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Direct Catalytic Asymmetric Doubly Vinylogous Michael Addition of α,β-Unsaturated γ-Butyrolactams to Dienones**

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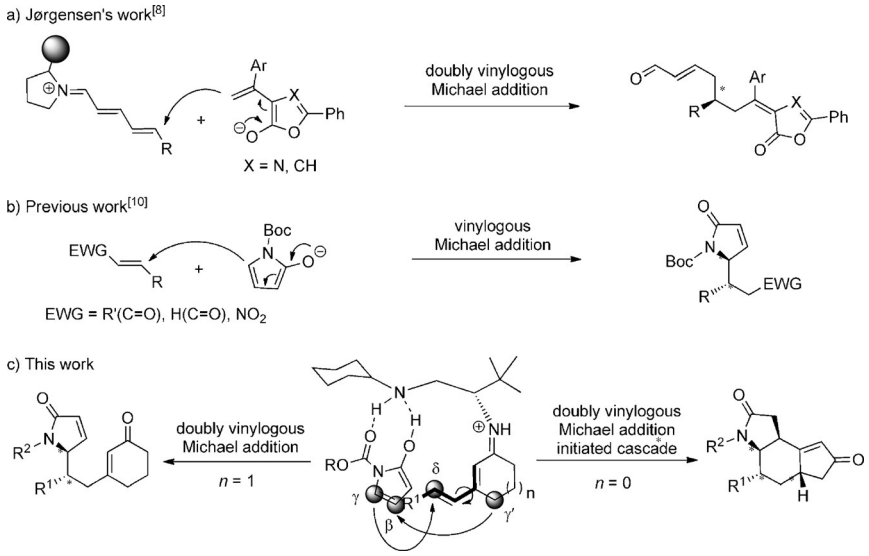
Abstract: *An asymmetric doubly vinylogous Michael addition (DVMA) of α,β-unsaturated γ-butyrolactams to sterically congested β-substituted cyclic dienones with high site-, diastereo-, and enantioselectivity has been achieved. An unprecedented DVMA/vinylogous Michael addition/isomerization cascade reaction affords chiral fused tricyclic γ-lactams with four newly formed stereocenters.*

Remote stereocontrol in catalytic asymmetric reactions is a major challenge in modern organic synthesis.[1,2] Recently, asymmetric organocatalysis has been successfully applied to the functionalization of unsaturated carbonyl compounds at their γ-, δ-, and ε-positions with high stereo- and site-selectivity.[1] The two basic activation strategies exploit LUMO-lowering and HOMO-raising effects, whereby iminium ions and either di- or trienamines are formed by condensation of the carbonyl substrates with the amine function of chiral organocatalysts.[1,3] Melchiorre and co-workers achieved the δ-functionalization of enones by using a cinchona-based primary amine, which forms an iminium ion with the polyunsaturated carbonyl substrate, thus delivering the LUMO-lowering effect through the conjugated π system.[4] Enamine catalysis[5] was also successfully applied to vinylogous systems. Di- and trienamine catalysis,[5b,c] usually employing chiral secondary amines to activate the γ and ε sites of unsaturated aldehydes, has led for instance to a series of Diels–Alder cycloadditions[5e] and other remote functionalization reactions.[6]



Scheme 1. a) First asymmetric organocatalytic doubly vinylogous Michael addition. b) Use of α,β-unsaturated γ-butyrolactams in vinylogous Michael additions. c) This work: unprecedented asymmetric organocatalytic DVMA and a related cascade between α,β-unsaturated γ-butyrolactams and dienones. Boc = *tert*-butoxycarbonyl.

In most studies a single vinylogous substrate, either the electrophilic or nucleophilic partner, was used.[1,3–7] In 2013 Jørgensen and co-workers reported the first organocatalytic doubly vinylogous Michael-type reaction, namely the 1,6-addition of alkylidene lactones to 2,4-dienals with the formation of a new stereocenter (Scheme 1 a).[8] It is significantly difficult to simultaneously activate the two vinylogous partners at their remote reactive sites whilst achieving high regio-, diastereo-, and enantiocontrol. Indeed, to the best of our knowledge there are no precedents for the catalytic, asymmetric doubly vinylogous Michael addition (DVMA) to 2,4-dienones, the much less reactive analogues of 2,4-dienals. The realization of such a reaction would prove the broad applicability of the organocatalytic vinylogous activation patterns, thus representing a significant advance in the field. Moreover, asymmetric doubly vinylogous reactions naturally leave two unsaturated C–C bonds in the product and provide

