Synthetic Methods

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Targeting Structural and Stereochemical Complexity by Organocascade Catalysis: Construction of Spirocyclic Oxindoles Having Multiple Stereocenters**

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Dedicated to Professor Alfredo Ricci on the occasion of his 70th birthday

The structural complexity and well-defined three-dimensional architecture of natural molecules are generally correlated with specificity of action and potentially useful biological properties.[1] This complexity has inspired generations of synthetic chemists to design novel enantioselective strategies for assembling challenging target structures and reproducing the rich structural diversity inherent in natural molecules. This symbiotic correlation between natural compounds synthesis and the discovery of effective asymmetric—generally catalytic[2]—technologies lies at the heart of the synthetic chemistry innovation.[3] Despite the substantial advances made thus far, the construction of highly strained polycyclic structures (particularly those that contain spiro-stereocenters) and the generation of all-carbon quaternary stereocenters still remain daunting targets for synthesis.[4,5]

The spirocyclic oxindole core is featured in a number of natural products[6] as well as medicinally relevant compounds[7] (Figure 1), but its stereocontrolled synthesis, particularly installing the challenging spiro-quaternary stereocenter, poses a great synthetic problem. Only a few venerable asymmetric transformations, such as cycloaddition processes[8] or the intramolecular Heck reaction,[9] have proven suitable for achieving this challenging goal.

Herein we show that asymmetric organocascade catalysis,[10] which exploits the ability of chiral amines to efficiently combine two modes of catalyst activation of carbonyl compounds (iminium and enamine catalysis) into one mechanism,[11] allows the direct, one-step synthesis of complex spirooxindolic cyclohexane derivatives; these products have three or four stereogenic carbon atoms and are obtained with extraordinary levels of stereocontrol starting from simple precursors. Specifically, we developed complementary organocatalytic multicomponent domino reactions based on two distinct organocatalysts, **A** and **B**, which efficiently activate carbonyl compounds such as ketones and aldehydes, respectively, toward multiple asymmetric transformations in a well-defined cascade sequence. Both strategies provide straightforward access to natural product inspired compound collections,[12] which would be difficult to synthesize by other enantioselective methods.

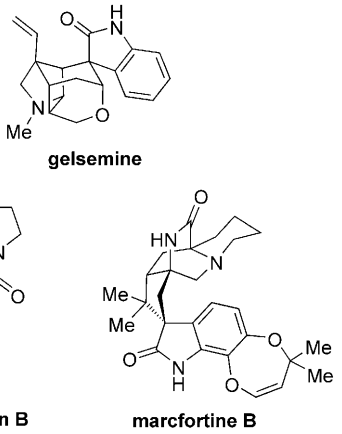
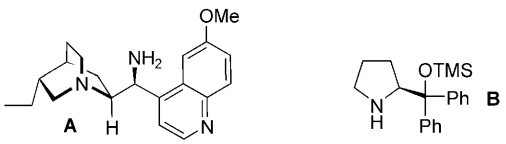


Figure 1. Naturally occurring and biologically active spirocyclic oxindoles.



The recent advances achieved in the field of chiral secondary amine catalysis[13] have set the conditions for the development of many asymmetric cascade reactions based on the efficient activation of aldehydes.[11] However, minor progress has been achieved in the corresponding transformations of ketones.[14] This lack in progress is a result of the

