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Amino acids and peptides as asymmetric organocatalysts

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Contents

1. Introduction

Many enzymes are remarkable asymmetric catalysts, performing reactions effectively and selectively. Aspiring to imitate enzymatic efficiencies, chemists have delved into Nature's toolbox, transforming amino acids into innumerable auxiliaries, catalysts, and ligands. In the majority of examples, the amino acid is used purely as a source of chirality and both the amine and acid functionality are altered or eliminated. Unmodified amino acids and peptides have been used as catalysts much less frequently. Early studies of peptide-based catalysis appear to have been focused on two ends of a spectrum of possible catalysts: small, conformationally rigid amino acids and cyclic dipeptides, and large peptides which, by virtue of their increased size, likely adopt a specific tertiary structure in solution. At the lower end of the complexity spectrum, Hajos and Wiechert reported the use of proline as a catalyst for the Robinson annulation as early as 1970. Inoue used diketopiperazines as catalysts in the Strecker reaction in the late 1970s and early 1980s. At the same time, and at the other end of the spectrum, Juliá and Colonna employed poly(amino acids) (>10 amino acids in length) as epoxidation catalysts. These polymers had rather ill defined solution state structures and were, to an extent, viewed as a chiral medium for the reaction.

Use of a short peptide as a catalyst would allow expansion beyond the (still uncharted) repertoire of single amino acids, while conserving the advantages of a small molecule catalyst. The ability of a tiny subset of an enzyme's primary structure to mediate catalysis suggests that short peptides could also be successful catalysts. However, the idea that a peptide would be able to function as a pared-down version of an enzyme has been met with considerable skepticism.[1] The development of de novo design of short peptide

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sequences that fold into defined secondary structures in organic or aqueous solution[2] has enabled the push forward into this middle ground. These designed secondary and tertiary structures have been used as chiral scaffolds for the assembly of catalytically active functionality.[3] As with larger enzyme counterparts, a degree of flexibility may benefit these catalysts.[4] More recently, examination of libraries of short peptide catalysts that are not biased towards one secondary structure has resulted in the discovery of very selective catalysts.

Interest in organocatalysis has increased over the past decade. The use of peptidic ligands for enantioselective metal catalysts has also increased.[5] This review will focus on catalysis by amino acids, peptides (<50 amino acids in length), and relatively simple derivatives of amino acids. Our coverage in this review is not comprehensive, and focuses on representative examples. We elect to focus on metal-free amino acid and peptide-based catalysts as a subset of the larger field of organocatalysts. We refer interested readers to a number of other excellent reviews and minireviews of this subject.[6] Given the successes outlined in this review, it appears that amino acid- and peptide-based catalysis will continue to thrive.

2. Aldol reaction

2.1. Robinson annulation

In the early 1970s, two groups independently reported the asymmetric Robinson annulation of *meso*-triones using (*S*)-proline as a catalyst. Hajos and Parrish at Hoffmann–LaRoche isolated intermediate ketol **2**,[7] while Wiechert and co-workers at Schering AG reported direct conversion to enone **3**.[8] A catalytic quantity of (*S*)-proline (3 mol%) was sufficient to mediate the aldol cyclization of **1**, yielding bicyclic ketol **2** in 100% yield and 93% ee (Scheme 1). The ketol can be converted to the enone without loss of enantiomeric excess. The polar aprotic solvent DMF was found to give the shortest reaction time and highest enantioselectivity and yield. The Wieland–Miescher ketone may be prepared in optically pure form (after recrystallization) by this route.[9,10] This reaction has thus enabled numerous asymmetric syntheses of steroids and terpenoids[11] and is a seminal example of asymmetric catalysis.

Elucidation of the mechanism of action of this catalyst began with the idea that enamine intermediates were involved.[12] Both the secondary amine and carboxylate functionalities were found to be critical for catalysis. The reaction displays second order kinetic dependence on (*S*)-proline[13] and exhibits a negative non-linear effect.[14] Agami and co-workers proposed a mechanism that involves attack of an intermediate enamine on one enantioface of a prochiral ketone. Proton transfer is facilitated by a bifurcated hydrogen bond between the enamine, the ketone, and the amine of a second molecule of (*S*)-proline (see Fig. 1).[15] This is reminiscent of the mechanism of action of the Type I aldolases, wherein the ketone is activated by formation of an enamine intermediate.[16]

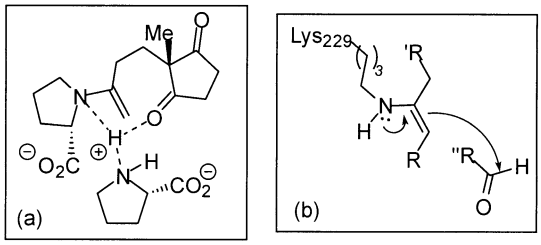
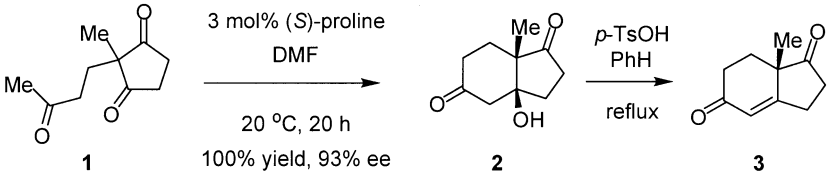


Figure 1. Proposed enamine intermediates in (a) proline catalyzed intramolecular aldol and (b) Type I aldolase.

