The Juliá-Colonna Reaction: A Phase-Transfer Catalyzed Enantioselective Olefin Epoxidation

Rosa M. Claramunt [a] , Concepción López [a] , Dolores Santa María [a*] and José Elguero [b*]

[a] Departamento de Química Orgánica y Bio-Orgánica, Facultad de Ciencias, UNED, Avda. Esparta s/n, E- 28232 Las Rozas, Madrid, Spain

[b] Instituto de Química Médica, CSIC, Juan de la Cierva, 3, E-28006 Madrid, Spain

The Juliá-Colonna Reaction: A Phase-Transfer Catalyzed Enantioselective Olefin Epoxidation

The Juliá-Colonna Reaction: A Phase-Transfer Catalyzed Enantioselective Olefin Epoxidation

RECEIVED: 21 JUNE 2023; ACCEPTED: 14 SEPTEMBER 2023; HTTPS://DOI.ORG/10.55815/428767

SUMMARY

Juliá and Colonna were one of the firsts chemists reporting examples of enantioselective organocatalyzed reactions, namely the **Phase-Transfer Catalysis (PTC) olefin epoxidation**. Although some reviews exist on the Juliá-Colonna reaction, none is devoted specifically to it. After an introduction reporting the main publications gathered in three tables, this review is organized into a) *olefin epoxidation;* b) *other enantioselective catalysts*; c) *Juliá-Colonna papers*; d, e) *papers citing the "Juliá-Colonna" epoxidation with special stress on those by Stanley M. Roberts*. This review summarizes the papers by these authors and reports the most relevant improvements.

Keywords: Enantioselective epoxidation; Juliá-Colonna; Weitz-Scheffer; biphasic; triphasic; phase transfer catalysis.

RESUMEN

Juliá y Colonna fueron de los primeros químicos que publicaron ejemplos de reacciones organocatalizadas enantioselectivas, a saber, la epoxidación de olefinas mediante catálisis por transferencia de fase (PTC). Aunque existen algunas revisiones sobre la reacción de Juliá-Colonna, ninguna está dedicada específicamente a ella. Después de una introducción que reporta las principales publicaciones reunidas en tres tablas, esta revisión se organiza en a) epoxidación de olefinas, b) otros catalizadores enantioselectivos, c) artículos de Juliá-Colonna y d, e) trabajos que citan la epoxidación "Juliá-Colonna" con especial énfasis en los de Stanley M. Roberts, resumiendo los artículos de estos autores y destacando las mejoras más relevantes.

Palabras clave: Epoxidación enantioselectiva; Juliá-Colonna; Weitz-Scheffer; bifásico; trifásico; catálisis por transferencia de fase.

RESUM

Juliá i Colonna van ser dels primers químics que van publicar exemples de reaccions organocatalitzades enantioselectives, és a dir, l'epoxidació d'olefines mitjançant la catàlisi per transferència de fase (PTC). Tot i que existeixen algunes revisions sobre la reacció Juliá-Colonna, cap no li està dedicada específicament. Després d'una introducció que informa de les principals publicacions reunides en tres taules, aquesta revisió s'organitza en a) epoxidació d'olefines, b) altres catalitzadors enantioselectivos, c) articles de Juliá-Colonna i d, e) treballs que citen l'epoxidació "Juliá-Colonna" amb especial atenció als de Stanley M. Roberts. Aquesta

*Corresponding author: iqmbe17@iqm.csic.es

revisió resumeix els articles d'aquests autors i en destaca les millores més rellevants.

Paraules clau: epoxidació enantioselectiva; Juliá-Colonna; Weitz-Scheffer; bifàsica; trifàsica; catàlisi per transferència de fase.

TABLE OF CONTENTS

1. INTRODUCTION

This is not a classical review similar to those we published in different journals[1,2,3] The present review is an "historical" review because the Juliá-Colonna reaction has two faces. On one side, it is one of the best methods to prepare enantioenriched or even enantiopure epoxides and for this reason has been cited 941 times as of 2022 (see Tables 1 and 3 further on). On the other side, it is scarcely cited in textbooks as well as in named-reactions books as one of the first and most successful enantioselective organocatalyzed reaction.

Sebastián Juliá and Stefano Colonna published 17 papers ranging from 1978 to 2009 reporting phase transfer reactions using chiral organocatalysts, those concerning the Juliá-Colonna reaction will be reported and discussed in this review.[4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20] Some of these papers have been frequently cited, others less so (Table 1). First collaborating with Colonna then alone this reaction was explored by many other authors, the most relevant being Stanley M. Roberts whose papers are marked in Tables 1 and 2 with an asterisk. Only the JC reactions will be usually discussed in this review although some Michael addition reactions and the use of cyclodextrins will be commented.

All these references correspond to phase transfer catalyzed reactions[21] of the solid-liquid variety, a field to which we have contributed in collaboration with Juliá.[22,23,24,25,26,27]

Table 1 *Number of citations of Juliá and/or Colonna papers*

Year	Main authors	Roberts	Reference	Nº of citations [a]	Reaction
1978	Colonna	---	4	82	C=O reduction
1980	Juliá	---	5	319	JC reaction
1981	Colonna & Juliá	---	6	6	C=O reduction
1981	Juliá & Colonna	---	7	37	C=O reduction
1982	Juliá & Colonna	---	8	226	JC reaction
1983	Juliá & Colonna	---	9	9	JC reaction
1983	Colonna & Juliá	---	10	13	C=O reduction
1983	Colonna & Juliá	---	11	22	Cyclodextrins
1983	Colonna & Juliá	---	12	135	JC reaction
1984	Colonna & Juliá	---	13	2	JC reaction
1984	Colonna & Juliá	---	14	137	JC reaction
1985	Colonna & Juliá	---	15	12	Michael
2004	Colonna	*	16	21	JC reaction
2004	Colonna	*	17	26	JC reaction
2005	Colonna	*	18	44	JC reaction
2007	Colonna	---	19	15	Aldol
2009	Colonna	---	20	22	JC reaction

[a] *Search 2 June 2023.*

Table 2 *Publications including in their title, abstract and/or keywords the "Juliá-Colonna" name*

Year	Title	Ref
1996	Development of the asymmetric epoxidation reaction. Part 1. Application of the oxidation to enones other than chalcones. *	28
1997	Improved procedure for Julia-Colonna asymmetric epoxidation of α,β-unsaturated ketones: Total synthesis of diltiazem and Taxol (TM) side-chain. *	29
1997	Preparation of polyamino acid catalysts for use in Juliá asymmetric epoxidation. *	30
1998	New procedures for the Julia-Colonna asymmetric epoxidation: Synthesis of (+)-clausenamide. *	31
1998	Towards a mechanistic insight into the Julia-Colonna asymmetric epoxidation of α,β-unsaturated ketones using discrete lengths of poly-leucine. *	32
1998	Julia-Colonna asymmetric epoxidation reactions under non-aqueous conditions: Rapid, highly regio- and stereo-selective transformations using a cheap, recyclable catalyst. *	33
1999	A new procedure for the Julia-Colonna stereoselective epoxidation reaction under non-aqueous conditions: The development of a catalyst comprising polyamino acid on silica (PaaSiCat). *	34
1999	Julia-Colonna asymmetric epoxidation of furyl styryl ketone as a route to intermediates to naturally-occurring styryl lactones. *	35
2000	The Julia-Colonna type asymmetric epoxidation reaction catalyzed by soluble oligo-L-leucines containing an alpha-aminoisobutyric acid residue: Importance of helical structure of the catalyst on asymmetric induction.	36
2000	The Julia-Colonna asymmetric epoxidation reaction of chalcone catalyzed by length defined oligo-L-leucine: Importance of the N-terminal functional group and helical structure of the catalyst in the asymmetric induction.	37
2001	β-Peptides as catalysts: Poly-β-leucine as a catalyst for the Julia-Colonna asymmetric epoxidation of enones. *	38
2001	Efficient asymmetric epoxidation of α,β-unsaturated ketones using a soluble triblock polyethylene glycol-polyamino acid catalyst. *	39
2001	Asymmetric epoxidation of a geminally-disubstituted and some trisubstituted enones catalyzed by poly-L-leucine. *	40
2001	The effect of the primary structure of the polypeptide catalyst on the enantioselectivity of the Julia-Colonna asymmetric epoxidation of enones. *	41
2001	Highly enantioselective enone epoxidation catalyzed by short solid phase-bound peptides: Dominant role of peptide helicity.	42
2001	Julia-Colonna stereoselective epoxidation of some α,β-unsaturated enones possessing a stereogenic center at the gamma-position: Synthesis of a protected galactonic acid derivative. *	43
2002	Biomimetic reactions in organic synthesis: Semi-pinacol rearrangements of some spirocyclic epoxyalcohols derived from Julia-Colonna asymmetric epoxidations.	44
2002	Julia-Colonna asymmetric epoxidation in a continuously operated chemzyme membrane reactor.	45
2002	Asymmetric epoxidation of α,β-unsaturated ketones catalyzed by poly(amino acids). *	46
2003	A route to the structure proposed for puetuberosanol and approaches to the natural products Marshrin and Phebalosin.*	47
2003	Julia-Colonna oxidation reaction: Efficient access to chiral epoxides.	48
2003	Development of the Julia-Colonna asymmetric epoxidation reaction: Part 1. Preparation and activation of the polyleucine catalyst. *	49
2004	Novel conditions for the Julia-Colonna epoxidation reaction providing efficient access to chiral, nonracemic epoxides.	50
2004	Scoping the triphasic/PTC conditions for the Julia-Colonna epoxidation reaction.	51
2004	Asymmetric epoxidation of some arylalkenyl sulfones using a modified Julia-Colonna procedure. *	52
2004	Influence of polymerization degree of poly-L-leucine catalyst and substituent effect on the Julia-Colonna asymmetric epoxidation of benzalacetophenones.	53
2004	Scale-up studies for the asymmetric Julia-Colonna epoxidation reaction.	54
2004	Chiral amplification by polypeptides and its relevance to prebiotic catalysis.*	55
2004	Structure and catalytic activity of some soluble polyethylene glycol-peptide conjugates. *	56
2004	The mechanism of polyleucine catalyzed asymmetric epoxidation. *	57
2005	Asymmetric synthesis of (−)-(4*R*, 5*R*)-4-[5-(benzo[1, 3]dioxo1-5-y1)-4-hydroxyl-1-(pyridin-2-yl)-4, 5-dihydro-1*H*-pyrazol-3-yl]benzamide.	58
2005	Asymmetric epoxidation of α,β-unsaturated ketones catalyzed by silica-grafted poly-(L)-leucine catalysts.	59
2006	The Julia-Colonna epoxidation: Access to chiral, non-racemic epoxides.	60
2006	Asymmetric enone epoxidation by short solid-phase bound peptides: Further evidence for catalyst helicity and catalytic activity of individual peptide strands.	61
2006	Oligopeptides as catalysts for asymmetric epoxidation. *	62
2008	Asymmetric epoxidation of electron-deficient olefins.	63
2008	Organocatalytic asymmetric oxidation.	64
2009	Imidazolium-modified poly(L-leucine) catalyst: An efficient and recoverable catalyst for Julia-Colonna reactions.	65
2011	Enantioselective epoxidation of electron-deficient olefins: An organocatalytic approach.	66
2011	Asymmetric epoxidation of chalcone catalyzed by reusable poly-L-leucine immobilized on hydrotalcite.	67
2011	Novel nanohybrid materials based on L-leucine on hydrotalcite clays: Asymmetric epoxidation reaction of chalcone.	68
2012	The L-Leu hexamer, a short and highly enantioselective peptide catalyst for the Julia-Colonna epoxidation: Stabilization of a helical conformation in DMSO.	69
2014	Organocatalytic asymmetric epoxidation and aziridination of olefins and their synthetic applications.	70
2016	In-situ study of substrate - catalyst interactions in a Julia-Colonna epoxidation using quartz crystal microbalance with dissipation.	71
2016	Peptides as asymmetric organocatalysts.	72
2016	Asymmetric epoxidation of enones by peptide-based catalyst: A strategy inverting Julia-Colonna stereoselectivity.	73
2016	The isomerization of (*Z*)-3-[H-2(1)]-phenylprop-2-enone as a measure of the rate of hydroperoxide addition in Weitz-Scheffer and Julia-Colonna epoxidations. *	74
2017	Catalytic asymmetric oxygenations with the environmentally benign oxidants H_2O_2 and O_2.	75
2017	Revisiting the Julia-Colonna enantioselective epoxidation: Supramolecular catalysis in water.	76
2018	Papain-catalyzed mechanochemical synthesis of oligopeptides by milling and twin-screw extrusion: Application in the Julia-Colonna enantioselective epoxidation.	77
2018	An artificial molecular machine that builds an asymmetric catalyst.	78
2019	Peptide-based catalysts reach the outer sphere through remote desymmetrization and atroposelectivity.	79
2020	Synthesis of functionalized 1-aryl-3-phenylthiazolylpropanoids and their potential as anticancer agents.	80

**The twenty-two S. M. Roberts' papers.*

A search in the Web of Science of publications including in their title, in their abstract and/or in the keywords the "Juliá-Colonna" reaction affords 53 references (Table 2).

There are also three books that discuss very briefly the Juliá-Colonna reaction.[81,82,83] The last one is a collection of Wikipedia reports. C. Rose Kennedy (then in Harvard, now at the University of Rochester) wrote that on the Juliá-Colonna reaction in 2010. The following papers of Tables 1 and 2 were cited in her report:[4,8,16,29,31,32,33,34,41,42,50,52,55,59]

With some exceptions, the two most recent references to the seventeen papers of Table 1 to build up Table 3 have been selected. If they are quoted in Table 2, we will cite the following most recent reference.

The present review will be organized as follows: a) olefin epoxidation; b) other enantioselective catalysts; c) Juliá-Colonna papers (Table 1); d) papers citing the Juliá-Colonna epoxidation in the title, abstract and/or keywords (Table 2), and e) papers citing the Juliá-Colonna epoxidation in the text or in the bibliography (Table 3).

Table 3 *The two most recent publications citing in their bibliography at least one of the Juliá and/or Colonna 17 papers*

Table 1 cited	Title	Year	Ref
4	Enantioselective acetalization by dynamic kinetic resolution for the synthesis of γ-alkoxybutenolides by thiourea/quaternary ammonium salt catalysts: Application to strigolactones.	2020	84
4 [a]	Chiral tertiary sulfonium salts as effective catalysts for asymmetric base-free neutral phase-transfer reactions.	2017	85
5	Single-crystal-to-single-crystal translation of a helical supramolecular polymer to a helical covalent polymer.	2022	86
5	Stereoselective peptide catalysis in complex environments - from river water to cell lysates.	2022	87
6	Kinetic resolution of α-bromophenylacetamides using quinine or Cinchona alkaloid salts.	2012	88
6	A new active catalyst species for enantioselective alkylation by phase-transfer catalysis.	1994	89
7 [b]	Ephedrines and their acyclic derivatives.	2011	90
7	Enantioselective reductions by chirally modified alumino- and borohydrides.	2001	91
8 [c]	Asymmetric 1,4-addition reactions catalyzed by *N*-terminal thiourea-modified helical L-Leu peptide with cyclic amino acids.	2021	92
8 [d]	Foldamer catalysis.	2020	93
9	Preparation of TADOOH, a hydroperoxide from TADDOL, and use in highly enantioface- and enantiomer-differentiating oxidations.	2001	94
9	Asymmetric epoxidation of electron-deficient olefins.	2000	95
10	Scalable synthesis of amaryllidaceae isocarbostyril alkaloids from enantiomerically pure 7-azabicyclo[2.2.1]heptanone scaffold: Total synthesis of (+)-7-deoxypancratistatin.	2018	96
10	Ionic activation of tin hydrides.	2002	97
11	Polymerization of lactones initiated by cyclodextrins: Effects of cyclodextrins on the initiation and propagation reactions.	2007	98
11	Enantioselective oxidation of sulfides catalyzed by chiral Mo-V and Cu-II complexes of catechol-appended β-cyclodextrin derivatives in water.	2006	99
12	The synthesis of hydrobenzoin-based monoaza crown ethers and their application as recyclable enantioselective catalysts.	2020	100
12	Secondary structures in synthetic polypeptides from *N*-carboxyanhydrides: design, modulation, association, and material applications.	2018	101
13	Synthetic applications of polymeric α-amino acids.	1997	102
13	Asymmetric epoxidation.	1991	103
14 [e]	Selective synthesis of Botryococcene pentaepoxide - The chemical modifications of the algal biomass oil.	2018	104
15	Nanocrystalline MgO for asymmetric Henry and Michael reactions.	2005	105
15	Effect of microwaves in the chiral switching asymmetric Michael reaction.	2003	106
16	Catalytic foldamers: When the structure guides the function.	2020	107
16	Biologically inspired oxidation catalysis using metallopeptides.	2018	108
17 [f]	One-pot synthesis of α,β-epoxy ketones through domino reaction between alkenes and aldehydes catalyzed by proline based chiral organocatalysts.	2017	109
17	Highly selective multifunctional nanohybrid catalysts for the one-pot synthesis of α,β-epoxy-chalcones.	2016	110
18	Enantioselective nitro-Michael addition catalyzed by *N*-Terminal guanidinylated helical peptide.	2022	111
18	Inhibitive properties comparison of different polyamino acids in water-based drilling fluids.	2020	112
19 [g]	Proline based organocatalysis: Supported and unsupported approach.	2016	113
19	Chitosan-supported cinchonine as an efficient organocatalyst for direct asymmetric aldol reaction in water.	2015	114
20	Insight into substrate recognition by urea-based helical foldamer catalysts using a DFT global optimization approach.	2022	115
20	Asymmetric catalysis mediated by synthetic peptides, Version 2.0: Expansion of scope and mechanisms.	2020	116

[a] There is an older but important review;[117] [b] also ref.[81]; [c] also ref.[87]; [d] also refs.[70,75]; [e] also refs.[101,118]; [f] also refs.[71,76]; [g] also ref.[73]

2. RESULTS

2.1. Olefin epoxidation

The racemic version of the epoxidation of electron-deficient olefins by the HOO^- anion is known as the Weitz-Scheffer reaction,[119,120,121,122] often cited by Colonna and Roberts,[17,20,123] who described that reaction as the achiral progenitor of Juliá–Colonna epoxidation.[18]

The original reactions discussed in this review belong to the field of Phase Transfer Reactions and the subclass of triphasic or liquid-liquid-solid reactions.[124,125,126] Based on the Wikipedia document [83] the following Scheme 1 is a summary of the Juliá-Colonna epoxidation of olefins.

