ASYMMETRIC DOMINO REACTIONS: WHAT DO ORGANOCATALYSTS HAVE TO OFFER?

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INTRODUCTION

Organic reactions are traditionally viewed as linear and stepwise processes in which isolation and purification of key intermediates often lead to reduced yields. Domino reactions, on the other hand, allow access to a myriad of complex molecules with high stereocontrol in an efficient, atom-economical manner. Nicolaou noted that the descriptors *domino*, *cascade*, *tandem*, and *sequential* are often used indistinguishably from one another in the literature.[1] Indeed, a variety of opinions exist on how such reactions should be classified. According to Tietze, a domino (or cascade) reaction is defined as a process in which two or more bond-forming transformations occur based on functionalities formed in the previous step. Furthermore, no additional reagents, catalysts, or additives can be added to the reaction vessel, nor can reaction conditions be changed.[2,3] Denmark further posits that most domino reactions, as defined by Tietze, fall under the broader category of tandem processes.[4] Other tandem reactions that are not cascades involve the isolation of intermediates, a change in reaction conditions, or the addition of reagents or coupling partners. Others classify domino reactions with even stricter conditions;[5,6] however, for the sake of this discussion of organocatalyzed domino reactions, the definition according to Tietze is suitable.

Biosyntheses, such as that of the steroid scaffold formed from squalene epoxide, demonstrate the elegant manner in which molecules are stitched together through cascade processes in nature with amazing selectivity.[7] In the laboratory, efforts to develop efficient and stereoselective domino reactions have been propelled predominantly by metal catalysts. Enzyme catalysts have also made a mark on the development of cascade transformations.[8] However, until recently, few domino reactions have been catalyzed by chiral organic molecules.[9,10]

Herein are described examples of organocatalysts that facilitate asymmetric domino reactions to afford a variety of complex structures in an efficient and elegant fashion. This abstract will focus in particular on the use of iminium and enamine catalysis, followed by a brief survey of other organic catalysts utilized in cascade reactions.

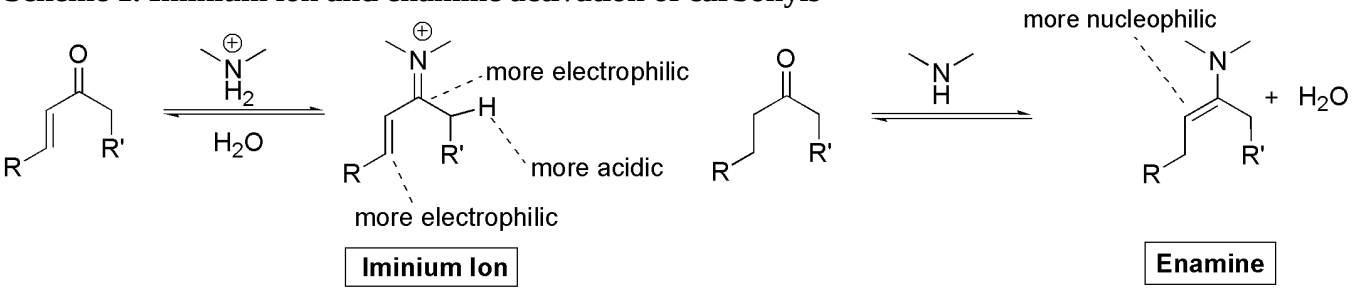
THE DEVELOPMENT OF ORGANOCATALYZED DOMINO REACTIONS

Background on iminium and enamine catalysis

Chiral amine catalysts and their derivatives dominate the emerging field of asymmetric organocatalysis. This technology, initially based upon the discovery of proline-catalyzed aldol reactions,[11] has been expanded to a variety of amine catalysts, many of which have been derived from

proline itself. Amine catalysts activate carbonyls by the formation of an iminium ion or an enamine. List compares iminium and enamine catalysis to the yin and yang, in that they are closely related yet contrasting processes.[12] Iminium ion formation increases the electrophilicity of the carbonyl carbon and lowers the LUMO energy. This allows access to pericyclic reactions and electrophilic addition reactions, particularly conjugate additions. Conversely, enamine formation raises the HOMO energy, increases nucleophilicity, and facilitates nucleophilic addition and substitutions reactions (Scheme 1).

