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Organocatalyzed Transformations of α,β-Unsaturated Carbonyl Compounds through Iminium Ion Intermediates

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α,β-Unsaturated carbonyl compounds represent the most versatile electrophilic building● blocks in organic synthesis. Traditional methods for the activation of these substrates in catalytic asymmetric synthesis● involve treatment of the carbonyl compound with a chiral Lewis acid. This lowers the energy level of the LUMO associated with the π-system activating it to 1,2-addition, 1,4-addition, and cycloaddition across either of the π-bonds [1]. In a seminal publication in 2000, MacMillan and coworkers described the concept of *iminium ion activation,* whereby a secondary amine salt (**1**) reacts with an α,β-unsaturated aldehyde (**2**) forming the corresponding iminium ion (**3**) simulating the π-electronics and equilibrium dynamics associated with Lewis acid catalysis (Step 1) [2]. The iminium ion (**3**) can undergo cycloaddition to give the iminium ion of the Diels–Alder adduct **4** (Step 2). Hydrolysis of **4** leads to the observed product **5** and the secondary amine salt (**1**), turning over the catalytic cycle (Step 3).[1] Since this landmark contribution, there has been intense interest in the area, with over 50 distinct transformations being developed [3]. This overview● describes the knowledge developed on the catalytic cycle, the active iminium ion, and the sense of asymmetric induction using imidazolidinone catalysts (Scheme 1).

Two primary classes of secondary amines have been widely investigated using this mode of catalysis: imidazolidinones and diarylprolinol ethers. Within the imidazolidinone series, two principal structures have been reported: imidazolidinone (**6**), which has been used in the acceleration of cycloadditions and closed transition state conjugate addition reactions, and the pivaldehyde-derived imidazolidinone (**7**), which has been used for conjugate addition processes and intramolecular cycloadditions [4, 5].

Reaction of amine **6**·HX with an α,β-unsaturated aldehyde can lead to either the (*E*)- iminium ion (**8**) or (*Z*)-iminium ion (**9**). It has been shown that steric interaction between the geminal dimethyl group of the catalyst and the C−H α- to the aldehyde disfavors **9** and that at equilibrium the ratio of **8/9** is 98 : 2 [6].

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1) A similar catalytic cycle can be proposed for conjugate addition reactions, see Ref. [3] for examples.
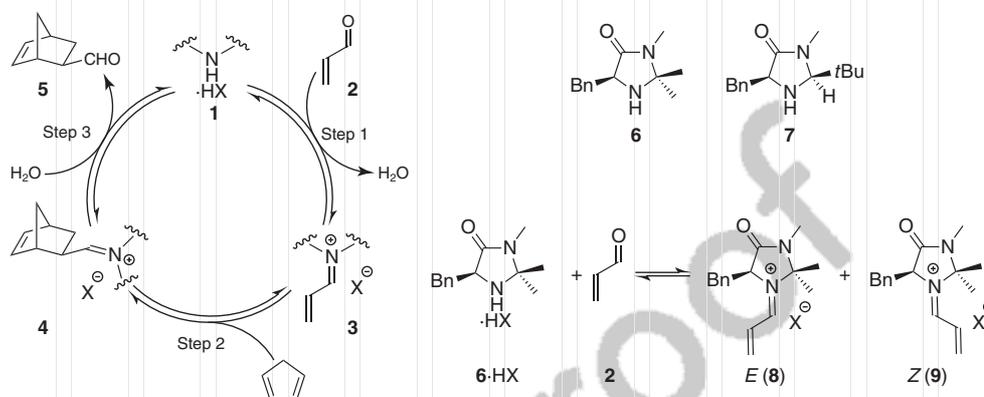
Scheme 1 Catalytic cycle of the iminium ion activation, amine catalysts, and iminium ion formation.

Within a Diels−Alder reaction, the approach of the diene is directed by the benzyl group on the catalyst. On selective formation of the (*E*)-iminium ion (**8**), the benzyl arm can adopt three low-energy conformations **10**−**12**. Molecular modeling (DF-SCS-LMP2/aug-cc-pVTZ) has shown that the lowest energy conformation is where the benzyl arm is located over the imidazolidinone ring (**11**), rather than over the reactive π-system (**10**: 5 kJ mol^{-1}) or back toward the carbonyl group (**12**: 20 kJ mol^{-1}). This is also the case in the solid state. For example, **13** shows the X-ray structure of three different iminium ion salts superimposed (rmsd < 0.6 Å). With the computational and solid-state evidence described above, VT-NMR• experiments suggest that in solution the low-energy conformation of the iminium ion is consistent with **11** [7]. In this low-energy and reactive conformation, the benzyl arm directs approach of the incoming diene to the lower *Si* face of the iminium ion, leading to the observed Diels−Alder adducts in high enantiomeric excess.