The most important paper, outside the enantioselective epoxidations, is entitled "Quantum chemical modeling of ethene epoxidation with hydrogen peroxide: The effect of microsolvation with water". [127] In it, at a very high theoretical level reaching CCSD(T) and CASSCF, a mechanism was established where hydrogen peroxide becomes polarized in the transition state upon binding to the ethene molecule; microsolvation by water up to four molecules, decreases the activation energy from 140 kJ·mol^{-1} to 44 kJ·mol^{-1}. In what concerns the helicity of supramolecular polymers see [86].

2.2. Other enantioselective catalysts using PTC protocols

Epoxidation with hydrogen peroxide of α,β-unsaturated ketones and other olefins whose double bond is conjugated with strongly electronegative substituents yields chiral epoxy compounds when a two-phase system and an optically active phase-transfer catalyst are used. For a review on Asymmetric Epoxidation of Electron-Deficient Olefins see [63].

In this case the enantioselectivity of the reaction varies from 1.2–5.4% e.e. (quaternary salts of quinone added to a polystyrene matrix comprise the phase-transfer catalyst), [128] 11% e.e. in the presence of cyclodextrins,[11,129,130] up to values of 55–78% e.e. when phase-transfer catalysts based on cinchona alkaloids [131,132] and quinine derivatives [133,134,135,136,137,138] are used. Best results were obtained with monoaza-15-crown ethers prepared from (*R,R*)-(+)- and (*S,S*)-(–)-hydrobenzoin, up to 68-88" e.e.[100]

Much more effective triphasic transfer catalysts are the synthetic enzymes, the polyamino acids of Juliá, which can be used to epoxidize prochiral olefins with a high enantiomeric purity (e.e. up to 100%, see following section).

Asymmetric syntheses catalyzed by synthetic polypeptides [139,140] are considered to be closely related to stereospecific enzymatic reactions. Hence, many organic reactions in which optically active polypeptides take part, such as hydrogenation,[139,140] addition of an active hydrogen compounds to carbon-carbon double bonds,[141,142,143,144] oxidation,[145,146] and reduction [147,148,149,150] have been investigated.

2.3. The Juliá-Colonna papers of Table 1

In 1978 Colonna and Fornasier reported the use of chiral ammonium salts in two-phase systems to reduce phenyl *t*-butyl ketone with sodium borohydride to yield the corresponding carbinols with moderate enantiomeric excess.[1] The best catalyst is benzylquininium chloride, Fig. 1, with yields of 95-100% and e.e. of 32 to 25. This compound and related ones were utilized in the Juliá-Colonna papers on olefin epoxidation.[6,7]

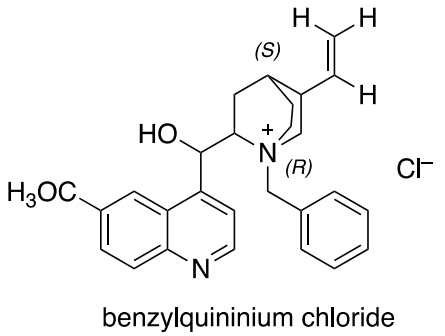
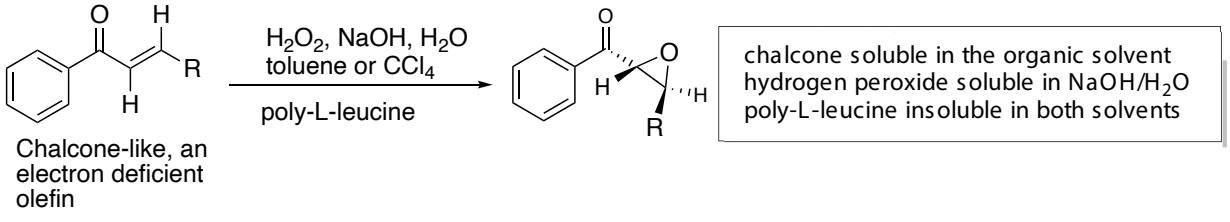


Fig. 1 *Benzylquininium chloride*

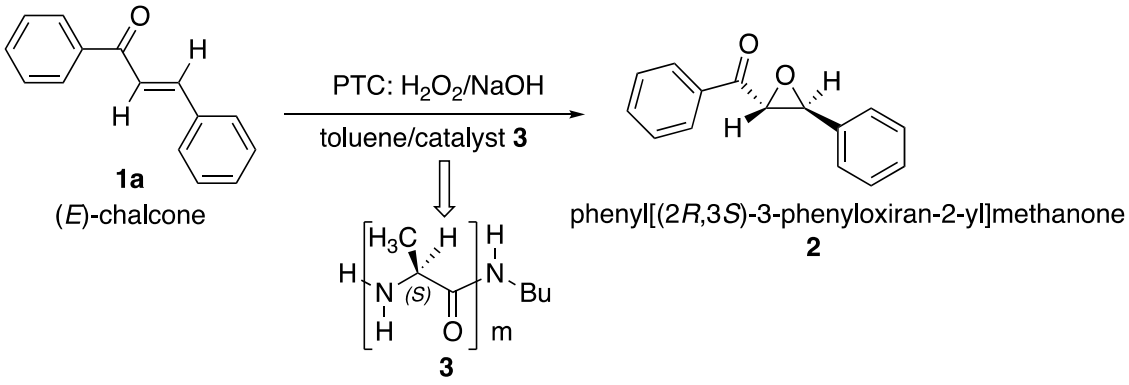
In 1980, Juliá, Masana and Vega published their seminal paper entitled "Synthetic enzymes. Highly stereoselective epoxidation of chalcone in a triphasic toluene-water-poly[(S)-alanine system", Scheme 2.[5] In subsequent papers the (*S*)-alanine will be named L-alanine or L-(+)-alanine. The synthesis of **3** was reported in references[4,8].

After Colonna and Juliá collaborated in other type of reactions (borohydride reduction carbonyl compounds, the reaction of ethyl 2-bromopropionate with potassium phthalimide) they moved to the topic of this review.

In 1982[8] they reported the systematic study of i) different chalcones (**1a**, **4**-**10**), (*E*)-(2-nitroprop)-1-enyl) benzene (**11**) and the 2-methylnaphthalene-1,4-dione (**12**), Fig. 2; ii) different polypeptide catalysts (**13**-**16**,



Scheme 1 *The origin of the Juliá-Colonna reaction*



Scheme 2 *The first example of the use of synthetic enzymes*

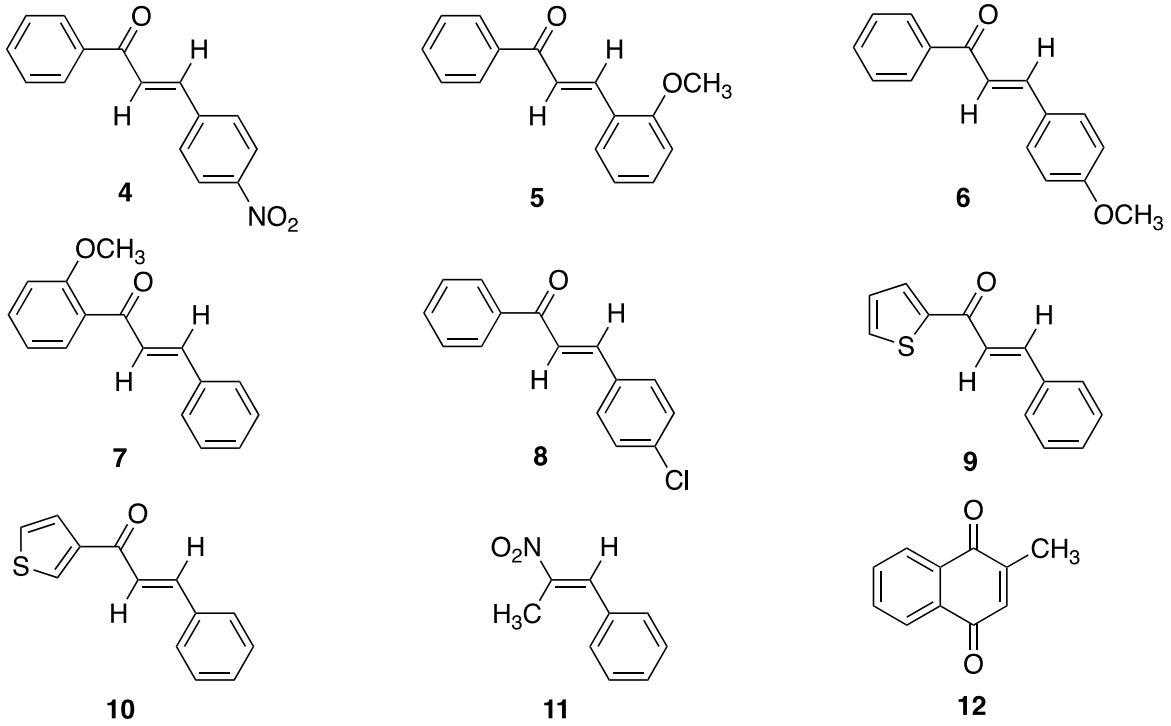


Fig. 2 *Different conjugated carbonyl compounds*

Fig. 3); iii) different solvents (toluene, CCl_4, chlorobenzene, CH_2Cl_2, cyclohexane, hexane); iv) different temperatures (0, 25, 50 °C); v) different ratios (chalcone/catalyst), and vi) different oxidants (H_2O_2-NaOH, MCPBA-$NaHCO_3$-H_2O, *t*-BuO_2H-NaOH-H_2O, *t*-BuO_2H (80%), *t*-BuO_2H-K_2CO_3).

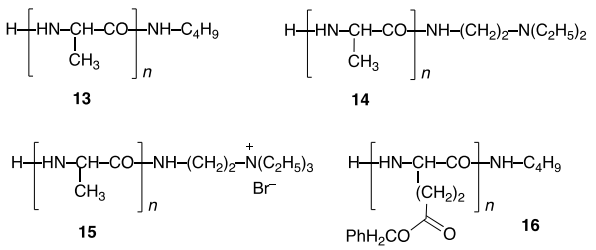


Fig. 3 *Polypeptide catalysts*

The conclusions were: i) three chalcones that yield the higher e.e., about 80%, are **1a**, **4** and **9**; ii) the best catalyst is the simpler one **13**, the degree of polymerization also plays a role, the best results are obtained with n = 30, e.e. = 96% (see also reference[53]); iii) toluene and carbon tetrachloride are the solvents of choice; iv) concerning the temperature, the e.e. decreases when the temperature increases; v) there is no substantial change in the stereoselectivity of the reaction when different substrate/catalyst ratios are employed and vi) H_2O_2-NaOH is the best system among those tested, the reaction does not occur using 80% *t*-BuO_2H. If solid K_2CO_3 is added to the system, the chemical conversion is complete, but the epoxychalcone obtained is racemic. This fact shows that a triphasic system is necessary for asymmetric induction.

Colonna and Juliá published a note[9] where a set of 10 compounds most of them chalcones, including **1a**, were studied (Fig. 2). Using the reaction of Scheme 1 they obtain the following e.e.(%): **1a** between 78 and 93 depending on the optical purity of poly[(S)-alanine; **4** 82 (after one crystallization in ethanol); **5** and **6** not reported; **7** 50; **8** 66; **9** 80; **10** 70; **11** 7, and **12** 0. When the stereoselectivity is higher than e.e. > 80%, optically pure epoxides can be obtained by crystallization in hexane.

All the epoxides are levorotatory; since (–)-epoxychalcone has (2*R*,3*S*) absolute configuration,[136] the same configuration can be tentatively assigned to other epoxides. They also note that the polypeptide increases considerably the reaction yield.

The next publication concerns highly stereoselective synthesis of optically active α,β-epoxy alcohols from the preceding epoxides.[10] The method uses zinc borohydride and the reduction is almost completely stereoselective; thus, the (2*R*,3*S*) epoxides afford erythro alcohols.

Then Colonna, Juliá and their coworkers decided to study systematically different polypeptides, they named synthetic enzymes, compounds **17**-**32** (Fig. 4).[12,13] All the epoxidations were carried out at room temperature in a triphase system with carbon tetrachloride, water, catalytic amount of polypeptide and a large excess of oxidant (H_2O_2/NaOH). Their results are reported in Table 4; note that change of sign between **17**(L) and **17**(D).

These results indicate that the enantioselectivity reaches its maximum with catalysts having a high content of α-helical conformation.[151]

Table 4 *Epoxidation of chalcone **1a***

Catalyst	$[\alpha]^{20}_{578}$ (CH_2Cl_2)	e.e. (%)
17 (L)	–199.5	93
17 (D)	+193.5	90
17 (D,L)	0	0
18	–205.4	96
19	–22.0	10
20	–70.5	33
21	–181.2	84
22	–189.8	88
23	–204.5	95
24	–1.9	1
25	–7.4	3
26	–23.4	11.6
Copolymers		
27	+5.0	2
28	–204.0	95
29	–190.2	88
30	–83.9	17
31	–25.8	17
32	–1.4	0.7

The following year they extended the catalyst to a related family, **33** to **41** (Fig. 5) replacing in most cases the NHR by OH or OR (in compound **39** the polyaminoacid is anchored on a polymeric matrix).[14]

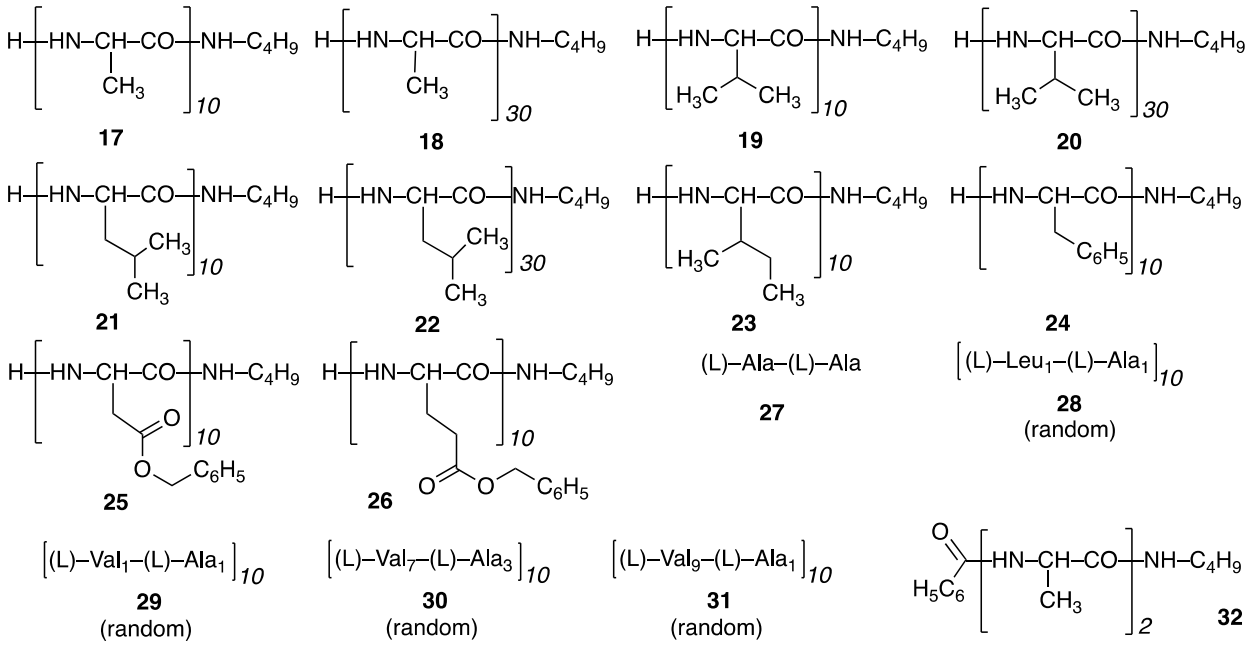


Fig. 4 *New catalysts. A random copolymer is one in which the monomer residues are located randomly in the polymer molecule*

Catalysts **33**-**41** were tested in the epoxidation of *trans*-chalcone **1a** with H_2O_2 in NaOH at room temperature in toluene. They always afford (–)-**2**, having the (2*R*,3*S*) absolute configuration. The results are reported in Table 5.

