Asymmetric Organocatalysis

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Organocascade Reactions of Enones Catalyzed by a Chiral Primary Amine**

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Enantioselective catalysis is one of the most efficient chemical approaches to the challenging issues associated with structural and stereochemical complexity.[1] This approach is attractive as it is the only rational means of producing useful chiral compounds with high optical purity in an economical, energy-saving, and environmentally benign way.[2] Recently, the potential of asymmetric catalysis has been expanded by the introduction of simple chiral small organic molecules as highly efficient catalysts for many transformations.[3] One of the most powerful organocatalytic strategies is organocascade catalysis.[4] This process exploits the ability of chiral amines to efficiently combine two modes of catalytic activation of carbonyl compounds (iminium and enamine catalysis)[5] into one mechanism, thereby allowing the rapid conversion of simple achiral starting materials into stereochemically complex products with multiple stereocenters and very high optical purity. This one-step strategy requires neither protection/deprotection steps, which can be time-consuming and costly, nor isolation of intermediates.

The recent advances in the field of chiral secondary amine catalysis[5] have set the scene for the development of many highly efficient organocascade reactions based on the selective activation of aldehydes.[6] However, little progress has been achieved in the corresponding transformations of ketones, mainly because of the inherent difficulties in generating congested covalent intermediates from secondary amines and ketones.

Herein, we show that chiral primary amine catalysis offers a powerful alternative in the design of novel and synthetically useful organocascade reactions, thus providing a practical solution to the issue of activating α,β-unsaturated ketones toward a well-defined enamine–iminium tandem sequence. Specifically, we have developed a series of organocascade approaches that affords straightforward access to a range of formal Diels–Alder adducts **4a**–**i**, which have three or four stereogenic centers, with very high optical purity (Figure 1). Importantly, we found that catalyst **1**, a chiral primary amine directly derived from natural cinchona alkaloids, efficiently activates acyclic enones while selectively directing the reaction manifold toward a stepwise double-Michael addition sequence instead of a pericyclic path. The resulting unique stereochemical outcome renders the presented methodology, which complements the venerable [4+2] cycloaddition transformations, a novel synthetic route to valuable cyclohexane derivatives.[7]

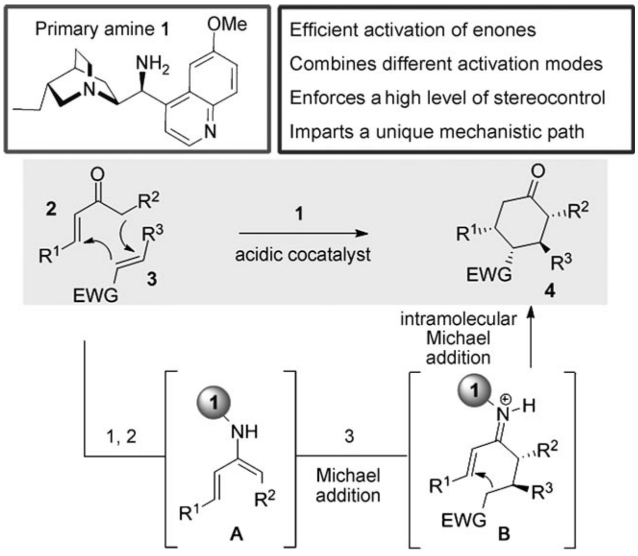

Figure 1. Organocascade with enones promoted by chiral primary amine **1**: enamine–iminium activation for a double-Michael sequence. EWG = electron-withdrawing group.