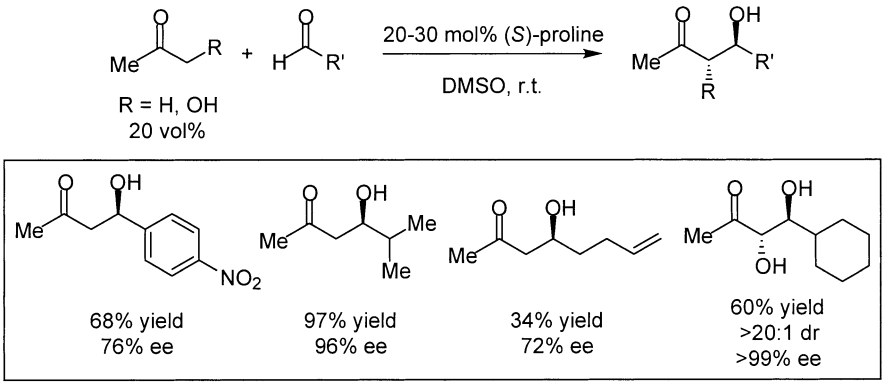
2.2. Intermolecular aldol reaction

Catalytic antibodies that mediate asymmetric aldol reactions in a fashion similar to Type I aldolases have been reported by Lerner and Barbas et al. Based on these studies and the Hajos–Wiechert reaction, List et al. investigated the use of proline as a catalyst for the intermolecular aldol reaction between acetone and a series of aldehydes.[17] As was found in the Hajos–Wiechert reaction, both the 5-membered ring and carboxylate of the catalyst were required to maintain good enantioselectivities and yields. Unlike most catalytic asymmetric aldol reactions, this variant does not require a preformed enolate, and constitutes a direct aldol reaction.[18]

Aromatic aldehydes give the aldol products with moderate yields and enantioselectivities (60–70% yield and ee, see Scheme 2).[19] Using (*S*)-proline as catalyst, α-branched isobutyraldehyde is processed with excellent yield and enantioselectivity (97% yield, 96% ee). A rather high catalyst loading (20–30 mol%) is required, and the ketone, acetone, is used as a co-solvent (20 vol% in DMSO). However, from a practical point of view, the low cost of the catalyst mitigates this issue. α-Unbranched, enolizable aldehydes generally suffer lower yields due to competing self-aldolization. Switching the solvent to $CHCl_3$ suppresses this side reaction for some substrates; these substrates are processed with improved yields and moderate enantioselectivities (generally 60–70% ee).[20] Diminished yields are due to formation of the aldol condensation product.[21] Switching the ketone to hydroxyacetone extends this reaction to the preparation of *anti*-1,2-diols with no protecting group manipulations.[22] α-Branched aldehydes yield



Scheme 1. Proline catalyzed asymmetric Robinson annulation.



Scheme 2. Intermolecular aldol reaction catalyzed by proline.

aldol products with high regioselectivites, diastereoselectivities and enantioselectivities in moderate yields. Recycling of the catalyst by adsorption onto silica has proved promising, allowing reuse for one cycle while maintaining enantioselectivity and yield.[23] These impressive transformations represent an important contribution to aldol methodology since they allow the direct conversion of ketones and aldehydes to optically enriched aldol products using a readily available and moisture-tolerant catalyst.

This reaction is postulated to proceed through a metal-free Zimmerman–Traxler-like transition state (Fig. 2).[24] A bifurcated hydrogen bond involving the carboxylate, enamine, and aldehyde organizes the transition state. Unlike the proline catalyzed intramolecular aldol, this reaction shows an absence of a non-linear effect,[25] consistent with the involvement of only one equivalent of catalyst in the transition state.

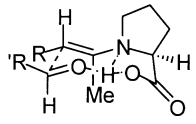
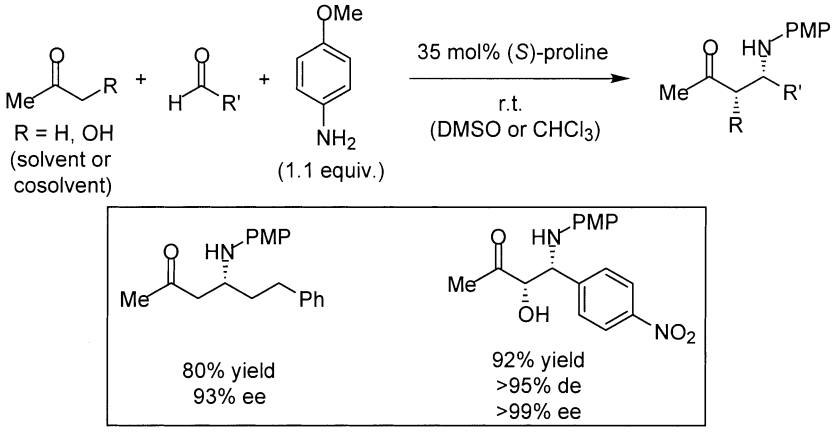


Figure 2. Proposed transition state for proline-catalyzed intermolecular aldol reaction.

2.3. Mannich reaction

Proline has also been used as a catalyst for the direct Mannich reaction.[26,27] Preformed enolates and imines are not required. It is thus possible to mix together a substoichiometric quantity of proline (35 mol%), a ketone (acetone or hydroxyacetone), an aldehyde, and a primary amine (*p*-anisidine), and isolate the desired PMP-protected amine in good to excellent enantioselectivity (70–96%) and modest to excellent yield (35–90%, Scheme 3). This is particularly interesting considering both catalyst and primary amines are able to form Schiff bases with both ketone and aldehyde, opening various avenues for undesired reactivity. DMSO and $CHCl_3$ are used as co-solvents in some cases.

This reaction exhibits opposite enantiofacial selectivity to the proline-catalyzed aldol reaction (attack on *si*-enantioface as compared to *re*-enantioface). A number of models have been proposed, culminating in the view presented in Fig. 3. List proposes that the reaction of (*E*)-imine (which will be present in higher concentrations than the (*Z*)-imine) with the (*E*)-enamine could proceed as shown in Fig. 3(a). Comparison of this transition state to the proposed transition state for the aldol reaction (Fig. 3(b)) provides an explanation for the opposite enantiofacial selectivity of the two reactions: in the Mannich reaction steric interactions between the aromatic and pyrrolidine ring dominate while



Scheme 3. Three component catalytic asymmetric Mannich reaction.