Table 5 *Other data on the epoxidation of chalcone **1a***

Catalyst	$[\alpha]^{20}_{578}$ (CH_2Cl_2)	e.e. (%)
33	–23	12
34	–171	80
35	–205	96
36	–191	89
37	–201	94
38	–166	78
39	–181	84
40	–208	97
41	–116	54

Even when the polyaminoacid is anchored on a polymeric matrix **39** the obtained oxirane **2** has a high optical purity, the e.e. being 84%. These results, as a whole, lead to the conclusion that the nature of the terminal group of the home polypeptide does not affect the degree of asymmetric synthesis.

The optical yield drops dramatically, as in catalyst **33**, when the polymer has less than 10 units.[14] This behavior is related to the fact that polyaminoacids with degree of polymerization (DP) > 10 have a higher content of α-helix conformation, the secondary structure usually favoring asymmetric induction in the epoxidation reaction.

Then it follows a paper on the Michael reaction,[15] not being discussed in this review as explained previously, together with references in Table 3 citing this paper.[105,106,111] We will not comment on another article on the aldol reaction catalyzed by polyleucines[19] cited in Table 3.[114]

Between 2004 and 2009, Colonna published four important papers.[16,17,18,20]

In the two firsts,[16,17] they report the use of chiral liquid catalysts a field already explored by other authors, *e.g.*, by Roberts [polyethylene glycol (PEG)-bound poly-L-leucine, **42**][41] and by Tsogoeva (two novel soluble polymer-bound oligo-L-leucines).[45] Roberts' polymer contains different lengths of polyamino acid chains, averaging 15.[29,30]

They reached a number of important conclusions using the catalyst **42** (PLL) in the reaction between chalcone, hydrogen peroxide and a base in THF; the base is essential to induce the dissociation of hydrogen peroxide to the hydrogen peroxide anion, which is the actual oxidant (Scheme 3). The bases tested were 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 2-*t*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diaza-phosphorine (BEMP) and the phosphazene base [P_2-*t*-Bu, 1-*t*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene)]. The use of the very strong phosphazene base P_2-*t*-Bu was prevented by the fact that, contrary to the other two bases, it was unstable under the conditions used for the kinetic experiments.

Kinetic experiments lead the authors to conclude that in THF solution PLL behaves as an enzyme-like catalyst with a behavior that fits a steady state random bi-reactant system with one of the pathways (HOO^- binding first) being kinetically preferred to the other (chalcone binding first), Scheme 3, framed.[16,18,20,62]

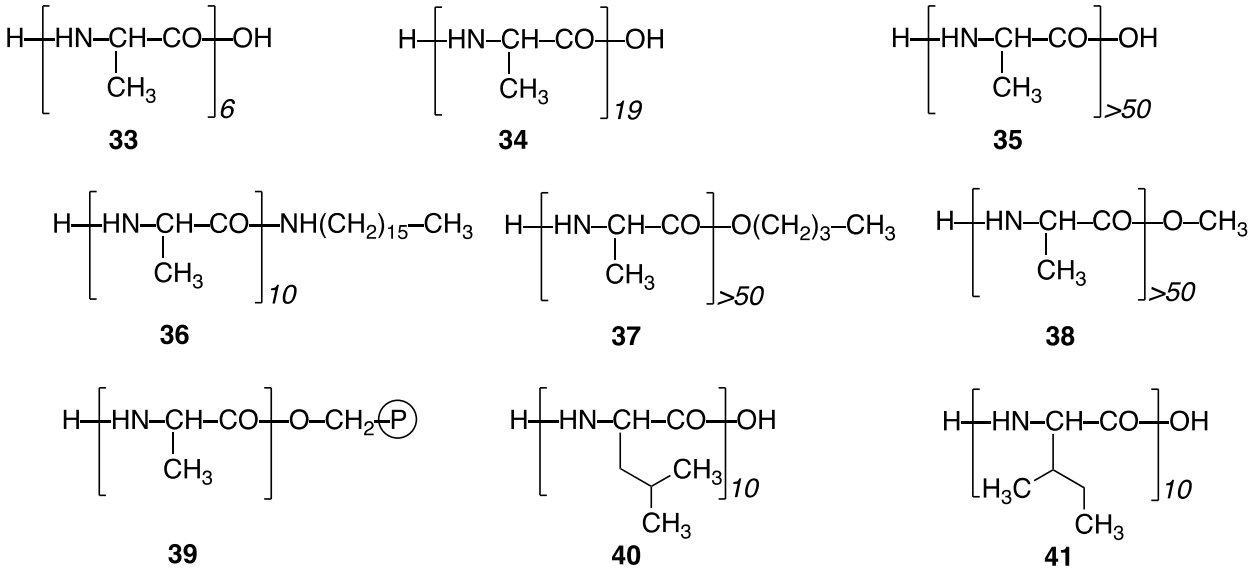
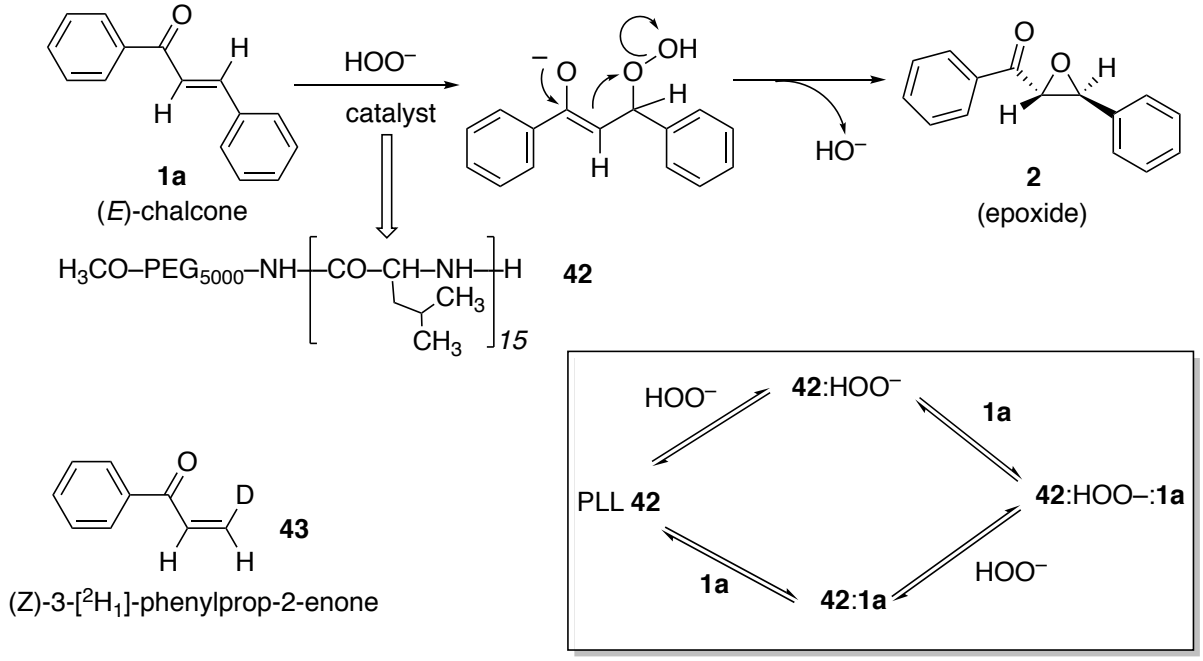
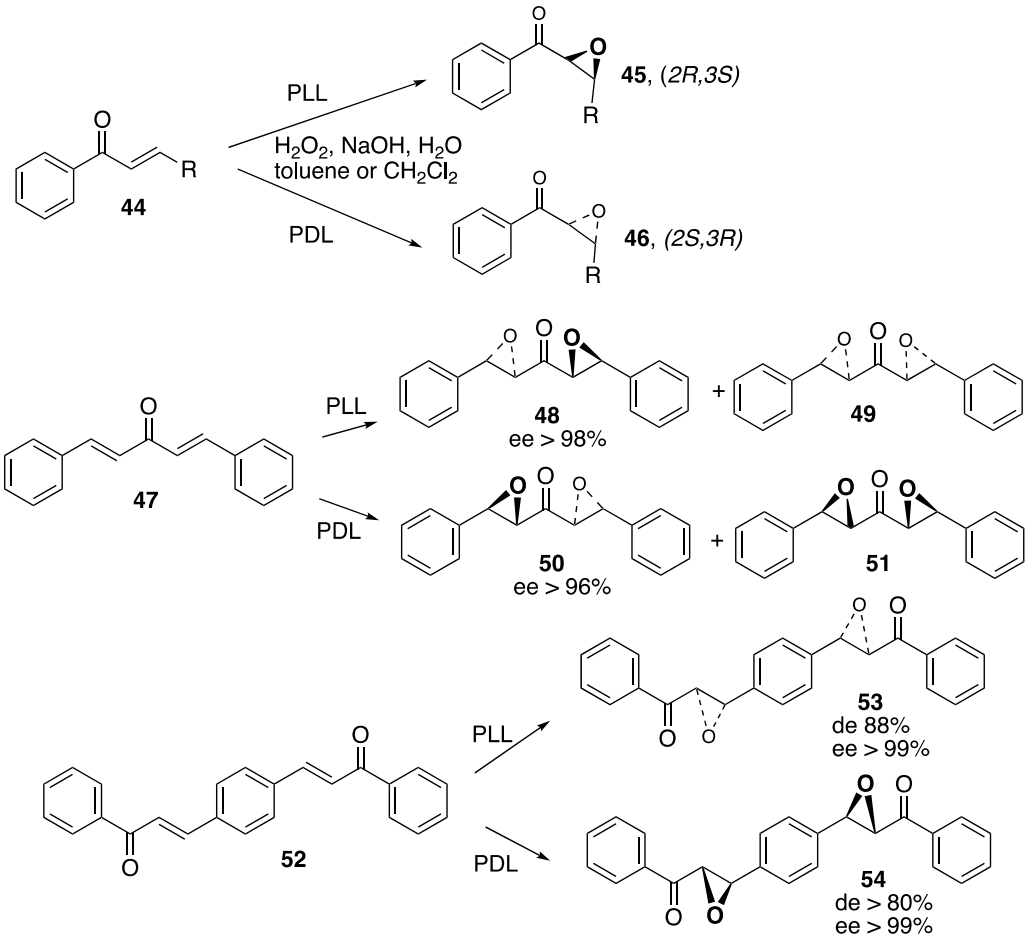


Fig. 5 *A new crop of catalysts*



Scheme 3 *The use of soluble catalysts in the Juliá-Colonna reaction*



Scheme 4 *Enantiocomplementary asymmetric epoxidation*

The last two papers are highly significant concerning the mechanism of the Juliá-Colonna reaction using the soluble PEG-polyleucine conjugate **42** and an isotopically labeled phenylvinyl ketone **43**.[18,20,74] To determine the mechanism, not only of the Juliá-Colonna reaction but that of the racemic Weitz-Scheffer reaction (formation of the epimeric epoxides (*E*) and (*Z*), they established from kinetic and isotopic experiments the mechanism represented in Fig. 6.[20,62] They proved that the Juliá-Colonna reaction showed chiral amplification. The enantiomeric excess increases with the number *n* of leucine residues following the Bernoulli asymptotic law, which tends to 1 (pure enantiomer) when $n \rightarrow \infty$: $e.e._n = (L^n - D^n)/(L^n + D^n)$.

Both articles, but specially the second[20] entitled "Enantioselective reactions catalyzed by synthetic enzymes. A model for chemical evolution" considers that the Juliá-Colonna reaction could be a good model for studies about the emergence of homochirality in the prebiotic world, still a major open problem.

2.4. Papers citing the "Juliá-Colonna" epoxidation in the title, abstract and/or keywords of Table 2.

2.4.1. Roberts' publications.

All Roberts' publications are relevant and two are reviews,[46,123] only three have been already discussed.[29,30,41]

As early as 1995, Robert [152] started his investigations on the Juliá-Colonna reaction publishing with Lasterra-Sánchez a note entitled "Enantiocomplementary asymmetric epoxidation of selected enones using poly-L-leucine and poly-D-leucine" where their demonstrated that the use of PLL (**42**) and PDL (the D-leucine analog of PLL) catalysts lead to 2*R*,3*S* and 2*S*,3*R* epoxides, respectively (Scheme 4, **45** and **46** from **44**).

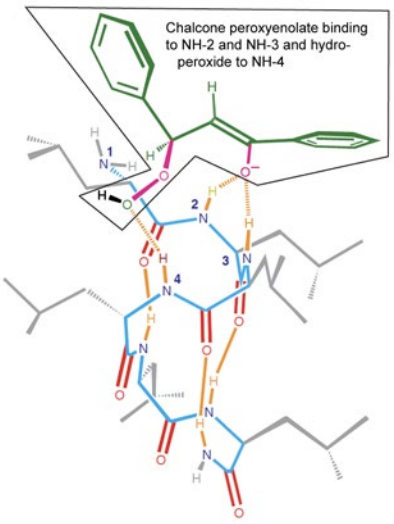


Fig. 6 *Model of the 3-hydroperoxy-chalcone enolate bound to hexaleucine carboxamide (adapted from references[18,57,62])*

As shown in Scheme 4 the olefins **47** and **52** afforded the corresponding diepoxides, **48-51** and **53**,**54** with good diastereoselectivity and excellent enantioselectivity. The formation of the diepoxides **48-51** is the first example showing that an aromatic or conjugated alkene substituent is not necessary for the epoxidation to occur.

The following paper extends the use of the PLL and PDL catalysts to a large series of enones **55-63** (Fig. 7).[28]

In the following paper,[28] the reaction represented in Scheme 5 was reported.

