Synthetic Methods

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Controlling the Molecular Topology of Vinylogous Iminium Ions by Logical Substrate Design: Highly Regio- and Stereoselective Aminocatalytic 1,6-Addition to Linear 2,4-Dienals**

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This work was prompted by our interest in devising a versatile catalytic strategy for stereoselectively accessing tetrahydrofuran spirooxindole derivatives.[1] In spite of their promising biological activities (Figure 1 a),[2] the direct and stereocontrolled synthesis of these molecular scaffolds is a difficult goal, and there are few catalytic asymmetric methodologies

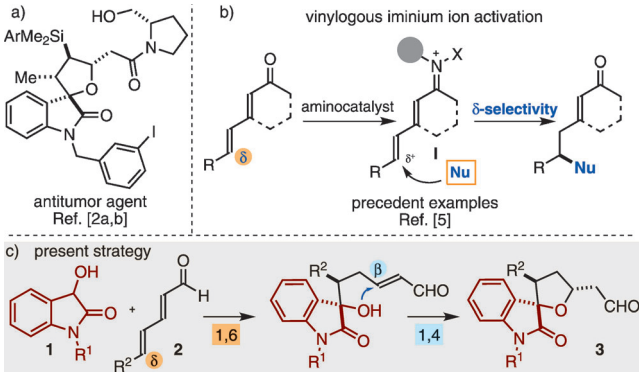

Figure 1. a) A biologically active tetrahydrofuranyl spirooxindole; Ar: anisyl. b) The vinylogous iminium ion strategy; X = H or alkyl. c) The proposed design plan for vinylogous organocascade catalysis: 1,6-addition/oxa-Michael sequence driven by vinylogous iminium ion/iminium ion activation.

available.[3] We recently discovered that dioxindole (3-hydroxy-2-oxindole; **1**) is characterized by a strong nucleophilic behavior.[4] This reactivity offers efficient pathways for the preparation of versatile optically enriched complex molecules such as spirooxindole γ-butyrolactones[4a,c] and 3-substituted 3-hydroxyoxindole derivatives.[4b] We wondered if the synthetic potential of the dioxindole reactivity could be further harnessed to directly access tetrahydrofuranyl spirooxindoles. Specifically, we sought to apply the recently identified vinylogous iminium ion strategy[5] (Figure 1 b) to promote the regio- and stereoselective 1,6-addition of **1** to polyunsaturated linear enals (**2**) upon activation by a chiral aminocatalyst. The design plan, based on the cascade reaction[6] detailed in Figure 1 c, would conclude with an intramolecular oxa-Michael cyclization event to forge the spiro-stereocenter within the product **3**. The main difficulty is that the chiral catalyst must forge a remote stereocenter[7] with high fidelity while inducing exclusive δ-site selectivity in the 1,6-addition manifold.[8] To date, the only effective catalytic strategy has capitalized upon the ability of a chiral amine to stereochemically bias intermediary cyclic vinylogous iminium ion intermediates (species **I** in Figure 1 b), which are generated upon condensation with cyclic α,β,γ,δ-unsaturated dienones.[5] However, controlling the molecular topology of an acyclic intermediate, so as to ensure highly predictable reaction outcomes, poses a more challenging problem.[9]

Herein, we describe how this synthetic issue has been successfully addressed. Spectroscopic conformational analyses were crucial to understanding how the structural features of the 2,4-dienal substrate **2** could be modulated to encode for a given molecular topology of the transient vinylogous iminium ion intermediate, which is formed upon condensation with the chiral aminocatalyst.[10] This understanding was critical to the rational design of an optimal linear dienal which allowed the development of a highly regio- and stereoselective 1,6-addition/oxa-Michael cascade with dioxindole (**1**), thus directly leading to tetrahydrofuran spirooxindole derivatives (**3**).

In our initial experiments, we examined the reactivity of *N*-methyl dioxindole (**1a**) toward the proposed vinylogous cascade reaction with (*E*,*E*)-hexa-2,4-dienal (**2a**; Figure 2 a). The commercially available diphenyl prolinol silylether catalyst **A** was selected because of its established ability to activate α,β-unsaturated aldehydes toward asymmetric transformations.[11] The reaction did indeed proceed with high reactivity, but followed an exclusive β-site-selective pathway.[4a] Only the classical Michael addition product **4** was detected. This result is consonant with the established catalytic profile of amine **A**, which is not generally able to induce a 1,6-addition manifold when activating unbiased dienals of type **2a**.[12]

We next considered the possibility of structurally modifying the substrate scaffold in **2** to direct the dioxindole attack