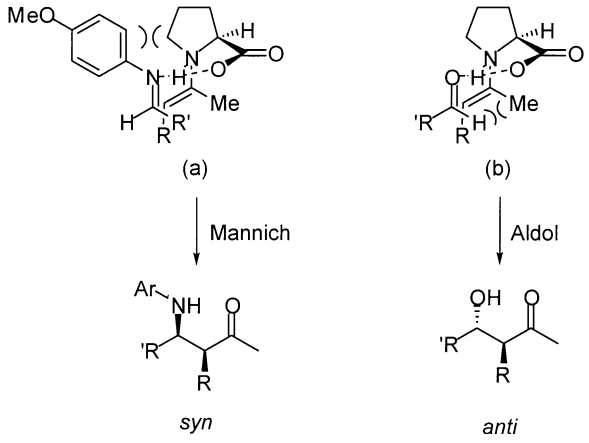
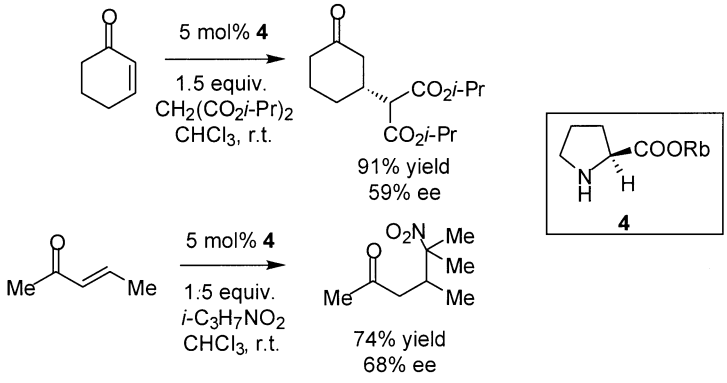


Figure 3. Proposed transition states for the proline-catalyzed asymmetric Mannich and aldol reactions.

selectivities and yields. Both the carboxylate and secondary amine were found to be essential for catalysis. Various countercations, including alkali metals and tetraalkylammoniums were examined, with the rubidium salt proving the most enantioselective.[29] Rigorous exclusion of water slows the reaction rate, suggesting that the reaction may proceed through an intermediate iminium ion. The reaction exhibits an absence of a non-linear effect. This salt has also been used as a catalyst for the addition of nitroalkanes to enones,[30] with modest to good enantioselectivities and yields (ees ranging from 41–84%, yields 47–91%, Scheme 4). Use of prochiral nitroalkanes yields products with low diastereoselectivities.

Hanessian and Pham have examined a related system, using a catalytic quantity of L-proline and a stoichiometric amount of *trans*-2,5-dimethylpiperazine as an additive.[31] Enantio-

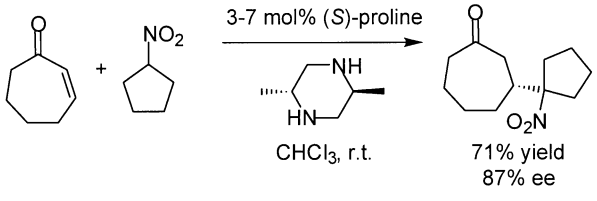


Scheme 4. Rb-Prolinate catalyzed conjugate additions.

in the aldol reaction steric interactions between the aldehyde and enamine substituents may be the most important.

2.4. Michael addition

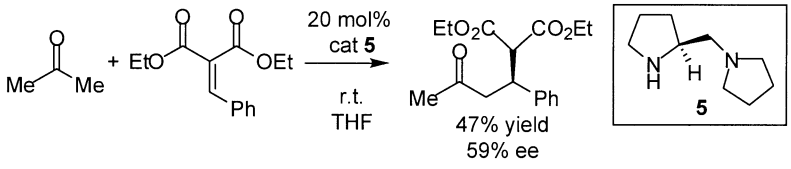
The rubidium salt of (*S*)-proline has been used as a catalyst for the enantioselective addition of malonate to enones by Yamaguchi and co-workers (Scheme 4).[28] Michael addition products are formed with moderate to good enantio-



Scheme 5. Proline catalyzed conjugate additions of nitroalkanes.

selectivities in the conjugate additions of nitroalkanes to cyclic enones are improved compared to Rb-prolinate systems, with ees ranging from 62–93% (Scheme 5). Diastereoselectivities in reactions with primary nitroalkanes remain low. This reaction exhibits a pronounced nonlinear effect suggesting the involvement of a multicomponent catalyst. Furthermore, alcoholic solvents decrease enantioselectivities. Rigorous exclusion of water inhibits the reaction, lending credence to a hydrolytic step in the catalytic cycle.

A small molecule (**5**) derived from (*S*)-proline has been shown to catalyze the Michael addition of ketones to alkylidene malonates.[32,33] Addition of acetone to aryl substituted diethylmalonates proved to be the best system with enantioselectivities ranging from 31 to 70% and yields ranging from 17 to 70% (Scheme 6).



Scheme 6. Bisamine catalyzed Michael addition.

3. Hydrocyanation

3.1. Hydrocyanation of aldehydes

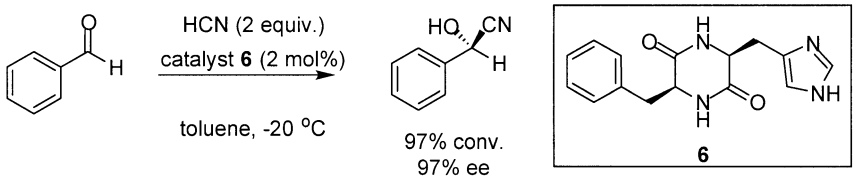
In 1981, Inoue reported the enantioselective addition of HCN to benzaldehyde catalyzed by diketopiperazine **6**, cyclo(L-phenylalanine-L-histidine).[34] This catalyst was designed to be a small molecule alternative to oxynitrilase, an enzyme that was a known catalyst for the process.[35] While the cyclic dipeptide is structurally much less complex than the enzyme, it is successful in achieving high levels of enantioselection. The cyanohydrin product of this reaction is a useful chiral building block as a precursor to α-hydroxy acids and amino alcohols.[36] Diketopiperazine catalyst **6** displays a reasonably broad substrate scope and is required in low catalyst loadings (2 mol%), giving good yields of the optically enriched cyanohydrins.[37] Electron rich aromatic aldehydes are the best substrates (ees ranging from 78 to 98%, Scheme 7), while aliphatic and electron poor aromatic aldehydes are processed with lower enantioselectivities (ranging from 18 to 71% ee). A preliminary mechanistic model and mnemonic device was proposed to predict the observed absolute stereoselectivities (Fig. 4(a)).[38]

