Synthetic Methods

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Control of Remote Stereochemistry in the Synthesis of Spirocyclic Oxindoles: Vinylogous Organocascade Catalysis**

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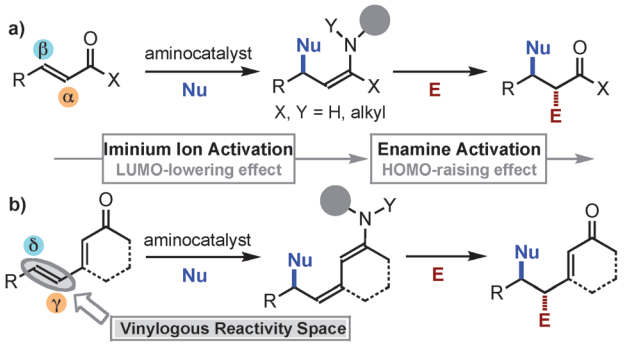
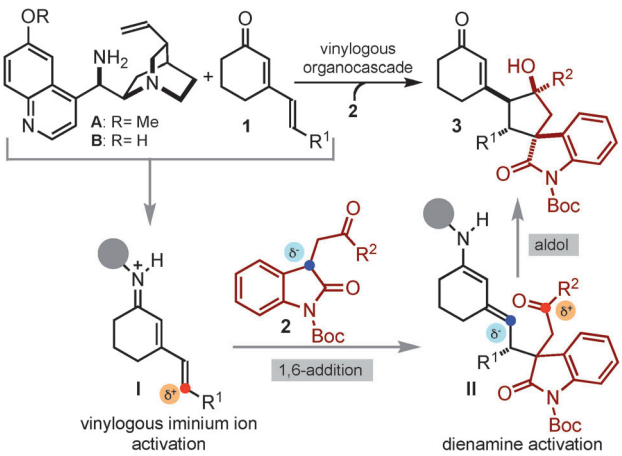
Cascade reactions are powerful tools for rapidly achieving molecular complexity since multiple chemical bonds are formed in a single synthetic operation.[1] Their recent marriage to asymmetric organocatalysis[2] has led to highly innovative techniques, which are now recognized as reliable strategies for the one-step enantioselective synthesis of stereochemically dense molecules.[3] To fully harness the synthetic power of organocascade catalysis, it was crucial to identify the iminium ion/enamine activation sequence as an enabling approach to highly efficient domino reactions (Scheme 1 a).[4] The strategy is based on the conjugated addition of a nucleophile to α,β-unsaturated aldehydes or ketones and subsequent α functionalization of the resulting saturated carbonyls. In this well-defined sequence, the chiral amine catalyst has an active role in both steps, initially forming the activated iminium ion species (not shown in Scheme 1 a) and later the electron-rich enamine intermediate. The strategy has been extensively applied by the synthetic community to access α- and β-functionalized carbonyl chiral building blocks.[2–4]



Scheme 1. a) The established strategy of iminium ion/enamine activation for designing organocascade reactions. b) Proposed approach for targeting multiple stereocenters remote from the catalyst's point of action: transferring the technique into a vinylogous reactivity pattern. The gray circle represents the chiral fragment of the aminocatalyst scaffold. Nu = nucleophile, E = electrophile.

Herein, we expand the potential of organocascade catalysis by including vinylogous reactivity[5] as a new design principle to conceive unprecedented asymmetric domino reactions (Scheme 1 b). Key to our achievements was the ability of a cinchona-based primary amine catalyst[6] to propagate the electronic effects inherent in the iminium ion and the enamine reactivity modes (i.e., the LUMO-lowering and the HOMO-raising activating effects, respectively)[7] through the conjugated π system of cyclic α,β,γ,δ-unsaturated dienones while transmitting the stereochemical information to distant positions. This strategy allowed us to selectively forge multiple stereocenters far away from the catalyst's point of action.[8] The resulting vinylogous iminium ion/dienamine activation sequence contributed a direct entry into highly enantioenriched δ- and γ-functionalized chiral carbonyls while preserving an α,β-unsaturated system.