A further example was represented in Scheme 6.[118]

PEG-polystyrene supported 15-mer of L-leucine and a PEG-polystyrene supported 20-mer of L-leucine were

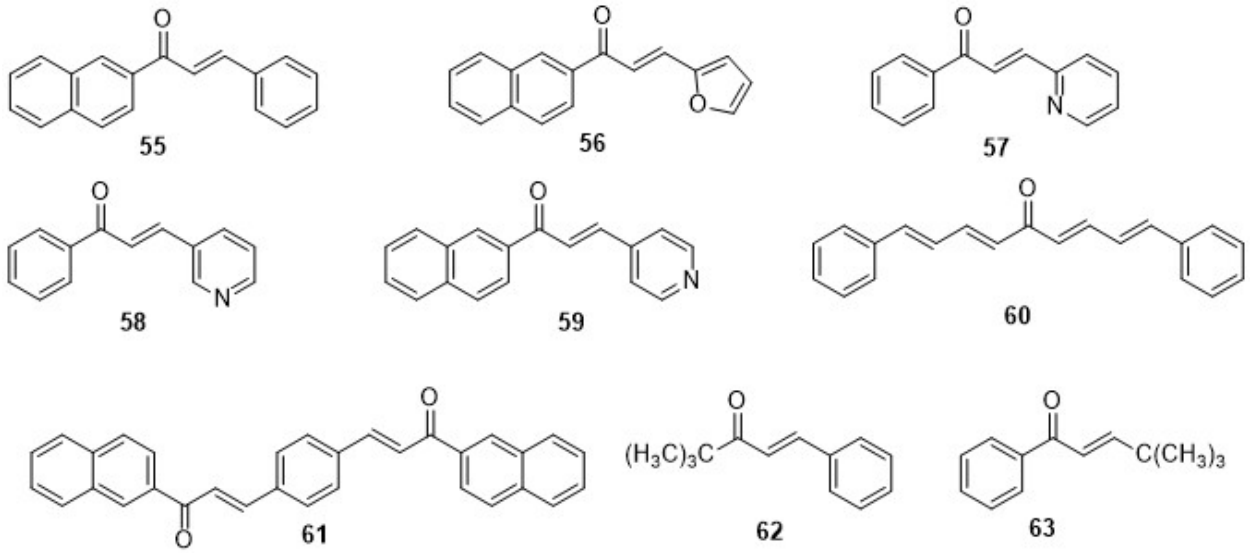
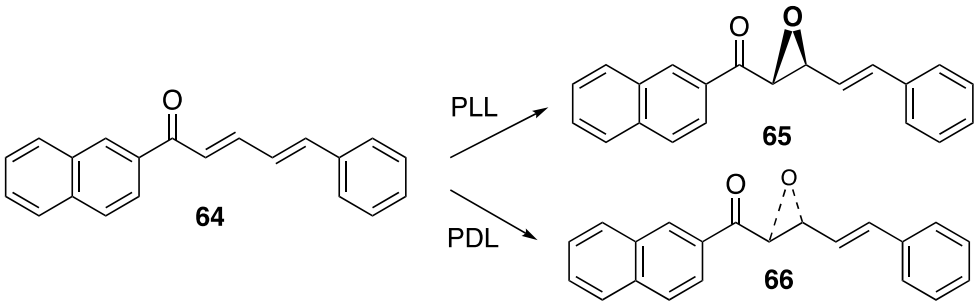
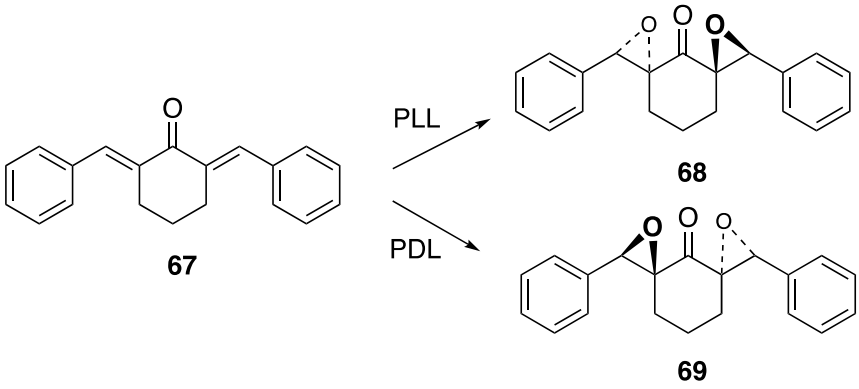


Fig. 7 *New enones used in the Juliá-Colonna epoxidation*



Scheme 5 *Enantiocomplementary asymmetric epoxidation of dienone* ***64*** *affording epoxides* ***65*** *and* ***66***



Scheme 6 *Epoxidation of 2,6-di[(E)-benzylidene]cyclohexan-1-one*

prepared to oxidize chalcone **1a**; the resulting optically active epoxide **2** is a precursor of (+)-clausenamide.[31]

Roberts *et al*. published a series of papers that can be classified as general as they use the Juliá-Colonna to prepare new epoxides or to use epoxides for further synthetic process: epoxides from furyl styryl ketones like **56**;[34] epoxides from enones with a stereogenic center;[40] transformation of epoxides into epoxyalcohols;[44] asymmetric epoxidation of a geminally-disubstituted and some trisubstituted enones;[43] transformation of epoxides into natural products;[47] asymmetric epoxidation of some arylalkenyl sulfones using a modified Juliá–Colonna procedure.[52]

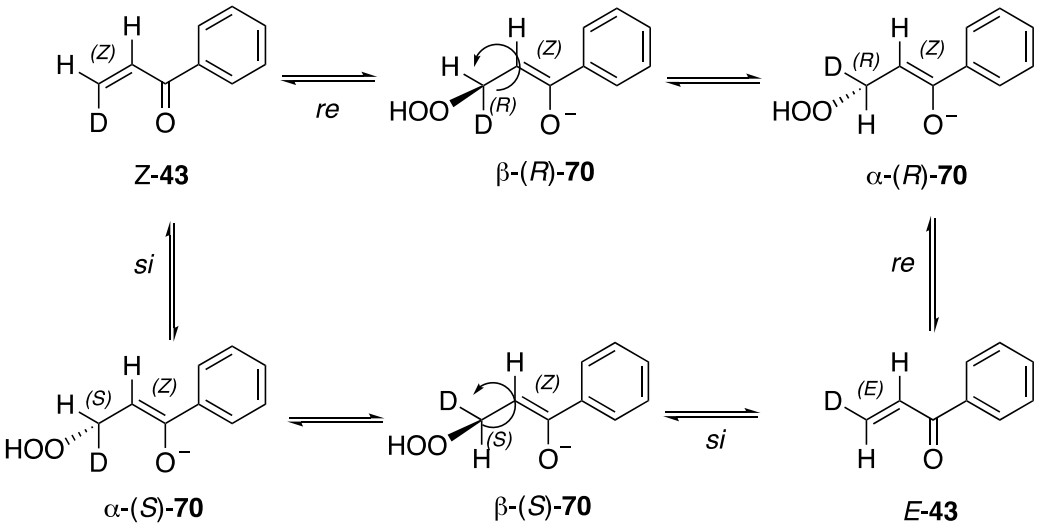
A second and important series of papers concerns Roberts systematic exploration of new catalysts: recyclable catalysts;[33] polyamino acids as catalysts in asymmetric synthesis;[123] catalysts comprising polyamino acid on silica (PaaSiCat);[35] β-Peptides as catalysts;[38] primary structure of the polypeptide catalyst (the residues in the chain near to the *N*-terminus determine the stereochemical outcome of the reaction);[39] soluble triblock polyethylene glycol-polyamino acid catalyst;[41] preparation of the polyleucine catalyst,[49] and catalytic activity of some soluble polyethylene glycol–peptide conjugates.[56]

Finally there are five important papers concerning the reaction mechanism. However, note that in what concerns the mechanism of Fig. 6 and the given references[18] and [62], the first is by Colonna and Roberts (year 2005) and the second one by Kelly and Roberts (year 2006). These last authors point out that the model they have proposed for their mechanism is significantly different from that of Berkessel *et al*.[42]

Similarly, Bernoulli equation was cited in reference[18] (year 2005). Reference[32] (year 1998) reports that length-accurate poly-leucines have been used to evaluate mechanistic features of the asymmetric epoxidation of chalcone, in particular, this work has been aimed towards the influence of the length of the chain, the stereochemistry of the amino acid residues and the nature of the terminal amino group. These studies have been used to establish the mechanism of Scheme 7. Kelly and Roberts published a preliminary communication in 2004[57] before their full paper.[62] Similarly, the full paper on the Bernoulli law,[18] published in 2005 was preceded by a communication in 2004.[55]

In the last Roberts *et al*. paper of Table 2 (2016),[74] some difficulties about the mechanism of epoxidation of chalcone and related enones were solved. The authors used their biphasic system with urea-hydrogen peroxide complex (UHP),[29] DBU as base and THF as solvent (Scheme 7). Using (*E*)-chalcone **1a** and (*Z*)-chalcone **1b**, under both Weitz–Scheffer and Juliá–Colonna conditions, the *trans*-epoxide **2** (racemic or scalemic, respectively) was formed via the (*E*)-chalcone **1a** (see also Scheme 1).

There are two distinguishable mechanisms for alkene isomerization/epoxidation, Scheme 7. The first possibility involves face selective addition (*re* or *si*, Scheme 7), followed by random elimination or epoxidation while the second invokes random facial addition, followed by conformationally controlled elimination of hydroper-



Scheme 7 *Stereochemistry of alkene isomerization; α and β refer to the orientation of the hydroperoxy moiety*

oxide or hydroxyl from the α- or β-conformers. Additionally, when epoxide is formed the O–O bond must be anti-periplanar to the π-system to enable overlap with the O–O anti-bonding orbital.

To conclude this part it must be remembered that Roberts is the responsible of discovering the improved biphasic Juliá-Colonna reaction using a soluble chiral catalyst.[29,35,153] The biphasic system exhibits impressively short reaction times and chalcone epoxide **2** is produced in remarkably high enantiomeric excess (> 95%).

2.4.2. Publications by other authors.

Other authors have discussed the Juliá-Colonna reaction, those, who published more than one paper were Geller (5), Sagarra (3), Tsogoeva (3) and Berkessel (3). Some of their publications were already cited,[42,45,70,71,73] others were reviews (c).[48,63,64,66,72,79] The last review is very interesting but the Juliá-Colonna reaction is only cited in the Abstract (Conspectus).[79] On the other hand, the review published in 2014[70] entitled "Organocatalytic asymmetric epoxidation and aziridination of olefins and their synthetic applications" is a complete summary of "Polypeptide-Catalyzed Epoxidation under Triphasic Conditions"; "Polypeptide-catalyzed epoxidation under biphasic conditions" (Roberts' works), and the "Mechanistic insights".

Most publications are related to the search for new catalysts.[36,37,61,65,67,68,69,71,73,78]

Ohkata *et al*. published two papers on the importance of the helical structure of the catalyst on asymmetric induction.[36,37] The Juliá-Colonna type asymmetric epoxidation reactions were catalyzed by soluble oligo-L-leucines containing an α-aminoisobutyric acid residue (Boc-L-Leu$_{m+n}$-OBz, OBz = benzyl ester). The yield and enantioselectivity rose by increasing the number of amino acid units in the catalyst. The enantioselectivity was very sensitive to the reaction solvent (THF 94% e.e., toluene 84% e.e., CH_2Cl_2 76% e.e., $CHCl_3$ 15% e.e.). The IR characteristic bands (the amide I region) in CH_2Cl_2 indicated the soluble catalysts to be of α-helical structure in solution. This improvement in solubility of the catalyst brings in a new dimension to the Juliá-Colonna reaction and should lead to further understanding of the reaction.

Berkessel *et al*.[42] also reported the dominant role of peptide helicity (cited in a review), [154] based in the study of the effect of chain length of oligo-L-Leu on catalytic performance; the blue columns denote the enantiomeric excess of **(**2*R*,3*S*)-**2** and the black columns refer to the yield of epoxide **2** obtained after 24 h, Fig. 8, left.

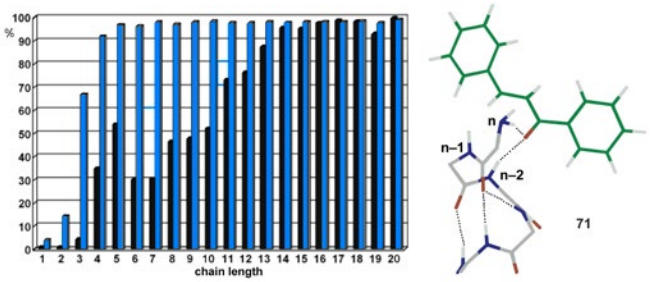


Fig. 8 *Results of Berkessel publications.*[42,61]

Fig. 8 right shows structure **71** where chalcone (green) is bound to the *N*-terminus of a peptide α-helix and besides hydrogen bonds between the carbonyl O-atom, the *N*-terminus, and NH (n–2). This mechanism,[42,61,107] is an alternative proposal to that of Kelly and Roberts (Fig. 6).[18,57,62] Berkessel *et al*.[69] determined by NMR NOESY experiments in DMSO that the L-Leu hexamer, a short and highly enantioselective peptide catalyst for the Juliá–Colonna epoxidation, adopts a helical conformation in DMSO.

It has been described an efficient epoxidation process leading to chiral epoxyketones, **2** and other chalcones with substituents in the phenyl rings, using the reusable homo-oligopeptide poly-L-leucine (PLL) in pure water, without any organic co-solvent.[76] The authors conclude

that the Roberts' mechanism for the triphasic system, Fig. 6, cannot explain their results in pure water and put forward a new mechanism (Fig. 9).

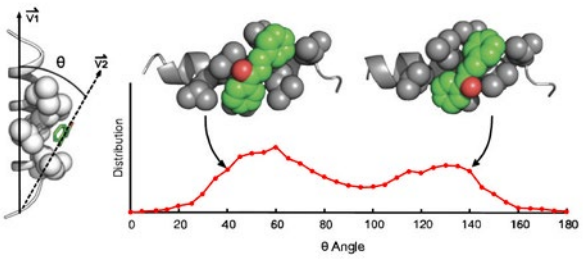
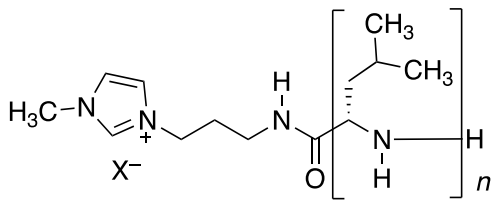


Fig. 9 *Angular distribution of angle y between trans-chalcone **1a** (green) carbonyl (red) and PLL helix. PLL is represented in gray. Leucine side chains interacting with trans-chalcone **1a** are represented as spheres.*

The angular distribution presented in Fig. 9 shows that *trans*-chalcone **1a**, upon binding to PLL, adopts various orientations, with no clear preference for the solvent-exposed side that is accessible to nucleophilic species. The authors suggest a mechanism in which the hydroperoxide anion would accumulate at the *N*-terminal of PLL. The *trans*-chalcone **1a** would move in the hydrophobic groove of the leucine side chain until reaching the *N*-terminal to react there with the hydroperoxide anion. This "groove displacement" mechanism leads to a reactive supramolecular complex consisting of PLL, hydroperoxide, and *trans*-chalcone **1a**.

Imidazolium-modified poly(L-leucine) **72**, Fig. 10, is an efficient and easily recyclable catalyst for Juliá–Colonna reactions.[65] This catalyst exhibits high activity for the asymmetric epoxidation of α,β-unsaturated ketones without any pre-activation. The enantioselectivity was up to 99% e.e. for epoxidation of *p*-methoxy-chalcone. Compared to classical Juliá–Colonna catalysts, this insoluble, powdery catalyst can dramatically reduce the reaction time and can be easily recycled by a simple filtration after the reaction. More importantly, the recycled catalyst has been successfully reused for seven cycles without deterioration in catalytic efficiency.



[3-apmim][X]-PLL **72**

Fig. 10 *Structure of catalyst **72***

Segarra *et al*. used a different approach.[67,68] who prepared a *synzyme* (synthetic enzyme) consisting in a nanohybrid material of L-leucine, PLL, on hydrotalcite clays; hydrotalcite, HTr, is a layered double hydroxide (LDH) of general formula $Mg_6Al_2CO_3(OH)_{16}{\cdot}4H_2O$. The obtained PLLs/HTr synzyme showed excellent activity and enantioselectivity when used as a catalyst in the asymmetric Juliá–Colonna epoxidation reaction of chalcone.

Segarra with other coworkers,[71] carried out experiments using a quartz crystal microbalance with dissipation (QCM-D) to analyze the two mechanism of Scheme 3 (framed) to demonstrate, as was proposed by Colonna and by Roberts,[16,18,20,62] that the hexa-L-Leucine (PLL) catalyzed epoxidation of chalcone **1a** proceeds mainly *via* the formation of a PLL-bound hydroperoxide complex (PLL**:**HOO^-**)** followed by the reversible addition of chalcone **1a**.

A surprising result was obtained by Kudo *et al*.,[73] a resin-supported peptide catalyst with an *N*-terminal primary amino group was developed for asymmetric epoxidation of enones through iminium activation. The peptide has *N*-terminal L-3-(1-pyrenyl)alanine, a non-natural amino acid with a bulky side chain, which is connected to L-proline and then to 3_{10}-helical (L-Leu-L-Leu-Aib)$_2$ (Aib: 2-aminoisobutyric acid). This peptide successfully catalyzes the asymmetric epoxidation of β-aryl-substituted enones with electron-withdrawing groups on the aryl group. The feature of the present peptide catalyst is that **the sense of the enantioselectivity is opposite to that of Juliá–Colonna reaction**, oligo-L-Leu-catalyzed epoxidation of enones, although both of the peptide catalysts consist of L-amino acids.

Leigh *et al*.[78] prepared molecular machines that build as asymmetric catalysts, Fig. 11.

Compounds **73** and **75** have ~6-7 leucine residues while **74** is shorter having ~2-3 leucine resides; they are attached to AlaGlyGly and CysGlyGly. Furyl styryl ketone **76** was employed for epoxidation experiments to prepare **77** with the results reported in the framed table of Fig. 11.

The beautiful but expensive catalyst **75**, 92% e.e. is similar to the classical catalysts (using chalcone **1a**) of Table 4, 96% e.e. and Table 5, 97% e.e., but this is not the important aspect of Leigh publication, which opens a new window in the field of enantioselective epoxidation. As written by the journal editor "The authors have made a molecule that can synthesize a second molecule, which in turn assumes a characteristic conformation that can catalyze the formation of a third molecule. In other words, the work shows a molecule that can synthesize a chemically functional molecule. This is the closest we have been to being able to mimic the behavior of a ribosome".

