Organocatalysis

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Enantiodivergent Organocascade Reactions**

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Nature is superior when it comes to performing enzyme-catalyzed cascade reactions, and such course of reaction is in sharp contrast to classical multistep, often lengthy and tedious, organic synthesis. Not surprisingly, the use of enzymes in organic synthesis has increased tremendously over the last few years. Besides performing single-step transformations, the combination of multiple enzymes, for example, in a so-called bionanoreactor, has been used to perform cascade reactions.[1]

Another possible feature of enzyme catalysis is enantioconvergency, that is, a single-step transformation of a racemic stereogenic substrate into an enantiomerically enriched product in a theoretical yield of 100%.[2] For example, enantiocomplementary epoxide hydrolases exhibit dissimilar hydrolysis mechanisms, but nevertheless, will still generate the same enantiomeric diols.[3]

Following in the footsteps of multienzyme catalysis, closely related organocatalytic systems have emerged as powerful alternatives to address various challenging synthetic problems, and have resulted in the synthesis of complex molecular architectures in a single step.[4,5] In these protocols a clever selection of reagents and a modest catalytic push can lead to a synthetic setup in which a high degree of stereocontrol can be realized without elaboration on protecting group strategies and functional group conversions.

In the reports on organocatalytic cascade reactions two major modes of catalyst activation can be distinguished. These modes of activation mainly differ in their mechanisms for activation of the carbonyl group. Combination of these two catalytic activation pathways in one protocol allows for rapid conversion of simple achiral starting materials into stereochemically complex, highly enantioenriched products.[6] Most commonly used catalysts are secondary amines, usually of proline origin, which allow the formation of enamines upon condensation with aldehydes (raising the HOMO). Alternatively, the formation of iminium ions is carried out by treating α,β-unsaturated aldehydes with imidazolidines (lowering the LUMO). This dual-mode activation thus enables a variety of chemical transformations that are otherwise not possible using single-mode activation pathways. Either a dual catalyst system **1** and **2** (Scheme 1a)[7,8] or a single bifunctional catalyst **3** (Scheme 1b)[9] has been utilized for the organocatalytic cascade reactions. Imidazolidinones (e.g. **1**) serve as LUMO-lowering iminium catalysts, however, they lack essential structural features to effect the second catalytic cycle which involves enamine catalysis. In contrast, proline, which is available in both stereoisomeric forms, has a successful record as enamine catalyst. Unfortunately, proline is less effective in iminium catalysis particularly with enals or enones. A combination of catalysts **1** and **2**, however, leads to diastereomeric products **4** and **5** depending upon which proline enantiomer is used.

Bifunctional catalyst **3**, possessing both the imidazolidine and proline functionality, was elegantly put to use in the synthesis of stereochemically congested, optically active, cyclohexanones and cyclohexanediols.[9] The products were obtained as single diastereoisomers as a result of epimerization of the intermediate Michael adduct (*syn*/*anti* products). The diastereoselectivity in the subsequent intramolecular aldol reaction is thus controlled by the stable stereogenic center (*syn* configuration) of the Michael adduct which was previously formed.

The idea of organocatalytic cascade reactions that mimic enzyme catalysis was further developed by Fréchet and coworkers.[10] By using starlike polymers to generate "compartments", undesired interactions between the two catalysts, which might lead to mutual deactivation, were avoided (Scheme 2). By employing this "site isolation" concept, they succeeded in using a combination of otherwise incompatible catalysts and circumvented intercatalyst interactions. By applying the combination of encapsulated catalysts they were able to produce indole derivative **8** with high diastereo- and enantioselectivity in a one-pot double Michael reaction.