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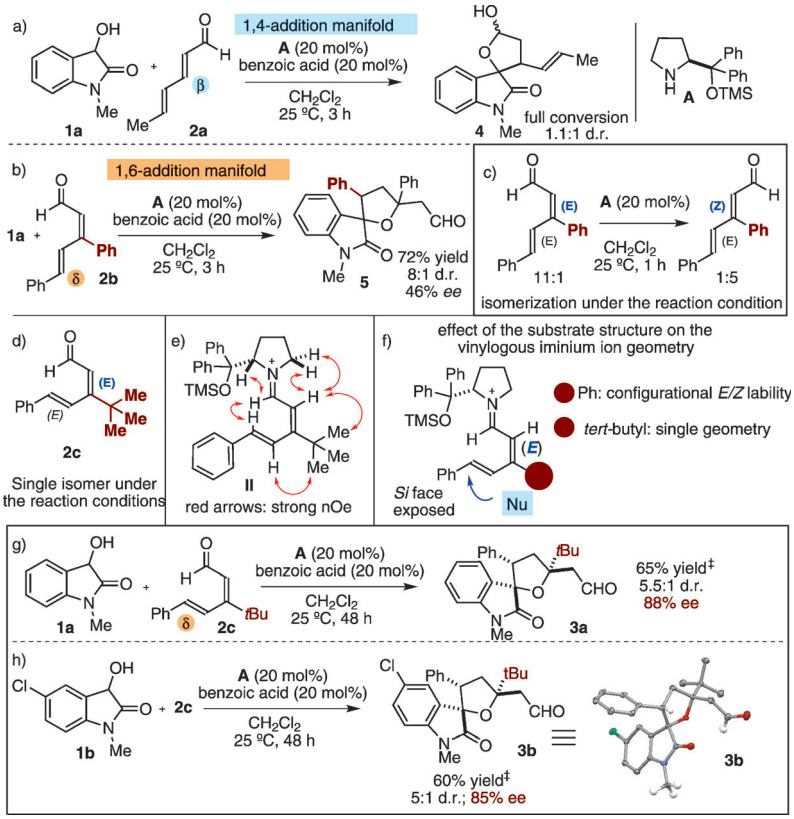


Figure 2. Progress towards an effective vinylogous cascade initiated by a δ-selective 1,6-addition under vinylogous iminium ion activation of linear 2,4-dienals (**2**). [+]Yield of the single, major diastereomer of **3** isolated after purification on silica gel. TMS = trimethylsilyl.

toward a 1,6-addition pathway. We reasoned that the inherent steric bias of a β-substituent on the dienal **2** could provide a suitable control element for securing δ-site selectivity by suppressing the competing 1,4-addition manifold. The results shown in Figure 2b validate the feasibility of this idea. Introducing a phenyl moiety at the β-position of **2b** completely switched the site selectivity toward the desired 1,6-addition driven by vinylogous iminium ion activation. The tetrahydrofuran spirooxindole **5** was quantitatively formed with a good control over the relative stereochemistry of the three stereogenic centers (8:1 d.r.). However, the enantioselectivity of the process was far below a synthetically useful level (46% *ee*). During these investigations, we noticed that **2b** was not configurationally stable, since a scrambling of the double-bond geometry of the α,β-olefin was observed in the presence of the catalyst **A** (from an *E*- to a *Z*-configured double bond, Figure 2c).[13] We ascribed the low enantioselectivity observed in the cascade reaction of **2b** to the configurational lability of the substrate. NMR spectroscopic studies of the covalent vinylogous iminium ion intermediate, formed in $CDCl_3$ by condensation of **A** and **2b** in the presence of molecular sieves, confirmed that the geometrical promiscuity of **2b** is translated into the catalytically active species: two geometries for the iminium ion were detected (details can be found in Figures S10–12 of the Supporting Information). The lack of structural preorganization makes it difficult for the chiral catalyst **A** to ensure configurational control and π-facial discrimination of the covalent intermediate, factors which are essential in enforcing high levels of enantioselectivity in iminium ion-based chemistry (Figure 2f).