Two novel soluble polymer-bound oligo-L-leucines **78** and **79** (Fig. 12) have been prepared and used as catalysts for the continuously operated **chemzyme** (a chemical enzyme) asymmetric epoxidation of chalcone **1a**. The optimized batch reaction conditions yield epoxychalcone in high enantioselectivities (up to 94%) and conversions (over 99%) after 15 minutes.[45]

Urea hydrogen peroxide (UHP), proposed by Adger,[29] was used successfully in two publications. In a multi-step synthesis of molecule inhibitors with a pyrazoline skeleton an improved Juliá-Colonna asymmetric epoxidation was successfully used; the conditions were MeONa/MeOH, PLL/UHP/DBU/THF (DBU).[58] The same oxidant and silica-grafted poly-(L)-leucine catalyst

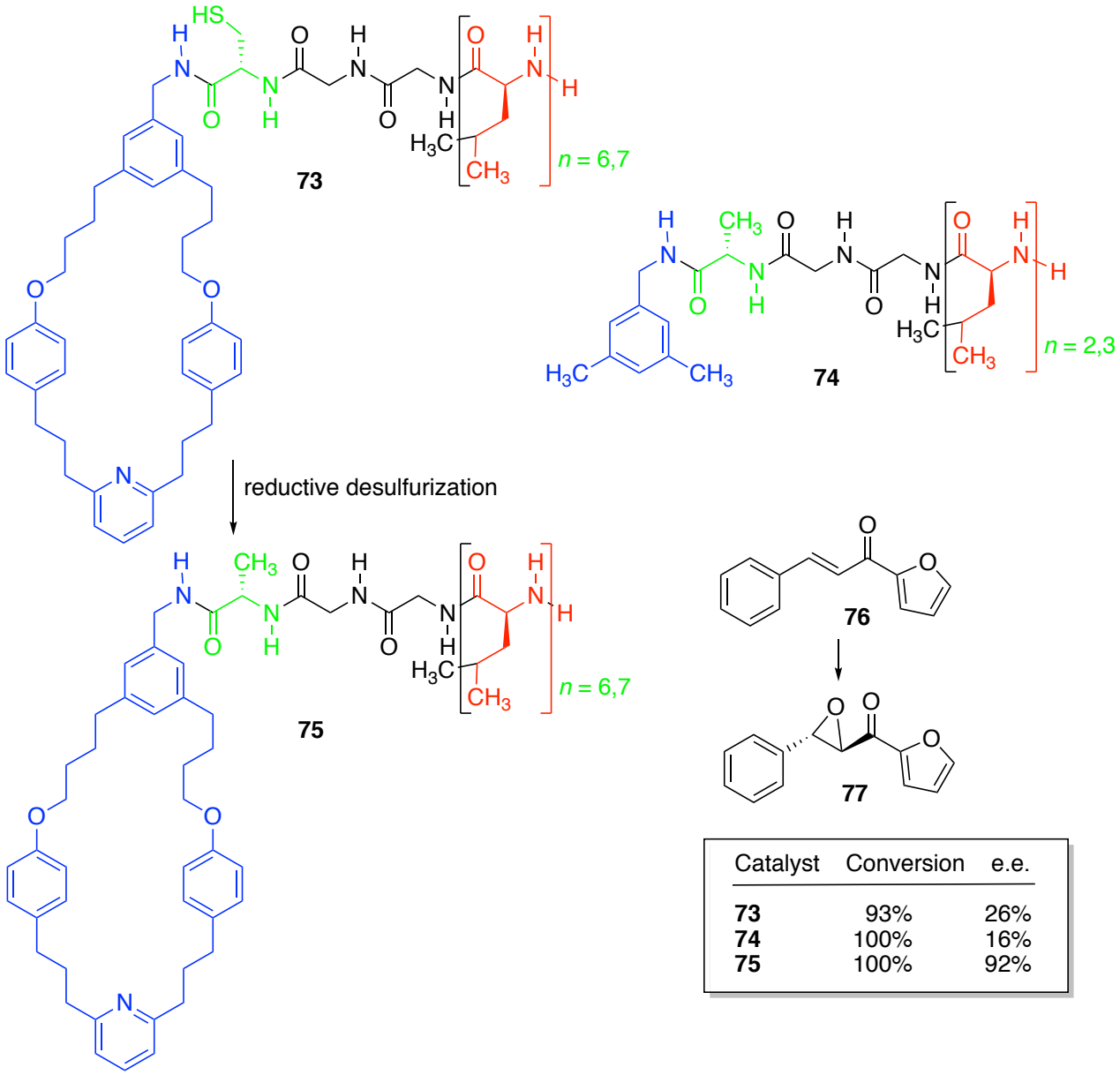


Fig. 11 *Catalysts **73**, **74**, **75** and their corresponding reactions, with the conversion and e.e. percentages*

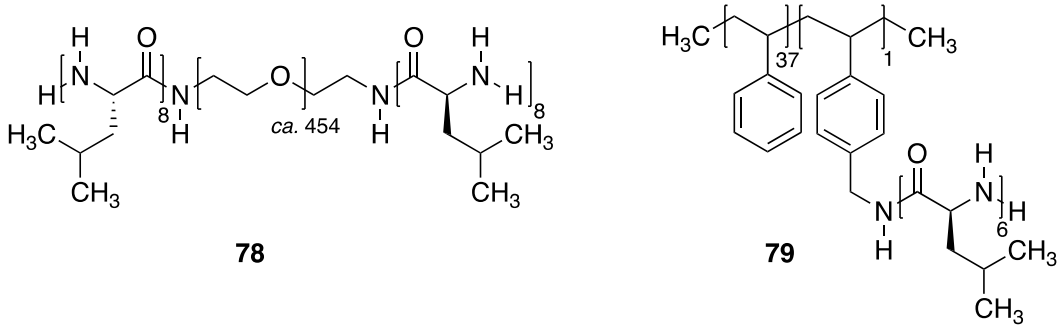
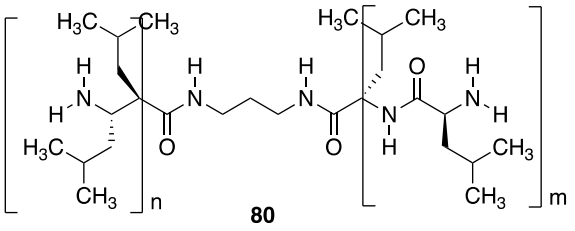


Fig. 12 *Structure of chemzymes **78** and **79***

was used for the asymmetric epoxidation of α,β-unsaturated ketones like benzalacetophenone; utilizing sodium percarbonate as both oxidant and base.[59]



80

Fig. 13 *Statistical polymerization to poly-L-leu* ***80***

Addition of a phase-transfer catalyst (PTC) such as TBAB resulted in triphasic conditions; using L-leucine-*N*-carboxyanhydride (L-leu-NCA), **80**, Fig. 13, resulted in a dramatic increase of reactivity and sometimes also in a higher enantiomeric excess of the product.[50,60] The same *Bayer CropScience* group also report that the required amount of polyamino acid can be significantly reduced under the new conditions, such that large scale industrial application of the method are feasible to prepare epoxides **81**-**85**, Fig. 14.[51] The procedure reported in reference[60] was successfully applied to functionalized 1-aryl-3-phenylthiazolylpropanoids potential anticancer agents.[80]

Papain-catalyzed mechanochemical synthesis of oligopeptides by **milling** and **twin-screw extrusion** was applied to the Juliá-Colonna enantioselective epoxidation.[77] From a more general perspective, it is expected that the results of this work to be an excellent platform to pave the way for new mechanochemical polymerization protocols by ball milling and extrusion.

2.4.3. Reviews.

We have already cited some of the reviews related to the Juliá-Colonna reaction in precedent sections. Highlighting its importance many reviews and perspectives have been published about the Juliá and Colonna reactions, in general, as a part of a larger subject, the content of these reviews has been taken into account in the present review and will not be discussed here.[66,70,72,75,81,90,91,93,95,97,101,102,103,107,113,116,117,155] However, most of them are excellent.[66,70,72,75]

2.5. Papers citing the Juliá-Colonna epoxidation in the text or in the bibliography of Table 3

Exceptionally some recent references cited on the notes of Table 3 will be discussed here. However, references that mention Juliá-Colonna only in the introduction are not being considered.

There are some references to Juliá/Colonna cited only in the introduction of the publications,[87,104,109,112] such as synthetic procedures,[84,92,96,115] and others that concern fields different of olefin epoxidation: Michael, Henry,[105,106,111] as well as aldol reactions.[114]

The remaining publications can be separated in two fields:

2.5.1. Catalysts.

Some publications [88,89,98,99] dealing with Colonna reactions different from epoxidations or with Juliá works cited only in the introduction of the corresponding papers will be no longer considered.[85]

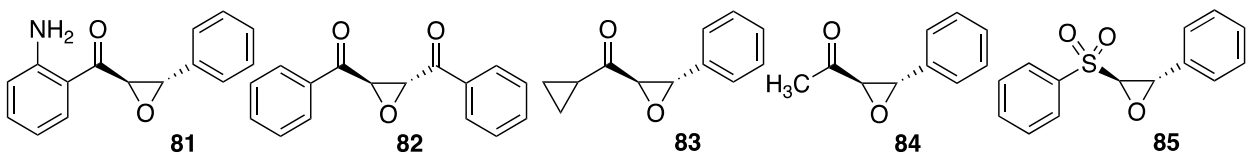
The most interesting is one from Segarra *et al*.[110] We have already cited three publications of these authors;[67,68,71] in their last contribution also using nanohybrid materials based on poly-L-leucine immobilized into rehydrated hydrotalcites, IPL, they continue the progress starting from Juliá-Colonna method of 1981 (triphasic system),[6,7] to that of Roberts of 1996 (biphasic system with an organic base and UHP),[28] to that if Geller of 1999 (chiral)[35] to, finally, that of Segarra of 2011 (triphasic with a new catalyst).

In 2016 they carried out a one-pot Claisen-Schmidt condensation/Juliá-Colonna epoxidation reaction (Scheme 8). Their nanohybrid materials based on PLL did not require any pre-activation time, were easily separated from the reaction media and, unlike the PLL-supported catalyst, were reusable, exhibiting high stability after five consecutive runs without any apparent deactivation.[110]

Costas *et al*. have reported that combining iron coordination complexes, like **88**, and peptides it is possible to oxidize non-functionalized olefins like α-methylstyrene **87** into epoxides **89** (Scheme 9).[108,156] The authors consider the catalytic system a bottom up approach towards the design of artificial oxygenases.

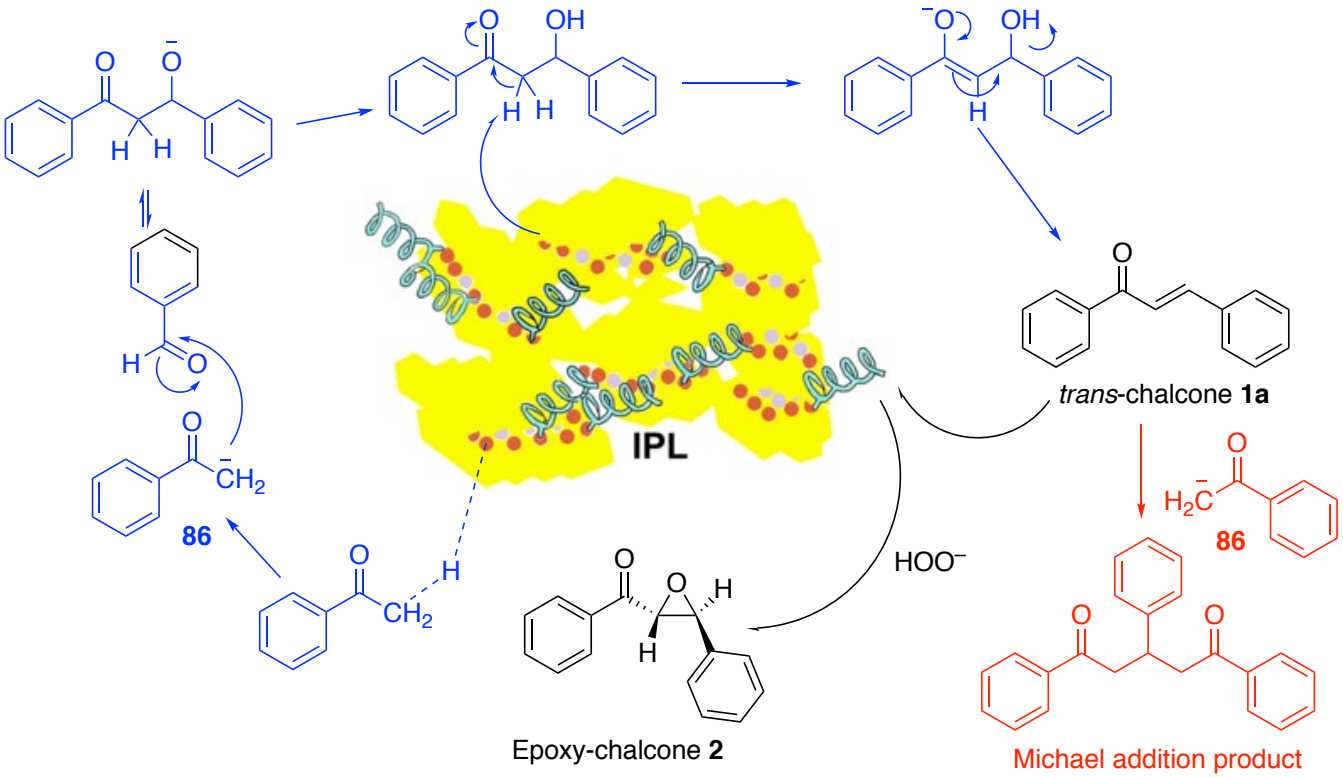
2.5.2. Oxidants.

In 2002 Aoki and Seebach had the very original idea to introduce the chirality not in the catalyst, but in the oxidant {(*4R,5R*)-5-[(hydroperoxydiphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}diphenylmethanol)}, TADOOH **90**.[94] They obtained epoxides with interesting enantiomeric ratios, see Fig. 15. Their work has been often cited together with Juliá and Colonna.[63,157,158,159,160] Two epoxides, **2** and **84**, were already cited and the three other, **91**, **92** and **93**, are new.

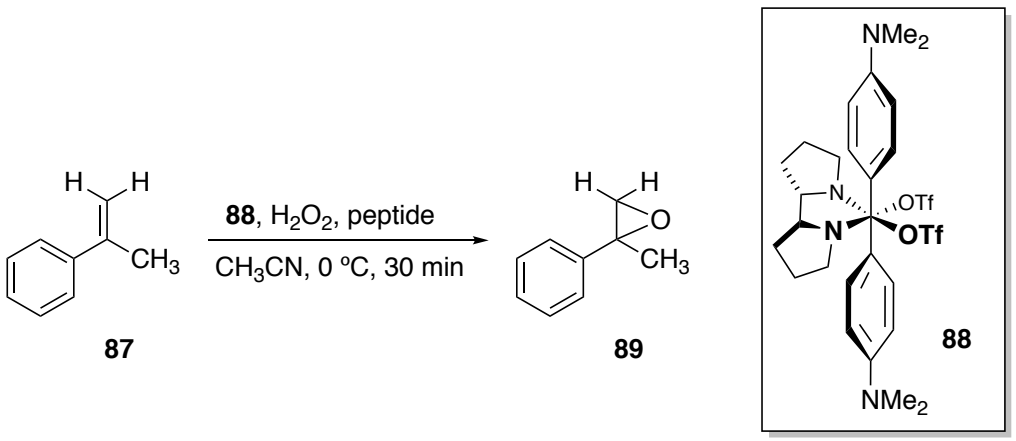


81 **82** **83** **84** **85**

Fig. 14 *Epoxides* ***81*** *to* ***85***



Scheme 8 *One-pot Claisen-Schmidt condensation (in blue)/Juliá-Colonna epoxidation reaction (in black) catalyzed by IPL. The very reactive enolate* ***86*** *can further give a Michael addition reaction with chalcone* ***1a*** *(in red)*