The elucidation of the mechanism of this reaction poses a formidable challenge that has been approached by several groups. Early reports from the Inoue group specified that the method of catalyst preparation has a profound effect on the enantioselectivity and yield of the reaction. Amorphous catalyst samples exhibit higher selectivities and activities than samples that are crystalline. Toluene is the best solvent for the reaction, and gel-like reaction mixtures are more successful than homogenous solutions. This gel is likely due to a hydrogen-bonded polymer of the diketopiperazine. Danda et al. reported that the reaction displays thixotropy, with highest enantioselectivities obtained from the least viscous (most vigorously stirred) reaction mixtures.[39] Furthermore, the reaction was found to exhibit asymmetric autocatalysis. As enantioenriched product is formed, the enantioselectivity and rate of the reaction increase significantly. In fact, it is possible to obtain cyanohydrin in 82% ee using a catalyst of only 2% ee by doping the reaction mixture with 9 mol% of optically enriched product (92% ee).[40] Subsequent studies showed that addition of an achiral protic additive also eliminates the observed induction period, presumably functioning similarly to the product of the reaction.[41]

In attempts to unravel the intricacies of this reaction, solution state NMR spectroscopy,[42] solid state NMR spectroscopy,[43] and molecular modeling[44] (primarily of monomeric diketopiperazines) have been used to study the possible catalyst conformations. Unfortunately, interpretation of the significance of these results is complicated by the reaction's heterogeneity. An alternative mechanism, involving a hemiaminal intermediate, was proposed by North and co-workers when they found that dipeptide **6** catalyzes the oxidation of benzaldehyde to benzoic acid,[45] presumably through an aminal intermediate (Fig. 4(b)). Perhaps the most conclusive experimental evidence was obtained when Shvo showed that the reaction displays a second order kinetic dependence on catalyst.[46] This supports a mechanism wherein the aldehyde is activated by one histidine side chain while the cyanide nucleophile is activated by a second histidine side chain, from a second diketopiperazine (Fig. 4(c)). Conceivably, the aldehyde could be activated by either a hydrogen bond to imidazolium or by formation of the hemiaminal intermediate. This confirms that the isolated monomer is not responsible for the observed reaction. The exact structure of the catalytically active species, be it a dimer, an oligomer or a polymer, remains undefined.[47] Twenty years after the first report of this catalytic process, a clear and rigorous understanding of the mechanism of action of the catalyst remains elusive. Nonetheless, this reaction is an early example of the capability of simple peptide-based catalysts to perform asymmetric transformations.[48]

3.2. Hydrocyanation of imines

In 1996, Lipton and co-workers reported the use of a cyclic dipeptide as a catalyst for the asymmetric Strecker amino acid synthesis.[49] The use of unnatural α-amino acids as tools in enzymology[50] and their prevalence as building blocks for



Scheme 7. Inoue's hydrocyanation of aldehydes.

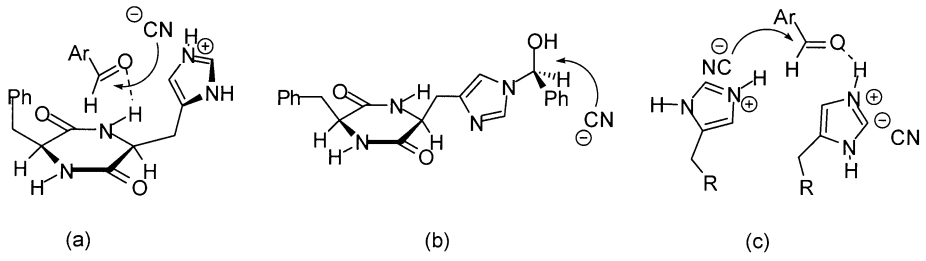
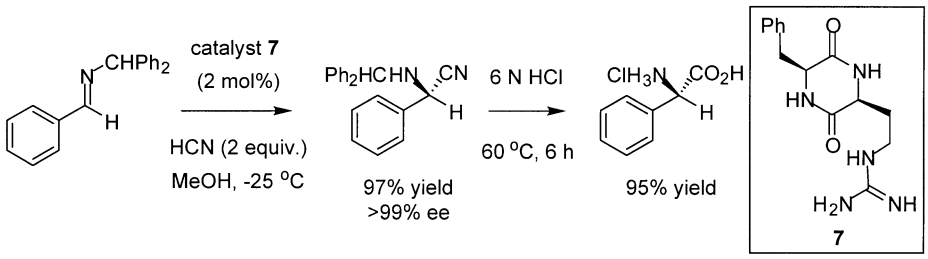


Figure 4. Proposed transition states for Inoue's hydrocyanation of aldehydes.



Scheme 8. Lipton's asymmetric Strecker synthesis of amino acids.

synthetic targets and ligands and makes their asymmetric synthesis an attractive target. The mechanistic similarity between the hydrocyanation of aldehydes and imines suggested that perhaps similar catalysts would be effective for both processes. However, early studies with Inoue's histidine containing diketopiperazine **6** did not afford enantiomerically enriched product. Replacement of (*S*)-histidine with (*S*)-norargenine, which substitutes a guanidine moiety for the imidazole (catalyst **7**), led to a successful catalyst. The authors speculate that this is due to the increased basicity of guanidine, which allows it to participate in proton transfer. Benzaldimine is substantially more basic than benzaldehyde and is more basic than imidazole. While imidazolium ion can serve as an acid catalyst with benzaldehyde, in the case of benzaldimine, proton transfer and subsequent addition of cyanide can occur without the intervention of the catalyst. Increased basicity of the catalyst ensures that cyanide addition precedes proton transfer from catalyst to substrate.

N-Benzhydryl aromatic imines treated with catalyst **7** (2 mol%) and HCN (2 equiv.) in methanol at −25 or −75°C form α-aminonitriles in high yields and high selectivities (Scheme 8). α-Aminonitriles lacking an *N*-protecting group are configurationally unstable and the benzhydryl protecting group was chosen since it can be removed without racemization of the products. This reaction allows the synthesis of (*S*)-phenylglycine in three steps from benzaldehyde in 97% ee and 92% overall yield. Aliphatic aldimines and some electron poor aldimines yield products with lower ees. Nonetheless, this reaction provides facile access to the important class of optically enriched arylglycines.

While several similarities exist between this reaction and the diketopiperazine catalyzed cyanohydrin formation, their mechanisms may be different. Cyanohydrin formation is performed as a gel in toluene, and enantioselectivity was eliminated in methanol. The hydrocyanation of imines with catalyst **7**, however, is performed as a homogeneous reaction mixture in methanol. While catalysts **6** and **7** both contain all (*S*)-amino acids, they promote addition to enantiotopic faces of the substrates (formation of (*R*)-cyanohydrin versus (*S*)-aminonitrile).