Scheme 1. Iminium ion and enamine activation of carbonyls



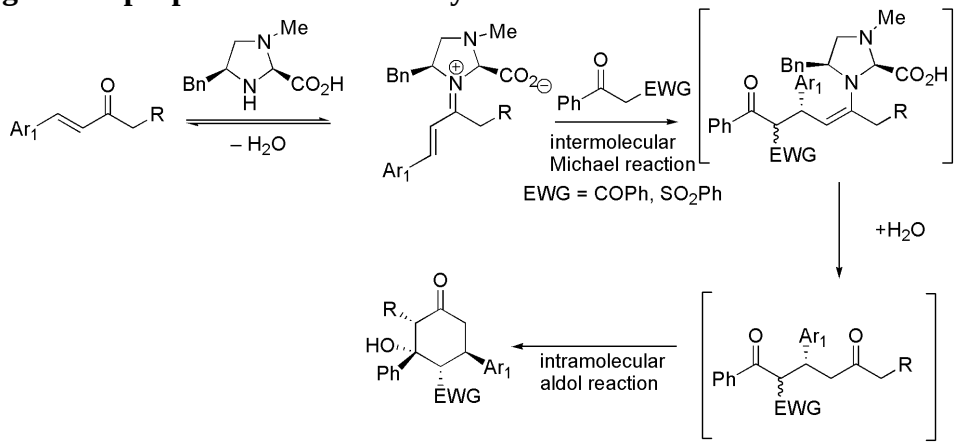
Domino reactions that utilize iminium and enamine catalysis

Many recent synthetic efforts take advantage of the orthogonal modes of carbonyl activation in the context of a domino reaction. In 2004, Jørgensen and coworkers published two reports of organocatalyzed enantioselective Michael-aldol cascade reactions. The reaction of α,β-unsaturated ketones with β-ketoesters,[13] β-diketones, or β-ketosulfones[14] yields cyclohexanones with up to four contiguous stereocenters. In these accounts, the authors propose that the phenylalanine-derived imidazolidine catalyst and Michael acceptor form an iminium ion that facilitates conjugate addition by activating the carbonyl and deprotonating the Michael donor. After hydrolysis, the catalyst was originally thought serve as a base for an intramolecular aldolization (Scheme 2). According to this proposed pathway, the stereoselectivity of the aldol reaction is influenced by a stable stereogenic center on the Michael intermediate.[13]

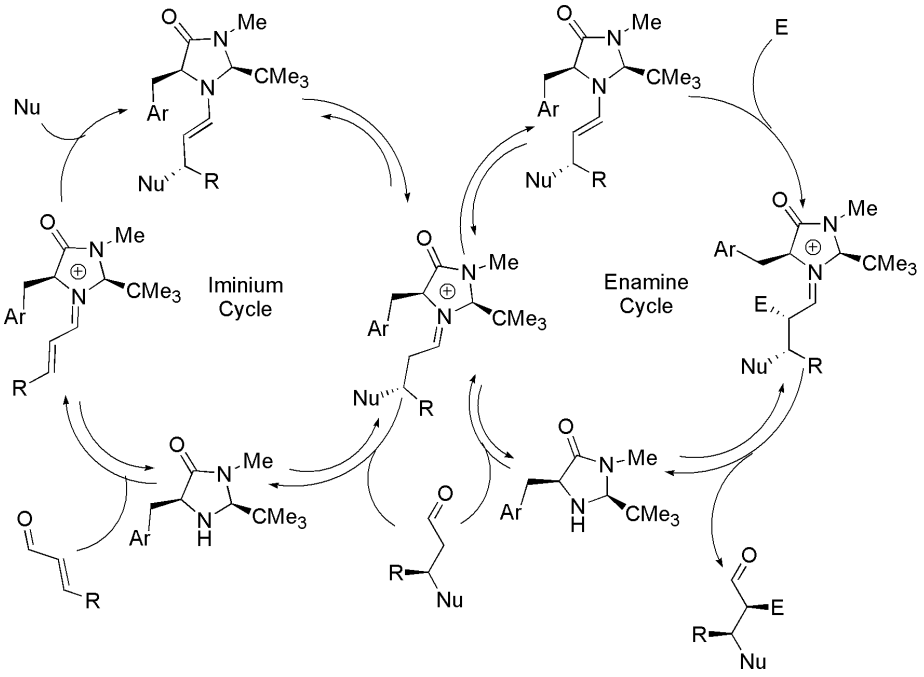
Gryko subsequently published a cascade Michael-aldol transformation to form asymmetric cyclohexanones from 1,3-diketones and methyl vinyl ketone (MVK) using L-proline as a chiral catalyst and *N*-methyl-2-pyrrolidone (NMP) as a solvent.[15] The Michael intermediate lacks a stereocenter to influence stereoselectivity of the cyclohexanone product, providing evidence that selectivity of the aldol reaction is not substrate-controlled as in Jørgensen's proposed pathway. Additionally, only the Michael adduct is observed when MVK reacts with the 1,3-dione in pyrrolidine as an organic base. Gryko thus modified Jørgensen's pathway to propose that the chiral catalyst is not hydrolyzed after the initial Michael addition, but rather forms an enamine that activates the donor to facilitate the aldolization. Furthermore, MacMillan posited that the enamine-catalyzed step utilizes catalyst control rather than