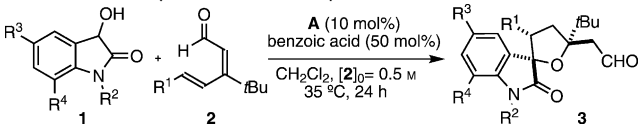
We hypothesized that the presence of a bulky substituent at the β-position of **2** could be useful for freezing out a specific geometry of the molecular iminium ion assembly by enhancing repulsive interactions with the catalyst framework. The dienal **2c**, bearing a *tert*-butyl moiety, was purposely synthesized (Figure 2d). We were pleased to confirm that the defined *E*,*E* double bond geometry was stable under the reaction conditions, since no isomerization was observed in the presence of **A**. NMR spectroscopic analyses were then used to gain information on the geometry of the covalent vinylogous iminium ion intermediate **II**, which is actively involved in the stereodefining step (Figure 2e). When mixing **A** with **2c** in $CDCl_3$ and in the presence of 4 Å molecular sieves, the corresponding intermediate **II** was formed. A single isomer was detected, and the conformational behavior was investigated by conventional NMR techniques, particularly vicinal coupling constant analysis, nuclear Overhauser enhancement (nOe) spectroscopy, and deuterium-labeling experiments (see Figures S5–S9 in the Supporting Information). Overall, the NMR studies indicated that the dominant ground-state conformer in solution has an *E*,*E*,*E* topology, with the same configuration for the three double bonds. Interestingly, the steric prominence of the *tert*-butyl group makes it a topologically dominant element, since it is able to enforce an uncommon *s*-cis conformation around the single C(β)–C(γ) bond.[14] Collectively, these features contribute to a highly preorganized, configurationally stable, transient intermediate (**II**), which may be crucial to reaction development. Indeed, the chiral fragment in **A** seems positioned close enough to the reactive δ-carbon atom to determine an effective shielding of the *Re* face of the extended iminium ion, thus leaving the opposite *Si* face available for the approach of the dioxindole **1a** (see the model in Figure 2f).

We then evaluated the impact of the *tert*-butyl group of **2c** on the stereochemical outcome of the vinylogous cascade reaction. As seen in Figure 2g, the spirocompound **3a** was obtained with perfect δ-site selectivity and an enantioselectivity as high as 88% *ee*. The use of the chloro-containing dioxindole **1b** resulted in similar reaction efficiency. The corresponding tetrahydrofuran spirooxindole **3b** was obtained with synthetically useful results (Figure 2h). The absolute and relative configuration for the major diastereomer of compound **3b** was unambiguously determined by anomalous dispersion X-ray crystallographic analysis: an *S* absolute configuration at the newly formed δ-stereocenter was inferred.[15] The sense of asymmetric induction is in agreement with the stereochemical model extrapolated from the conformational analysis discussed above (Figure 2f).

Having identified a viable strategy to control the regio- and stereoselectivity of the vinylogous cascade, we sought to increase the efficiency of the catalytic system. Starting from the conditions detailed in Figure 2g, we evaluated variations of the standard reaction parameters. The complete progress towards the optimized reaction conditions for the reaction of **1a** with **2c** is detailed in Tables S1–3 within the Supporting Information. Dichloromethane emerged as the most appropriate solvent for this transformation. The use of 50% of the benzoic acid cocatalyst with 35°C as the reaction temperature positively influenced the reactivity, thus allowing a decrease in the catalyst **A** loading to 10 mol%. These reaction conditions were selected to evaluate the scope of the vinylogous cascade.

As highlighted in Table 1, there appears to be significant tolerance for structural and electronic variations of both substrates to access a variety of complex spirotetrahydrofurans (**3**) with good diastereomeric ratio, a high optical purity, and exquisite site selectivity. It is of synthetic relevance that a simple chromatographic purification on silica gel afforded the isolation of the pure major diastereomer. A wide range of dioxindole derivatives are compatible with the catalytic system. The presence of a different substituent at the nitrogen atom or the use of unprotected dioxindole (R^2 = Bn or H, respectively; entries 2 and 3) preserved the stereoselectivity of the process, while substrates with different substituents at C5 and C7 (entries 4–8) performed well under the reaction conditions. As for the δ-position of the dienal substrate **2**, different substitution patterns at the aromatic moiety were well-tolerated regardless of their electronic properties and position on the phenyl ring (products **3i–m**). A heteroaryl framework can be included in the final product as shown for the thienyl-substituted adduct **3n** (entry 14).

