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Organocatalysis

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Abstract

Reactions carried out with substoichiometric quantities of organic molecules as catalysts have received much attention since the organocatalysis phrase was coined in 2000. This review highlights progress in 2012 on highly enantioselective and achiral organocatalytic processes.

1.0 Introduction

The literature for 2012 once again contains a vast number of reports regarding organocatalysis, and it is clear that this area continues to be an important and popular strand of research. Several excellent reviews have been reported in this highly topical area;¹ most notably Jørgensen has reviewed the use of the diarylprolinol silyl ether catalyst system.² An interesting report by Bode has reviewed recent developments in the field of catalytic selective synthesis (both metal and non-metal mediated processes) in which reactions with the same substrate, under otherwise nearly identical conditions, give rise to different products by a change in the structure or type of catalyst.³ Nagasawa has reviewed dynamic asymmetric organocatalysis, looking at the cooperative effects of weak interactions and conformational flexibility in asymmetric organocatalysts,⁴ and Bella has reviewed non-asymmetric organocatalysis.⁵ Recent efforts directed towards the development of more sustainable asymmetric organocatalysis have been reviewed by Hernández and Juaristi.⁶

The present review covers achievements from 2012, but regrettably, with the considerable number of publications in this area, it is not possible to report every contribution to the field. A cross-section of reports is therefore described below to give a flavour of the exciting research being carried out in this arena.

2.0 Enamine Catalysis

Since the original term organocatalysis was coined in 2000 enamine catalysis is perhaps still the area of most activity owing to the ability of amine catalysts, such as proline, to condense with α,β -unsaturated aldehydes or ketones, so forming iminium ion or enamine intermediates that can be captured by incoming nucleophiles or electrophiles yielding excellent levels of enantiomeric excess; below is a selected set of examples.

Jørgensen has, in 2012, developed a conceptually new approach in organocatalysis, termed cross-conjugated trienamines (See Figure 1 for a general example).⁷ The group has demonstrated that these intermediates can undergo highly enantioselective Diels–Alder reactions with oxindoles substituted at the 3-position with olefins and with 5-olefinic azlactones, providing an attractive route towards bicyclic structures. Jørgensen has also shown that cross-trienamines can react in a highly enantioselective γ' -addition with vinyl bis-sulfones. The work was supported by calculations and NMR studies, and involves the use of the diarylprolinol catalyst **1** and the inclusion of a benzoic acid additive. Excellent yields, and diastereomer and enantiomer ratios were obtained for a variety of substrates; an example is shown in Scheme 1.

Scheme 1

On the sustainability front, Lipshutz has reported a new designer surfactant that contains a covalently bound organocatalyst **2** (a proline derivative).⁸ This catalyst is water-soluble and, through spontaneous nanomicelle formation, catalyses aldol reactions with water-soluble or -insoluble substrates with high enantio- and diastereo-control (Scheme 2). The catalyst can be recycled several times without loss of activity through simple extraction of the reaction products from the aqueous reaction phase (as the catalyst remains in water), and has been shown to outperform the previous standard catalyst (**3**) for water reactions reported by Babas.⁹

Catalyst	Run	Yield	<i>anti:syn</i>	<i>er</i>	Ref
2	1	94	92:8	98:2	8
	2	94	94:6	98:2	8
	3	93	91:9	98:2	8
	4	91	90:10	98:2	8
3	1	99	89:11	97:3	9

Scheme 2

An asymmetric formal [3+2] cycloaddition of 4-hydroxybut-2-enal, a succinaldehyde surrogate, and a range of nitroalkenes with an organocatalyst **1** has been reported to provide cyclopentanecarbaldehydes containing four consecutive stereogenic centers with excellent enantioselectivities (Scheme 10).¹⁰ Hong *et. al.* have shown that this reaction not only adds to the limited reports of dienamine organocatalysis, but also demonstrates for the first time the utilization of a succinaldehyde surrogate in synthesis. This process is attractive as the reactions are carried out at ambient temperature, although they do require the use of halogenated solvents.

Scheme 3

The authors have proposed a mechanism for the transformation in which iminium activation is followed by dienamine activation, which in turn enables the enantioselective Michael reaction to occur. Simple tautomerisation and a Henry reaction regenerates the catalyst and produces the highly functionalized enantio- and diastereo-enriched cyclopentane ring system (Scheme 4).