In an excellent seminal paper by Enders et al. a new variant of organocascade catalysis was introduced (Scheme 3).[11] By using a triple activation sequence the control of four newly formed stereogenic centers was possible. The cascade sequence starts with enamine formation (**10**) from an aldehyde and (*S*)-proline-derived catalyst **9**, which then adds to nitrostyrene **11** in a selective fashion to generate

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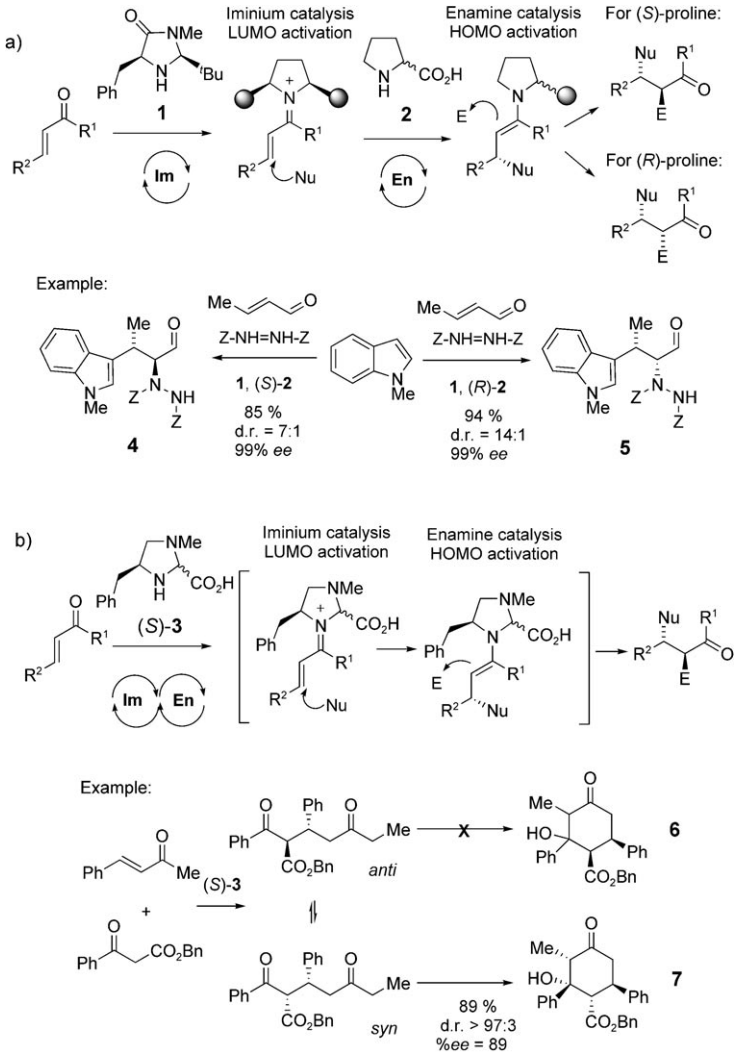
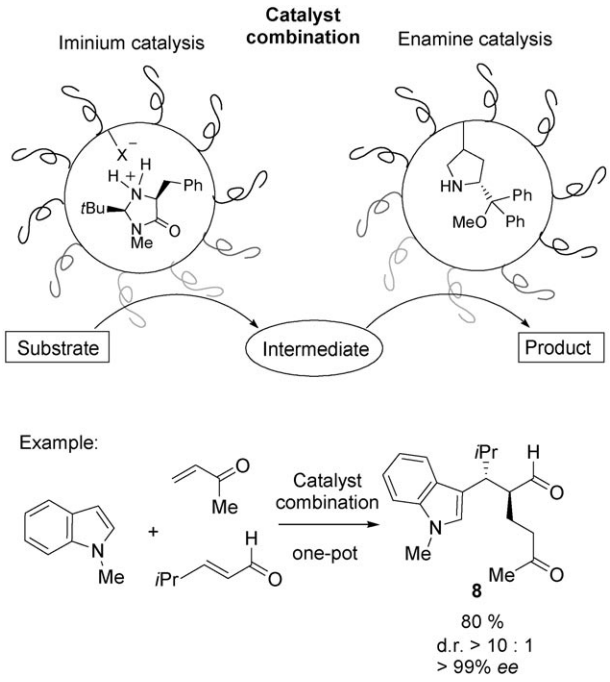