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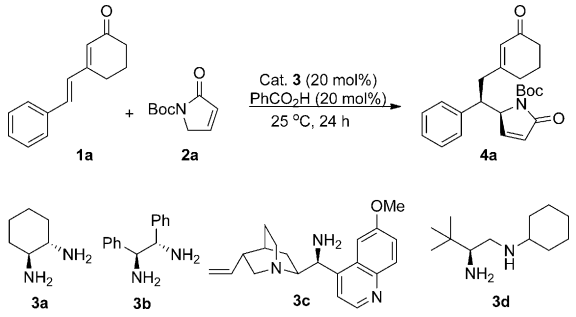
a potential opportunity for additional transformations for the construction of complex chiral molecules.

Herein we report the first doubly vinylogous Michael addition to 2,4-dienones by using a diamine derived from *tert*-leucine as an organocatalyst (Scheme 1c).[9] The challenging γ to δ 1,6-addition reaction of N-protected α,β-unsaturated γ-butyrolactams[10] to sterically congested β-substituted cyclic dienones proceeds with high regio- and stereoselectivity wherein strong hydrogen-bonding interactions between the N-protected, deprotonated butyrolactam and the catalyst are believed to be responsible for the observed control. In addition we report that by using 3-alkenyl cyclopent-2-enones as substrates, the initial DVMA is followed by a vinylogous Michael addition/isomerization cascade, thus affording tricyclic γ-lactams with four new stereocenters.

Our investigations began with a screen of a set of chiral diamines (**3a–d**) in the DVMA of the dienone **1a** and the N-protected α,β-unsaturated γ-butyrolactam **2a** as shown in Table 1. The L-*tert*-leucine derivative **3d** afforded the desired product **4a** with encouraging conversion and good stereoselectivity (entry 4). This catalyst performed well in most solvents, but provided the best *ee* values in chlorinated solvents (89–91% *ee*, entries 4–6), compared to the 85% *ee* obtained with ethers and the less than 80% *ee* obtained with

Table 1: Catalyst screening and optimization of the doubly vinylogous Michael addition (DVMA) between **1a** and **2a**.[a]



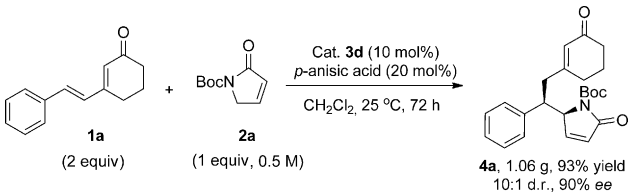
Entry	Cat.	Solvent	Conv. [%][b]	d.r.[b]	*ee* [%][c]
1	**3a**	$CDCl_3$	16	4:1	−7
2	**3b**	$CDCl_3$	trace	n.d.	n.d.
3	**3c**	$CDCl_3$	trace	n.d.	n.d.
4	**3d**	$CDCl_3$	55	7:1	89
5	**3d**	CH_2Cl_2	74	19:1	90
6	**3d**	1,2-DCE	88	12:1	91
7	**3d**	toluene	96	9:1	79
8	**3d**	MTBE	95	7:1	82
9	**3d**	EtOAc	86	6:1	86
10	**3d**	*i*-PrOH	65	2:1	79
11[d,e]	**3d**	1,2-DCE	86	16:1	91
12[d]	**3d**	CH_2Cl_2	91	19:1	89
13[d,e]	**3d**	CH_2Cl_2	76	19:1	91
14[e,f]	**3d**	CH_2Cl_2	88	>19:1	92

[a] Reactions performed using 1.0 equiv of **2a** (0.15 mmol, 0.5 M), 1.5 equiv of **1a**, 0.2 equiv of catalyst **3**, and 0.2 equiv of $PhCO_2H$ at 25 °C for 24 h, unless otherwise stated. [b] Conversion and d.r. values determined by ^1H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis using a chiral stationary phase. [d] With 0.2 equiv of *p*-anisic acid. [e] Reaction performed at 4 °C for 48 h. [f] With 0.4 equiv of *p*-anisic acid and 2.0 equiv of **1a**. 1,2-DCE = 1,2-dichloroethane, MTBE = methyl *tert*-butyl ether.