substrate control for stereoinduction.[16] Therefore, the domino Michael-aldol process is now accepted to utilize both iminium and enamine catalysis (Scheme 3).

Scheme 2. Jørgensen's proposed iminium-catalyzed domino reaction

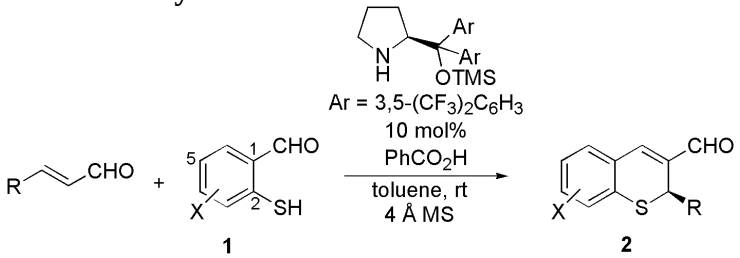


Scheme 3. Iminium-enamine catalysis in a nucleophilic-electrophilic addition cascade

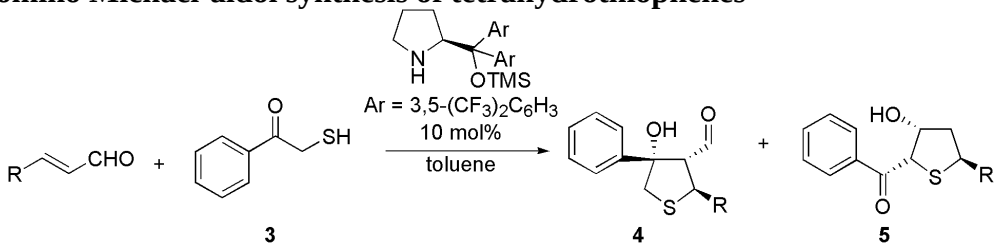


Both iminium ion and enamine formation are used in cascade reactions to develop products with high enantio- and diasteroselectivities. Wang recently reported a cascade Michael-aldol synthesis of chiral thiochromenes (Scheme 4).[17] The reaction between an enal and a thiophenol aldehyde **1** with chiral pyrrolinol silyl ether catalysts afforded thiochromene **2** products in yields ranging from 72-96% and enantiomeric excesses (ee) of 86-94%. Jørgensen also used a pyrrolinol silyl ether to catalyze the reaction between an α,β-unsaturated aldehyde and 2-mercapto-acetophenone **3** to yield functionalized tetrahydrothiophenes.[18] Under acidic conditions, the cascade yielded tetrahydrothiophene carbaldehydes **4**, whereas the same reagents under basic conditions afforded tetrahydrothiophen-3-ols **5** (Scheme 5).