Scheme 4

Using another secondary amine catalyst (the MacMillan oxazolidinone **4**) an enantioselective organocatalytic $\text{Csp}^3\text{-H}$ α -functionalization of ethers has been developed by Jiao *et al.*¹¹ A series of chiral spiroethers with various substituents and ring sizes was prepared using racemic ethers producing good to excellent enantiomeric ratios; a selection is shown in Scheme 5. This transformation is tolerant of a range of bulky substituents and proceeds under mild reaction conditions.

Scheme 5

The authors have proposed a mechanism in which a 1,5-hydride shift leads to favoured enantioselective spirocycle centre formation through the generation of an enamine intermediate that selectively reacts with one of two possible oxocarbenium ions (Scheme 6). The favoured route is thought to contain less dipole repulsion and therefore leads to the spirocyclic centre in high enantiomeric ratios.

3.0 Enamine/H-Bonding Hybrid Catalysis

Jørgensen and coworkers have also reported the first H-bond-directed inverse-electron-demand hetero-Diels–Alder reaction that proceeds through a diene-amine intermediate (Scheme 7).¹² These dienamine species were able to undergo highly regio- and stereo-selective functionalization at the remote double bond, five bonds away from the stereogenic center of the catalyst, to give dihydropyran derivatives bearing three contiguous stereogenic centers. The high stereoselectivities were obtained by employing a bifunctional squaramide-containing aminocatalyst **5**, and the rationalization for the

Scheme 6

stereochemical outcome of the reaction was believed to be due to the π - π stacking of the dienamide and substrate as shown in the groups proposed mechanism (Scheme 8). The group was also able to employ the chiral framework produced in the synthesis of tetrahydropyrans and polycyclic compounds. A selection of accessible aryl enals is shown in Scheme 7; both heteroaryl and sterically demanding *ortho*-aryl systems are tolerated.

Scheme 7

Scheme 8

4.0 H-Bonding Catalysis

Interest in and applications of hydrogen bonding catalysis have increased significantly over the last few years; below is an interesting report from 2012. Barbas and coworkers have reported a safe and practical method for the stereospecific dibromination of alkenes (Scheme 9).¹³ Organocatalytic stereospecific dibromination of a wide variety of functionalized alkenes was achieved using a stable, inexpensive halogen source, 1,3-dibromo-5,5-dimethylhydantoin **6**, and a simple thiourea catalyst **7** at room temperature. The presence of a tertiary amine enhanced the rate of the dibromination reaction, and yields were good for various substrates including oxindoles in a variety of solvents, including water. The procedure was extended to alkynes, aromatic systems and to dichlorination reactions. Scheme 9 shows selected examples with excellent diastereomeric ratios.

5.0 Bifunctional Organocatalysis

Smith and co-workers reported in 2009 that the presence of an intra-molecular hydrogen bond in catalysts such as **8** provides significant improvements in the hydrogen-bond-donor capacity of thioureas through cooperative effects.¹⁴ Building upon this Pihko and co-workers have described their findings in this area, centered around enantioselective Mannich reactions with aliphatic and aromatic imines (Scheme 10).¹⁵ The group found that catalysts that contain a rigid *trans*-1,2-aminoindanol scaffold and a urea group that activates the thiourea group through intramolecular hydrogen bonds (such as **9**) promote the enantioselective Mannich reaction between malonates and both aliphatic and aromatic imines. This offers a useful direct route to a wide variety

Scheme 9

of protected β^3 -amino acids. They also obtained computational and X-ray data which suggest that the intramolecular hydrogen bonds and the overall fold of these catalysts are maintained when the catalysts are bound to the anionic substrate, and also during the C–C bond forming process.

Scheme 10

6.0 Tandem Metal/Organocatalysis

Since we reported last year that a new vista for organocatalysis was emerging in which metal catalysed reactions were being used in tandem with organic based catalysts, other areas utilising a tandem approach have emerged. For example, König and co-workers have reported that heterogeneous photocatalysis has been combined with organocatalysis to promote stereoselective alkylation with visiblelight (Scheme

11).¹⁶ This work was extended to the asymmetric synthesis of α -functionalised aldehydes using the MacMillan oxazolidinone catalyst **10**, PbBiO₂Br and light (Scheme 12).