polar solvents (see Table S1 in the Supporting Information). An extensive screening of acidic additives (see Table S2 in the Supporting Information) allowed identification of *p*-anisic acid as ideal. By using 20 mol% of *p*-anisic acid in CH_2Cl_2 at 4 °C, the product was obtained with 19:1 d.r. and 91% *ee* (Table 1, entry 13; see Tables S3–S6 in the Supporting Information for full optimization studies). Finally, by increasing the amount of *p*-anisic acid to 40 mol% and adjusting the dienone/butyrolactam ratio to 2:1, the d.r. and *ee* values were slightly increased (entry 14). When the reaction was run under these optimized reaction conditions for 60 hours, the desired product was obtained with 95% yield upon isolation, in greater than 19:1 d.r. and 91% *ee* (see Table 2).

Next, the scope of the asymmetric DVMA with respect to dienone reaction partners was explored. By using the N-Boc-protected γ-butyrolactam **2a** as the reacting partner, an extensive range of 3-alkenyl cyclohex-2-enones were transformed into the desired products **4** with good to excellent stereoselectivity (Table 2). Aryl-substituted dienones with electron-donating substituents in the *para*- and *meta*-positions of the aromatic ring gave excellent enantioselectivities and diastereoselectivities (**4b**,**c**,**f**), whilst substrates with substituents in the *ortho*-position resulted in a slightly diminished *ee* value (**4d**,**e**). The enantioselectivity remained excellent when the aryl ring bore electron-withdrawing and halogen substituents (**4g–j**), although in the presence of the nitro group the d.r. value was reduced. Also, less reactive aliphatic substituted dienones (**4k**,**l**) and bulky substrates with gem-dimethyl groups on the cyclohexenone (**4m**,**n**) were well-tolerated. The absolute configuration of **4p** was determined by X-ray crystallographic analysis.[11]

The reaction was scaled up to obtain 1.06 grams of **4a** (Scheme 2). By lowering the catalyst loading to 10 mol%,



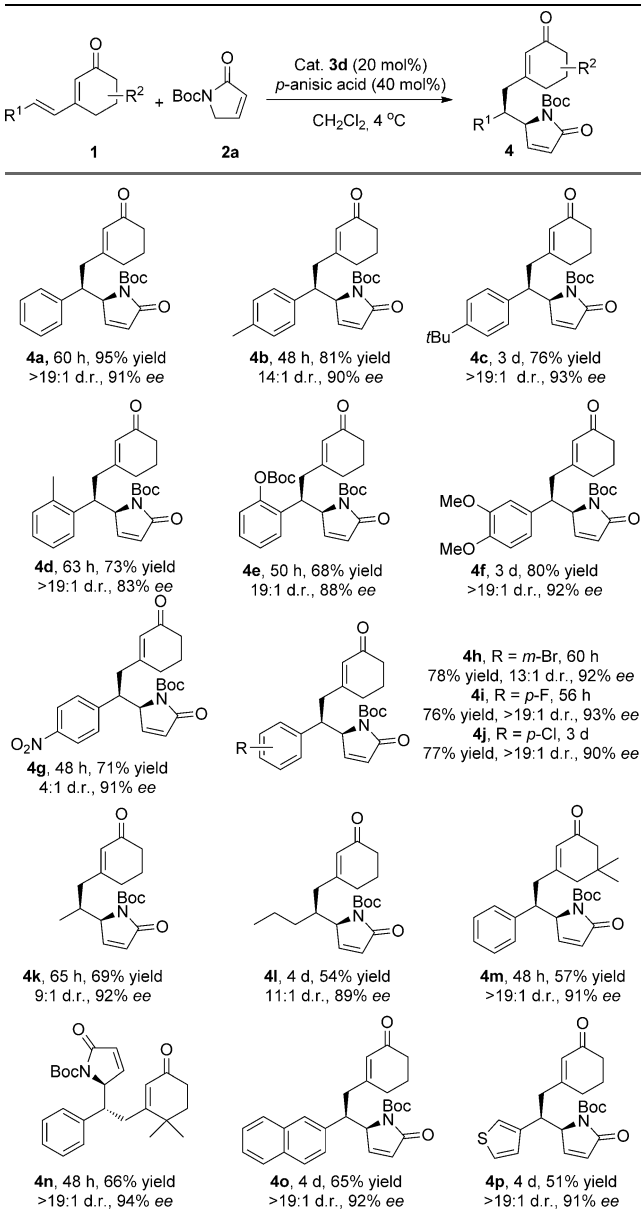
Scheme 2. Large-scale preparation of **4a**.

raising the temperature to 25 °C, and prolonging the reaction time to 72 hours the yield of the isolated product (93%) and enantioselectivity (90% *ee*) were comparable to those obtained on smaller scale.

