1 Organocatalysis

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Abstract

Reactions carried out with substoicheiometric quantities of organic molecules as catalysts have received much attention over the past decade. This review highlights progress in 2011 towards highly enantioselective organocatalytic systems and the natural product/biologically active compounds that can be prepared using these types of processes.

1.0 Introduction

Organocatalysis continues to be an important and popular strand of research in 2011 and the area is now well established in the academic as well as industrial sectors.[1,2] Several excellent reviews have again been reported in this highly topical area.[3] The present review covers achievements from 2011, but regrettably, with the considerable number of publications in this area, it is not possible to report every contribution to this 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 Iminium/Enamine Catalysis

This is perhaps the area of most activity over the past few years 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 which can be captured by incoming nucleophiles or electrophiles with excellent levels of enantiomeric excess. Although the first use of these generic modes of action was reported in 2000 there continues to be a large number of reports in this area. Below is a selected set of examples. In the majority of cases this mode is catalysed by proline or proline derivatives, however, some recent reports have now applied other catalysts in this area.

Jørgensen and coworkers have reported an asymmetric organocatalytic one-pot strategy to octahydroacridines such as **1**.[4] The reactions are catalysed by the silyl protected proline derivative **2**. The scope of the formation of octahydroacridines is outlined in Scheme 1. High levels of stereogenic control were obtained over a wide range of substrates and by probing the reaction the authors were able to verify that an *endo*-transition state in which

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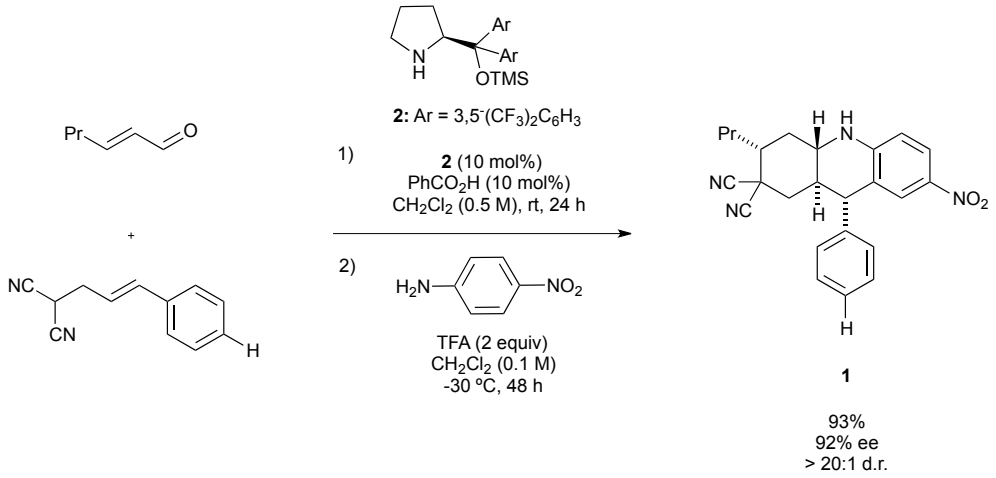
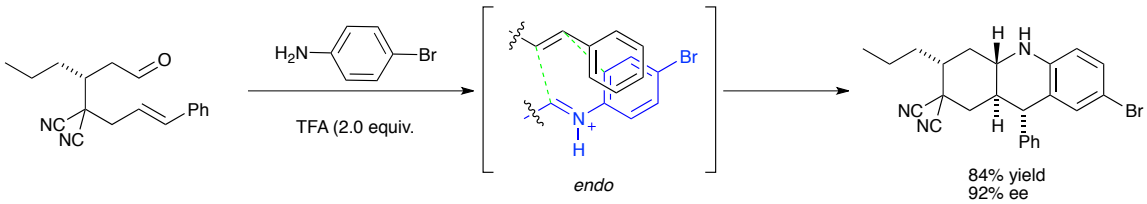
π-π overlap of the aromatics plays an important role in the reactivity and selectivity of the process (Scheme 2).

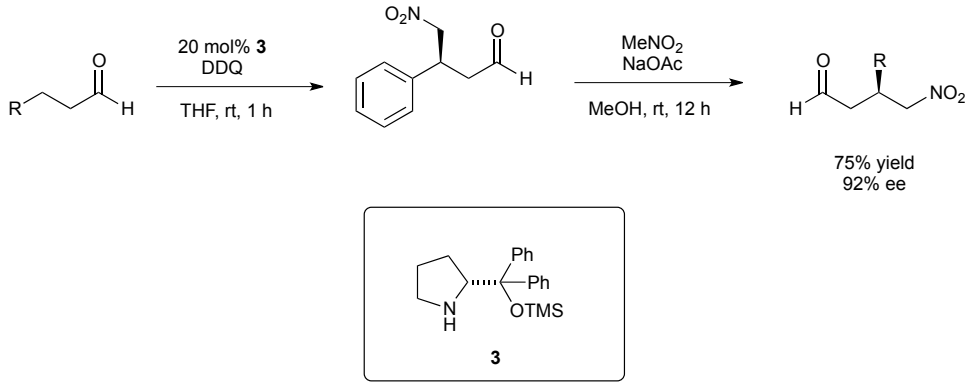


Scheme 1 Jørgensen's asymmetric organocatalytic one-pot strategy to octahydroacridines



Scheme 2 Jørgensen's proposed *endo*-transition state model

Using a related organocatalyst Hayashi has reported the oxidative and enantioselective cross-coupling of aldehydes and nitromethane catalysed by the diphenylprolinol silyl ether **3** (Scheme 3).[5] The authors describe the reaction as a synthetic equivalent to C-H activation at the β-carbon atom of an aldehyde, this approach is particularly attractive as it does not require the use of a metal for the oxidative C-C bond forming reaction. As such this report by Hayashi represents the first enantioselective one-pot transformation of a C-H bond at the β-carbon atom of an aldehyde into a new C-C bond.