Our design plan is detailed in Scheme 2. The inspiration for this approach arose from our previous experiences with vinylogous reactivity.[9] We recently established that the cinchona-based primary amine of type **A**[6] can condense with the β-substituted cyclic dienones **1**, thus facilitating the formation of an extended iminium ion intermediate **I**, with an enhanced electrophilic character at the δ-carbon atom. The



Scheme 2. Design plan for vinylogous organocascade catalysis: 1,6-addition/aldol sequence driven by vinylogous iminium ion/dienamine activation. The reactive carbon atoms are highlighted in different colors depending on their inherent reactivity: blue stands for a nucleophilic position, red for an electrophilic center. The gray circle represents the chiral cinchona scaffold. Boc = *tert*-butoxycarbonyl.

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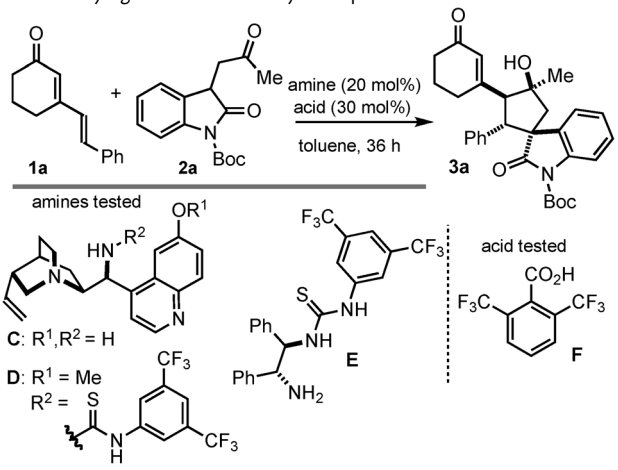
resulting vinylogous iminium ion activation accounted for a highly δ-site- and enantioselective 1,6-addition of alkyl thiols.[10] However, our attempts to expand this reactivity to include different types of nucleophiles were met with failure. We reasoned that the design of a cascade reaction initiated by vinylogous iminium ion activation might serve the dual objectives of 1) overriding the intrinsic low reactivity of the nucleophilic δ addition to the extended iminium ion **I**, by capitalizing upon the thermodynamic driving force provided by the subsequent reaction steps,[11] and 2) assembling complex molecules in a single step while setting remote stereocenters. We recognized that a well-suited substrate, characterized by a dichotomous reactivity profile, would be crucial to realizing this design plan. On the basis of the inspiring studies by Barbas III and colleagues,[12] the 3-substituted oxindole **2** seemed well tailored to first act as a carbon-centered nucleophile and then to develop, after the δ-site 1,6-addition, an electrophilic behavior. The pendant carbonyl moiety within the transiently generated nucleophilic dienamine intermediate **II** might drive an intramolecular aldol reaction, thus resulting in a fast cyclization. The product of the vinylogous cascade reaction is the complex spirocyclopentane oxindole **3**[13] bearing four contiguous stereocenters and a preserved α,β-unsaturated carbonyl system. Highly substituted carbocyclic spirooxindole units are featured in a large number of natural products[14a–b] as well as medicinally relevant compounds.[14c–d] A selection of biologically active spirocyclopentane oxindoles are shown in Figure S1 of the Supporting Information.

To test the feasibility of our plan, we investigated the potential of the quinidine-derived primary amine **A** (20 mol%) to activate the cyclic dienone **1a** toward a cascade reaction with **2a** (1.2 equiv). Optimization studies are reported in Tables S1-3 of the Supporting Information, with selected results summarized in Table 1.

Running the reaction in the presence of benzoic acid as the acid cocatalyst (30 mol%) in toluene at 60 °C afforded the complex product **3a** with good yield and promising control over the relative and absolute configuration (Table 1, entry 1).[11] Using the bifunctional catalyst **B** (entry 2) and a lower reaction temperature of 40 °C led to significantly improved stereoselectivity (entry 3). A larger excess of **2a** (1.5 equiv) further increased the reactivity of the catalytic system (entry 4). Importantly, the use of the pseudoenantiomeric quinine derivative **C** showed a similar catalytic efficiency, thus securing access to each product enantiomer individually (entry 5). In contrast, a different primary amine catalyst (**E**)[15] provided poor reactivity and stereocontrol (entry 6). We then conducted experiments to better elucidate the mechanism of the cascade reaction. The absence of the acid co-catalyst greatly reduced the rate of the reaction promoted by **B**, while affecting the stereoselectivity only slightly (entry 7). This result suggests a possible contribution from a noncovalent-based mode of catalysis, with the basic moiety of **B** activating **2a**.[12a,b] This path may synergistically add to the vinylogous iminium ion mechanism. The simultaneous activation of both substrates, **1a** and **2a**, may increase both the reactivity and the stereoselectivity. However, the total lack of catalytic activity of quinine (entry 8) and the bifunctional cinchona thiourea **D** (entry 9), a catalyst with an established ability for noncovalent activation, is consistent with the view that the vinylogous iminium ion activation of **1a** is mainly responsible for reactivity and stereoselectivity.[16]