Recently, chiral secondary amine catalysis has proved efficient in promoting the stereoselective Diels–Alder reactions that use cyclic enones as dienes and involve in situ dienamine activation.[8] On the other hand, the corresponding transformations with linear α,β-unsaturated ketones proceeded with essentially no enantioselectivity.[9] We then investigated whether the versatility of 9-amino(9-deoxy)-*epi*-hydroquinine **1**, which we and other research groups have independently established as an effective catalyst for ketone activation,[10] may be exploited to combine enamine–iminium activations of acyclic enones, as this cascade sequence would lead to a formal Diels–Alder adduct (Figure 1). This idea was mainly driven by our recent application of **1**[11a] to catalyze an intramolecular tandem reaction of linear enones, based on an iminium–enamine pathway.[11]

Initially, we focused on the identification of a suitable compound **3**, which was able to initially act as a Michael

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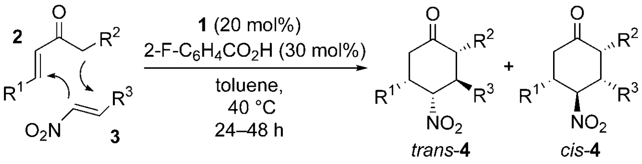
acceptor that could intercept the nucleophilic enamine intermediate **A** generated in situ by the condensation of catalyst **1** with the α,β-unsaturated ketones **2a–i** (Figure 1). The resulting carbon nucleophile **B** should then selectively engage in an intramolecular, iminium-catalyzed conjugate addition to afford the derivatives **4a–i**. Therefore, the reaction between acyclic α,β-unsaturated ketones **2a–i** and nitroalkenes **3** to furnish complex cyclohexanones **4a–i** was studied (Table 1).

Table 1: Organocascade with chiral primary amine **1**: combinations of linear α,β-unsaturated ketones and nitroalkenes.[a]



Entry	4	R^1	R^2	R^3	Yield [%][b]	d.r.[c] trans/cis	*ee* [%][d]
1	**a**	Ph	H	Ph	78	> 19:1	96
2	**b**	Ph	H	4-MeO-C_6H_4	69[e]	3:1	93
3	**c**	Ph	H	2,6-Cl_2-C_6H_3	85	13:1	95
4	**d**	4-Cl-C_6H_4	H	Ph	77[e]	2:1	94
5[f]	**d**	4-Cl-C_6H_4	H	Ph	40	> 19:1	90
6	**e**	4-Cl-C_6H_4	H	2,6-Cl_2-C_6H_3	92	> 19:1	96
7	**f**	thiophenyl	H	Ph	50	3:1	96
8[f]	**f**	thiophenyl	H	Ph	53	> 19:1	88
9	**g**	Ph	Me	Ph	58	15:1	99
10	**h**	Ph	Me	4-Br-C_6H_4	47	6:1	99
11	**i**	thiophenyl	Me	Ph	65	14:1	99

[a] Reactions conducted on a 0.2 mmol scale with 2 equiv of **2** and [**3**]$_0$ = 1 м. [b] Yield of the isolated single, major diastereoisomer. The yields reflect the degree of conversion. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases. [e] Yield refers to the sum of diastereoisomers. [f] Reaction carried out at RT using 30 mol% of salicylic acid (2-OH-$C_6H_4CO_2H$) as cocatalyst.

Barbas and co-workers[9a] used the same transformation to demonstrate, for the first time, the ability of chiral secondary amine catalysts to activate linear enones toward a Diels–Alder process, thus exploiting the transient formation of the activated diene **A** (Figure 1). Such a type of [4+2] cycloaddition reaction led to the selective formation of the expected *exo* cycloadducts *cis*-**4** with very poor enantioselectivity (38% *ee*).[9a] We were pleased to find that the reaction catalyzed by the chiral primary amine **1** (20 mol%), in combination with 30 mol% of 2-fluorobenzoic acid as the cocatalyst, showed a very high enantiocontrol and the opposite stereochemical behavior, with preferential formation of the formal *endo* product *trans*-**4**. As highlighted in Table 1, the combination of a series of acyclic enones **2** and aromatic nitroalkenes **3** afforded complex cyclohexanones **4** with high diastereomeric ratio and in almost enantiomerically pure form (*ee* values ranging from 93 to 99%). We also found that the nature of the acidic cocatalyst strongly influences both the reactivity and the stereochemical outcome of the cascade.[12] By carrying out the reaction in the presence of 30 mol% salicylic acid, a very high diasterocontrol and an increased reaction rate were obtained, albeit with slightly lower enantioselectivity (compare Table 1, entries 4,5 and 7,8). Interestingly, the use of enones that bear an ethyl α-substituent (R^2 = Me, Table 1, entries 9–11) promotes the selective formation of cyclic products **4g–i**, which have four stereogenic centers.