Subsequent to Lipton and co-workers disclosure of the asymmetric Strecker synthesis, several groups have published catalysts for the addition of cyanide to imines. Several of these rely on the use of metal-based catalysts where the ligands are peptide-like, that is, they contain one or more amino acids. However they also incorporate other functional groups (e.g. Schiff bases, ureas), in part to ensure potential metal-binding sites.[51] In the course of exploring such catalyst structures, Jacobsen et al. discovered a ligand that did not require a metal salt to catalyze the reaction.[52–54] This peptide-like catalyst **8** displays excellent enantioselectivities with aliphatic aldimines. In addition, these findings support the possibility that a linear, flexible peptide could function as an effective catalyst for this reaction (Fig. 5).

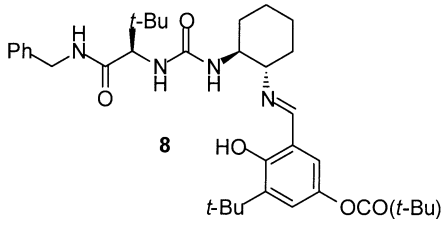
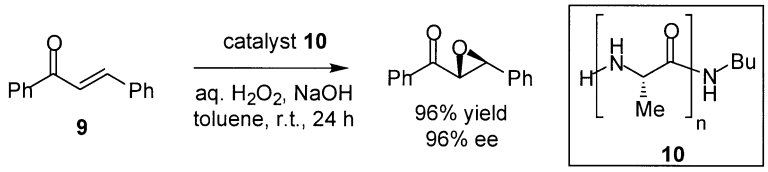


Figure 5. Organocatalyst **8** for the asymmetric Strecker reaction.

4. Epoxidation[55]

In 1980, Juliá reported the epoxidation of chalcones using poly-L-alanine (**10**) as catalyst.[56,57] Reactions are a triphasic mixture—organic, aqueous, and the polymeric catalyst that swells to form a gel. Non-polar solvents such as toluene were found to be the best, with selectivities and yields suffering in methanol, perhaps due to interruption of hydrogen bonding between catalyst and the ketone of the substrate. An excess of $NaOH–H_2O_2$ is used at room temperature to afford epoxides of substrates such as **9** with very good enantioselectivities and yields (Scheme 9). Exploration of suitable amino acids for catalyst monomers showed that poly-L-leucine displayed the most promise.[58] In general, α-helical peptides proved more successful than



Scheme 9. Juliá–Colonna epoxidation of chalcones.

peptides that have a propensity to form β-sheets.[59] Polypeptides of lengths >10 amino acids were found to be the best catalysts, with catalysts having mean lengths of approximately 30 amino acids proving most enantioselective.[60,61] This may be due in part to the increased stability of the α-helical secondary structure.[62,63]

The nature of the C-terminus does not appear to have a large effect on the catalyst's efficiency. Juliá, Colonna and co-workers used this as a point of attachment to hydroxymethylated polystyrene through an ester linkage, thus facilitating retrieval of the catalyst by filtration.[64] Itsuno and co-workers prepared a resin-bound poly-L-leucine (**12**), linking the polypeptide to aminomethylated polystyrene crosslinked with divinylbenzene.[65]

In an effort to expand the scope of this reaction to include enolizable ketones and other substrates that are sensitive to aqueous base, Roberts and co-workers developed the use of a two-phase system.[66] The terminal oxidant was switched to urea–H_2O_2 and is no longer required in excess. The Itsuno catalyst (**12**) is used with DBU in THF. Under these reaction conditions, the catalyst is a paste that may be isolated by decanting the reaction mixture. Epoxidation of substrates such as **11** may be achieved with good yields and enantioselectivities (Scheme 10, no desired product was obtained with this substrate under triphasic conditions).

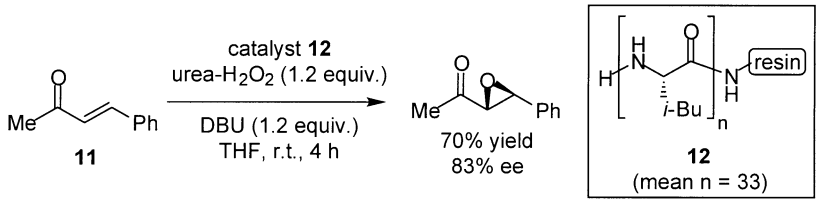
Smaller amounts of catalyst (~10% per run) are lost under biphasic conditions than under the original three-phase system. The catalyst may be regenerated by washing with 4 M NaOH and adding an aliquot of fresh catalyst (10% of original weight), thus allowing for catalyst recycling.[67] Roberts et al. have reported adsorption of poly-L-leucine onto silica gel, making possible more efficient recovery of catalyst by filtration.[68] Preliminary experiments suggest that this catalyst retains both activity and enantioselectivity when reused. Furthermore, the activity of the catalyst is reported to be higher than the resin-bound catalyst, so that catalyst loading may be decreased to as low as 2.5 mol%. A soluble polymer catalyst, poly-L-leucine bound to polyethylene glycol, has recently been reported.[69] Short average peptide chain lengths (four amino acids) are sufficient to yield products in high enantioselectivities and yields.

5. Acyl transfer reaction

5.1. Kinetic resolution by hydrolysis of *p*-nitrophenyl esters

Over the past three decades, a body of work has been published concerning catalysis of transesterification by peptide-based catalysts. This may not be surprising since lipases and esterases are perhaps the most commonly utilized enzymes for synthetic applications.[70] Early studies using short peptides or cyclic dipeptides as catalysts were often performed in aqueous solution, and capitalized on hydrophobic effects.[71] Surfactants were used to form micelles and vesicles, thus increasing the rate of catalysis by localizing catalyst and substrate. While some catalysts exhibit very high selectivities (k_{rel}>100),[72] these systems generally suffered from a lack of catalytic activity, requiring multiple equivalents of catalyst.

An example of the melding of progress towards the de novo design of short peptides with defined secondary and tertiary structure and the use of such peptides as catalysts is the work of Baltzer and co-workers.[73] Peptides (42-mers) which adopt a helix–loop–helix conformation and which dimerize to form four helix bundles were designed.[74] Histidine residues were incorporated at positions where they could cooperate in catalysis. Using one of these catalysts, the *p*-nitrophenyl ester of D-Nle is hydrolyzed with a k_2(D-Nle)/k_2(L-Nle)=2.0.[75] This selectivity is proposed to stem from charge–charge repulsion that destabilizes the transition state for attack on L-Nle, slowing the reaction of that enantiomer (Fig. 6(a) versus (b)). The ammonium of the



Scheme 10. Two-phase Juliá–Colonna epoxidation.