Scheme 11

Scheme 12

Zhang *et. al.* have described a novel asymmetric oxidative cross-coupling reaction between simple amines and olefins (Scheme 13).¹⁷ The dual catalysis process employs an organo/metal cooperative system under mild conditions using molecular oxygen as a terminal oxidant, with moderate to good yields (47–82%) and excellent enantiomeric ratios (up to 99.5:0.5 er) when employing copper(II) triflate and quinine **11** as catalysts. A range of alkenes was tolerated, but the rigid isoquinoline backbone was required for the reaction to proceed, for example, the benzylamine derivative afforded less than 10% of the desired product.

Scheme 13

A tandem metal-organo-catalytic reaction has been reported by Xiao and coworkers;

they have employed this approach to effect α -alkylation of aldehydes (Scheme 14).¹⁸ A cooperative system of the diarylprolinol catalyst **12** with Lewis acids such as CuCl, IrCl₃, or InBr₃ was found to catalyse this highly enantioselective intermolecular alkylation of aldehydes. A large variety of aldehydes and alcohols can be transformed to the functionalized alcohols in high yields and excellent enantioselectivities, and an example is shown in Scheme 14.

Scheme 14

An enantioselective oxidative domino reaction of allylic alcohols to functionalized aldehydes has also been developed under the tandem metal-organo-catalytic banner (Scheme 15).¹⁹ The one pot domino oxidation-iminium activation is a useful approach to the highly enantioselective addition of malonates to allylic alcohols (using catalyst **12**) and the asymmetric formation of formyl cyclopropanes (using catalyst **1** Scheme 16). An advantage of this approach is reported to be the avoidance of the purification or distillation step normally associated with the use of aldehydes in asymmetric organocatalysis. The procedure allows the use of allylic alcohols, together with the cheap and readily available oxidant MnO₂, which can be simply separated by filtration at the end of the reaction. The authors believe that this new approach represents a viable alternative to other recently reported oxidative procedures that employ aldehydes and more expensive or difficult to handle oxidizing reagents, such as IBX and DDQ. A wide range of aryl substrates could be tolerated for both systems; a selection of products is shown in Schemes 15 and 16, all obtained with good to excellent yields and high enantiomeric ratios.

Scheme 15

Scheme 16

7.0 SOMO Catalysis

Originally we reported in volume 104 that MacMillan and coworkers had expanded the scope of aminocatalysis (iminium or enamine catalysis) by introducing a new mode of action, SOMO catalysis,²⁰ in which the intermediate enamine formed from the condensation of an aldehyde and a secondary amine can be intercepted by an

Scheme 17

oxidizing reagent to generate a singularly occupied molecular orbital (SOMO) at

nitrogen. Subsequent reaction with, for example, allylsilane affords α -allylated aldehydes with good yields and excellent levels of enantioselectivity. MacMillan has again in 2012 expanded the portfolio of this powerful approach to functionalized compounds derived from aldehydes. The group has reported a new protocol to rapidly construct enantioenriched pyrrolidines using β -amino aldehydes and π -nucleophilic olefins (Scheme 17).²¹ The authors report that “as a critical design feature, the starting materials and catalysts are commercial materials or easily prepared, allowing rapid and modular production of a variety of pyrrolidine cores”. A wide variety of substrates was screened, all yielding good to excellent enantiomer ratios, but with varying levels of diastereomeric control. A range of functional groups was tolerated under the reaction conditions and di- and tri-cyclic systems were prepared using this methodology; a selection of products is shown in Scheme 17.

8.0 Light Assisted Catalysis

Neilson and Bielawski have reported an interesting and rare example of a photoswitchable catalyst that operates through the remote photomodulation of its electronic structure (Scheme 18).²² By incorporating a dithienylethene moiety into the backbone of a NHC precursor, the activity of the corresponding organocatalyst was remotely tuned through exposure to UV or visible light. The rates of NHC-catalysed *trans*-esterification and amidation reactions were attenuated by 1 to 2 orders of magnitude upon exposure to UV light, while subsequent exposure to visible light restored the catalytic activity. The authors suggest, based on detailed spectroscopic analysis, that the resting state of the active catalyst is an imidazolium species, which converts to a NHC-alcohol adduct upon UV irradiation and effectively suspends the catalytic cycle.