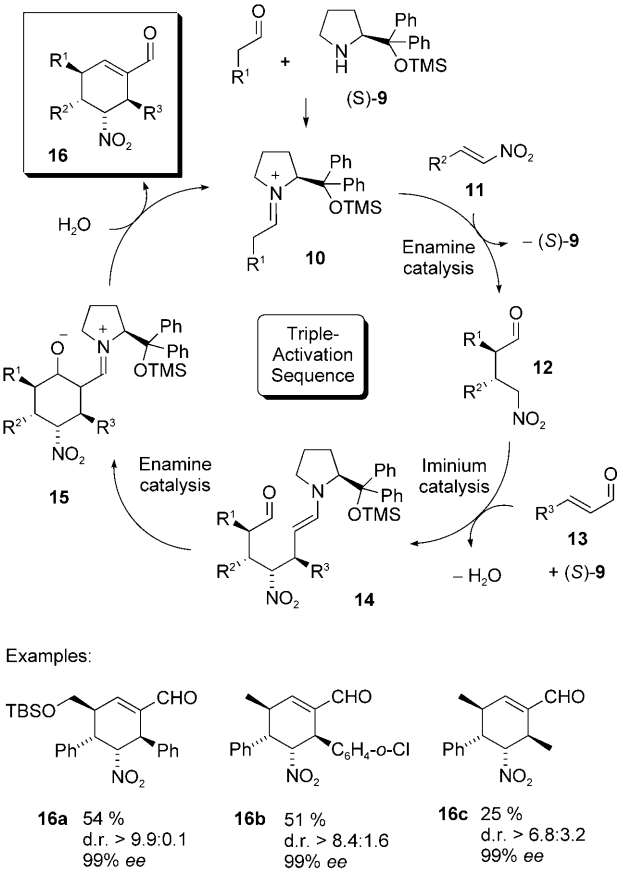
Scheme 1. Catalyst combinations **1** and **2** or bifunctional catalyst **3** perform iminium/enamine activation for the diastereoselective synthesis of indole derivatives or stereochemically congested cyclohexanone **7**. Bn = benzyl, En = enamine activation, Im = iminium activation, Z = carboxybenzoyl.

the Henry adduct **12**. After iminium formation of α,β-unsaturated aldehyde **13** with catalyst (*S*)-**9**, aldehyde **12** adds intermolecularly and forms intermediate enamine **14**. This enamine then undergoes an intramolecular ring-closure and furnishes diastereomerically and enantiomerically enriched cyclohexene derivatives **16** (e.g. **16a–c**).