Scheme 9 *Asymmetric epoxidation of* ***87***

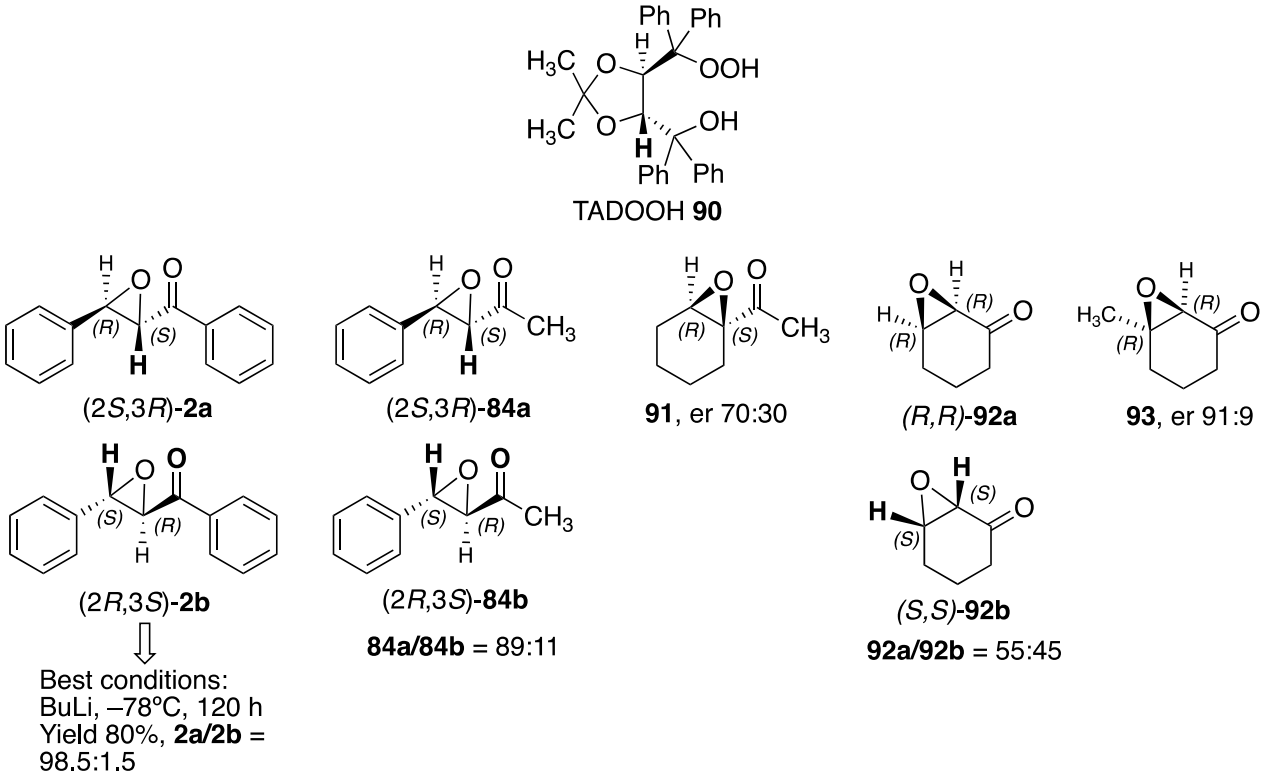


Fig. 15 *Results obtaining using **90** as chiral oxidant. er = enantiomer ratio*

3. CONCLUSIONS AND PERSPECTIVES

In 1980 Sebastián Juliá, Jaume Masana and Juan Carlos Vega, working in Barcelona, published a paper entitled *"Synthetic Enzymes". Highly Stereoselective Epoxidation of Chalcone in a Triphasic Toluene-Water-Poly[(S)-alanine System*.[5] Since in 1978, Stefano Colonna and Roberto Fornasier, working in Milano, published *Asymmetric Induction in the Borohydride Reduction of Carbonyl Compounds by Means of Chiral Phase-transfer Catalysts*,[4] they decided to collaborate, cooperation that resulted in ten papers [6-15] and in the name **Juliá-Colonna reaction**. After Juliá leaves for the industry, Colonna alone published five papers, [16-20] three of them with Stanley M. Roberts.[16-18] These ten papers (from Table 1 concerning the JC reaction) were cited 941 times.

Although Juliá, Colonna and their collaborators set the bar high, a whole host of chemists, notably Roberts, but also Geller, Sagarra, Tsogoeva, Berkessel, Seebach and Leigh improved different aspects of the reaction. The most relevant contributions concern catalysts: the use of PDL (the D-leucine analog of PLL) catalyst to obtain the opposite enantiomers;[150] the use of PEG-polystyrene supported n-mer of L-leucine;[31] many other related catalysts;[33,35,39,41,49,56,123] imidazolium-modified poly(L-leucine);[65] synzymes (hydrotalcite clays);[67,68,110] chemzymes;[45] resin-supported peptide catalysts,[73] and molecular machines.[78]

Regarding oxidants: hydrogen peroxide has been replaced by Adger urea-hydrogen peroxide complex (UHP)[29,58,59] and by chiral TADOOH[63,94,157,158,159,160] and the phase transfer catalysis conditions were modified from the original triphasic to biphasic[29,35,153] as well as by adding TBAB as co-catalyst[35] and using pure water without any organic co-solvent.[76]

Finally, the not too well understood mechanism was successfully explored,[32,55,57,62] in particular, concerning peptide helicity[36,37,42] and the importance of the angular distribution.[76]

It might appear that the field is exhausted, however there are many unexplored avenues: photoorganocatalysis; photobiocatalysis; polarized photocatalysis; organometallic compounds as oxidants and catalysts; computational studies of the mechanism; cascade reactions, etc. It is expected that some of these goals will be met in the coming years and is the hope of the authors that this review contributes to this.

4. ACKNOWLEDGEMENTS

We greatly acknowledge the Ministerio de Ciencia, Innovación y Universidades (PGC2018-094644-B-C22 and PID2021-125207NB-C32) and to Comunidad de Madrid (P2018/EMT-4329). The authors welcome the staff and services of the Central Library of the UNED for their continuous support. We thank Dr. Ibon Alkorta for helping us with some computational aspects.

ORCID

Rosa M. Claramunt https://orcid.org/0000-0001-6634-2677
Concepción López https://orcid.org/0000-0002-2343-902X
Dolores Santa María https://orcid.org/0000-0001-5125-2206
José Elguero https://orcid.org/0000-0002-9213-6858

5. REFERENCES

1. Alkorta, I.; Claramunt. R. M.; Díez-Barra, E.; Elguero, J.; de la Hoz, A.; López, C., The organic chemistry of poly(1H-pyrazol-1-yl)methanes. Coord. Chem. Rev. 2017, 339, 153–182. https://doi.org/10.1016/j.ccr.2017.03.011.
2. de la Hoz, A.; Claramunt, R. M.; Elguero, J.; Alkorta, I., 3-Pyrazolines (2,3-dihydro-1H-pyrazoles): Synthesis, reactivity, and physical and biological properties. Arkivoc 2021, ix, 75–129. https://doi.org/10.24820/ark.5550190.p011.521.
3. Nieto, C.; Sanz, D.; Claramunt, R. M.; Alkorta, I.; Elguero, J., Pyrazaboles and pyrazolylboranes. Coord. Chem. Rev. 2022, 473, 214812. https://doi.org/10.1016/j.ccr.2022.214812.
4. Colonna, S.; Fornasier, R., Asymmetric induction in the borohydride reduction of carbonyl compounds by means of chiral phase-transfer catalysts. Part 2. J. Chem. Soc., Perkin I 1978, 371–373. https://doi.org/10.1039/P19780000371.
5. Juliá, S.; Masana, J.; Vega, J. C., "Synthetic Enzymes". Highly stereoselective epoxidation of chalcone in a triphasic toluene-water-poly[(S)-alanine] system. Angew. Chem. Int. Ed. Engl. 1980, 19, 929–931. https://doi.org/10.1002/anie.198009291.
6. Colonna, S.; Annuziata, R.; Juliá, S.; Guixer, J., Phase transfer catalysis using chiral catalysts. Part 6. The effect of the hydroxyl group in asymmetric phase transfer catalysis. Afinidad 1981, 38, 501–502.
7. Juliá, S.; Ginebreda, A.; Guixer, J.; Masana, J.; Tomás, A.; Colonna, S., Phase-transfer catalysis using chiral catalysts. Influence of the structure of the catalyst on stereoselectivity. Part 3. J. Chem. Soc., Perkin Trans. 1 1981, 574–577. https://doi.org/10.1039/P19810000574.
8. Juliá, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H., Synthetic enzymes. Part 2. Catalytic asymmetric epoxidation by means of polyamino-acids in a triphase system. J. Chem. Soc., Perkin Trans. 1 1982, 1317–1324. https://doi.org/10.1039/P19820001317.
9. Juliá, S.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H., Synthetic enzymes. Part 3. Highly stereoselective epoxidation of chalcones in a triphasic toluene-water-poly[(S)-alanine] system. Anal. Quim. Ser. C 1983, 79, 102–104. https://doi.org/10.2307/293765.
10. Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S., Highly stereoselective synthesis of optically active α,β-epoxy alcohols. Synth. Comm. 1983, 13, 901–904. https://doi.org/10.1080/00397918308059543.
11. Banfi, S.; Colonna, S.; Juliá, S., Asymmetric catalytic epoxidation by means of cyclodextrins Synth. Comm. 1983, 13, 1049–1052. https://doi.org/10.1080/00397918308082725.
12. Colonna, S.; Molinari, H.; Banfi, S.; Juliá, S.; Masana, J.; Alvarez, A., Synthetic enzymes. 4. Highly enantioselective epoxidation by means of polyaminoacids in a triphase system: Influence of structural variations within the catalysts. Tetrahedron 1983, 39, 1635–1641. https://doi.org/10.1016/S0040-4020(01)88574-4.
13. Colonna, S.; Juliá, S.; Molinari, H.; Banfi, S., Catalytic asymmetric epoxidation by means of polyaminoacids in a triphase system. Heterocycles 1984, 21, 548–548. https://doi.org/10.3987/S-1984-02-0548.
14. Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S.; Guixer, J., Asymmetric epoxidation of electron-poor olefins. V. Influence on stereoselectivity of the structure of poly-α-aminoacids used as catalysts. Tetrahedron 1984, 40, 5207–5211. https://doi.org/10.1016/S0040-4020(01)91272-4.
15. Papagni, A.; Colonna, S.; Juliá, S.; Rocas, J., Asymmetric catalytic Michael reaction by means of natural proteins. Synth. Comm. 1985, 15, 891–897. https://doi.org/10.1080/00397918508063887.
16. Carrea, G.; Colonna, S.; Meek, A. D.; Ottolina, G.; Roberts, S. M., Kinetics of chalcone oxidation by peroxide anion catalysed by poly-L-leucine. Chem. Commun. 2004, 1412–1413. https://doi.org/10.1039/B401497A.
17. Carrea, G.; Colonna, S.; Meek, A. D.; Ottolina, G.; Roberts, S. M., Enantioselective epoxidation of chalcone catalysed by the artificial enzyme poly-L-leucine: Kinetic mechanism. Tetrahedron Asymmetry 2004, 15, 2945–2949. https://doi.org/10.1016/j.tetasy.2004.06.046.
18. Carrea, G.; Colonna, S.; Kelly, D. R.; Lazcano, A.; Ottolina, G.; Roberts, S. M., Polyamino acids as synthetic enzymes: Mechanism, applications and relevance to prebiotic catalysis. Trends Biotechnol. 2005, 23, 507–513. https://doi.org/10.1016/j.tibtech.2005.07.010.
19. Carrea, G.; Ottolina, G.; Lezcano, A.; Pironti, V.; Colonna, S., Enantioselective aldol reaction catalysed by polyleucines. Tetrahedron Asymmetry 2007, 18, 1265–1268. https://doi.org/10.1016/j.tetasy.2007.05.024.
20. Colonna, S.; Perdicchia, D.; Di Mauro, E., Enantioselective reactions catalyzed by synthetic enzymes. A model for chemical evolution. Tetrahedron Asymmetry 2009, 20, 1709–1714. https://doi.org/10.1016/j.tetasy.2009.07.007.
21. Makosza, M., Phase-transfer catalysis. A general green methodology in organic synthesis. Pure Appl. Chem. 2000, 72, 1399–1403. https://doi.org/10.1351/pac200072071399.
22. Juliá, S.; Sala, P.; del Mazo, J.; Sancho, M.; Ochoa, C.; Elguero, J.; Fayet, J. P.; Vertut, M. C., N-Polyazolylmethanes. 1. Synthesis and NMR study of N,N'-

diazolylmethanes. J. Heterocycl. Chem. 1981, 19, 1141–1145. https://doi.org/10.1002/jhet.5570190531.
23. Claramunt, R. M.; Hernández, R.; Elguero, J.; Juliá, S., (N-polyazolyl)methanes. II. Synthèse et réactivité de methylène-1,1'-dipyrazoles. Bull. Soc. Chim. Fr. II 1983, 5–10. https://doi.org/10.1002/chin.198326198.
24. Ávila, L.; Elguero, J.; Juliá, S.; del Mazo, J. M., N-Polyazolylmethanes. IV. Reaction of benzotriazole with methylene chloride and chloroform under phase transfer conditions. Heterocycles 1983, 20, 1787–1792. https://doi.org/10.3987/R-1983-09-1787.
25. Juliá, S.; Del Mazo, J. M.; Avila, L.; Elguero, J., Improved synthesis of polyazolylmethanes under solid-liquid phase-transfer catalysis. Org. Prep. Proc. Int. 1984, 16, 299–307. https://doi.org/10.1080/00304948409457886.
26. Juliá, S.; Martínez-Martorell, C.; Elguero, J., A selective synthesis of unsymmetrical 1,1'-methylenebisazoles by solid-liquid phase transfer catalysis. Heterocycles 1986, 24, 2233–2237. https://doi.org/10.3987/R-1986-08-2233.
27. Elguero, J.; Claramunt, R. M.; Garcerán, R.; Juliá, S.; Avila, L.; del Mazo, J. M., Polyazolyl-methanes. 7. 13C NMR study of polyphenyl-, poly-N-azolyl- and poly-N-benzazolylmethanes. Magn. Reson. Chem. 1987, 25, 260–268. https://doi.org/10.1002/mrc.1260250317.
28. Lasterra-Sánchez, M. E.; Felfer, U.; Mayon, P.; Roberts, S. M.; Thornton, S. R.; Todd, C. J., Development of the Juliá asymmetric epoxidation reaction. Part 1. Application of the oxidation to enones other than chalcones. J. Chem. Soc., Perkin Trans. 1 1996, 343–348. https://doi.org/10.1039/P19960000343.
29. Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; McCague, R.; Nugent, T. C.; Roberts, S. M., Improved procedure for Juliá–Colonna asymmetric epoxidation of α,β-unsaturated ketones: Total synthesis of diltiazem and Taxol TM side-chain. J. Chem. Soc., Perkin Trans. 1 1997, 3501–3507. https://doi.org/10.1039/A704413E.
30. Bentley, P. A.; Kroutil, W.; Littlechild, J. A.; Roberts, S. M., Preparation of polyamino acid catalysts for use in Juliá asymmetric epoxidation. Chirality 1997, 9, 198–202. https://doi.org/10.1002/(SICI)1520-636X.
31. Cappi, M. W.; Chen, W. P.; Food, R. W.; Liao, Y.-W.; Roberts, S. M.; Skidmore, J.; Smith, J. A.; Williamson, N. M., New procedures for the Juliá-Colonna asymmetric epoxidation: Synthesis of (+)-clausenamide. Chem. Commun. 1998, 1159–1160. https://doi.org/10.1039/A801450G.
32. Bentley, P. A.; Cappi, M. W.; Flood, R. W.; Roberts, S. M.; Smith, J. A., Towards a mechanistic insight into the Juliá-Colonna asymmetric epoxidation of α,β-unsaturated ketones using discrete lengths of polyleucine. Tetrahedron Lett. 1998, 39, 9297–9300. https://doi.org/10.1016/S0040-4039(98)02090-5.
33. Allen, J. V.; Bergeron, S.; Griffiths, M. J.; Mukherjee, S.; Roberts, S. M.; Williamson, N. M.; Wu, L. E., Juliá–Colonna asymmetric epoxidation reactions under non-aqueous conditions: Rapid, highly regio- and stereo-selective transformations using a cheap, recyclable catalyst. J. Chem. Soc., Perkin Trans. 1 1998, 3171–3179. https://doi.org/10.1039/A805407J.
34. Chen, W. P.; Roberts, S. M., Julia–Colonna asymmetric epoxidation of furyl styryl ketone as a route to intermediates to naturally occurring styryl lactones. J. Chem. Soc., Perkin Trans. 1 1999, 103–106. https://doi.org/10.1039/A808436J.
35. Geller, T.; Roberts, S. M., A new procedure for the Juliá–Colonna stereoselective epoxidation reaction under non-aqueous conditions: The development of a catalyst comprising polyamino acid on silica (PaaSiCat). J. Chem. Soc., Perkin Trans. 1 1999, 1397–1398. https://doi.org/10.1039/A903219C.
36. Takagi, R.; Shiraki, A.; Manabe, T.; Kojima, S.; Ohkata, K., The Juliá-Colonna type asymmetric epoxidation reaction catalyzed by soluble oligo-L-leucines containing an α-aminoisobutyric acid residue: importance of helical structure of the catalyst on asymmetric induction. Chem. Lett. 2000, 366–367. https://doi.org/10.1246/cl.2000.366.
37. Takagi, R.; Manabe, T.; Shiraki, A.; Yoneshige, A.; Hiraga, Y.; Kojima, K.; Ohkata, K., The Juliá-Colonna asymmetric epoxidation reaction of chalcone catalyzed by length defined oligo-L-leucine: Importance of the N-terminal functional group and helical structure of the catalyst in the asymmetric induction. Bull. Chem. Soc. Japan 2000, 73, 2115–2121. https://doi.org/10.1246/bcsj.73.2115.
38. Coffey, P. E.; Drauz, K. H.; Roberts, S. M.; Skidmore, J.; Smith, J. A., β-Peptides as catalysts: Poly-β-leucine as a catalyst for the Juliá–Colonna asymmetric epoxidation of enones. Chem. Commun. 2001, 2330–2331. https://doi.org/10.1039/B106368P.
39. Bentley, P. A.; Flood, R. W.; Roberts, S. M.; Skidmore, J.; Smith, C. B.; Smith, J. A., The effect of the primary structure of the polypeptide catalyst on the enantioselectivity of the Juliá–Colonna asymmetric epoxidation of enones. Chem. Commun. 2001, 1616–1617. https://doi.org/10.1039/B104123C.
40. Ray, P. C.; Roberts, S. M., Juliá–Colonna stereoselective epoxidation of some α,β-unsaturated enones possessing a stereogenic centre at the γ-position: Synthesis of a protected galactonic acid derivative. J. Chem. Soc., Perkin Trans. 1 2001, 149–153. https://doi.org/10.1039/B007100P.
41. Flood, R. W.; Geller, T. P.; Petty, S. A.; Roberts, S. M.; Skidmore, J.; Volk, M., Efficient asymmetric epoxidation of α,β-unsaturated ketones using a soluble triblock polyethylene glycol-polyamino acid catalyst. Org. Lett. 2001, 3, 683–686. https://doi.org/10.1021/ol007005l.
42. Berkessel, A.; Gasch, N.; Glaubitz, K.; Koch, C., Highly enantioselective enone epoxidation catalyzed by short solid phase-bound peptides: Dominant role of peptide helicity. Org. Lett. 2001, 3, 3839–3842. https://doi.org/10.1021/ol0166451.
43. Bentley, P. A.; Bickley, J. F.; Roberts, S. M.; Steiner, A., Asymmetric epoxidation of a geminally-disubstituted and some trisubstituted enones catalysed by poly-L-leucine. Tetrahedron Lett. 2001,