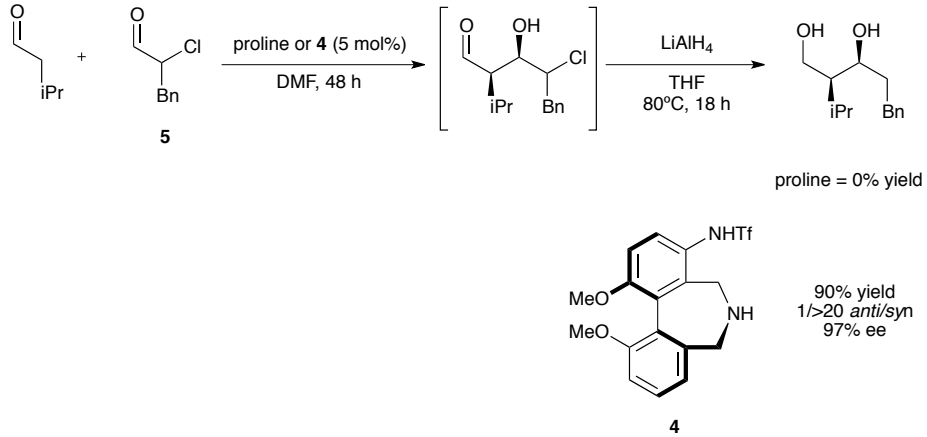


Scheme 3 Hayashi's one-pot oxidative asymmetric Michael reaction

Maruoka and coworkers have recently introduced a new route to access crossed-aldol products, employing the biaryl organocatalyst **4**.[6] The highly enantioselective organocatalytic crossed-aldol reaction of aldehydes through the enamine intermediate was originally reported by MacMillan.[7] However, these reactions required the use of sterically hindered aliphatic aldehydes (from which the enamine intermediates are rather difficult to form) or aromatic aldehydes. In the direct aldol reaction between simple aliphatic aldehydes, both aldehydes can act as either nucleophile and electrophile, and consequently, two crossed-aldol adducts and two homoaldol adducts are possible.

In order to combat this issue Maruoka has differentiated the two aldehydes by introducing a halogen group at the α-position of an acceptor aldehyde such as **5**. Thus the formation of the enamine intermediate of the sterically hindered α-haloaldehyde and an amine catalyst is suppressed. The α-haloaldehyde reacts predominantly with the enamine intermediate and in the final reductive step the halogen group on the crossed-aldol adduct is removed.

Interestingly the reactions could not be catalysed by proline but introduction of Maruoka's biaryl triflamide catalyst **4** afforded the desired products in excellent yield and high enantio- and diasteromeric excess (Scheme 4). A proposed transition state model is shown in Figure 1.



Scheme 4 Maruoka's crossed-aldol reaction, utilizing α-haloaldehydes

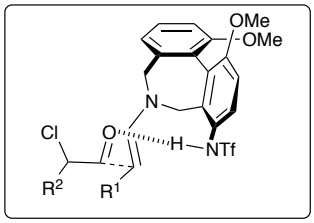
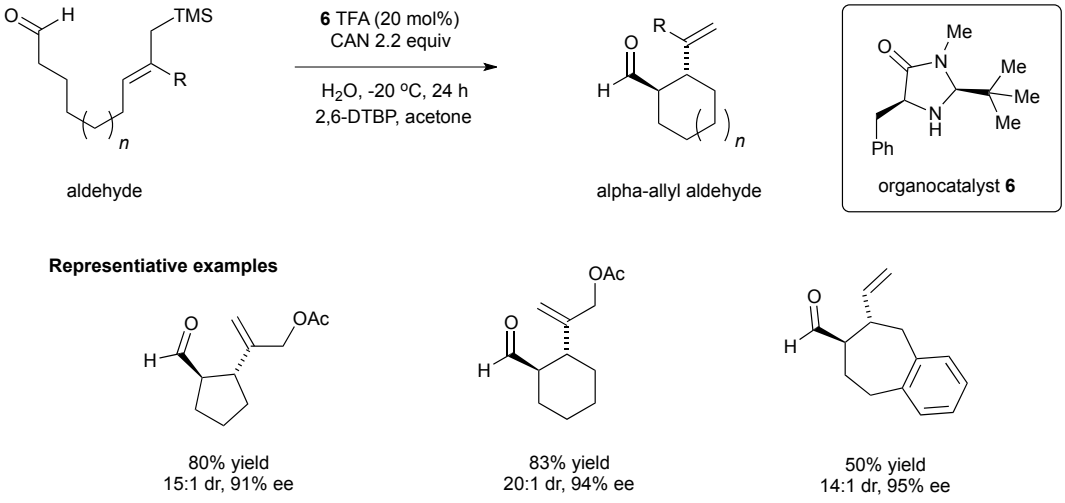