Scheme 18

Restoration of activity observed upon visible light irradiation suggests that the

photocyclized adduct may be converted back to an imidazolium species that then re-engages the catalytic cycle. Due to the wide array of NHC mediated reactions, as either organocatalyst or transition metal ligand, the authors envisage a variety of applications of this technique.

9.0 Mechanistic Rationale in Organocatalysis

A wide variety of organocatalytic reactions have been reported over the years, sometimes with little or no explanation for the observed reaction outcomes, and therefore no real understanding of reaction mechanisms involved. However in 2012, Armstrong and Blackmond reported detailed mechanistic studies of two reactions catalysed by diarylprolinol ether catalysts;^{23,24} the conjugate addition of aldehydes to nitro-olefins (also studied by Seebach²⁵); and the α -chlorination of aldehydes. Their report leads to the proposal that the stereochemical outcome in these cases is not determined by the transition state of the step in which the stereogenic center is formed from enamine attack on the electrophile, but rather is correlated with the relative stability and reactivity of diastereomeric intermediates in the catalytic cycle. This combination of kinetic and thermodynamic factors illustrates a Curtin–Hammett scenario that can result in either an enhancement or erosion of the selectivity that would be predicted by consideration of the transition state for enamine attack on the electrophile. This study thus has implications for future design of organocatalysts. The two detailed reaction mechanisms are shown in Schemes 19 and 20;²⁶ the latter showing the various diastereomeric intermediates.

Scheme 19

Scheme 20

10.0 Miscellaneous Organocatalytic Processes

Barbas and coworkers have developed an organocatalytic cross-coupling reaction between aldehydes and *N*-hydroxyimides, hexa-fluoroisopropyl alcohol, and sulfonimides that provide active esters and imides in moderate to excellent yields (Scheme 21).²⁷ The resulting active intermediates can be directly converted into amides or esters in one pot. The authors report that this “straightforward process....is simple, highly effective, and makes use of readily available starting materials, all of which should render this method attractive to synthetic chemists”. These newly

discovered active imide reagents could therefore be useful for amide and ester formation. Barbas suggests that this reaction proceeds through radical intermediates after the addition of the nucleophile to the aldehyde; at this point *tert*-butylhydroperoxide (TBHP) oxidises the intermediate to the final product (Scheme 22).

Scheme 21

Scheme 22

Clark has reported a simple organocatalytic synthesis of substituted furans.²⁸ The novel features of the procedure include the use of a simple thioether as the organocatalyst **13**, the formation of a furan under neutral conditions rather than the anionic or acidic conditions employed in conventional syntheses, and the intermediacy of a versatile sulfonium ylide that has the potential to be intercepted directly by a variety of electrophiles instead of being protonated to give a sulfonium

ion. The reaction proceeds with a wide range of substrates and nucleophiles to give highly decorated furans in good yield. The mild nature of the process is exemplified by Scheme 23, which describes the formation of a fragile, biologically relevant epoxyfuran motif related to the natural product lopotoxin.

Scheme 23

Ooi and coworkers have developed a 1,6-addition of azlactones to δ -monosubstituted dienyl N-acylpyrroles with essentially complete control of regio-, diastereo-, and enantio-selectivity through the employment of a P-spiro triaminoimino-phosphorane as a strong organic base catalyst **14** (Scheme 24).²⁹ This methodology has further been evolved into the highly regio- and stereoselective 1,8-addition to ζ -substituted trienyl acceptors (Scheme 25).

Scheme 24

Scheme 25

11.0 Conclusion

As stated in the introduction the development of organocatalysed reactions has again been heavily reported in the literature for 2012. The level of enantiomeric ratio and product yield obtained are now in many cases at excellent levels, with ees of over 95% commonplace. As can be seen from the examples presented in this review, enamine ion catalysis remains one of the most extensively studied areas within organocatalysis. However, as reported in previous organocatalysis chapters, with the use of hydrogen bonding catalysts, such as thioureas, and Brønsted acid/base catalysts, and now counterion catalysis, a wide range of new organocatalytic reactions has been discovered and these modes of organocatalysis are now firmly established protocols. The area of combining catalytic processes from both metal and organic mediators has emerged over the past few years, and as reported in 2011 this intriguing marriage, which has provided some excellent yields and selectivities for new transformations, looks set to move forward the organocatalysis arena perhaps even further over the next few years.

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