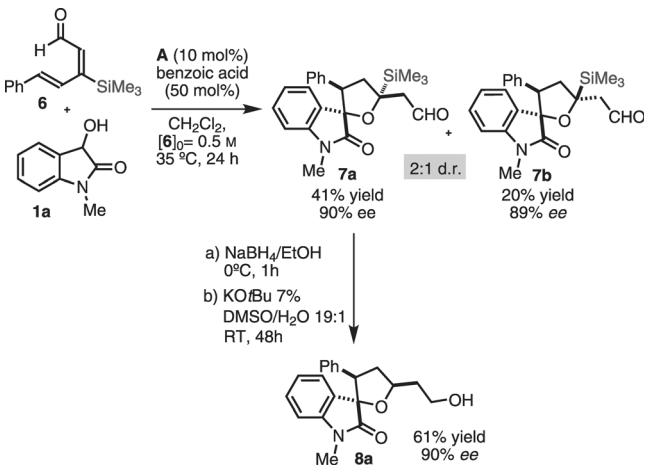
Table 1: Generality of the 1,6–1,4 sequential addition.[a]



Entry	R^1	R^2	R^3	R^4	**3**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	Me	H	H	**a**	72	6.1:1	91
2	Ph	Bn	H	H	**c**	75[e]	6.5:1	92
3	Ph	H	H	H	**d**	66	4.3:1	90
4[f]	Ph	Me	Me	H	**e**	56	5.3:1	90
5[g]	Ph	Me	Cl	H	**b**	66	6.3:1	90
6	Ph	Me	MeO	H	**f**	79	8.9:1	90
7[h]	Ph	Me	Me	Me	**g**	64	6.6:1	92
8	Ph	Me	H	Br	**h**	73	11:1	91
9	4-$MeOC_6H_4$	Me	H	H	**i**	74	6.7:1	90
10	4-BrC_6H_4	Me	H	H	**j**	84	9.4:1	93
11[g]	3-ClC_6H_4	Me	H	H	**k**	84	15:1	93
12	3-ClC_6H_4	H	H	H	**l**	71	5.4:1	94
13	2-MeC_6H_4	Me	H	H	**m**	82	8.7:1	93
14	3-thienyl	Me	H	H	**n**	76	5.6:1	92

[a] Reactions performed on a 0.1 mmol scale. Results represent the average of two runs per substrate. All the 2,4-dienals **2** used have a *E*/*E* configuration of the olefins. [b] Yield of the single, major diastereomer of **3** isolated after purification on silica gel. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Product **3c** was isolated as a 13.5:1 mixture of diastereomers. [f] Reaction time: 48 h. [g] The absolute and relative configuration for the major diastereomer of compounds **3b** and **3k** was unambiguously determined by anomalous dispersion X-ray crystallographic analysis, see Ref. [15]. [h] Reaction time: 72 h.

As a limitation of the system, an aliphatic R^1 substituent in **2** resulted in a complete loss of reactivity.[16] Replacing the *tert*-butyl moiety at the β-position of **2** with a less sterically prominent substituent profoundly influenced the selectivity of the process (see Table S4 in the Supporting Information). While an isopropyl group could still infer δ-site selectivity, albeit with a decreased stereocontrol (78% *ee*, 2.3:1.5:1 d.r.), a methyl group was not able to effectively partition the 1,6- and the 1,4-addition manifolds (products of type **3** and **4** in Figure 2 obtained in a 1:1 ratio).[16] These results highlight how strongly the steric profile of the β-substituent in **2** is connected with an effective control over the molecular topology of the vinylogous iminium ion intermediate. Consistent with this hypothesis, a trimethylsilyl group, characterized by a similar Charton steric parameter[17] of a *tert*-butyl moiety, directed the process exclusively toward a 1,6-addition manifold while preserving the high enantioselectivity (Scheme 1). This approach can be useful for directly accessing biologically relevant silicon-containing spirocompounds (see structure in Figure 1a).[2a,b] Remarkably, we could easily access the enantioenriched compound **8a** upon protiodesilylation of the isolated major diastereomer **7a** under basic conditions.[18] This highlights that the trimethylsilyl moiety can be used as a traceless directing group[19] to achieve δ-site selectivity, thus providing a formal 1,6-addition of geometrically unbiased, linear dienals.



Scheme 1. The trimethylsilyl group as a traceless stereocontrol element. The stereochemistry of **7a** was unambiguously determined by anomalous dispersion X-ray crystallographic analysis.[15] DMSO = dimethylsulfoxide.

In conclusion, we have developed a novel aminocatalytic vinylogous cascade reaction yielding valuable tetrahydrofuran spirooxindole derivatives. The chemistry is based on a rare example of asymmetric 1,6-addition to linear 2,4-dienals proceeding with high δ-site and stereoselectivity.

Central to this study was the rational design of the substrate, as inspired by conformational studies. A steering group at the β-dienal position ensured molecular preorganization of the catalytically active vinylogous iminium ion intermediate, which was essential to achieve highly predictable reaction outcomes. Expanding upon these findings, we are pursuing the possibility of using traceless silyl-based directing groups to design other vinylogous cascade reactions of linear 2,4-dienals.

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