Figure 1 Maruoka's proposed transition state model

3.0 SOMO Catalysis

As reported in volumes 104 and 106, MacMillan expanded the scope of aminocatalysis (iminium or enamine catalysis) by introducing a new mode of action.[8] The intermediate enamine formed from the condensation of an aldehyde and a secondary amine can be intercepted by an 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 expanded the scope of this key organocatalytic technology with the intermolecular asymmetric allylation of aldehydes catalysed by **6** and applied to the synthesis of cyclic ring systems (Scheme 5).[9] The process is able to deliver five-, six- and seven-membered carbocycles and also tetrahydropyran and piperidine ring systems with high levels of enantio- and diastereocontrol.



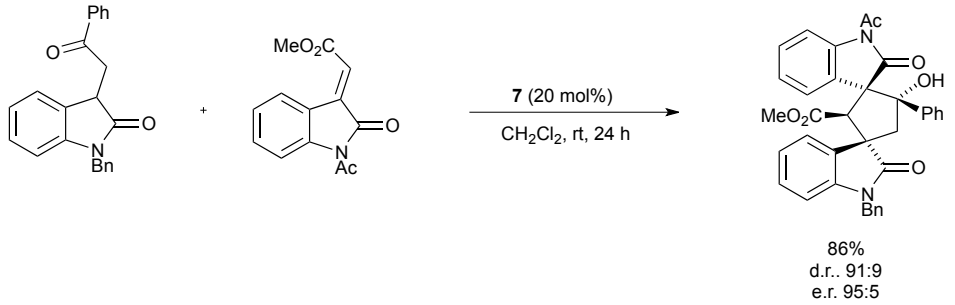
Scheme 5 MacMillan's Organo-SOMO intermolecular asymmetric allylation of aldehydes

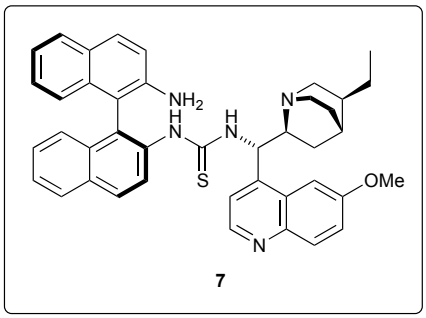
4.0 Hydrogen Bonding Catalysis

Over the last few years interest and applications of in hydrogen bonding catalysis have increased significantly, below are several interesting reports that push the boundary of this novel area from 2011.

Barbas and coworkers have reported the construction of bispirooxindoles containing three quaternary stereocentres in a cascade using a single multifunctional organocatalyst (Scheme 6).[10] Inspired by Melchiorre's results that a binaphthyl primary amine and a thiourea can hydrogen bond with the oxindole unit, the group designed a trifunctional *S*-binaphthyl diamine catalyst containing a binaphthyl primary amine, a thiourea and a tertiary amine **7**. In the presence of this new catalyst, the reaction proceeded smoothly

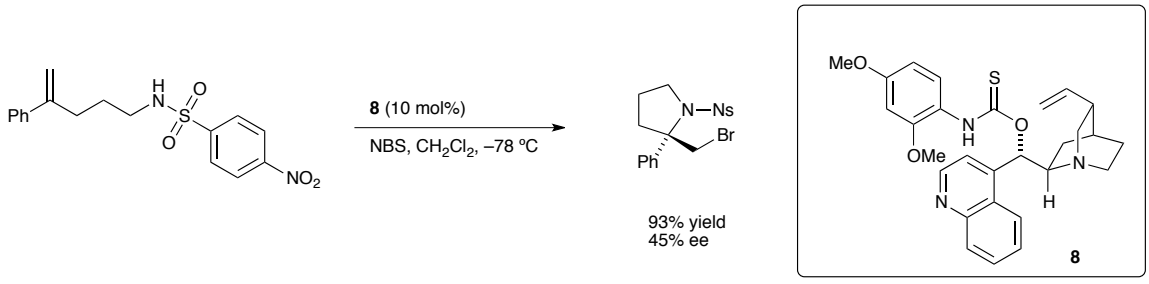
and gave rise to the desired product in high yield with good enantioselectivity (95:5 e.r.) and diastereoselectivity. The process was then applied to a wide range of substrates that were also prepared with high enantio- and diastereoselectivity.



