) 3183, 3051, 2869, 1661, 1511, 1458, 1266, 1121, 801 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.09 (d, *J* = 2.5 Hz, 1H), 8.06 (d, *J* = 2.3 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 6.63 (dd, *J* = 8.2, 1.8 Hz, 1H), 4.10 (br, 1H), 4.04–3.96 (m, 4H), 3.75–3.69 (m, 4H), 3.64–3.57 (m, 4H), 3.57–3.52 (m, 4H), 3.51–3.46 (m, 9H), 3.03 (dd, *J* = 13.5, 3.8 Hz, 1H), 2.74 (dd, *J* = 13.5, 4.7 Hz, 1H), 1.44 (ddt, *J* = 15.6, 13.2, 6.4 Hz, 1H), 0.85–0.80 (m, 1H), 0.64 (d, *J* = 6.6 Hz, 3H), 0.62 (d, *J* = 6.6 Hz, 3H), 0.25–0.16 (m, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.0, 166.8, 148.3, 147.9, 128.9, 123.2, 116.5, 113.5, 70.7, 70.3, 69.4, 69.3, 68.9, 68.8, 56.0, 52.7, 44.2, 38.7, 23.4, 23.2, 21.8. **HRMS** (ESI) m/z calcd for $C_{47}H_{46}N_3O_9$ $(M + NH_4)^+$: 556.3229, found 556.3263. **HPLC** (Retention time, purity): 21.40 min, 90%.

4.2.5.4. cyclo[D-Leu-L-DOPA(21-C-7)] (24). Pale yellow powder, 67% yield. **mp** 148 °C. $[\alpha]_D^{22}$ + 15.6° (c 0.1 in MeOH). **ATR** (ZnSe) 3180, 3049, 2921, 2870, 1665, 1515, 1458, 1260, 1120 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.02–8.00 (m, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.79 (d, *J* = 2 Hz, 1H), 6.69 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.09 (brt, 1H), 4.03–4.00 (m, 4H), 3.74–3.71 (m, 4H), 3.61–3.58 (m, 4H), 3.56–3.53 (m, 4H), 3.51 (s, 8H), 3.03 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.97–2.94 (m, 1H), 2.79 (dd, *J* = 13.6, 4.7 Hz, 1H), 1.73–1.68 (m, 1H), 1.47–1.42 (m, 1H), 1.40–1.34 (m, 1H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.3, 167.9, 148.0, 147.6, 129.0, 123.0, 116.0, 113.4, 70.7, 70.3, 69.4, 69.3, 68.7, 68.6, 55.8, 52.4, 41.9, 38.1, 23.8, 23.2, 22.4. **HRMS** (ESI) m/z calcd for $C_{47}H_{46}N_3O_9$ $(M + NH_4)^+$: 556.3229, found 556.3443. **HPLC** (Retention time, %): 19.30 min, purity 91% .

4.2.5.5. cyclo[L-Leu-L-DOPA(15-C-5)](25). Brown powder, 81% yield. **mp** 161 °C. $[\alpha]_D^{22}$ + 6.3° (c 0.1 in MeOH). **ATR** (ZnSe) 3180, 3054, 2919, 2869, 1666, 1530, 1452, 1256, 1123 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.08 (d, *J* = 2.7 Hz, 1H), 8.06 (d, *J* = 2.5 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 6.63 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.11–4.09 (m, 1H), 4.01–3.93 (m, 4H), 3.75–3.72 (m, 4H), 3.61–3.58 (m, 8H), 3.49–3.46 (m, 1H), 3.03 (dd, *J* = 13.5, 3.8 Hz, 1H), 2.73 (dd, *J* = 13.5, 3.8 Hz, 1H), 1.45–1.41 (m, 1H), 1.26–1.23 (m, 2H), 0.65 (d, *J* = 6.5 Hz, 3H), 0.63 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 167.9, 166.7, 148.7, 148.3, 129.1, 123.4, 116.9, 113.9, 70.9, 70.4, 69.4, 69.2, 56.0, 52.7, 44.2, 38.5, 23.3, 21.9, 21.5. **HRMS** (ESI) m/z calcd for $C_{23}H_{35}N_2O_7$ $(M + H)^+$: 451.2439, found 451.2438. **HPLC** (Retention time, %): 17.98 min, purity 80%.