Table 1: Vinylogous cascade catalysis: Optimization studies.[a]



Entry	Amine	Acid	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**A**	$PhCO_2H$	60	55	7.5:1	85
2	**B**	$PhCO_2H$	60	78	7:1	91
3	**B**	$PhCO_2H$	40	71	12:1	97
4[e]	**B**	$PhCO_2H$	40	85	12:1	97
5[e]	**C**	$PhCO_2H$	40	86	11:1	95[f]
6	**E**	$PhCO_2H$	40	54	5:1	35
7	**B**	none	40	23	12:1	95
8	quinine	none	40	<5	–	–
9	**D**	none	40	<5	–	–
10[e]	**B**	TFA	40	14	–	–
11[e]	**B**	**F**	40	89	11.5:1	97
12[e,g]	**B**	**F**	40	66	13:1	97
13[e,g,h]	**B**	**F**	40	84[i]	12.5:1	97

[a] Reactions performed on a 0.05 mmol scale over 36 h using 1.2 equiv of **2a** and $[\mathbf{1a}]_0 = 0.5$ M in toluene. Catalysts **A**–**C** were used with 1.5 equiv of acid (30 mol%), while **E** required a 1:1 combination with the acid (20 mol%). [b] Yield determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral column. [e] Reaction performed using a 1.5 equiv of **2a**. [f] The opposite antipode of product **3a** was obtained. [g] Used 10 mol% of **B** and 15 mol% of **F**. [h] $[\mathbf{1a}]_0 = 1$ M, 48 h reaction time. [i] Yield of the isolated **3a**. TFA = trifluoroacetic acid.

These initial results confirmed the unique ability of cinchona-derived primary amines to ensure highly predictable reaction outcomes, even when targeting stereocenters six and five bond lengths away from the catalyst chiral fragment (δ- and- γ-carbon atoms in **I** and **II**, respectively). We thus focused on optimization of the standard reaction parameters using the cinchona-based catalyst **B**. Evaluation of the reaction media confirmed that the catalytic process performed better in toluene. Other solvents such as chloroform, THF, and acetone significantly diminished the chemical yield (see Table S1 in the Supporting Information). We found that the nature of the acidic additive greatly affected catalyst efficiency (an extensive screening is detailed in Table S2). While a strong acid such as TFA almost completely inhibited the vinylogous cascade process (entry 10), the use of 2,6-

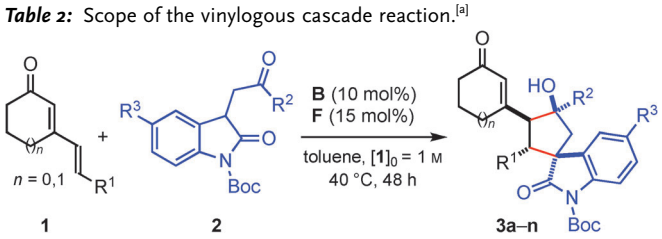
bis(trifluoromethyl)benzoic acid (**F**) positively influenced the reactivity while maintaining a high stereocontrol (entry 11). This acid allowed us to lower the catalyst loading to 10 mol% (entry 12). The use of a 1:1.5 combination of **B** (10 mol%) and **F**, and a more concentrated reaction system ($[\mathbf{1a}]_0 = 1$ M in toluene) provided the spirocyclopentane oxindole with synthetically useful results over a 48 hour reaction time (entry 13). These reaction conditions were selected to evaluate the scope of the vinylogous cascade.