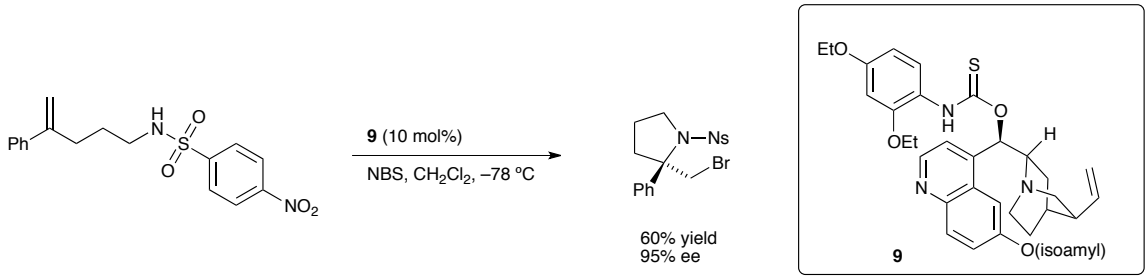


Scheme 6 A trifunctional *S*-binaphthyl diamine catalyst for multifunctional organocatalysis

Yeung and coworkers have reported the highly enantioselective bromoaminocyclization reaction employing amino-thiocarbamate catalysts, for example catalysts **8** and **9**.[11] Based on their previous study of the bromolactonization reaction,[12] the optimized conditions were applied to the amino variant of the process to afford the desired product in 93% yield and 45% ee (Scheme 7). Slight modification of the catalyst had a dramatic effect, enhancing the ee of the process up to 94% (Scheme 8). This report represents the first practical example of a catalytic, enantioselective, halo-*N*-cyclization.

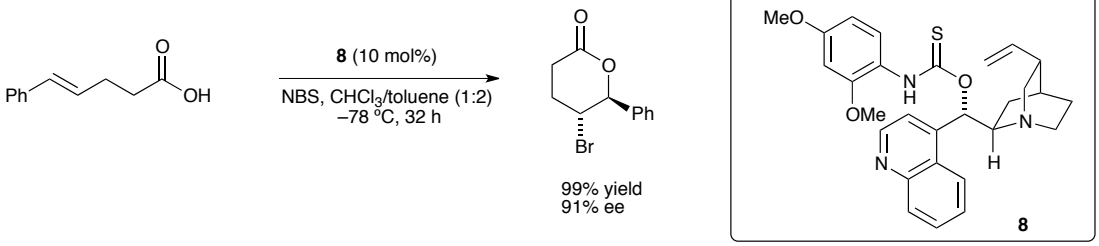


Scheme 7 Yeung's initial bromoaminocyclization process



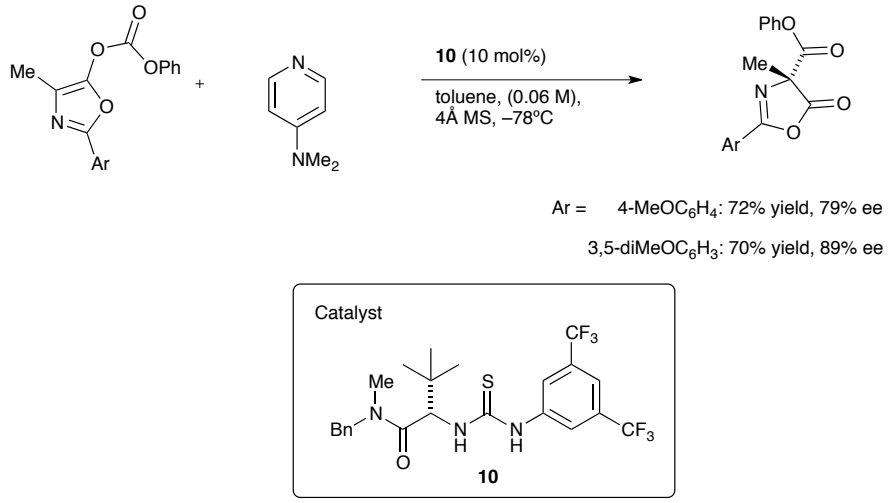
Scheme 8 Yeung's highly enantioselective amino-thiocarbamate catalysed bromoaminocyclization employing the modified catalyst X

The same group have also extended their earlier work[12] with the asymmetric bromolactonization of 1,2-disubstituted olefinic acids.[13] The level of enantioselectivities observed were high (typically 90%) for a range of substituted olefins, however only the six-membered ring products were studied (Scheme 9).



Scheme 9 Yeung's amino-thiocarbamate catalysed bromolactonization of 1,2-disubstituted olefinic acids.

Siedel has reported a dual-catalysed approach to the asymmetric Steglich rearrangement (Scheme 10) and using an analogous system developed a catalytic enantioselective addition of *O*-acylated azlactones to isoquinolines (Scheme 11).[14] The group initially proposed the simultaneous activation of an azalactone by both DMAP and a chiral thiourea as shown in figure 2. The group subsequently found that the Jacobsen thiourea **10** imparted high yield and enantioselectivity for azalactone rearrangement. Capitalizing on the ion pair formed during the reaction the group postulated that replacement of DMAP with an isoquinoline could lead to the addition of the azalactone to the isoquinoline. Hence, the Jacobsen thiourea was again employed in the modified reactions to afford a wide range of isoquinoline adducts in excellent yield, diasteroselectivity and enantioselectivity (Scheme 11).



Scheme 10 Siedel's highly enantioselective Steglich rearrangement.