4.2.5.6. cyclo[D-Leu-L-DOPA(15-C-5)](26). Brown powder, 74% yield. **mp** 169 °C. $[\alpha]_D^{22}$ + 24.9° (c 0.1 in MeOH). **ATR** (ZnSe) 3179, 3051, 2927, 2877, 1669, 1518, 1461, 1258, 1122 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.02 (m, 2H), 6.63 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 6.69 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.10–4.08 (m, 1H), 3.99–3.96 (m, 5H), 3.75–3.72 (m, 4H), 3.61–3.59 (m, 8H), 3.03 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.79 (dd, *J* = 13.7, 4.8 Hz, 1H), 1.71–1.68 (m, 1H), 1.26–1.23 (m, 2H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.9, 167.9, 148.5, 148.0, 129.1, 123.1, 116.6, 114.0, 70.9, 70.3, 69.3, 69.0, 55.8, 52.3, 41.8, 38.1, 23.8, 23.2, 22.3. **HRMS** (ESI) m/z calcd for $C_{23}H_{35}N_2O_7$ $(M + H)^+$: 451.2439, found 451.2438. **HPLC** (Retention time, %): 18.58 min, purity 86%.

4.2.5.7. cyclo[L-Ala-L-DOPA(18-C-6)] (27). Pale yellow powder, 40% yield. **mp** 169 °C. $[\alpha]_D^{22}$ + 30° (c 0.1 in MeOH). **ATR** (ZnSe) 3183, 3045, 2921, 1664, 1512, 1461, 1264, 1125, 877 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.05 (d, *J* = 1.3 Hz, 1H), 8.02 (d, *J* = 1.3 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.75 (d, J = 1.8 Hz, 1H), 6.65 (dd, *J* = 8.2, 1.8 Hz, 1H),

4.11 (brt, 1H), 4.05–4.00 (m, 5H), 3.76–3.70 (m, 4H), 3.61–3.57 (m, 4H), 3.56–3.52 (m, 4H), 3.52 (s, 4H), 3.02 (dd, *J* = 13.5, 3.8 Hz, 1H), 2.77 (dd, *J* = 13.5, 4.6 Hz, 1H), 0.58 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.2, 166.5, 148.3, 147.7, 129.0, 123.2, 116.4, 113.8, 70.3, 69.2, 69.1, 68.7, 68.6, 55.9, 50.2, 38.3, 20.3. **HRMS** (ESI) m/z calcd for $C_{22}H_{36}N_3O_8$ $(M + NH_4)^+$: 470.2497, found 470.2514. **HPLC** (Retention time, purity): 17.03 min, 84%.

4.2.5.8. cyclo[L-Phe-L-DOPA(18-C-6)] (28). Pale yellow powder, 67% yield. **mp** 170 °C. $[\alpha]_D^{22}$ – 83.1° (c 0.1 in MeOH). **ATR** (ZnSe) 3188, 3053, 2875, 1665, 1513, 1452, 1261, 1121, 799 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.91 (d, *J* = 1.9 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 7.25 (t, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.55 (s, 1H), 6.46 (d, *J* = 8.3 Hz, 1H), 4.01–3.94 (m, 5H), 3.86 (brt, 1H), 3.76–3.63 (m, 4H), 3.60–3.55 (m, 2H), 3.53–3.49 (m, 2H), 3.47–3.42 (m, 8H), 2.60 (dd, *J* = 13.4, 4.7 Hz, 1H), 2.50 (dd, *J* = 13.8, 4.5 Hz, 1H), 2.30 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.94 (dd, *J* = 13.5, 6.9 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.7, 166.5, 148.3, 147.4, 136.9, 130.3, 129.3, 128.6, 127.0, 122.4, 115.2, 113.6, 70.3, 70.2, 69.1, 68.6, 68.4, 56.0, 55.8. **HRMS** (ESI) m/z calcd for $C_{28}H_{40}N_3O_8$ $(M + NH_4)^+$: 546.2810, found 546.3151. **HPLC** (Retention time, purity): 23.79 min, 82%.