As highlighted in entry 1 of Table 2, the method is amenable to synthetically useful purposes, since a high efficiency was maintained when running the reaction on a 1 mmol scale. As for the generality of the approach, there appears to be significant tolerance for structural and electronic variations of both substrates to access a variety of complex spirocompounds (**3**) with four contiguous stereocenters with high diastereomeric ratio and optical purity. A wide range of dienone δ substituents are compatible with the catalytic system. Different substitution patterns at the aromatic moiety of **1** were well tolerated, regardless of their electronic properties and position on the phenyl ring (entries 1–7). A heteroaryl framework can be included in the final product, as shown for the thienyl-substituted adduct **3h** (entry 8). Remarkably, the chemistry can be successfully extended to include an aliphatic δ substituent in **1**, thus maintaining a high enantioselectivity, but partially affecting the relative stereocontrol (**3i**; entry 9). It is also possible to modify the cyclic scaffold of the electrophilic component to a five-membered ring (**3j**; entry 10). As a limitation of the system, a linear 2,4-dienone remained completely unreacted under the optimized reaction conditions (Figure S2 in the Supporting Information). The cascade reaction also tolerates the use of a phenyl-substituted ketone-derived oxindole, as testified to by the preparation of **3k** with almost perfect stereocontrol (entry 11). As for the oxindole core of **2**,[17] different substituents are tolerated, since electronic modification of the aromatic ring can be accomplished without affecting the efficiency of the system (entries 12–14).

Crystals of **3d** (entry 4) were suitable for X-ray crystallographic analysis. This analysis established the stereochemical outcome of the vinylogous cascade as well as the absolute configuration of the four stereogenic centers.[18]

We have reported the first example of vinylogous organocascade catalysis. Key to developing the chemistry was the ability of a cinchona primary amine to propagate the aminocatalytic activation modes through the conjugated π system of β-substituted cyclic dienones while transmitting the stereochemical information to distant positions. The cascade, which is based on a δ addition/aldolization sequence, is initiated by a rare example of an organocatalytic 1,6-addition of a carbon-centered nucleophile.[19] The strategy allowed the one-step preparation of the highly enantioenriched spirocyclopentane oxindoles **3**. Application of vinylogous reactivities in organocascade catalysis is expected to open new avenues for reaction design in the field of asymmetric domino processes.

Table 2: Scope of the vinylogous cascade reaction.[a]



1 **2** **3a–n**

Entry	*n*	R^1	R^2	R^3	**3**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1[e]	1	Ph	Me	H	**3a**	83	12:1	97
2	1	4-ClC_6H_4	Me	H	**3b**	83	13.5:1	97
3	1	4-FC_6H_4	Me	H	**3c**	78	11:1	96
4	1	3-ClC_6H_4	Me	H	**3d**	80	7.2:1	97[f]
5[g]	1	2-BrC_6H_4	Me	H	**3e**	65	19:1	91
6	1	4-MeC_6H_4	Me	H	**3f**	84	13.5:1	96
7	1	4-MeOC_6H_4	Me	H	**3g**	75	16:1	93
8	1	3-thienyl	Me	H	**3h**	78	12.5:1	96
9[g]	1	Me	Me	H	**3i**	62	3.2:1	94
10	0	Ph	Me	H	**3j**	50	6.8:1	87
11	1	Ph	Ph	H	**3k**	66	>20:1	96
12	1	Ph	Me	Cl	**3l**	80	13.5:1	91
13	1	Ph	Me	OMe	**3m**	80	9.5:1	96
14	1	Ph	Me	Me	**3n**	86	9.5:1	97

[a] Reactions performed on a 0.1 mmol scale over 48 h using 10 mol% of **B**, 15 mol% of **F**, 1.5 equiv of **2**, and $[\mathbf{1}]_0 = 1$ M in toluene at 40 °C. [b] Yield of isolated compound, as an inseparable mixture of diastereoisomers, after purification on silica gel. The d.r. of the isolated product is specified within the Supporting Information. The yields reflect the degree of reaction conversion. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral column. [e] 1 mmol scale reaction. [f] The absolute configuration of **3d** was unambiguously inferred by X-ray analysis. See Ref. [18]. [g] Reactions conducted with 20 mol% of **B** and 30 mol% of **F** over 60 h.

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[17] The use of different nitrogen substituents on **2** resulted in much lower stereoselectivity. For example, replacing the Boc group in **2a** with a methyl group gave a spirocyclic adduct with 50% *ee* and 3.5:1 d.r.

[18] CCDC 918015 (**3d**) contains 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.

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