Scheme 4. Cascade Michael-aldol synthesis of thiochromenes



Scheme 5. Domino Michael-aldol synthesis of tetrahydrothiophenes



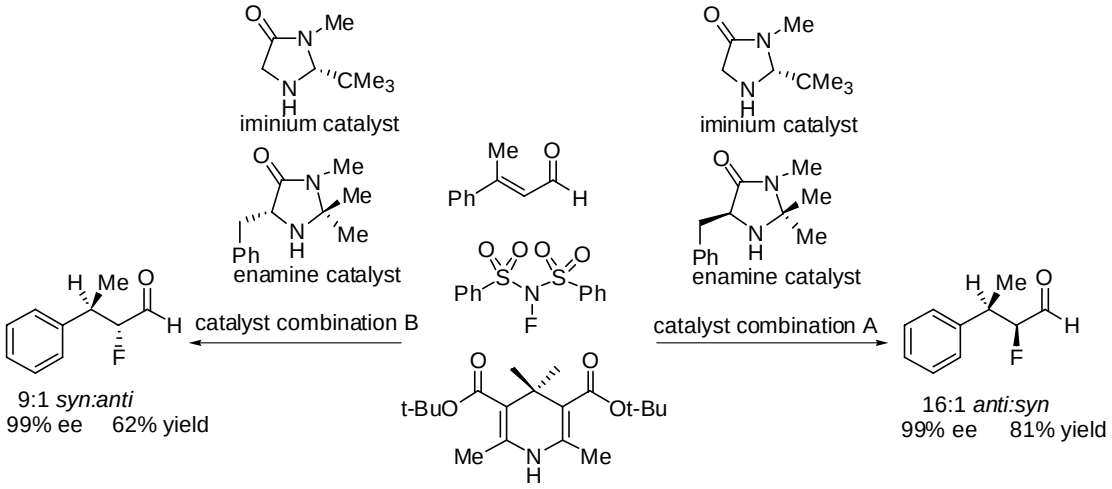
In 2005, MacMillan and coworkers reported enantioselective domino nucleophilic addition-electrophilic addition reactions of α,β-unsaturated aldehydes using imidazolidinone catalysts.[16] Although a single amine catalyst could successfully perform both iminium and enamine catalysis through a cascade reaction, it was proposed and indeed observed that the stereocontrol could be enhanced with two different amine catalysts specific to the iminium and enamine catalytic cycles, respectively. The authors were able to obtain 9:1 *syn* selectivity in the transfer hydrogenation and electrophilic addition of fluorine to the enals for one combination of imidazolidinone catalysts, and 16:1 *anti* selectivity by switching the stereochemistry of either catalyst in the combination (Scheme 6). However, this modification of using two catalysts is not a true cascade reaction in that the enamine catalyst is added along with the electrophile sequentially after the iminium catalyst and nucleophile have first reacted with the enal.

The products of iminium- and enamine-catalyzed cascade reactions have been applied to small-molecule syntheses. In 2003, MacMillan and coworkers presented an imidazolidinone-catalyzed conjugate addition-cyclization of tryptamine and functionalized enals to afford the pyrroloindoline scaffold of (–)-flustramine B.[19] Hong and coworkers reported a proline-catalyzed domino formal [3+3] cycloaddition of enals to yield chiral cyclohexadiene products that were used in the syntheses of (–)-isopulegol hydrate and (–)-cubebaol (Scheme 7).[20]

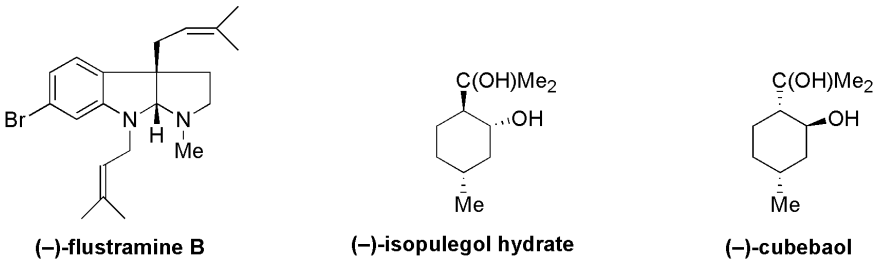
The remarkable power of iminium and enamine catalysis is demonstrated in triple cascade reactions. Jørgensen and coworkers recently reported a iminium-iminium-enamine triple domino reaction, catalyzed by a pyrrolinol silyl ether, in which the reaction of two α,β–unsaturated aldehydes with an activated methylene compound afforded cyclohexenecarbaldehyde products through the

formation of three new carbon-carbon bonds.[21] Beginning with symmetrical activated methylene compounds, nearly enantiopure cyclohexenecarbaldehydes were obtained with a variety of enal substrates (Scheme 8). The scope of the activated methylene was then extended to include two unique electron-withdrawing groups such as cyanoacetates, resulting in products with three stereogenic centers obtained in excellent enantioselectivities and moderate to good diastereoselectivities.