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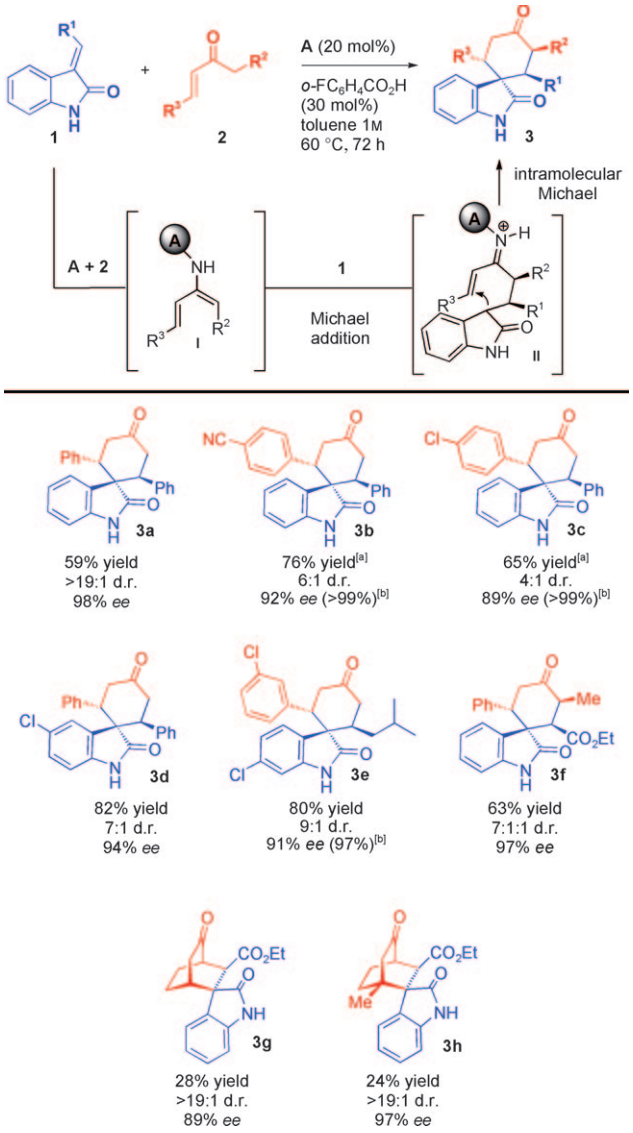
inherent difficulties in generating congested covalent intermediates from chiral secondary amines and ketones. Recently, we introduced 9-amino(9-deoxy)*epi*-hydroquinine **A**, a chiral primary amine derived in a single step from the cinchona alkaloid hydroquinine, as a general and selective catalyst for ketone activations.[15] Catalyst **A** proved efficient even for the catalysis of an intramolecular tandem reaction of α,β-unsaturated ketones through an iminium–enamine pathway.[16] We speculated that the versatility of **A** may be additionally exploited to design a novel organocascade to access valuable, spirocyclic scaffolds.[14b]

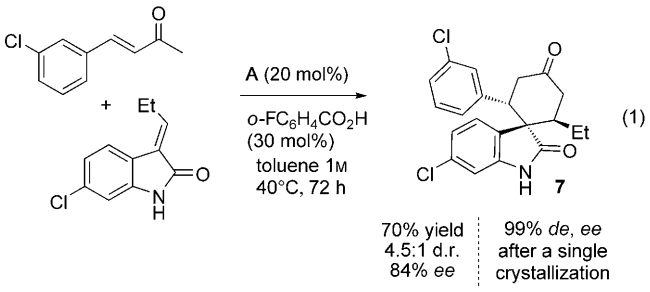
From the outset, a central tenet of our approach was the identification of a suitable compound, **1**, bearing the oxindole moiety. As shown in Scheme 1, we anticipated that compound **1** would first act as a Michael acceptor, intercepting the nucleophilic dienamine intermediate **I** generated by the condensation of catalyst **A** with the α,β-unsaturated ketone **2**.[14] The resulting carbon nucleophile **II** would then selectively engage itself in an intramolecular, iminium-catalyzed conjugate addition to afford the spiro-oxindole derivative **3**.[17] Our organocascade strategy with enones was evaluated by conducting the tandem reactions in toluene at 60 °C for 48–72 hours, under an aerobic atmosphere. Optimization experiments revealed that the best results in terms of both yield and stereoselectivity were achieved using 20 mol % of amine **A** in combination with an acidic co-catalyst, such as *ortho*-fluorobenzoic acid (30 mol %). Importantly, using the pseudo-enantiomeric amine catalyst, prepared from hydroquinidine, affords the opposite antipode of the spyrooxindole product, *ent*-**3**, with similar results (see Figure 1 in the Supporting Information). As highlighted in Scheme 1, there appears to be significant tolerance toward structural and electronic variations of both the precursors, **1** and **2**, to enable access to a variety of complex spiro-oxindoles (**3a**–**e**) having three and even four (compound **3f**) stereocenters with high diastereomeric ratio and excellent optical purity. Notably, the main diastereomer can be easily isolated by simple column chromatography.

Moreover, the presented organocascade is also effective with cyclohexenone derivatives, giving access to the highly congested bicyclo[2.2.2]octanes **3g** and **3h** adorned with a spiro-oxindole moiety. The spiro-bicycle **3h** is a completely unknown complex scaffold possessing two contiguous all-carbon quaternary stereocentres, a daunting synthetic challenge for which only a few direct strategies have been devised to date.[18]

To illustrate the value of our organocascade in the synthesis of biologically relevant compounds, we carried out the one-step preparation of the chiral spiro-oxindole **7** [Eq. (1)]. The spiro-oxindole **7** (recently patented by Hoffmann-La Roche)[19] serves as a specific and potent inhibitor of the MDM2–p53 interaction, an innovative target for the discovery of anticancer agents.[20] The biological properties of this compound have been evaluated on the racemic mixture, hence the availability of a fast and easy method for obtaining stereochemistry-based structure and activity relationships might enable the identification of a more selective and potent antitumor lead.