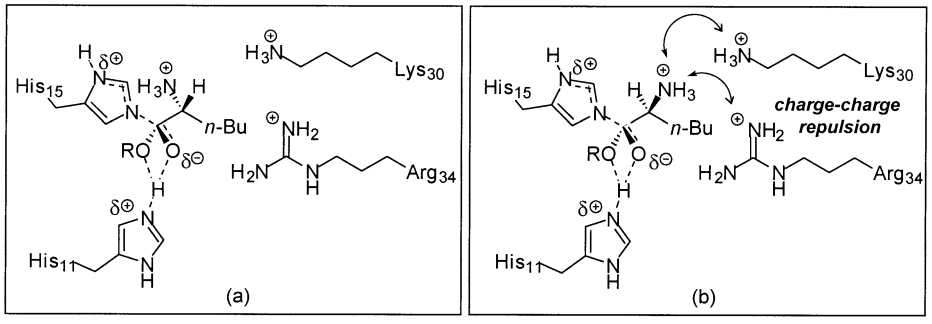


Figure 6. Proposed diastereomeric transition states for transesterification of *p*-nitrophenyl esters (a) favored; (b) disfavored.

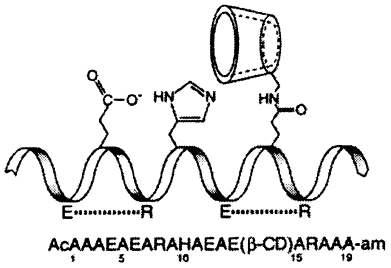


Figure 7. β-Cyclodextrin functionalized peptide catalyst **13**. Reprinted with permission. Copyright (2000) Royal Society of Chemistry.

substrate is thought to interact with the positively charged Lys and Arg residues of the adjacent helix. Catalysts of this type are interesting examples of the use of designed secondary structure in catalysis, and foreshadow further developments in this area.

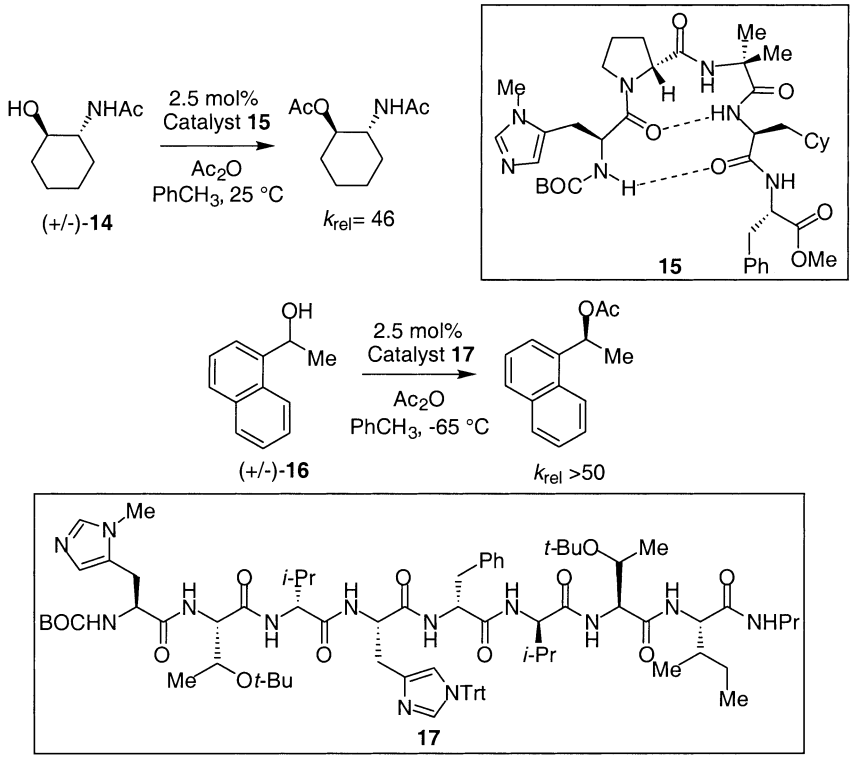
An interesting example of a peptide–cyclodextrin hybrid was reported by Ueno et al.[76,77] An α-helical 16-mer, **13**, was prepared wherein a β-cyclodextrin was included as a substrate binding site. Carboxylate and histidine functionality were included to promote nucleophilic catalysis of ester hydrolysis. Using a catalytic quantity of **13**, the *p*-nitrophenyl ester of D-alanine is hydrolyzed with a seven-fold higher k_{cat}/K_m than that of L-alanine (Fig. 7).

While not in the small-molecule catalyst regime, Reetz, Jaeger, and co-workers have used directed evolution to modify a lipase to increase the enzyme's selectivity for a desired substrate.[78] After six generations, the wild-type k_{rel} of 1.1 had been increased to 25.8. This is an exciting alternative to the investigation of small molecule catalysts for these processes.

5.2. Kinetic resolution by acylation of alcohols

Results from our laboratory have shown that short peptides containing alkylated histidine residues can be used as catalysts for the kinetic resolutions of secondary and some tertiary alcohols.[79] These catalysts are postulated to facilitate catalysis by a nucleophilic mechanism. The backbone amides and ancillary functionality are proposed to govern selectivity through enantiomer-specific secondary contacts (e.g. hydrogen bonding, π-stacking, ion pairing, etc.) that stabilize the transition state for reaction of one enantiomer. Preliminary studies drew heavily from the peptide design literature, focusing on catalysts that were biased towards β-turn conformations in solution, thus decreasing catalyst flexibility.[80,81] Furthermore, substrates were chosen which could participate in hydrogen bonds with the catalyst. Pentapeptide **15** exhibits high selectivity with amide functionalized substrate **14** (k_{rel}=46, Scheme 11).[82] Octapeptides were found that provide k_{rel}>50 for substrates of this class. Unfunctionalized substrates, such as aryl-alkylcarbinols, are resolved efficiently by catalyst **17**.[83] Octapeptide **17** was discovered by screening a split-pool library of peptide catalyst candidates for acylation of *sec*-phenylethanol, using a reactivity-based fluorescence screen,[84] followed by structure optimization by examining directed libraries. Catalyst **17** resolves α-napthyl-substituted alcohol **16** with k_{rel}>50 (Scheme 11).