Scheme 6. Combinations of amine catalysts lead to enhanced selectivity



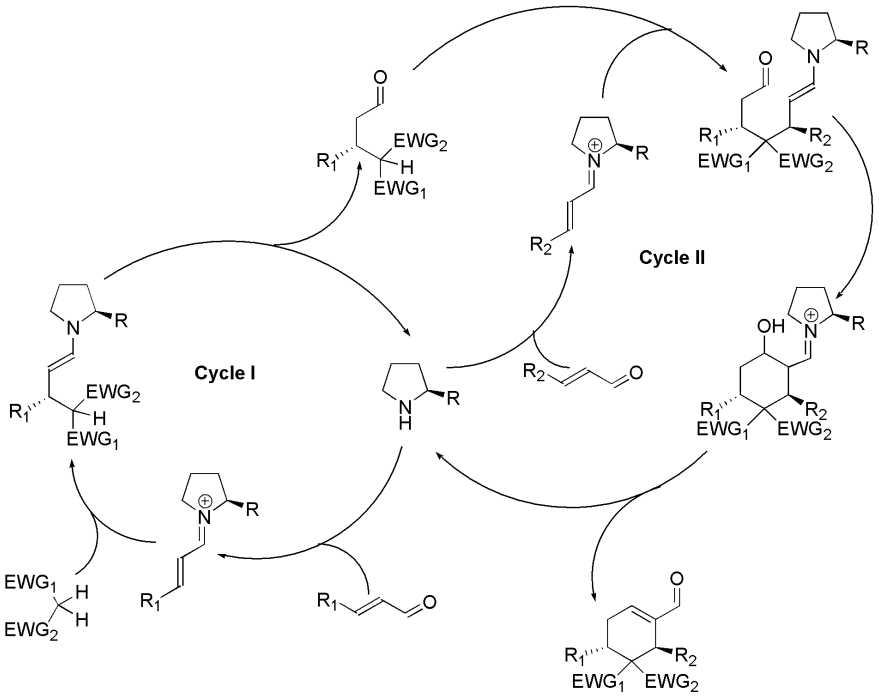
Scheme 7. Products formed in syntheses which utilize domino reactions



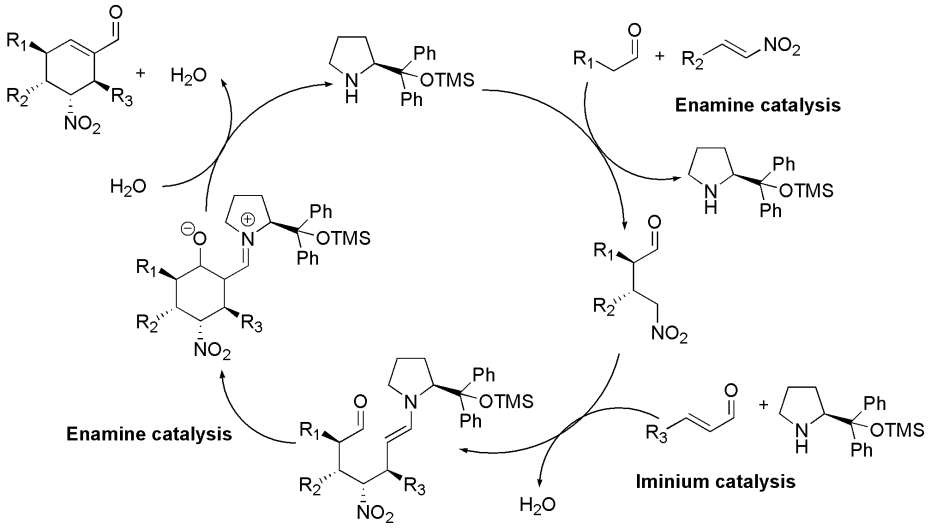
Another striking example of an organocatalyzed triple cascade reaction was reported in 2006 when Enders and coworkers utilized an enamine-iminium-enamine strategy to form three new carbon-carbon bonds, thus synthesizing cyclohexenecarbaldeydes with four stereogenic centers.[22] This report is one of only a few examples in which enamine activation is the first step in the cascade. Using a pyrrolinol silyl ether catalyst, the reaction between linear aldehydes, nitroalkenes, and α,β-unsaturated aldehydes yielded products in high diastereo- and enantioselectivities. The catalytic cycle is thought to proceed as follows. The linear aldehyde forms an enamine with the chiral catalyst and undergoes a conjugate addition into the nitroalkene to form a nitroalkane. Upon hydrolysis, the catalyst activates the enal, forming an iminium ion that undergoes a conjugate addition with the nitroalkane product from the previous step, yielding a substituted enamine intermediate. This enamine facilitates an intramolecular

aldolization to afford the cyclohexenecarbaldeyde product after hydrolysis (Scheme 9). Enders and coworkers applied this triple cascade to a one-pot synthetic sequence in which the cyclohexenecarbaldeyde product contains a diene. Upon a subsequent intramolecular Diels-Alder transformation, tricyclic carbaldehydes with up to eight stereocenters are formed in remarkably high diastero- and enantioselectivities.[23]