42, 3741–3743. https://doi.org/10 .1016/S0040-4039(01)00535-4.
44. Hauer, B.; Bickley, J. F.; Massue, J. P.; Pena, C. A.; Roberts, S. M.; Skidmore, J., Biomimetic reactions in organic synthesis: Semi-pinacol rearrangements of some spirocyclic epoxyalcohols derived from Juliá–Colonna asymmetric epoxidations. Can. J. Chem. 2002, 80, 546–550. https://doi.org/10.1139/v02-061.
45. Tsogoeva, S. B.; Woltinger, J.; Jost, C.; Reichert, D.; Kühnle, A.; Krimmer, H.-P.; Drauz, K., Juliá–Colonna asymmetric epoxidation in a continuously operated chemzyme membrane reactor. Synlett 2002, 707–710. https://doi.org/10.1055/s-2002-25352.
46. Lauret, C.; Roberts, S. M., Asymmetric epoxidation of α,β-unsaturated ketones catalyzed by poly(amino acids). Aldrichimica Acta 2002, 35, 47–51.
47. Gillmore, A.; Lauret, C.; Roberts, S. M., A route to the structure proposed for puetuberosanol and approaches to the natural products marshrin and phebalosin. Tetrahedron 2003, 59, 4363–4375. https://doi.org/10.1016/S0040-4020(03)00624-0.
48. Geller, T.; Gerlach, A.; Krüger, C. M.; Militzer, H. C., Juliá-Colonna oxidation reaction: Efficient access to chiral epoxides. Chem. Today 2003, 21, 6–8.
49. Baars, S.; Drauz, K. H.; Krimmer, H. P.; Roberts, S. M.; Sander, J.; Skidmore, J.; Zanardi, G., Development of the Juliá-Colonna asymmetric epoxidation reaction: Part 1. Preparation and activation of the polyleucine catalyst. Org. Proc. Res. Develop. 2003, 7, 509–513. https://doi.org/10.1021/op0300037.
50. Geller, T.; Gerlach, A.; Kruger, C. M.; Militzer, H. C., Novel conditions for the Juliá–Colonna epoxidation reaction providing efficient access to chiral, nonracemic epoxides. Tetrahedron Lett. 2004, 45, 5065–5067. https://doi.org/10.1016/j.tetlet.2004.04.188.
51. Geller, T.; Kruger, C. M.; Militzer, H. C., Scoping the triphasic/PTC conditions for the Juliá–Colonna epoxidation reaction. Tetrahedron Lett. 2004, 45, 5069–5071. https://doi.org/10. 1016/j.tetlet.2004.04.189.
52. López-Pedrosa, J. M.; Pitts, M. R.; Pitts, S. M.; Roberts, S. M.; Saminathan, S.; Whittall, J., Asymmetric epoxidation of some arylalkenyl sulfones using a modified Juliá–Colonna procedure. Tetrahedron Lett. 2004, 45, 5073–5075. https://doi.org/10.1016/j.tetlet.2004.04.190.
53. Takagi, R.; Begum, S.; Siraki, A.; Yoneshige, A.; Koyama, K.; Ohkata, K., Asymmetric epoxidation of some arylalkenyl sulfones using a modified Juliá–Colonna procedure. Heterocycles 2004, 64, 129–141. https://doi.org/10.3987/COM-04-S(P)5.
54. Gerlach, A.; Geller, T., Scale-up studies for the asymmetric Juliá–Colonna epoxidation reaction. Adv. Synth. Catal. 2004, 346, 1247–1249. https://doi.o;rg/10.1002/adsc.200404079.
55. Kelly, D. R.; Meek, A.; Roberts, S. M., Chiral amplification by polypeptides and its relevance to prebiotic catalysis. Chem. Commun. 2004, 2021–2022. https://doi.org/10.1039/B404379K.
56. Kelly, D. R.; Bui, T. T. T.; Caroff, E.; Drake, A. F.; Roberts, S. M., Structure and catalytic activity of some soluble polyethylene glycol–peptide conjugates. Tetrahedron Lett. 2004, 45, 3885–3888. https://doi.org/10.1016/j.tetlet.2004.03.120.
57. Kelly, D. R.; Roberts, S. M., The mechanism of polyleucine catalysed asymmetric epoxidation. Chem. Commun. 2004, 2018–2020. https://doi.org/10.1039/B404390C
58. Li, X. Z.; Dai, X. P.; Xiao, J. H.; Li, S., Asymmetric synthesis of (–)-(4R,5R)-4-[5-(benzo[1,3]dioxol-5-yl)-4-hydroxyl-1-(pyridin-2-yl)-4,5-dihydro-1H-pyrazol-3-yl]benzamide. Chin. Chem. Lett. 2005, 16, 1137–1139.
59. Yi, H.; Zou, G.; He, M. Y., Asymmetric epoxidation of α,β-unsaturated ketones catalyzed by silica-grafted poly-(L)-leucine catalysts. Tetrahedron Lett. 2005, 46, 5665–5668. https://doi.org/10.1016/j.tetlet.2005.06.096.
60. Geller, T.; Gerlach, A.; Kruger, C. M.; Militzer, H. C., The Juliá-Colonna epoxidation: Access to chiral, non-racemic epoxides. J. Mol. Catal. A 2006, 251, 71–77. https://doi.org/10.1016/j.molcata.2006.02.003.
61. Berkessel, A.; Koch, B.; Toniolo, C.; Rainaldi, M.; Broxterman, Q. B.; Kaptein, B., Asymmetric enone epoxidation by short solid-phase bound peptides: Further evidence for catalyst helicity and catalytic activity of individual peptide strands. Biopolymers 2006, 84, 90–96. https://doi.org/10.1002/bip.20413.
62. Kelly, D. R.; Roberts, S. M., Oligopeptides as catalysts for asymmetric epoxidation. Biopolymers (Peptide Science) 2006, 84, 74–89. https://doi.org/10.1002/bip.20373.
63. Díez, D.; Núñez, M. G.; Antón, A. B.; García, P.; Moro, R. F.; Garrido, N. M.; Marcos, I. S.; Basabe, P.; Urones, J. G., Asymmetric epoxidation of electron-deficient olefins. Curr. Org. Synth. 2008, 5, 186–216. https://doi.org/10.2174/157017908785133429.
64. Gong, B.; Meng, Q. W.; Gao, Z. X., Organocatalytic asymmetric oxidation. Chin. J. Org. Chem. 2008, 28, 588–597.
65. Qiu, W. W.; He, L. M.; Chen, Q.; Luo, W. R.; Yu, Z. C.; Yang, F.; Tang, J., Imidazolium-modified poly(L-leucine) catalyst: An efficient and recoverable catalyst for Juliá–Colonna reactions. Tetrahedron Lett. 2009, 50, 5225–5227. https://doi.org/10.1016/j.tetlet.2009.06.127.
66. Weiss, K. M.; Tsogoeva, S. B., Enantioselective epoxidation of electron-deficient olefins: An organocatalytic approach. Chem. Record 2011, 11, 18–39. https://doi.org/10.1002/tcr.201000006.
67. Miranda, R. A.; Llorca, J.; Medina, F.; Sueiras, J. E.; Segarra, A. M., Asymmetric epoxidation of chalcone catalyzed by reusable poly-L-leucine immobilized on hydrotalcite. J. Catal. 2011, 282, 65–73. https://doi.org/10.1016/j.jcat.2011.05.026.
68. Miranda, R. A.; Llorca, J.; Finocchiio, E.; Ramis, G.; Medina, F.; Sueiras, J. E.; Segarra, A. M., Catal. Today 2011, 172, 48–52. https://doi.org/10.1016/j.cattod.2011.02.040.

69. Weyer, A.; Díaz, D.; Nierth, A.; Schlorer, N. E.; Berkessel, A. ChemCatChem 2012, 4, 337–340. https://doi.org/10.1002/cctc.201100243.
70. Zhu, Y. G.; Wang, Q., Cornwall, R. G.; Shi, Y. Chem. Rev. 2014, 114, 8199–8256. https://doi.org/10.1021/cr500064w.
71. Wakeham, D.; Crivio, D. G.; Medina, F.; Segarra, A. M.; Rutland, M. W. J. Colloid Interface Sci. 2016, 469, 263–268. https://doi.org/10.1016/j.jcis.2016.01.076.
72. Fingerhut, A.; Grau, D.; Tsogoeva, S. B., Peptides as Asymmetric Organocatalysts, Chapter 13 of Sustainable Catalysis: Without Metals or Other Endangered Elements, Part 1: Volume 40. M. North, Editor, Royal Society of Chemistry, 2016, 309–353.
73. Akagawa, K.; Hirata, T.; Kudo, K., Synlett 2016, 27, 1217–1222. https://doi.org/10.1055/s-0035-1560597.
74. Kelly, D. R.; Caroff, E.; Flood, R. W.; Heal, W.; Roberts, S. M., Chem. Commun. 2004, 2016–2017. https://doi.org/10.1039/B404389H.
75. Bryliakov, K. P., Chem. Rev. 2017, 117, 11406–11459. https://doi.org/10.1021/acs.chemrev.7b00167.
76. Bérubé, C.; Barbeau, X.; Lagüe, P.; Voyer, N., Chem. Commun. 2017, 5099–5102. https://doi.org/10.1039/C7CC01168G.
77. Ardila-Fierro, J.; Crawford, D. E.; Korner, A.; James, S. L.; Bolm, C.; Hernández, J. G., Green Chem. 2018, 20, 1262–1269. https://doi.org/10.1039/C7GC03205F.
78. De Bo, G.; Gall, M. A. Y.; Kuschel, S.; De Winter, J.; Gerbaux, P.; Leigh, D. A., An artificial molecular machine that builds an asymmetric catalyst. Nature Nanotech. 2018, 13, 381. https://doi.org/10.1038/s41565-018-0105-3.
79. Metrano, A. J.; Miller, S. J., Peptide-based catalysts reach the outer sphere through remote desymmetrization and atroposelectivity. Acc. Chem. Res. 2019, 52, 199–215. https://doi.org/10.1021/acs.accounts.8b00473.
80. Nana, F.; Kuete, V.; Zaharia, V.; Ngamebi, B.; Sandjo, L. P., Synthesis of functionalized 1-aryl-3-phenylthiazolylpropanoids and their potential as anticancer agents. ChemistrySelect 2020, 5, 7675–7678. https://doi.org/10.1002/slct.202002060.
81. Berkessel, A.; Gröger, H., Nucleophilic substitution at aliphatic carbon, in Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis, Wiley-VCH, Weinheim, 2005, pp. 13–44.
82. Enantioselective Organocatalysis: Reactions and Experimental Procedures, Ed. P. I. Dalko, Wiley-VCH, Weinheim, 2007, pp. 6 and 416.
83. Name Reactions: Swern Oxidation, Sharpless Epoxidation, Pinner Reaction, Sharpless Asymmetric Dihydroxylation, source Wikipedia, Books LLC, Memphis, 2011.
84. Yasui, M.; Yamada, A.; Tsukano, C.; Hamza, A.; Papai, I.; Yakemoto, Y., Enantioselective acetalization by dynamic kinetic resolution for the synthesis of γ-alkoxybutenolides by thiourea/ quaternary ammonium salt catalysts: Application to strigolactones. Angew. Chem. Int. Ed. 2020, 59, 13479–13483. https://doi.org/10.1002/anie.202002129.
85. Liu, S. Y.; Maruoka, K.; Shirakawa, S., Chiral tertiary sulfonium salts as effective catalysts for asymmetric base-free neutral phase-transfer reactions. Angew. Chem. Int. Ed. 2017, 56, 4819–4823. https://doi.org/10.1002/anie.201612328.
86. Khazeber, R.; Sureshan, K. M., Single-crystal-to-single-crystal translation of a helical supramolecular polymer to a helical covalent polymer. Proc. Natl. Acad. Sci. USA 2022, 119, e2205320119. https://doi.org/10.1073/pnas.2205320119.
87. Schnitzer, T.; Rackl, J. W.; Wennemers, H., Stereoselective peptide catalysis in complex environments – from river water to cell lysates. Chem. Sci. 2022, 13, 8963–8967. https://doi.org/10.1039/d2sc02044k.
88. Marzorati, L.; Fejfar, J. L.; Tormena, C. F.; Di Vitta, C., Kinetic resolution of α-bromophenylacetamides using quinine or Cinchona alkaloid salts. Tetrahedron Asymmetry 2012, 23, 748–753. https://doi.org/10.1016/j.tetasy.2012.05.009.
89. O'Donnell, M. J.; Wu, S. D.; Huffman, J. C., A new active catalyst species for enantioselective alkylation by phase-transfer catalysis. Tetrahedron 1994, 50, 4507–4518. https://doi.org/10.1016/S0040-4020(01)89382-0.
90. Cruz, A.; Ramírez, M. E. B., Ephedrines and their acyclic derivatives. Curr. Org. Synth. 2011, 8, 901–928. https://doi.org/10.2174/157017941110806090l.
91. Daverio, P.; Zanda, M., Enantioselective reductions by chirally modified alumino- and borohydrides. Tetrahedron Asymmetry 2001, 12, 2225–2259. https://doi.org/10.1016/S0957-4166(01)00395-0.
92. Sato, K.; Umeno, T.; Ueda, A.; Kato, T.; Doi, M.; Tanaka, M., Asymmetric 1,4-addition reactions catalyzed by N-terminal thiourea-modified helical L-Leu Peptide with cyclic amino acids. Chem. Eur. J. 2021, 27, 11216–11220. https://doi.org/10.1002/chem.202101252.
93. Girvin, Z. C.; Gellman, S. H., Foldamer catalysis. J. Am. Chem. Soc. 2020, 142, 17211–17223. https://doi.org/10.1021/jacs.0c10589.
94. Aoki, M.; Seebach, D., Preparation of TADOOH, a hydroperoxide from TADDOL, and use in highly enantioface- and enantiomer-differentiating oxidations. Helv. Chim. Acta 2001, 84, 187–207. https://doi.org/10.1002/1522-2675.
95. Porter, M. J.; Skidmore, J., Asymmetric epoxidation of electron-deficient olefins. Chem. Commun. 2000, 1215–1225. https://doi.org/10.1039/B001780I.
96. Pandey, G.; Fernandes, R.; Dey, D., Scalable synthesis of amaryllidaceae isocarbostyril alkaloids from enantiomerically pure 7-azabicyclo[2.2.1]heptanone scaffold: total synthesis of (+)-7-deoxy-pancratistatin. Synlett 2018, 29, 805–809. https://doi.org/10.1055/s-0036-1591022.
97. Shibata, I.; Baba, A., Ionic activation of tin hydrides. Curr. Org. Chem. 2002, 6, 665–693. https://doi.org/10.2174/1385272023374003.
98. Osaki, M.; Takashima, Y.; Yamaguchi, H.; Harada, A., Polymerization of lactones initiated by cyclodextrins: Effects of cyclodextrins on the initiation