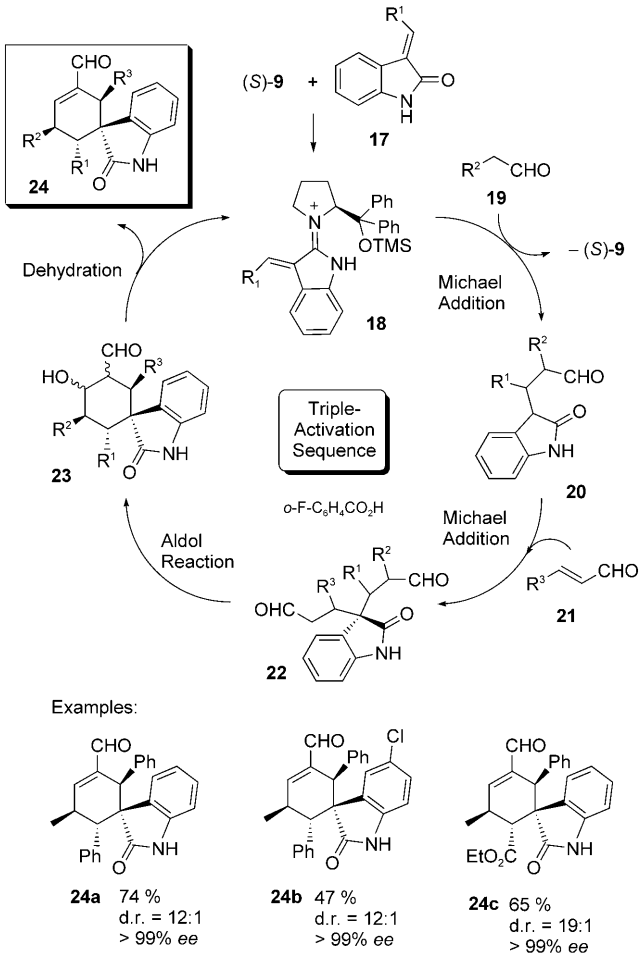
This strategy was adopted and substantially extended by Melchiorre and co-workers for the stereocontrolled formation of quaternary carbon centers (Scheme 4).[12] By employing an oxindole **17**, an aldehyde **19**, and an α,β-unsaturated aldehyde **21**, the modified triple activation cascade lead to spirocyclic products **24**. The quaternary center as well as the other stereogenic centers were formed with excellent diastereo- and enantioselectivity (e.g. **24a–c**). The yields of this cascade reaction are considerably higher than the ones reported by Enders, probably because of the addition of 2-fluoro-benzoic acid, which was shown to be highly favorable for this process.



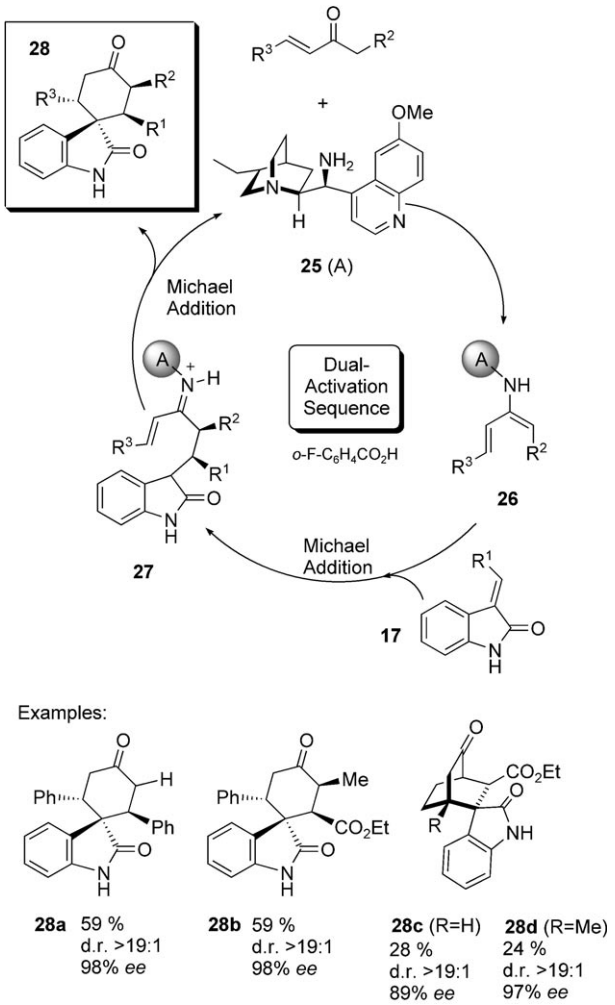
Scheme 2. Encapsulated iminium and enamine catalyst in a one-pot cascade reaction. X = C_6H_4-*p*-SO_3^-.



Scheme 3. Proposed mechanism of the triple-activation cascade reaction with control of four stereogenic centers (e.g. **16a–c**). TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.