Scheme 8. Iminium-iminium-enamine triple cascade



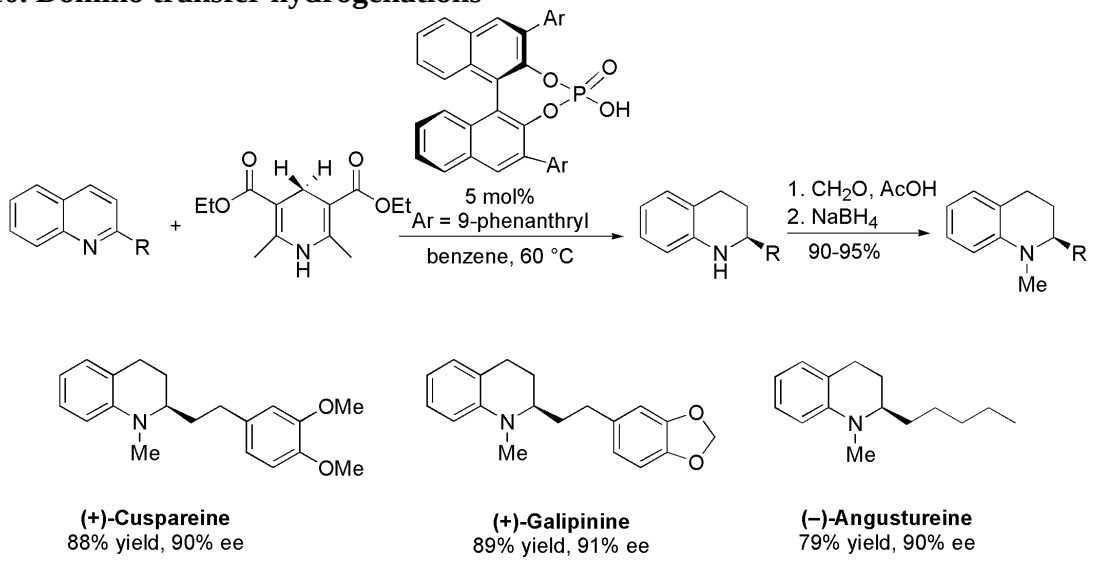
Scheme 9. Enamine-iminium-enamine triple cascade



Other examples of organocatalyzed domino reactions

In addition to iminium and enamine catalysis, which currently dominate organocatalyzed cascade reactions, other catalytic strategies are being investigated. One example is the application of some Brønsted acids as organocatalysts in cascade reactions. A Brønsted acid-catalyzed asymmetric domino transfer hydrogenation of quinolines was recently presented by Rueping and coworkers.[24] Using a BINOL-derived phosphoric acid catalyst and dihydropyridine as a hydride source, the quinoline underwent a 1,4-hydride addition followed by an isomerization and a 1,2-hydride addition, affording chiral tetrahydroquinolines. These products were then used in the syntheses of tetrahydroquinoline alkaloids (+)-cuspareine, (+)-galipinine, and (–)-angustureine (Scheme 10).

Scheme 10. Domino transfer hydrogenations



Asymmetric domino reactions have also profited from the development of catalysis mediated by hydrogen bonding. Wang and coworkers diverged from previous iminium-enamine catalytic studies[17] to present a chiral bifunctional thiourea-catalyzed thio-Michael-aldol reaction between oxazolidinones and thiophenol aldehydes, which afforded benzothiopyrans with three stereogenic centers.[25] Another example of a hydrogen-bonding-mediated domino reaction was reported by Deng.[26] Cinchona alkaloid-derived catalysts mediated the conjugate addition and protonation of a 2-chloroacrylonitrile with a variety of cyclic and acyclic Michael donors to yield products with 1,3-tertiary and quaternary stereocenters. The authors applied this method to the total synthesis of manzacidin A.

CONCLUSION

In recent years, asymmetric tandem cascade transformations have benefited from the rapidly growing field of organocatalysis, as exemplified by the impact of iminium and enamine catalysis. Chiral amine catalysts and their derivatives provide a highly controlled, efficient, and robust means of

accessing molecules with dense stereochemistry and functionality in a simple synthetic format. However, because iminium and enamine modes of activation dominate organocatalyzed cascades, the scope of reagents is strictly limited to enone and enal systems. Also, most processes first utilize an intermolecular reaction, followed by an intramolecular transformation. Furthermore, chiral secondary amines require high catalyst loadings (~20-50 mol%). Regardless of the apparent disadvantages, the further development of cascades, such as the notable triple cascades of Jørgensen[21] and Enders,[22] demonstrate how domino reactions will continue to impact organic synthesis in the future.

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