*4.2.5.9. cyclo[L-DOPA(15-C-5)-L-DOPA(15-C-5)](**22**) (29).* White powder, 72% yield. **mp** 116 °C. $[\alpha]_D^{22}$ – 28.0° (c 0.1 in MeOH). **ATR** (ZnSe) 3177, 3052, 2918, 2855, 1671, 1513, 1450, 1260, 1119 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.86 (d, *J* = 2.2 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 6.62 (d, *J* = 1.7 Hz, 2H), 6.52 (dd, *J* = 8.1, 2.0 Hz, 2H), 4.01–3.97 (m, 8H), 3.94–3.92 (m, 2H), 3.77–3.69 (m, 8H), 3.61–3.54 (m, 16H), 2.59 (dd, *J* = 13.5, 4.0 Hz, 2H), 2.09 (d, *J* = 13.6, 6.6 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.7, 148.9, 147.9, 122.7, 116.0, 114.5, 70.9, 70.8, 70.3, 69.3, 68.9, 56.0. **HRMS** (ESI) m/z calcd for $C_{34}H_{47}N_2O_{12}$ $(M + H)^+$: 675.3124, found 675.3123. **HPLC** (Retention time, %): 19.36 min, purity 88%.

4.2.5.10. cyclo[L-DOPA(15-C-5)-L-DOPA(18-C-6)] (30). Brown oil, 59% yield. $[\alpha]_D^{22}$ – 47.4° (c 0.1 in MeOH). **ATR** (ZnSe) 3181, 3050, 2930, 2850, 1669, 1510, 1454, 1259, 1121 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.87 (d, *J* = 2.6 Hz, 1H), 7.83 (d, *J* = 2.7 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 6.63 (d, *J* = 2.1 Hz, 1H), 6.61 (d, *J* = 2.0 Hz, 1H), 6.53 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.51 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.03–3.98 (m, 10H), 3.76–3.68 (m, 8H), 3.60–3.50 (m, 20H), 2.61–2.58 (m, 2H), 2.15 (dd, J = 13.5, 6.6 Hz, 1H), 2.03 (dd, J = 12.8, 6.0 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.7, 162.8, 148.9, 148.4, 147.9, 147.5, 129.7, 129.5, 122.7, 122.5, 116.1, 115.4, 114.5, 113.8, 70.9, 70.8, 70.3, 70.3, 70.2, 70.2, 69.3, 69.2, 68.9, 68.7, 68.5, 56.0. **HRMS** (ESI) m/z calcd for $C_{36}H_{50}N_2NaO_{13}$ $(M + Na)^+$: 741.3205, found 741.3232. **HPLC** (Retention time, %): 20.22 min, purity 89%.

4.2.5.11. cyclo[L-DOPA(15-C-5)-L-DOPA(21-C-7)] (31). Brown oil, 64% yield. $[\alpha]_D^{22}$ – 57.7° (c 0.1 in MeOH). **ATR** (ZnSe) 3181, 3051, 2917, 2853, 1667, 1515, 1453, 1258, 1123 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.88 (d, *J* = 2.6 Hz, 1H), 7.82 (d, *J* = 2.7 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 2.1 Hz, 1H), 6.54–6.50 (m, 2H), 4.02–3.91 (m, 10H), 3.76–3.68 (m, 12H), 3.60–3.48 (m, 20H), 2.60 (dd, *J* = 13.6, 4.4 Hz, 2H), 2.15 (dd, *J* = 12.6, 5.6 Hz, 1H), 2.02 (dd, *J* = 15.6, 7.1 Hz, 1H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.7, 162.8, 148.9, 148.4, 147.9, 147.4, 129.7, 129.6, 122.7, 122.5, 116.1, 115.6, 114.5, 113.9, 70.9, 70.8, 70.7, 70.6, 70.4, 70.3, 69.4, 69.3, 69.2, 68.9, 68.8, 68.7, 56.0. **HRMS** (ESI) m/z calcd for $C_{38}H_{54}N_2NaO_{14}$ $(M + Na)^+$: 785.3467, found 785.3508. **HPLC** (Retention time, %): 20.67 min, purity 80%.

4.2.5.12. cyclo[L-DOPA(18-C-6)-L-DOPA(18-C-6)] (32). Pale yellow powder; 40% yield. **mp** 64 °C. $[\alpha]_D^{22}$ – 58.0° (c 0.1 in MeOH). **ATR** (ZnSe) 2922, 2856, 1667, 1515, 1454, 1265, 1123, 1051, 946 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.84 (s, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.62 (s, 2H), 6.52 (d, *J* = 8.0 Hz, 2H), 4.03–4.01 (m, 8H), 3.93 (brt, 2H), 3.78–3.74 (m, 4H), 3.71–3.68 (m, 4H), 3.62–3.58 (m, 4H), 3.57–3.53 (m, 8H), 3.53–3.49 (m, 12H), 2.60 (dd, *J* = 13.6, 4.3 Hz, 2H), 2.09 (dd, *J* = 13.5, 6.7 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.7, 148.5, 147.5, 129.5, 122.5, 115.5, 113.8, 70.3, 70.2, 70.0, 69.2, 68.8, 68.7, 56.0. **HRMS** (ESI) m/z calcd for $C_{38}H_{58}N_3O_{14}$ $(M + NH_4)^+$: 780.3913, found 780.3917. **HPLC** (Retention time, purity): 22.77 min, 89%.