Solution state NMR studies suggest that the catalysts designed to adopt β-turn conformations do indeed adopt turns and hairpins in solution, and kinetic measurements



Scheme 11. Kinetic resolution of alcohols with peptide-based catalysts.

confirm that monomeric catalysts are active in the catalytic cycle. These catalysts exhibit enantiospecific rate acceleration, consistent with transition state stabilization by catalyst–substrate interactions. An isosteric replacement of an alkene for a backbone amide in a tetrapeptide catalyst (catalysts **18** and **19**, Fig. 8) has lent credence to a proposed mechanism of rate acceleration.[85] While catalyst **18** exhibits a k_{rel}=28 with substrate **14**, alkene-containing catalyst **19** is not selective in this kinetic resolution. This suggests that the prolyl amide is kinetically significant in the stereochemistry-determining step of the reaction.

Diamines derived from proline, **20** and **21**, catalyze the desymmetrization of *meso* diols[86] and the kinetic resolution of β-halohydrins (Scheme 12).[87] Acylation of the alcohols is achieved using benzoyl chloride at −78°C using a tertiary amine as an additive. Very low catalyst loadings (0.3 mol%) are tolerated and products are obtained with high levels of enantioselectivity.

6. Conjugate addition

6.1. Conjugate addition of thiol

Catalysis of the enantioselective addition of thiols to enones by chiral bases such as cinchonidine was pioneered by Wynberg and Hiemstra.[88,89] Mukaiyama and co-workers reported the use of catalyst **22**, derived from hydroxyproline, in the same reaction.[90] This catalyst affords ketone **23** in good yield and enantioselectivity (Scheme 13). The mechanistic model shown below was proposed to rationalize the observed stereoselectivity.

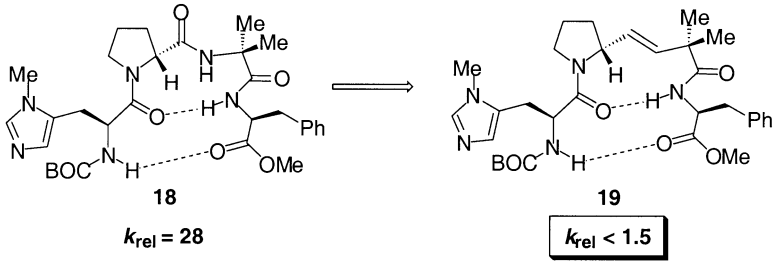
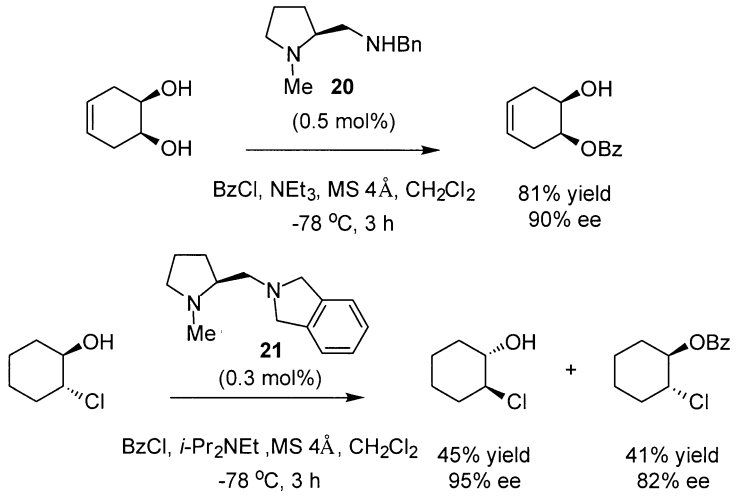
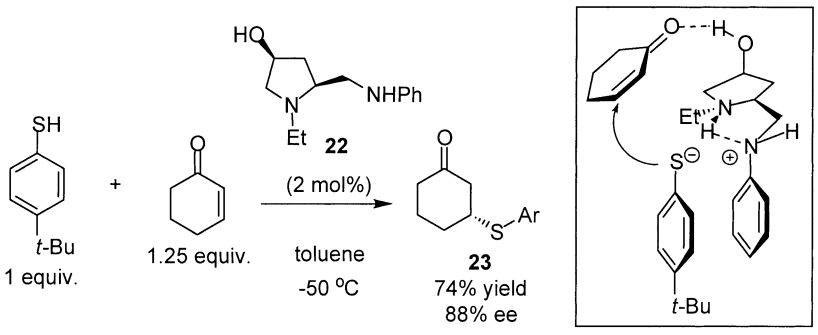


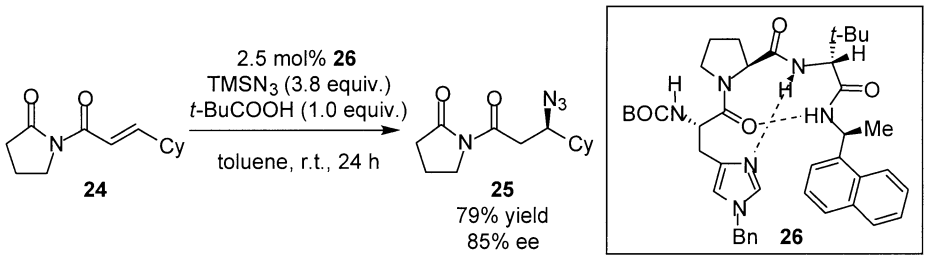
Figure 8. Isosteric alkene substitution eliminates catalyst selectivity.



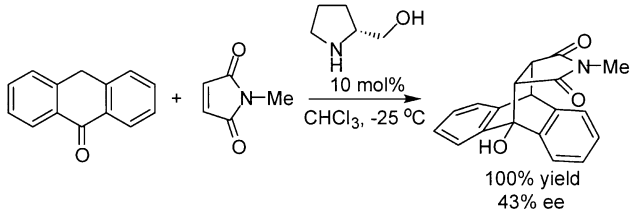
Scheme 12. Diamine catalyzed kinetic resolution and desymmetrization of alcohols.



Scheme 13. Conjugate addition of thiol catalyzed by **22**.



Scheme 14. Catalysis of asymmetric conjugate addition of azide by peptide **26**.



Scheme 15. Kagan's prolinol catalyzed Diels–Alder reaction.