Location of the benzyl arm over the imidazolidinone ring (**11**), rather than the reactive π-system of the iminium ion (e.g., **10**), provides a rationale for the poor enantiomeric excess observed when imidazolidinone (**6**) is used to catalyze conjugate addition reactions [8]. For such reactions, which have open transition states, the chiral space must be extended toward the reactive β-carbon of the iminium ion. This is achieved using catalyst **7** where the sterically demanding *tert*-butyl group of the catalyst forces the benzyl arm over the reactive π-system **14**. This highlights a critical consideration when selecting the appropriate imidazolidinone catalyst.

The majority of optimized conditions described within the literature for reactions that proceed through an iminium ion intermediate involve the use of a protic solvent in the reaction medium (water, methanol, ethanol, or isopropanol). From a practical perspective, the ability to perform these transformations without the rigorous exclusion of moisture makes them operationally simple and has undoubtedly been instrumental in the rapid development of the field. However, it is important to note that protic solvents can play a direct role within the reaction
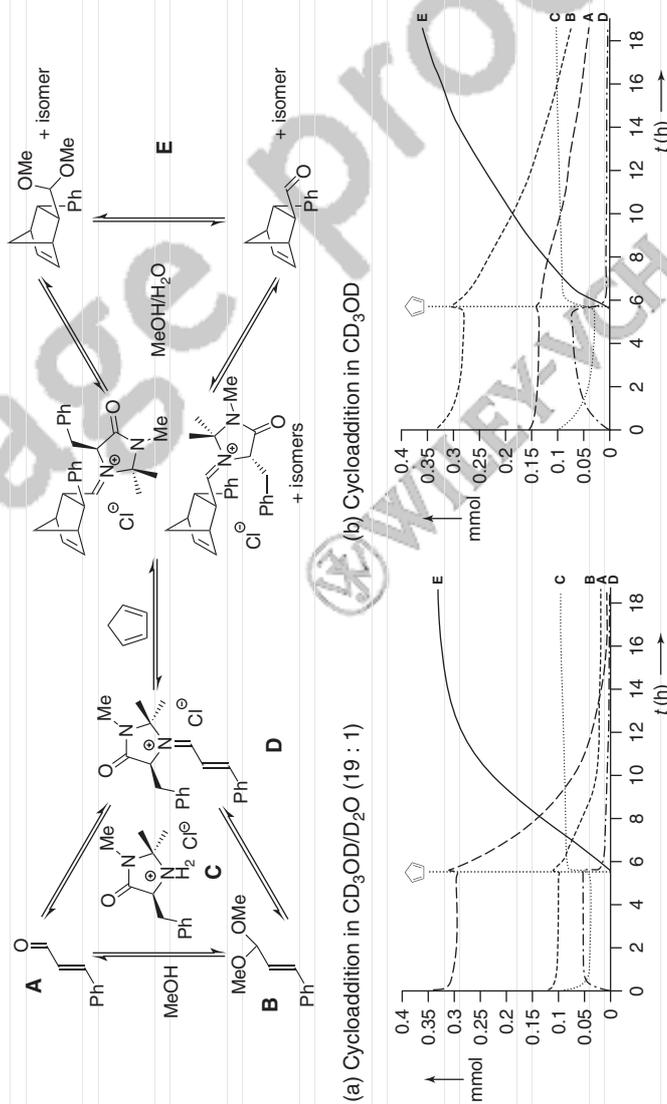
mechanism, increasing enantiomeric excess values and reaction rate as well as improving catalyst solubility [9].

The role of protic (nucleophilic) solvents in increasing the enantiomeric excess values of the products is due to rapid hydrolysis of the iminium ion adducts (**4**) before they can undergo retro Diels−Alder reaction (Step 2). This leads to the kinetic product. The presence of a protic solvent (such as methanol) in the reaction mixture increases the reaction rate by accelerating iminium ion formation through hydrogen bonding activation. Interestingly, a Diels−Alder reaction conducted in methanol proceeds slower than a reaction conducted in a methanol/water mixture (19 : 1). The basis of rate acceleration by addition of water to methanol is not obvious but was revealed by monitoring reaction progress. Scheme 2• shows two graphs for the reaction of cinnamaldehyde (**A**) (1 equiv) and cyclopentadiene (3 equiv) catalyzed by **6**·HCl (**C**) (20 mol%) in CD_3OD/D_2O (19 : 1) (Figure 1a) and CD_3OD (Figure 1b). Under these reaction concentrations, Diels−Alder cycloaddition is faster than iminium ion formation. In each reaction, before the addition of cyclopentadiene, equilibrium was established between cinnamaldehyde (**A**), cinnamaldehyde dimethyl acetal (**B**), and iminium ion (**D**). At equilibrium, the ratio of cinnamaldehyde/dimethyl acetal/iminium ion is 1.9 : 3.9 : 1 in CD_3OD and 5.8 : 1.9 : 1 in CD_3OD/D_2O (19:1). Water, therefore, alters the acid-catalyzed equilibrium position between cinnamaldehyde (**A**) and cinnamaldehyde dimethyl acetal (**B**). Iminium ion formation is the rate-determining step of the catalytic cycle; therefore, increasing the effective concentration of cinnamaldehyde (**A**) increases the rate of product formation (**E**).