The relative and absolute configuration of the trisubstituted cyclohexanone **4c** and the tetrasubstituted compound **4h** was unambiguously determined to be 3*S*,4*R*,5*S* and 2*R*,3*S*,4*R*,5*S*, respectively, by anomalous dispersion X-ray crystallography.[13]

The unique reaction pathway imparted by catalyst **1** introduces important features from both synthetic and mechanistic standpoints. The primary amine catalyzed organocascade furnishes a complementary approach to the classical Diels–Alder reaction for the asymmetric, one-step synthesis of complex cyclohexane scaffolds with multiple stereocenters. For example, the present reaction manifold allows the highly stereoselective access to the chiral compound **4a**, which has identical R^1 and R^3 substituents (Table 1, entry 1), whereas a cycloaddition path would lead to the *meso*-isomer *cis*-**4a**.[9a] On the basis of the experimental observations made thus far, we propose that the formal Diels–Alder reaction proceeds by the enamine–protioiminium mechanism depicted in Figure 1. In addition, to account for the unexpected stereochemical outcome of the process, this mechanistic scenario is consistent with the fact that the rate and enantioselectivity of the reaction strictly depend on the identity of the carboxylic acid cocatalyst,[12] a parameter that can strongly facilitate the equilibrium between imine (generated by catalyst condensation with enone **2**) and secondary enamine **A** during the reaction. Moreover, the catalytic activity of primary amine **1** is completely suppressed when carrying out the reaction in polar solvents (e.g., MeOH or H_2O), whereas a concerted cycloaddition pathway is generally accelerated in such reaction media.[7,8c,9] The proposed stepwise double-Michael sequential mechanism is finally corroborated by the isolation of the corresponding Michael adducts of α,β-unsaturated ketones and nitrostyrene[14] (see the Supporting Information for details).

A central goal of our organocascade catalysis studies has been to demonstrate the potential of this simple methodology to solve challenging synthetic problems. We thus applied the primary amine catalyzed organocascade strategy to target daunting issues in asymmetric synthesis, namely the generation of all-carbon quaternary stereocenters, and the asymmetric construction of polycyclic structures. These cyclic structures often pose distinct challenges owing to the unique strain and steric elements imparted by their connectivity. Meanwhile, the generation of a quaternary chiral carbon atom is always a demanding task, mainly because of the sterically congested environment in which C−C bonds must be formed and stereochemical information must be transferred.[15]

As shown in Table 2, our cascade-catalysis strategy provides a flexible and direct approach to innovate around the highly stereoselective construction of all-carbon quater-

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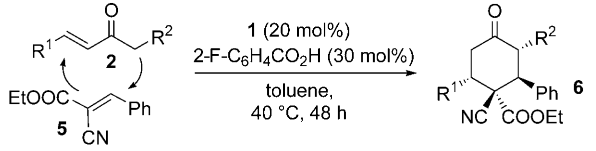
Table 2: Organocascade with chiral primary amine **1**: creation of all-carbon quaternary stereocenters in complex molecules.[a]



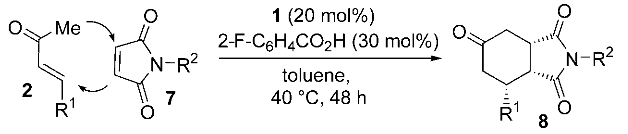
Entry	**6**	R^1	R^2	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**a**	Ph	H	83	14:1	94
2	**b**	thiophen-2-yl	H	77	>19:1	95
3	**c**	COOEt	H	86	>19:1	98
4	**d**	4-Cl-C$_6$H$_4$	H	67	>19:1	95
5	**e**	4-CN-C$_6$H$_4$	H	67	>19:1	94
6	**f**	Ph	Me	53	13:1	97
7	**g**	thiophen-2-yl	Me	75	9:1	97