N-Ts- and N-Cbz-protected α,β-unsaturated γ-butyrolactams were also compatible with the reaction conditions (Table 3, **4q–4v**). Compared to N-Boc-protected substrates, the enantioselectivity remained good (83–91% *ee*). However the yields (45–72%) and diastereoselectivities (7:1 to 10:1 d.r.) were slightly diminished.

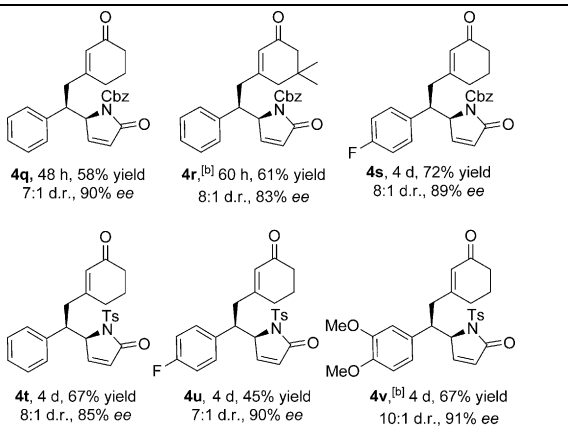
Interestingly, when switching from six- to five-membered cyclic dienones, a doubly vinylogous Michael addition/vinylogous Michael addition/isomerization cascade resulted (Table 4). The cascade reaction proceeded with excellent enantioselectivity (92–99% *ee*), but poor to moderate diaste-

Table 2: Scope of the DVMA with respect to the dienones.[a]



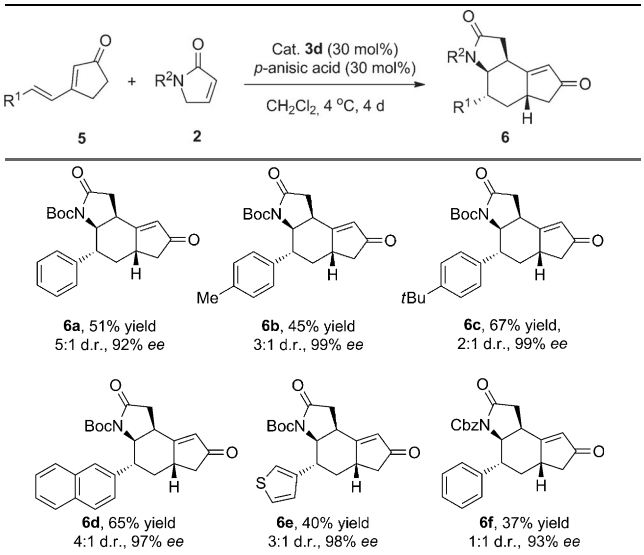
[a] Reactions performed using 1.0 equiv of **2** (0.2 mmol, 0.5 M), 2.0 equiv of **1**, 0.2 equiv of **3d**, and 0.4 equiv of *p*-anisic acid in CH_2Cl_2 at 4 °C. Yields of isolated products are given. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. The *ee* values were determined by HPLC analysis using a chiral stationary phase.

Table 3: Scope of the DVMA with respect to the N-protected α,β-unsaturated γ-butyrolactams.[a]



[a] Reactions performed using 1.0 equiv of **2** (0.2 mmol, 0.5 M), 2.0 equiv of **1**, 0.2 equiv of **3d**, and 0.2 equiv *p*-anisic acid in CH_2Cl_2 at 4 °C, unless otherwise stated. Yields of isolated products are given. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. The *ee* values were determined by HPLC analysis using a chiral stationary phase. [b] Reaction performed at RT. Cbz = carboxybenzyl, Ts = 4-toluenesulfonyl.