Scheme 1. Tandem double Michael additions (enamine–iminium activation sequence) toward spirocyclic oxindolic cyclohexanones. [a] Yield of isolated product calculated on the sum of the diastereomers, whereas other yields are given on the single major diastereomer. [b] Enantiomeric excess obtained after a single crystallization.

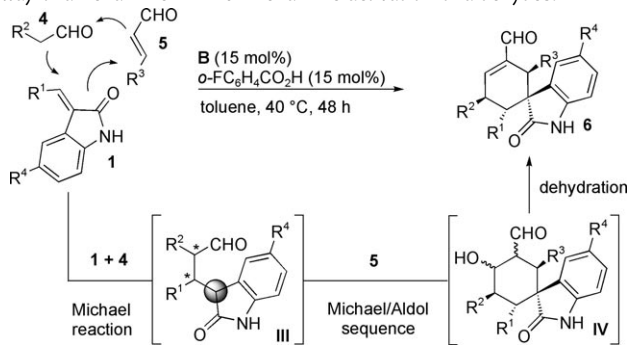


(1)

We then focused on the development of a complementary organocascade strategy based on the activation of aldehydic compounds, in which the spiro-oxindole cyclohexane architecture was constructed with the simultaneous creation of

three bonds and four stereogenic centers in a single chemical step (Table 1).

Table 1: Triple organocascade mediated by chiral secondary amine **B** by way of an enamine–iminium–enamine activation of aldehydes.[a]



6	R^1	R^2	R^3	R^4	Yield [%][b]	d.r.[c]	*de*, *ee* [%][d]
a	Ph	Me	Ph	H	74	12:1	>99
b	Ph	Me	*p*-MeOPh	H	70	16:1	>99
c	Ph	Me	*p*-NO_2Ph	H	35	>19:1	>99
d	Ph	Me	*p*-FPh	H	50	>19:1	>99
e	Ph	Me	*o*-MePh	H	50	>19:1	98
f	Ph	Me	Ph	Cl	47	12:1	>99
g	Ph	Me	Ph	Me	40	12:1	>99
h	propyl	Me	Ph	H	40	19:1	98
i	CO_2Et	Me	Ph	H	60	12:1	>99
j	C(=O)Ph	Me	Ph	H	46	>19:1	>99
k	CO_2Et	Me	Me	H	58	>19:1	98
l	CO_2Et	*n*-butyl	Ph	H	65	>19:1	>99
m	CO_2Et	benzyl	Ph	H	65	19:1	>99
n	CO_2Et	allyl	Ph	H	64	19:1	>99

[a] The triple organocascade proceeds by way of an enamine-catalyzed Michael addition of **4** to **1** and subsequent iminium-mediated Michael addition of the chiral nucleophilic intermediate **III** to **5**, and an enamine-catalyzed intramolecular aldol reaction to afford **IV**. The last dehydration step leads to the spirocyclic compounds **6**. [b] Yield of the isolated major diastereomer. [c] The diastereomeric ratio (d.r.) was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The diastereomeric and enantiomeric excess (*de*, *ee*) were determined by HPLC analysis on chiral stationary phases.

The rationale behind this approach arises from the studies by Enders and co-workers who demonstrated the catalytic ability of the chiral secondary amine **B** to realize an enamine–iminium–enamine sequential activation of aldehydes **4** and α,β-unsaturated aldehydes **5**.[11e] We later exploited the same catalytic machinery to stereoselectively install all-carbon quaternary stereocenters in complex molecules.[21] Here, by including compound **1** as the third component of the three-component cascade strategy, the triple organocascade provides a fast and easy access to challenging spirocyclohexene oxindoles. This three-component cascade reaction proceeds at 40 °C in the presence of the catalytic salt **B**·*o*-$FC_6H_4CO_2H$ (15 mol %) in toluene by way of a catalyzed Michael/Michael/aldol condensation sequence affording the complex products **6** with almost perfect stereocontrol.

The described complementary approaches demonstrate the potential of organocascade catalysis to face challenging synthetic problems using disparate tactics. Here the asymmetric one-step construction of multiple stereocenters in complex spirocyclic oxindoles was achieved with very high fidelity.[22] Such complexity- and diversity-generating processes, providing access to pre-validated nature-inspired compound collections with appropriate efficiency, scale, purity, and cost, and in a short period of time, may constitute a useful synthetic approach in other scientific domains such as medicinal chemistry and chemical biology research.[23]

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