4.2.5.13. cyclo[L-DOPA(18-C-6)-L-DOPA(21-C-7)] (33). Yellow gummy oil, 63% yield. $[\alpha]_D^{22}$ – 41.4° (c 0.1 in MeOH). **ATR** (ZnSe) 3177, 3051, 2920, 2853, 1668, 1518, 1452, 1259, 1119 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.85 (d, *J* = 2.3 Hz, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 6.86 (s, 1H), 6.85 (s, 1H), 6.62 (d, *J* = 1.8 Hz, 2H), 6.52–6.50 (m, 2H), 4.03–4.00 (m, 8H), 3.93–3.91 (m, 2H), 3.75–3.68 (m, 12H), 3.60–3.49 (m, 24H), 2.60 (dd, *J* = 14.1, 4.7 Hz, 2H), 2.08 (dd, *J* = 13.5, 6.8 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 166.7, 162.8, 148.5, 148.4, 147.5, 147.4, 129.6, 129.5, 122.6, 122.5, 115.7, 115.5, 114.0, 113.8, 70.7, 70.7, 70.6, 70.3, 70.3, 70.2, 70.2, 69.4, 69.2, 68.9, 68.7, 68.7, 68.6. **HRMS** (ESI) m/z calcd for $C_{40}H_{58}N_2NaO_{15}$ (M + Na)+: 829.3729, found 829.4056. **HPLC** (Retention time, %): 21.68 min, purity 93%.

4.2.5.14. cyclo-bis[L-DOPA(21-C-7)](34). Orange gummy oil, 50% yield. $[\alpha]_D^{22}$ – 53.4° (c 0.1 in MeOH). **ATR** (ZnSe) 3179, 3050, 2919, 2852, 1666, 1517, 1454, 1262, 1122 cm^{-1}. **^{1}H NMR** (500 MHz, DMSO-d_6) 7.84 (d,

J = 2.6 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 6.63 (d, *J* = 6.63 Hz, 2H), 6.52 (dd, *J* = 8.2, 2.0 Hz, 2H), 4.04–4.00 (m, 8H), 3.93 (brt, 2H), 3.76–3.68 (m, 10H), 3.62–3.60 (m, 4H), 3.56–3.54 (m, 8H), 3.52–3.48 (m, 18H), 2.60 (dd, *J* = 13.7, 4.5 Hz, 2H), 2.09 (dd, *J* = 13.6, 6.7 Hz, 2H). **^{13}C NMR** (126 MHz, DMSO-d6) δ 166.7, 148.4, 147.7, 129.6, 122.6, 115.7, 114.0, 70.7, 70.3, 70.3, 69.4, 68.9, 68.7, 56.0. **HRMS** (ESI) m/z calcd for $C_{42}H_{62}N_2NaO_{16}$ $(M + Na)^+$: 873.3992, found 873.3967. **HPLC** (Retention time, %): 21.89 min, purity 89%.

4.3. General procedure for epoxidation of unsaturated ketones

The catalyst **21** (0.005 mmol, 0.05 equiv.) was added to a solution of enone (0.1 mmol) in 0.3 mL of hexanes and stirred at room temperature for 30 min. Then, 0.2 mL of a solution of 8% LiOH (m/v) in 30% H_2O_2 (w/w) was added and the mixture was stirred at room temperature for 48 h. Twenty-five microliter of H_2O_2 30% were added to the solution after 24 h. The conversion and the enantiomeric excess of the corresponding epoxide were determined by chiral HPLC using a Hewlett Packard series 1050 instrument. Each epoxidation reaction was duplicated and the reported results correspond to the mean of the two experiments (conversions and enantiomeric excesses). The absolute configuration of epoxides **36a–36k** was determined by comparison of the HPLC retention times and the elution order of the corresponding epoxides with literature values.