Table 4: Scope of the cascade reaction between 3-alkenyl cyclopent-2-enones and N-protected α,β-unsaturated γ-butyrolactams.[a]

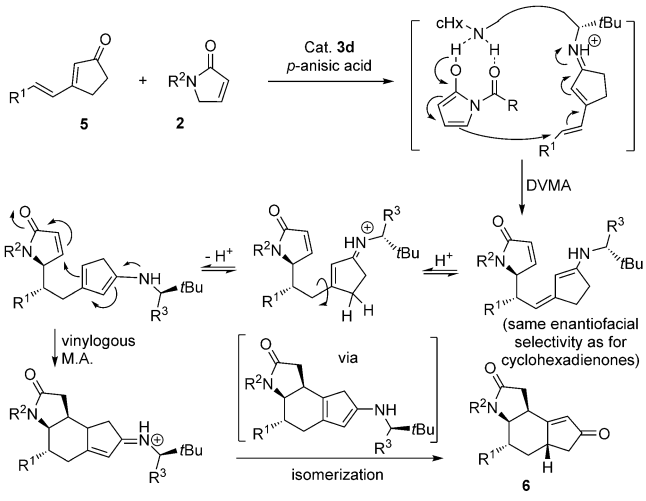


[a] Reactions performed using 1.0 equiv of **2** (0.2 mmol, 0.5 M), 2.0 equiv of **5**, 0.3 equiv of **3d**, and 0.3 equiv *p*-anisic acid in CH_2Cl_2 at 4 °C for 4 days. Yields of the isolated products are given. The d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. The *ee* values were determined by HPLC analysis using a chiral stationary phase.

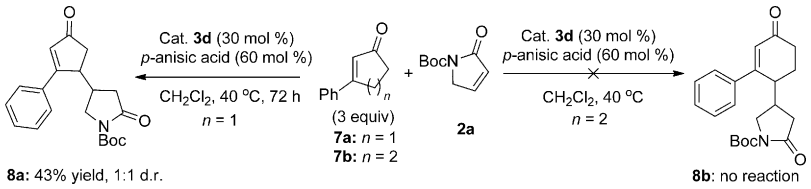
reoselectivity (d.r. from 1:1 to 5:1). In our proposed mechanism for the cascade reaction (Scheme 3), the initial DVMA is followed by a vinylogous Michael addition from the γ-position of the cyclopentenone to the β-position of the butyrolactam. Migration of the C–C double bond to the other side of the carbonyl group may be ascribed to an isomerization via the dienamine of cyclopentenone,[12] presumably driven by the thermodynamic stability of the product **6**.

This mechanism is supported by the outcomes of the intermolecular vinylogous additions of 3-phenylcyclopent-2-enone (**7a**) and 3-phenylcyclohex-2-enone (**7b**) to the α,β-unsaturated γ-butyrolactam **2a** (Scheme 4). A vinylogous Michael addition between **7a** and **2a**, which mimics the second step of the reaction cascade, took place with 30 mol% catalyst at 40 °C in 43% yield. On the contrary, no reaction was observed using **7b**.

The relative stereochemical configuration of the products of the cascade reaction (Table 4) was determined by single-crystal X-ray analysis of the compound **6d**. The absolute



Scheme 3. Postulated mechanism for the cascade reaction.



Scheme 4. Vinylogous Michael addition.

configuration was assigned by analogy with that determined for the six-membered ring analogues, under the assumption that 3-alkenyl cyclopent-2-enones undergo the DVMA with the same enantiofacial selectivity.

In conclusion, we have developed a novel asymmetric direct doubly vinylogous Michael addition between α,β-unsaturated γ-butyrolactams and sterically congested β-substituted cyclic dienones, affording products with significant levels of diastereo- and enantioselectivity. Remote transmission of the stereochemical information was successfully realized through the two conjugated π systems by taking advantage of a bifunctional diamine catalyst. In addition, this method has provided access to chiral tricyclic γ-lactams with up to four newly formed stereocenters, generated from 3-alkenyl cyclopentenones substrates by an unprecedented vinylogous Michael addition/vinylogous Michael addition/isomerization cascade.

Keywords: asymmetric catalysis · conjugation · cyclizations · nucleophilic addition · organocatalysis

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[11] See the Supporting Information. CCDC 1020721 (**4p**) and 1020722 (**6d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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