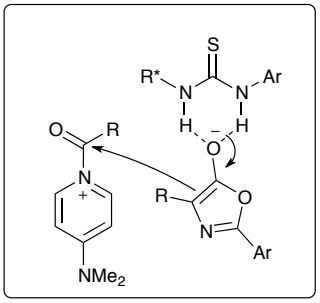
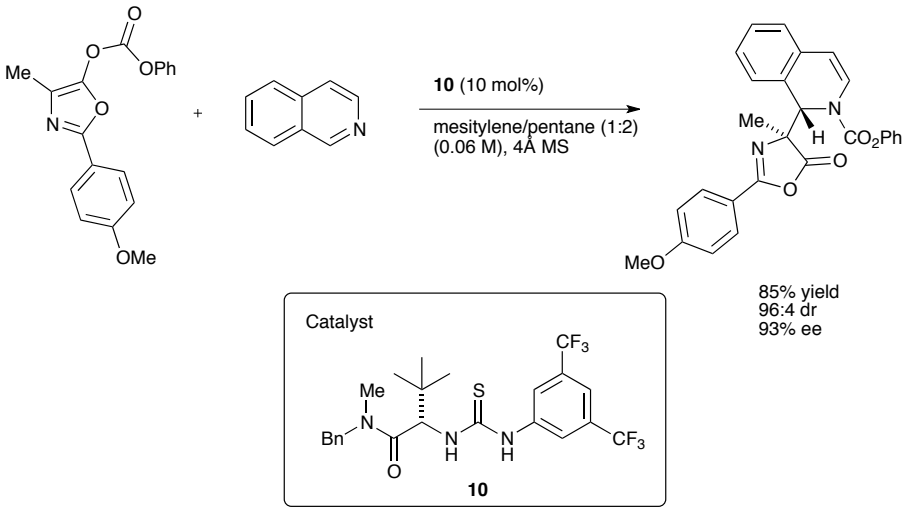


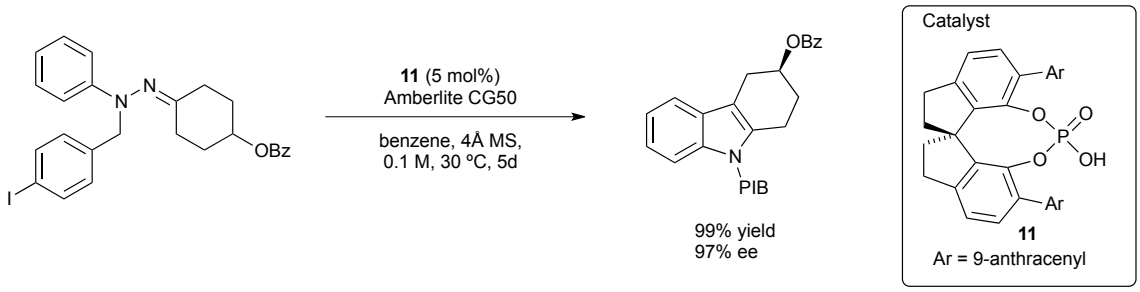
Figure 2 Siedel's proposed transition state model.



Scheme 11 Siedel's catalytic enantioselective addition of *O*-acylated azlactones to isoquinolines.

5.0 Counterion Catalysis

The concept of counterion catalysis was first reported 2007, and this area continues to provide some interesting applications. For example, the use of phosphoric acid catalysed processes has dramatically increased over the past few years. The List group have contributed significantly in this area and in 2011 reported the dynamic kinetic resolution Fischer indolization reaction, using the elaborate phosphoric acid X (Scheme X).[15] Wide ranges of systems were explored and the optimum protecting group at nitrogen was found to be the 4-iodobenzyl group, whilst the addition of 4Å molecular sieves were beneficial in slightly increasing the enantiocontrol of the process.

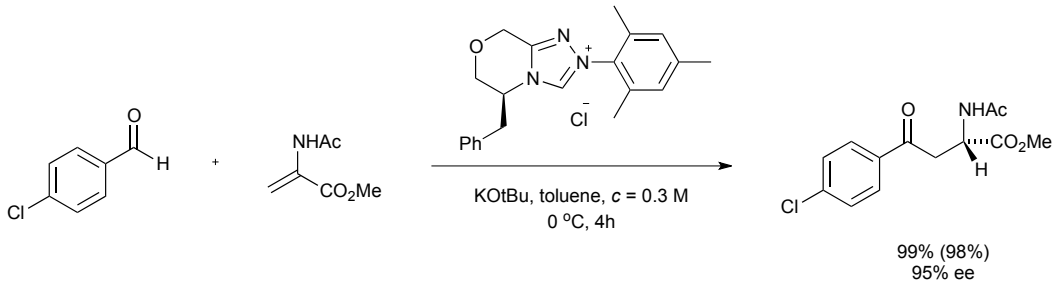


Scheme 12 List's dynamic kinetic resolution Fischer indolization reaction

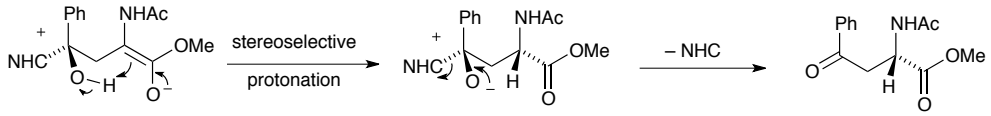
6.0 *N*-Heterocyclic Carbene (NHC) Mediated Organocatalysis

N-Heterocyclic carbene's have been successfully employed in organocatalysitc processes for sometime now, perhaps most famously in the Stetter and benzoin reactions. Below are some interesting examples from 2011.