With the imidazolidinone architecture, a number of alternative secondary amine salts have been reported to accelerate the reaction of α, β-unsaturated aldehydes through iminium ion intermediates. Of particular note among these are the diarylprolinol ethers [10]. Significantly less work has been carried out to understand the reactivity of this class of catalyst, where the mode of asymmetric induction appears significantly more complex than that delineated for imidazolidinones [6].

A substantial amount of data has been published to compare the relative reactivity of a number of different catalyst structures (including imidazolidinones and diarylprolinol ethers) for both cycloaddition and conjugate addition reactions [11]. It has also been shown that both proton affinity of the parent amine and LUMO energy level of the corresponding iminium ion can be used as useful ground state predictors of relative reactivity [12]. Direct comparison of the relative reactivities of imidazolidinones and diarylprolinol ethers in the Diels−Alder cycloaddition showed the imidazolidinone scaffold to possess significantly superior levels of activity when compared to diarylprolinol silyl ethers [13].

The nature of the co-acid involved within the reaction can also have a marked influence on both reaction rate and levels of asymmetric induction. Less effort has been devoted to understand this phenomenon, although an important work by Mayr [14] has shown that the basicity of the counterion can accelerate the rate-determining step in a conjugate addition reaction. A more general understanding of the effect of the co-acid would represent a significant contribution to the area.

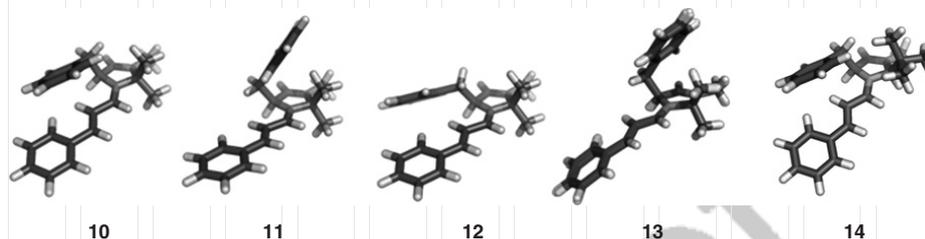**Scheme 2** Reaction mechanism and monitored reaction progress.

Figure 1 Possible conformations of the (*E*)-iminium ion regarding the location of the benzyl arm.

Despite the rapid progress within this area over the past 10 years, it is still a maturing field where significant challenges remain if it is to become a method of choice to synthetic chemists. Key chemical challenges within the area include (i) expansion of substrate scope, specifically with regard to the α, β-unsaturated carbonyl compound; (ii) further understanding of solvents and co-acids adopted within the reactions; and (iii) improving levels of catalyst activity. An important factor in the realization of these goals will come from a more intimate understanding of the mechanism, which offers great opportunities to those entering this exciting field of research.

CV of Nicholas C. O. Tomkinson

Nick Tomkinson was born in St. Andrews, Scotland in 1969. He studied Chemistry at The University of Sheffield and received his B.Sc. in 1992. His Ph.D. studies were under the supervision of Dr D. Neville Jones and Professor Jim Anderson, investigating asymmetric synthesis with unsaturated sulfur compounds. Postdoctoral studies on nuclear receptors were undertaken with Dr. Tim Willson at GlaxoSmithKline, Research Triangle Park, North Carolina (1996–1998). He was appointed as staff at the Cardiff University in 1999, and in 2004, he was awarded an EPSRC Advanced Research Fellowship. In June 2011, he took up a position in the Department of Pure and Applied Chemistry at the University of Strathclyde. His research interests are centered on the development of practical synthetic methodology.

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Julian Rowley was born in Oxford in 1988 and obtained an MChem with industrial experience at the Cardiff University in 2010. He then moved to the University of Strathclyde and is currently in his second year of Ph.D. studies under the supervision of Professor Nicholas Tomkinson. His current research interests focus on developing and understanding secondary-amine-catalyzed asymmetric transformations.

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