4.3.1. trans-(2R,3S)-Epoxy-1,3-diphenylpropan-1-one (**10**,**34**,**35**) (36a)

The ee of epoxide **36a** was determined by HPLC analysis using a Chiralcel OD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/i-PrOH 95/5, flow rate 0.6 mL/min, t_R minor (*2S,3R*) = 16.99 min, t_R major (*2R,3S*) = 18.70 min.

4.3.2. trans-(2R,3S)-Epoxy-3-(4-chlorophenyl)-1-phenyl-1-propan-1-one (**10**,**35**,**36**) (36b)

The ee of epoxide **36b** was determined by HPLC analysis using a Chiralcel OD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/*i*-PrOH 95/5, flow rate 0.6 mL/min, t_R minor (*2S,3R*) = 18.32 min, t_R major (*2R,3S*) = 19.74 min.

4.3.3. trans-(2R,3S)-Epoxy-3-(4-fluorophenyl)-1-phenyl-1-propan-1-one (**10**,**35**,**37**) (36c)

The ee of epoxide **36c** was determined by HPLC analysis using a Chiralcel AD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/*i*-PrOH 95/5, flow rate 0.6 mL/min, t_R minor (*2S,3R*) = 33.00 min, t_R major (*2R,3S*) = 35.73 min.

4.3.4. trans-(2R,3S)-2,3-epoxy-3-phenyl-1-(4-fluorophenyl)propan-1-one (**10**,**35**,**38**) (36d)

The ee of epoxide **36d** was determined by HPLC analysis using a Chiralcel OD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/*i*-PrOH 95/5, flow rate 0.6 mL/min, t_R minor (*2S,3R*) = 18.95 min, t_R major (*2R,3S*) = 20.89 min.

4.3.5. trans-(2R,3S)-2,3-epoxy-1-(4-methylphenyl)-3-(4-fluorophenyl)propan-1-one (**10**,**35**,**39**) (36e)

The ee of epoxide **36e** was determined by HPLC analysis using a Chiralcel AD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/*i*-PrOH 95/5, flow rate 0.6 mL/min, t_R minor (*2S,3R*) = 38.75 min, t_R major (*2R,3S*) = 42.07 min.

4.3.6. trans-(2R,3S)-Epoxy-3-(4-nitrophenyl)-1-phenyl-1-propan-1-one (**10**,**34**,**35**) (36f)

The ee of epoxide **36g** was determined by HPLC analysis using a Chiralcel OD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/*i*-PrOH 95/5, flow rate 0.6 mL/min, t_R minor (*2S,3R*) = 61.98 min, t_R major (*2R,3S*) = 67.98 min.

4.3.7. trans-(2R,3S)-Epoxy-3-(3-nitrophenyl)-1-phenyl-1-propan-1-one (**10**,**35**) (36g)

The ee of epoxide **36h** was determined by HPLC analysis using a Chiralcel OD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/*i*-PrOH 95/5, flow rate 0.6 mL/min, t_R minor (*2S,3R*) = 48.75 min, t_R major (*2R,3S*) = 55.02 min.

4.3.8. trans-(2R,3S)-Epoxy-3-(2-nitrophenyl)-1-phenyl-1-propan-1-one (**10**,**35**) (36h)

The ee of epoxide **36i** was determined by HPLC analysis using a Chiralcel OD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/*i*-PrOH 95/5, flow rate 0.6 mL/min, t_R major (*2R,3S*) = 44.55 min, t_R minor (*2S,3R*) = 50.27 min.

4.3.9. trans-(2R,3S)-Epoxy-3-(4-methoxyphenyl)-1-phenyl-1-propan-1-one (**10**,**35**,**36**) (36i)

The ee of epoxide **36j** was determined by HPLC analysis using a Chiralcel OD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/*i*-PrOH 95/5, flow rate 0.6 mL/min, t_R minor (*2S,3R*) = 22.59 min, t_R major (*2R,3S*) = 25.07 min.

4.3.10. trans-(2R,3S)-Epoxy-3-(naphthyl)-1-phenyl-1-propan-1-one (**35**,**40**) (36j)

The ee of epoxide **36k** was determined by HPLC analysis using a Chiralcel AD-H column (0.25 cm × 0.46 cm ID), conditions: λ 254 nm, hexanes/*i*-PrOH 95/5, flow rate 0.6 mL/min, t_R minor (*2S,3R*) = 27.69 min, t_R major (*2R,3S*) = 32.15 min.

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