Glorius and coworkers have reported the highly enantioselective synthesis of α-amino derivatives catalysed by an NHC intermolecular Stetter reaction (Scheme 13).[16] A wide veriety of substrates were tolerated under the reaction conditions and afforded the corresponding products in high ee and yield. The authors propose that the origin of enantioselectivity occurs through a stepwise protonation α to the nitrogen atom (Scheme 14).

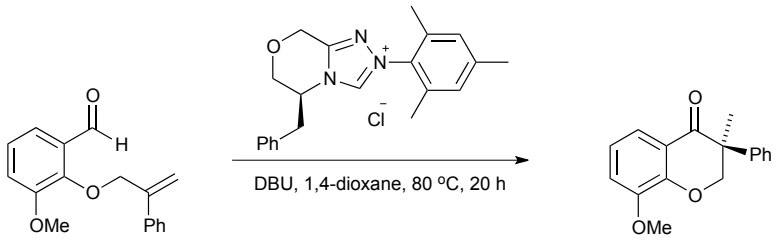


Scheme 13 Glorius' highly enantioselective synthesis of α-amino derivatives



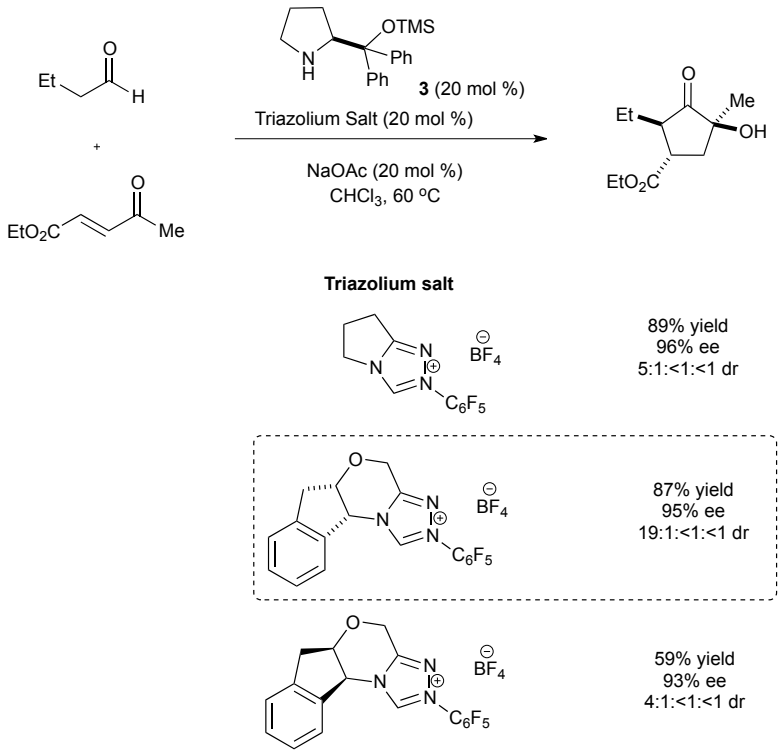
Scheme 14 Glorius' proposed stepwise stereoselective protonation mechanism

Glorius has also reported the highly asymmetric NHC-catalysed hydroacylation of unactivated alkenes using the same NHC catalyst derived from phenylalanol.[17] Up to 99% yield and 99% ee was obtained for the example shown in Scheme 15, again a wide range of substrates (although limited to a α-methylene group in the chromene product) were screened that in most cases were obtained with similar levels of enantiocontrol. In order to shed some light on the mechanism of the process calculations at the B2PLYP-D level were undertaken and suggest a concerted but asynchronous transition state.



Scheme 15 Glorius' highly enantioselective NHC-catalysed hydroacylation of unactivated alkenes

Ozboya and Rovis have reported enamine/carbene cascade catalysis in the diastereo- and enantioselective synthesis of functionalized cyclopentanones. The reaction utilizes the prolinol derived catalyst **3** and initially an achiral NHC co-catalyst derived from a triazolium salt (Scheme 16).[18] However, on addition of a chiral NHC the enantioselectivity remained constant (regardless of the NHC enantiomer employed) but significant enhancement in diastereoselectivity was observed (5:1:<1:<1 verses 19:1:<1<1).