6.2. Conjugate addition of azide

Base catalyzed addition of azide to enoates allows preparation of β-azido acids, synthons for β-amino acids. Short peptides containing τ-benzyl histidine have been used as asymmetric catalysts for this process.[91] This procedure avoids generation of stoichiometric quantities of explosive and highly toxic HN_3 by catalyzing the disproportionation of $TMSN_3$ and *t*-BuCOOH. β-Branched pyrrolidinone-derived imides are processed with the highest enantioselectivities. Azidation of substrate **24** employing catalyst **26** provides azide **25** with 85% ee in 79% yield (Scheme 14). Solution state NMR studies and crystal structure of a related catalyst suggest these peptides adopt Asx-Pro type turns.[92]

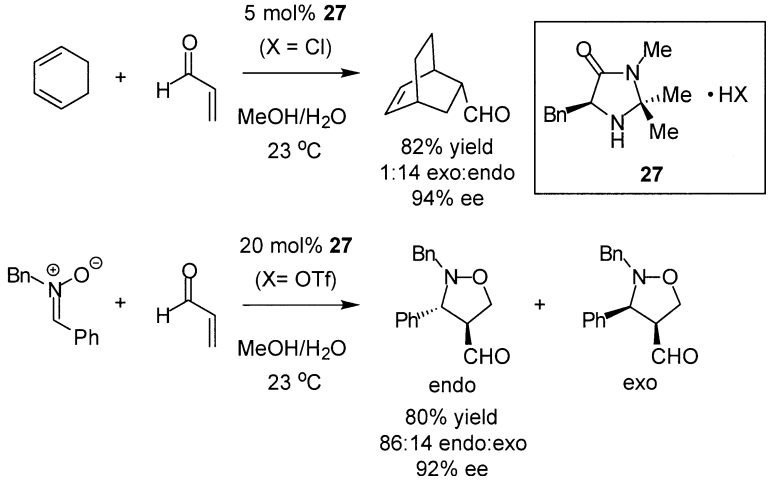
7. Cycloaddition

The first example of a base catalyzed enantioselective Diels–Alder reaction was published by Riant and Kagan in 1989.[93] Prolinol and quinidine were found to be the best catalysts. Moderate enantioselectivity was obtained for the reaction of anthrone with maleimide (Scheme 15). A bifunctional mechanism involving both ion pairing of the catalyst ammonium with the diene enolate and hydrogen bonding between the hydroxy group of the catalyst and the dienophile *N*-methyl maleimide was proposed.

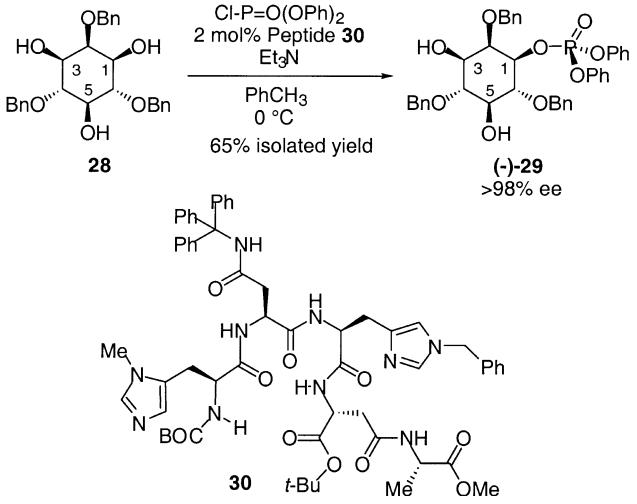
More recently, MacMillan and co-workers have reported the use of an amine catalyst for Diels–Alder reactions. Proline methyl ester and other secondary amines were screened, with phenylalanine derivative **27** proving the most selective, yielding products in very good enantioselectivities and yields (Scheme 16).[94] The imidazolidinone catalyst is postulated to activate the α,β-unsaturated aldehyde by formation of the iminium ion. Catalyst **27** also exhibits high enantioselectivities in 1,3-dipolar cycloadditions of nitrones (Scheme 16).[95,96] The success of this organocatalyst suggests that secondary amine containing peptides could be effective catalysts for processes that require activation of α,β-unsaturated carbonyl compounds.

8. Phosphorylation

In analogy to histidine-dependent kinases[97] and peptide-based catalysts for asymmetric acyl transfer, enantio- and regioselective phosphorylation has been achieved using peptide catalysts containing alkyl histidine moieties.[98] Selective phosphorylation of polyols could provide access to phosphorylated natural products without the need for



Scheme 16. Cycloadditions catalyzed by organocatalyst **27**.



Scheme 17. Enantioselective phosphorylation of *meso*-triol **28**.

extensive protective group manipulations. *meso* Triol **28** was chosen as a representative substrate, as a direct precursor to D-*myo*-inositol-1-phosphate, which is implicated in signal transduction pathways. A small library of catalysts (39 members) was screened, with peptide **30** proving the most selective. Phosphorylation of meso triol **28** in toluene provides monophosphate **29** in >98% ee and in 65% yield. This allows for an efficient synthesis of D-*myo*-inositol-1-phosphate in five steps from commercially available *myo*-inositol (Scheme 17).

9. Conclusions

Several decades after the first use of an amino acid as a catalyst, amino acids and simple peptides have become an important subset of asymmetric catalysts. Their ability to perform a variety of transformations is complimented by their ready availability, stability, and ease of handling. Currently, amino acids and all lengths of peptides are used as asymmetric catalysts. At present, the sequences of successful catalysts that have been reported are heavily biased towards proline. This is in part due to its unique status among the naturally occurring amino acids as a secondary amine and to its limited structural flexibility, a trait that has traditionally been considered advantageous in the search for asymmetric catalysts. The future undoubtedly holds catalysts that contain a wider variety of both natural and unnatural amino acids. Advances in the design of peptides with stable secondary and tertiary structures will be incorporated as new asymmetric environments for reactive functionality. Development and implementation of catalyst screening techniques will allow for exciting advances into a larger realm of diversity space, allowing for the discovery of unpredicted and unexpected peptide catalysts. The use of peptide–metal complexes as asymmetric catalysts will also progress as greater advances are demonstrated with peptide-based catalysts. Each new discovery of amino acid and peptide-based catalysts reinforces and intensifies organic chemists appreciation of the potential of Nature's catalysts of choice.

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