[a] Reactions conducted on a 0.2 mmol scale with 2 equiv of **2** and $[\mathbf{5}]_0 =$ 1 M. [b] Yield of the isolated single, major diastereoisomer. The yields reflect the degree of conversion. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases.

nary stereogenic centers in complex organic molecules.[16] Compound **1** catalyses the reaction of a series of α,β-unsaturated ketones with *trans*-α-cyanocinnamate **5** to furnish cyclohexanones **6a**–**g**, which have three or four stereogenic carbon atoms, in high yields and with excellent diastereomeric and enantiomeric control.

We next moved toward the one-step, asymmetric synthesis of valuable bicyclic scaffolds that have three contiguous stereocenters. To achieve this goal, we extended the organocascade strategy with enones to include *N*-phenyl or *N*-benzyl maleimides **7**, which is an unprecedented combination that allows the fast and selective production of bicyclic compounds **8** with very high fidelity (Table 3). From a mechanistic standpoint, it is worth mentioning that even in the presence of a strong dienophile such as maleimide **7**, we observed the formation of the Michael adduct derived from the enamine-mediated conjugate addition of the enones **2**.[17] This observation (see the Supporting Information for details) further illustrates the ability of primary amine **1** to selectively direct the reaction mechanism toward a peculiar stepwise double-Michael addition sequence.

Table 3: Organocascade with chiral primary amine **1**: combinations of enones and maleimides.[a]



Entry	**8**	R^1	R^2	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**a**	Ph	Ph	34	7:1	96
2	**b**	Ph	Bn	71	15:1	>99
3	**c**	4-CN-C$_6$H$_4$	Bn	72	>19:1	96
4	**d**	thiophenyl	Bn	37	>19:1	99
5	**e**	4-Cl-C$_6$H$_4$	Bn	56	>19:1	>99

[a] Reactions conducted on a 0.2 mmol scale with 2 equiv of **2** and $[\mathbf{7}]_0 =$ 1 M. [b] Yield of the isolated single, major diastereoisomer. The yields reflect the degree of conversion. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] Determined by HPLC analysis on chiral stationary phases.

The relative and absolute configurations of compounds **6f** and **8a** were assigned by NOE analyses and by means of time-dependent (TD) DFT calculations of the electronic circular dichroism (ECD) spectra (see the Supporting Information).

In summary, we have demonstrated that chiral primary amine catalysis offers a new avenue for the achievement of stereochemical and structural complexity through organocascade catalysis.[18] We anticipate that the versatility of catalyst **1** will be useful for the efficient, asymmetric construction of more challenging complex scaffolds, based on the design of novel organocascade reactions.[19]

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[12] The use of a strong acid as the cocatalyst resulted in a considerably lower reaction rate and reduced stereoselectivity; for instance, using TFA (30 mol %) in the reaction of Table 1, entry 1, led to *trans*-**4a** with 45 % conversion, 10:1 d.r. and 82 % *ee* at 70 °C after 72 h. Although the main role of the acidic cocatalyst is probably to facilitate the imine–enamine equilibrium, the positive influence of the salicylic acid on both the diastereoselectivity and the reaction rate suggests a possible electrophile activation through hydrogen-bond interaction with the nitrostyrene derivative.

[13] CCDC 736272 (**4c**) and 736273 (**4h**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] After isolation and characterization, the intermediate derived from the Michael addition of *trans*-4-phenyl-3-buten-2-one to nitrostryrene was completely converted into the cascade product *trans*-**4a** when mixed with the catalyst **1** under the standard reaction conditions.

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[19] In the following Communication, we exploit the synthetic power of **1**-mediated organocascade catalysis to directly access spirocyclic oxindoles with high optical purity from simple starting materials: G Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, 7336 – 7339; *Angew. Chem. Int. Ed.* **2009**, 7200 – 7203.

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