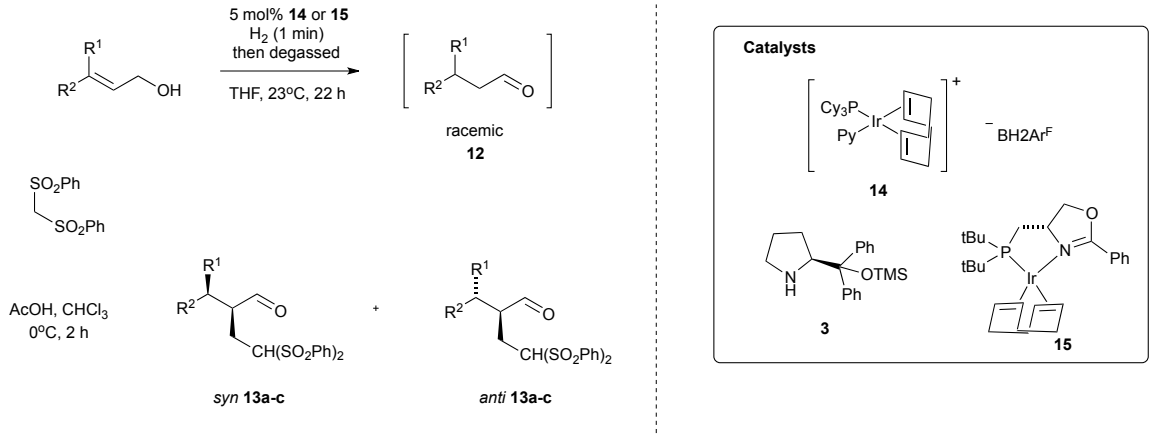


Scheme 16 Ozboya and Rovis' enamine/carbene cascade

7.0 A new vista for Organocatalysts: Tandem Metal-Organo-Catalysis

Alexakis and Mazet have recently reported access to high levels of molecular complexity by utilizing a one-pot iridium/enamine catalysed process. The initial metal catalysed process isomerizes the allyl alcohol to the corresponding aldehyde **12**, this aldehyde is then intercepted by a secondary amine derivative such as **3**. Enamine catalysed addition of a suitable electrophile affords *syn*- or *anti*-**13**, with varying levels of diastereo-and enantiocontrol. Initially the group employed the achiral iridium catalyst **14** to carry out the isomerization process relying on the chiral amine to control the selectivity of the reaction through what is in fact a kinetic resolution process. On reduction of the number of equivalents of the alkene acceptor (0.5 equiv.) and use of the chiral iridium complex **15** high levels of enantioselectivity were maintained but a large increase in diastereoselectivity was observed, this was however coupled with a reduction in overall yield (Table 1, entry 4).

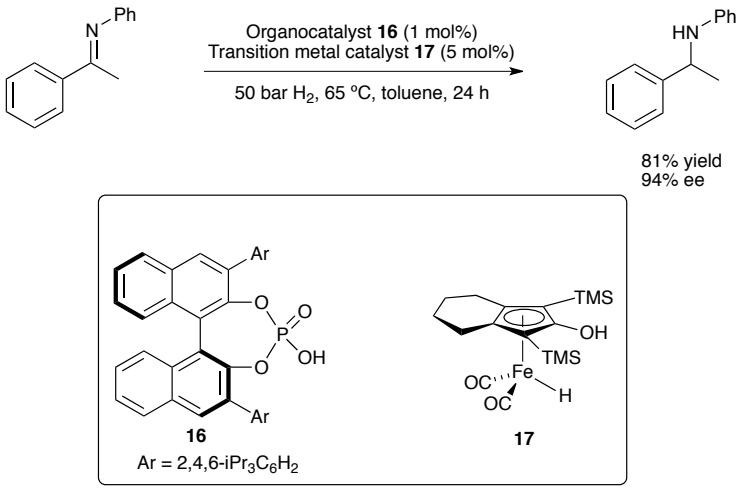
Table 1: Alexakis and Mazet's one-pot iridium/enamine catalysed process.



Entry	**13**	R^1	R^2	Yield (%)	*syn*-**13**/*anti*-**13**	ee (%)	
						syn-**13**	*anti*-**13**
1[a]	**13a**	*i*Pr	Ph	>99	1 : 1	92	96
2[a]	**13b**	Cy	Ph	>99	1 : 1	91	91
3[a]	**13c**	Me	tBu	73	1 : 4	66	47
4[b]	**13a**	*i*Pr	Ph	63	1 : 49	-	99

[a] Reaction carried out using iridium catalyst **14**; [b] reaction carried out using iridium catalyst **15**.

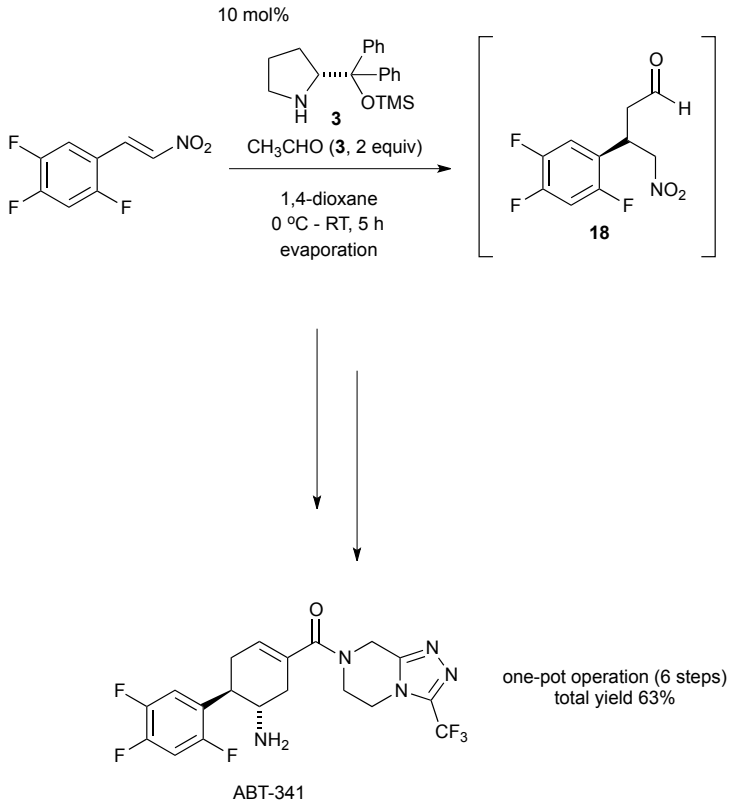
Another entry from this area has been reported by Beller and coworkers,[19] employing cooperative transition-metal and chiral Brønsted acid catalysis for the highly enantioselective hydrogenation of imines (Scheme 17). The authors suggest that the initial reports of Rueping, List, MacMillan and Antilla who have independently disclosed the asymmetric reduction of imines employing Brønsted acid catalysts that require a stoiceometric co-reductant, such as the expensive Hantzsch dihydropyridines, could be improved through the use of a cheap catalytic metal reductant. After screening a range of chiral Brønsted acid catalysts the group found the TRIP catalyst **16** in combination with the Knölker complex **17** gave excellent yields and enantioselectivities over a range of substrates.