and propagation reactions. Macromol. 2007, 40, 3154–3158. https://doi.org/10.1021/ma062650e.
99. Sakuraba, H.; Maekawa, H., Enantioselective oxidation of sulfides catalyzed by chiral MoV and CuII complexes of catechol-appended β-cyclodextrin derivatives in water. J. Incl. Phenom. Macrocycl. Chem. 2006, 54, 41–45. https://doi.org/10. 1007/s10847-005-3490-9.
100. Nemcsok, T.; Rapi, Z.; Bagi, P.; Oláh, A.; Kaglevich, G.; Bakó, P., The synthesis of hydrobenzoin-based monoaza crown ethers and their application as recyclable enantioselective catalysts. Catal. Lett. 2020, 150, 930–938. https://doi.org/10.1007/s10562-019-03013-0.
101. Song, Z.; Fu, H.; Wang, R.; Pacheco. L. A.; Wang, X.; Lin, Y.; Cheng, J., Secondary structures in synthetic polypeptides from N-carboxyanhydrides: Design, modulation, association, and material applications. Chem. Soc. Rev. 2018, 47, 7401–7425. https://doi.org/10.1039/C8CS00095F.
102. Ebrahim, S.; Wills, M., Synthetic applications of polymeric α-amino acids. Tetrahedron Asymmetry 1997, 8, 3163–3173. https://doi.org/10.1016/S0957-4166(97)00407-2.
103. Raifel'd, Y. E.; Vaisman, A. M., Asymmetric epoxidation. Russ. Chem. Rev. 1991, 60, 123–145. https://doi.org/10.1070/RC1991v060n02ABEH001035.
104. Kawashima, H.; Kijima, M. Selective synthesis of botryococcene pentaepoxide - The chemical modifications of the algal biomass oil. ChemistrySelect 2018, 3, 9589–9591. https://doi.org/10.1002/slct.201801823.
105. Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B., Nanocrystalline MgO for asymmetric Henry and Michael reactions. J. Am. Chem. Soc. 2005, 127, 13167–13171. https://doi.org/10.1021/ja0440248.
106. Narasimhan, S.; Velmathi, S., Effect of microwaves in the chiral switching asymmetric Michael reaction. Molecules 2003, 8, 256–262. https://doi.org/10.3390/80200256.
107. Legrand, B.; Aguesseau-Kondrotas, J.; Simon, M.; Maillard, L., Catalytic foldamers: When the structure guides the function. Catalysts 2020, 10, 700. https://doi.org/10.3390/catal10060700.
108. Vicens, L.; Costas, M., Biologically inspired oxidation catalysis using metallopeptides. Dalton Trans. 2018, 47, 1755–1763. https://doi.org/10.1039/C7DT03657D.
109. Ashokkumar, V.; Siva, A., One-pot synthesis of α,β-epoxy ketones through domino reaction between alkenes and aldehydes catalyzed by proline based chiral organocatalysts. Org. Biomol. Chem. 2017, 15, 2551–2561. https://doi.org/10.1039/C7OB00031F.
110. Crivoi, D.-G.; Segarra, A. M.; Medina, F., Highly selective multifunctional nanohybrid catalysts for the one-pot synthesis of α,β-epoxy-chalcones. J. Catal. 2016, 334, 120–128. https://doi.org/10.1016/j.jcat.2015.11.020.
111. Tamaribuchi, K.; Tian, J.; Akagawa, K.; Kudo, K., Enantioselective nitro-Michael addition catalyzed by N-terminal guanidinylated helical peptide. Adv. Synth. Catal. 2022, 364, 82–86. https://doi.org/10.1002/adsc.202101152.
112. Li, X. L.; Jiang, G. C.; Wang, J.; Ni, X. X., Inhibitive properties comparison of different polyamino acids in water-based drilling fluids. J. Nat. Gas Sci. Eng. 2020, 83, 103589. https://doi.org/10. 1016/j.jngse.2020.103589.
113. Upadhyay, P.; Srivastava, V., Proline based Organocatalysis: Supported and Unsupported Approach. Curr. Organocat. 2016, 3, 243–269. https://doi.org/10.2174/2213337202666150812230640.
114. Zhao, W. S.; Qu, C. K.; Yang, L. L.; Cui, Y. C., Chitosan-supported cinchonine as an efficient organocatalyst for direct asymmetric aldol reaction in water. Chin. J. Catal. 2015, 36, 367–371. https://doi.org/10.1016/S1872-2067(14)60248-5.
115. Toledo-Gonzalez, Y.; Sotiropoulos, J. M.; Becart, D.; Guichard, G.; Carbonnière, P., Insight into substrate recognition by urea-based helical foldamer catalysts using a DFT global optimization approach. J. Org. Chem. 2022, 87, 10726–10735. https://doi.org/10.1021/acs.joc.2c00562.
116. Metrano, A. J.; Chinn, A. J.; Shugrue, C. R.; Stone, E. A.; Kim, B.; Miller, S. J., Asymmetric catalysis mediated by synthetic peptides, version 2.0: Expansion of scope and mechanisms. Chem. Rev. 2020, 120, 11479–11615. https://doi.org/10.1021/acs.chemrev.0c00523.
117. Lasterra-Sánchez, M. E.; Roberts, S. M., An important niche in synthetic organic chemistry for some biomimetic oxidation reactions catalysed by polyamino acids. Curr. Org. Chem. 1997, 1, 187–196. https://doi.org/10.2174/1385272801666220120215606.
118. Kroutil, W.; Mayon, P.; Lasterra-Sánchez, M. E.; Maddrell, S. J.; Roberts, S. M.; Thorton, S. R.; Todd, C. J.; Tüter, M., Unexpected asymmetric epoxidation reactions catalysed by polyleucine-based systems. J. Chem. Soc. Chem. Commun. 1996, 845–846. https://doi.org/10.1039/P19960002837.
119. Weitz, E.; Scheffer, A., Über die Einwirkung von alkalischem Wasserstoffsuperoxyd auf ungesättigte Verbindungen. Chem. Ber. 1921, 54, 2327–2344. https://doi.org/10.1002/cber.19210540922.
120. Apeloig, Y.; Kerni, M.; Rappoport, Z., The role of hyperconjugation in determining the stereochemistry of nucleophilic epoxidation and cyclopropanation of electrophilic olefins. J. Am. Chem. Soc. 1983, 105, 2784–2793. https://doi.org/10.1021/ja00347a044.
121. Corma, A.; Iborra, S.; Mifsud, M.; Renz, M., Mesoporous molecular sieve Sn-MCM-41 as Baeyer-Villiger oxidation catalyst for sterically demanding aromatic and α,β-unsaturated aldehydes. Arkivoc 2005, ix, 124–132. https://doi.org/10.3998/ark.5550190.0006.913.
122. Wang, Z., Weitz-Scheffer Epoxidation, Comprehensive Organic Name Reactions and Reagents, John Wiley & Sons, West Sussex, U.K. 2010, pp. 2975–2979.
123. Porter, M. J.; Roberts, S. M.; Skidmore, J., Polyamino Acids as Catalysts in Asymmetric Synthesis.

Bioorg. Med. Chem. 1999, 7, 2145–2156. https://doi.org/10.1016/s0968-0896(99)00144-3.
124. Handbook of Phase Transfer Catalysis, Ed. Y. Sasson and R. Neumann, Chapman & Hall, London, 1997.
125. Jones, R. A., Quaternary Ammonium Salts: Their Use in Phase-Transfer Catalysis, Academic Press, San Diego, 2001.
126. Alkorta, I.; Elguero, J.; Gallo, R., A theoretical study of the limits of the acidity of carbon acids in phase transfer catalysis in water and in liquid ammonia. Cent. Eur. J. Chem. 2013, 11, 1711–1722. https://doi.org/10.2478/s11532-013-0311-7.
127. Lundin, A.; Panas, I.; Ahlberg, E., Quantum chemical modeling of ethene epoxidation with hydrogen peroxide: the effect of microsolvation with water. J. Phys. Chem. A 2007, 111, 9080–9086. https://doi.org/10.1039/B710784F.
128. Kobayashi, N.; Iwai, K., Functional polymers, 8. Asymmetric catalysis by quininium salts anchored to a polystyrene matrix. Makromol. Chem. Rapid Commun. 1981, 2, 105–108. https://doi.org/10.1002/marc.1981.030020121.
129. Colonna, S.; Banfi, S.; Papagni, A., Catalytic asymmetric epoxidation in the presence of cyclodextrins. Gazz. Chim. Ital. 1985, 115, 81–83. https://doi.org/10.1002/chin.198525089. https://doi.org/10.1002/chin.198525089.
130. Hu, Y.; Harada, A.; Takahashi, S., Cyclodextrin-H_2O_2: A new system for asymmetric epoxidation. Synth. Commun. 1988, 18, 1607–1610. https://doi.org/10.1080/00397918808081320.
131. Kobayashi, N., Asymmetric reactions catalysed by polymeric cinchona alkaloids. Br. Polym. J. 1984, 16, 205–211. https://doi.org/10.1002/pi.4980160409.
132. Baba, N.; Oda, J.; Kawaguchi, M. Asymmetric epoxidation of cyclic enones under chiral phase transfer conditions. Agric. Biol. Chem. 1986, 50, 3113–3117. https://doi.org/10.1080/00021369.1986.10867870.
133. Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering J. S.; Wynberg, H., Catalytic asymmetric induction in oxidation reactions. The synthesis of optically active epoxides. Tetrahedron Lett. 1976, 17, 1831–1834. https://doi.org/10.1016/S0040-4039(00)93796-1.
134. Wynberg, H.; Greijdanus, B., Solvent effects in homogeneous asymmetric catalysis. J. Chem. Soc, Chem. Commun. 1978, 427–428. https://doi.org/10.1039/C39780000427.
135. Igarashi, M.; Midorikawa, H., Asymmetric epoxidation of l-menthyl alkylidenecyanoacetates. Bull. Chem. Soc. Jpn. 1967, 40, 2624–2627. https://doi.org/10.1246.40.2624.
136. Marsman, B.; Wynberg, H., Absolute configuration of chalcone epoxide. Chemical correlation. J. Org. Chem. 1979, 44, 2312–2314. https://doi.org/10.1021/jo01327a070.
137. Harigaya, Y.; Yamaguchi, H.; Onda, M., Heterocycles IX. Asymmetric epoxidation of a quinone and syntheses of chiral lactones. Heterocycles 1981, 15, 183–185. https://doi.org/10.3987/S-1981-01-0183.
138. Harigaya, Y.; Yamaguchi, H.; Onda, M., Heterocycles. X. Syntheses and absolute configurations of a chiral naphthoquinone epoxide and chiral naphtho[1,2-c]isocumarins. Chem. Pharm. Bull. 1981, 29, 1321–1327. https://doi.org/10.1248/cpb.29.1321.
139. Inoue, S., Asymmetric reactions of synthetic polypeptides, in Mechanisms of Polyreactions-Polymer Characterization. Adv. Polym. Sci. 1976, 21, 77–106. https://doi.org/10.1007/3-540-07727-8_4.
140. Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J., Asymmetric catalysis mediated by synthetic peptides. Chem. Rev. 2007, 107, 5759–5812. https://doi.org/10.1021/cr068377w.
141. Ueyanagi, K.; Inoue, S., Asymmetric addition of 1-dodecanethiol to isopropenyl methyl ketone catalyzed by poly(α-amino acid)s: Determination of the enantiomeric purity of the product. Makromol. Chem. 1977, 178, 235–239. https://doi.org/10.1002/macp.1977.021780123 .
142. Oku, J.; Ito, N.; Inoue, S., Asymmetric cyanohydrin synthesis catalyzed by synthetic dipeptides, 1. Makromol Chem. 1979, 180, 1089–1091. https://doi.org/10.1002/macp.1979.021800431.
143. Heitbaum, M.; Glorius, F.; Escher, I., Asymmetric heterogeneous catalysis. Angew. Chem. Int. Ed. 2006, 45, 4732–4762. https://doi.org/10.1002/anie.200504212.
144. Zhang, Z. P.; Liu, Y. F.; Wang, Z.; Ding, K. L., Kinetic insights into cyanosilylation of aldehydes catalyzed by a covalently bridged dinuclear (salen)titanium complex. Asian J. Org. Chem. 2022, 11, e202100795. https://doi.org/10.1002/ajoc.202100795.
145. Sugimoto, T.; Kokubo, T.; Miyazaki, J.; Tanimoto, S.; Okano, M., Stereoselective formation of aromatic sulphoxides by oxidation of sulphides and sulphoxides in the presence of bovine serum albumin. J. Chem. Soc. Chem. Commun. 1979, 1052–1053. https://doi.org/10.1039/C39790001052.
146. Zhou, W.; Yerkes, N.; Chruma, J. J.; Liu, L.; Breslow, R., Chiral polyamines from reduction of polypeptides: Asymmetric pyridoxamine-mediated transaminations. Bioorg. Med. Chem. Lett. 2005, 15, 1351–1355. https://doi.org/10.1016/j.bmcl.2005.01.021.
147. Baba, N.; Matsumura, Y.; Sugimoto, T., Asymmetric reduction of aryl trifluoromethyl ketones with an achiral NADH model compound in a chiral hydrophobic binding site of sodiumcholate micelle, β-cyclodextrin and bovine serum albumin. Tetrahedron Lett. 1978, 19, 4281–4284. https://doi.org/10.1016/S0040-4039(01)95202-5.
148. Sugimoto, T.; Matsumura, Y.; Tanimoto, S.; Okano, M., Asymmetric reduction of aromatic ketones by sodium borohydride in the presence of bovine serum albumin. J. Chem. Soc. Chem. Commun. 1978, 926–927. https://doi.org/10.1039/C39780000926.
149. Ohno, A.; Ushida, S., Mechanistic Models of Asymmetric Reductions, Springer-Verlag, Berlin, 1986.
150. Albanese, C. M.; Gaggero, N., Albumin as a promiscuous biocatalyst in organic synthesis. RSC

Adv. 2015, 5, 10588–10598. https://doi.org/10.1039/C4RA11206G.
151. Freindorf, M.; Kraka, E., Mechanistic details of the Sharpless epoxidation of allylic alcohols - A combined URVA and local mode study. Catalysts 2022, 12, 789. https://doi.org/10.3390/catal12070789.
152. Lasterra-Sánchez, M. E.; Roberts, S. M., Enantiocomplementary asymmetric epoxidation of selected enones using poly-L-leucine and poly-D-leucine. J. Chem. Soc., Perkin Trans. 1 1995, 1467–1468. https://doi.org/10.1039/P19950001467.
153. Bentley, P. A.; Bergeron, S.; Cappi, M. W.; Hibbs, D. E.; Hurthouse, M. B.; Nugent, T. C.; Pulido, R.; Roberts, S. M.; Wu, L. E., Asymmetric epoxidation of enones employing polymeric a-amino acids in non-aqueous media. Chem. Commun. 1997, 739–740. https://doi.org/10.1039/A700550D.
154. Akagawa, K.; Kudo, K., Development of selective peptide catalysts with secondary structural frameworks. Acc. Chem. Res. 2017, 50, 2429–2439. https://doi.org/10.1021/acs.accounts.7b00211.
155. Bryliakov, K., Environmentally Sustainable Catalytic Asymmetric Oxidations, CRC Press, Taylor & Francis Group, Boca Raton, 2015.
156. Cussó, O.; Giulano, M. W.; Ribas, X.; Miller, S. J.; Costas, M., A bottom up approach towards artificial oxygenases by combining iron coordination complexes and peptides. Chem. Sci. 2017, 8, 3660–3667. https://doi.org/10.1039/c7sc00099e.
157. Wang, X.; Reisinger, C. M.; List, B., Catalytic asymmetric epoxidation of cyclic enones. J. Am. Chem. Soc. 2008, 130, 6070–6071. https://doi.org/10.1021/ja801181u.
158. De Fusco, C.; Tedesco, C.; Lattanzi, A., Organocatalytic stereoselective epoxidation of trisubstituted acrylonitriles. J. Org. Chem. 2011, 76, 676–679. https://doi.org/10.1021/jo102020a.
159. Cussó, O.; Cianfanelli, M.; Ribas, X.; Gebbink, R. J. M. K.; Costas, M., Iron catalyzed highly enantioselective epoxidation of cyclic aliphatic enones with aqueous H2O2. J. Am. Chem. Soc. 2016, 138, 2732–2738. https://doi.org/10.1021/jacs.5b12681.
160. Karaman, H. S.; Kiliç, H.; Sahin, E., Asymmetric epoxidation of enones using cumyl hydroperoxide and in situ generated zinc complexes of chiral pyrrolidinyl alcohols. Tetrahedron Asymmetry 2017, 28, 1626–1632. https://doi.org/10.1016/j.tetasy.2017.09.004.