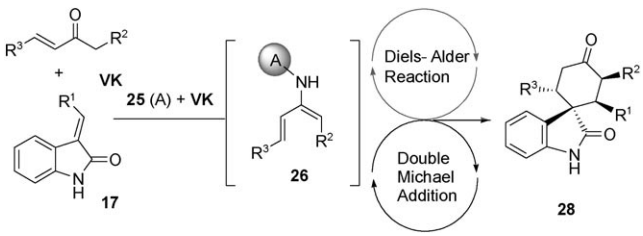
Scheme 4. Synthesis of spirocyclic oxindolic cyclohexanones through the triple cascade activation sequence with oxindoles **17**.



Scheme 5. Proposed mechanism for the dual-activation cascade reaction using catalyst **25**.

Intriguingly, by altering the activation cascade sequence using catalyst **25**, Melchiorre and co-workers were also able to generate similar spiro compounds through a dual-mode cascade reaction (Scheme 5).[12] Ketone activation, using the quinine-modified primary amine **25** and a vinyl ketone, results in the formation of diene–amine intermediate **26**. This compound then undergoes a first, intermolecular Michael addition reaction with oxindole **17** to produce precursor **27**. This resulting iminium intermediate (**27**) is ideal to activate the second, this time intramolecular Michael addition, to form the final product **28**, in which the participation of an oxindole compound is unique. Here, a twofold activation by primary amine catalyst **25** leads to the spirocyclic oxindole derivatives **28a–d**. The formation of the quaternary center is enantiodivergent to the one described in Scheme 4. By changing the amine catalyst to pseudo-*ent*-**25**, pseudo-enantioconvergent products can be made (see the Supporting Information in Ref. [9]). The high tolerance with respect to structural and electronic variations in the precursors **17** and **26** leads to congested bicyclic moieties **28a–d**, where bicyclic **28d** exhibits two contiguous all-carbon quaternary stereocenters—a framework otherwise extremely difficult to construct.

The high degree of stereoselectivity in the dual-activation cascade reaction prompted the authors to perform an extensive mechanistic study (see the Supporting Information in Ref. [9]). Unfortunately, the high reactivity of the intermediates formed in the activation cascade (e.g. **26** and **27**) hamper their analysis and thus made reaction monitoring extremely difficult.[13] The products formed, however, suggest either a double Michael addition (stepwise) or a concerted [4+2] cycloaddition reaction[14]—both of which start with the formation of the diene-amine intermediate **26** (see Scheme 6). Owing to the relative configurations of the products **28a–d**, the authors do not favor the concerted mechanism.



Scheme 6. Possible mechanisms for the formation of spirooxindole **28**: stepwise or concerted? **VK** = vinyl ketone.

Arguments which most likely rule out the concerted mechanism for the formation of the spirocyclic oxindoles are 1) the formation of **28a** (*trans* configuration), which can only be explained by the less favored *exo* transition state; 2) the formation of **28b** should originate from an unstable *E,E*, *s-cis* dienophile **26**, and 3) the formation of the *cis*-succinate moiety in products **28c** and **28d**. To support these mechanistic arguments more experiments are required, for example, starting from isomeric (de)activated dienes other than **26**.

To summarize, the significant developments in the area of organocascade catalysis, which only started a few years ago, is now coming to the point where it can be used to construct unique and complex architectures using robust and versatile chemical transformations. In the coming years, the use of organocatalysts other than proline derivatives is expected. Many organocatalysts with either cinchona-alkaloid-, binol-, or thiourea-based are nowadays successfully employed in catalysis. Nevertheless, they are still rarely applied in a cascade sequence.[6,15,16] Conversely, one should not expect that in the near future organocascade sequences will replace classical multistep synthesis altogether. The expansion of this rapidly growing field will, however, considerably assist the organic chemist in shortening the total time span required to carry out complex molecular synthesis, especially that of natural products.[17] Finally, organocatalytic cascade reactions are expected to increase the chemical and economical efficiency in the preparation of organic products.

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