Scheme 17 Beller's catalytic hydrogenation conditions

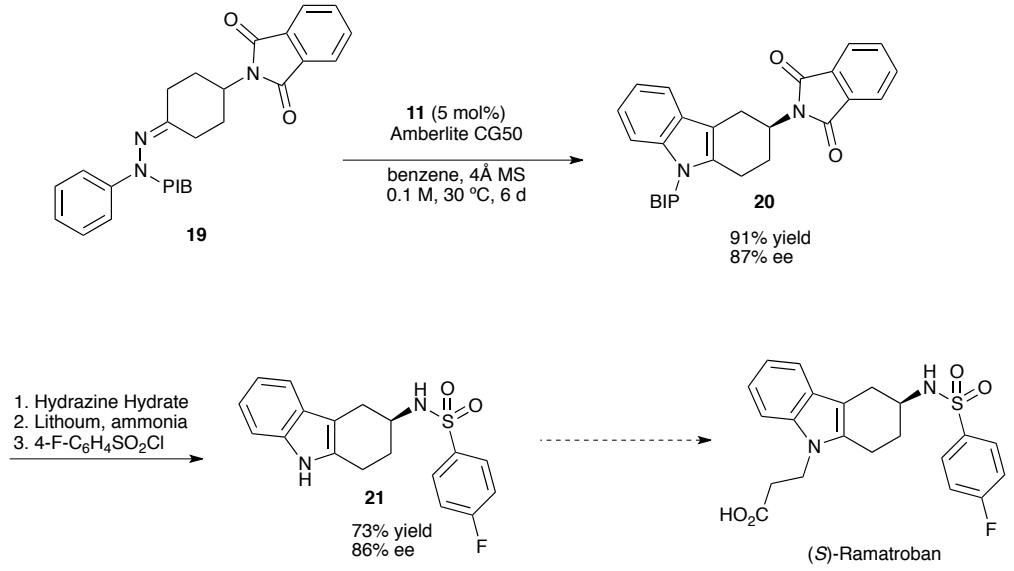
8.0 Natural Products/Biologically Active Compounds Synthesized by Organocatalytic Reactions

Given the developments outlined in this review, it is again perhaps not surprising that there is now the capacity for organocatlysts to be applied to the total synthesis of a wide variety of natural products/biologically active compounds. For example, Hayashi has reported the one-pot high yielding synthesis of the DPP4-selective inhibitor ABT-341 by employing a four-component coupling mediated by the diphenylprolinol silyl ether catalyst **3** (Scheme 18).[20] In the key enantiodefining step the catalyst affords the intermediate aldehyde **18** which after evapouration of the reaction solvent is treated with a range of classical reagents in a one-pot (6 step) operation to afford ABT-341 in an impressive 63% yield.



Scheme 18 The one-pot reaction for the synthesis of ABT-341 (1)

List has employed the asymmetric Fischer indolization reaction to the formal synthesis of the thromboxane receptor antagonist (S)-ramatroban (Scheme 19). Indolization of the hydrazine **19** on a followed by deprotection of the phthalimide **20**, debenzylation under Birch conditions and subsequent sulfonylation gave the literature intermediate **21** in good overall yield without erosion of the initial enantiomeric ratio and constituted a formal synthesis of (S)-ramatroban in 87% ee.



Scheme 19 List's route towards the formal synthesis of the thromboxane receptor antagonist (S)-ramatroban

9.0 Conclusions

As in previous years the development of organocatalysed reactions has been heavily reported in the literature for 2011. The level of enantiomeric excess and product yields obtained are generally at excellent levels, with ees of over 95% commonplace. As we can see from the examples presented in this review, enamine/iminium ion catalysis remains one of the most extensively studied areas within organocatalysis. However, 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 have been discovered and these modes of organocatalysis are now firmly established protocols.

In previous volumes we reported that the addition of combining catalytic processes both metal (see for example MacMillan's SOMO catlaysis volumes 104.105 & 106) and non-metal (see for example Melchiorre's cooperative organocatalysis 106) mediated has emerged was set to move forward the organocatalysis arena with significant vigour over the coming year. This has indeed been the case and the new vista reported in section 7.0 exemplifies the common use of organocatalysis so that it has now become a practical synthetic tool.

10.0 References

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