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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Beyond Classical Reactivity Patterns: Shifting from 1,4- to 1,6-Additions in Regio- and Enantioselective Organocatalyzed Vinylogous Reactions of Olefinic Lactones with Enals and 2,4-Dienals

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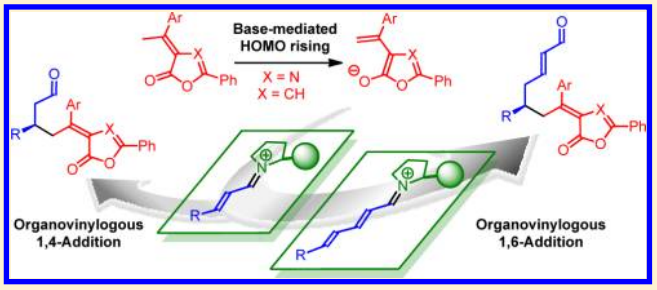
Supporting Information

ABSTRACT: Organocatalysis is shown to expand the classical reactivity pattern for conjugate addition reactions. It is demonstrated that the site selectivity can be extended from 1,4- to 1,6-additions for the enantioselective vinylogous additions of methyl-substituted vinylogous lactones to enals and 2,4-dienals. This novel reactivity is demonstrated for methyl-substituted olefinic azlactones and butyrolactones. Their synthetic potential is first highlighted by the development of the organocatalytic regioselective vinylogous 1,4-addition to enals which proceeds with a very high level of double-bond geometry control and excellent enantioselectivity. The concept is developed further for the unprecedented intermolecular enantioselective organocatalyzed vinylogous 1,6-addition to linear 2,4-dienals, by which the site selectivity of the process is extended from the β-position to the remote δ-position of the 2,4-dienal. The organocatalyst controls the newly generated stereocenter six bonds away from the stereocenter of the catalyst with a high level of enantiocontrol, and the products are obtained with full control of double-bonds configuration. The scope of these new reaction concepts is demonstrated for a series of aliphatic and aryl-substituted enals and 2,4-dienals undergoing enantioselective vinylogous reactions with methyl-substituted olefinic azlactones and butyrolactones. Furthermore, mechanistic considerations are presented which can account for the change from 1,4- to 1,6-selectivity. Finally, a number of different transformations of the optically active 1,4- and 1,6-addition products are demonstrated.

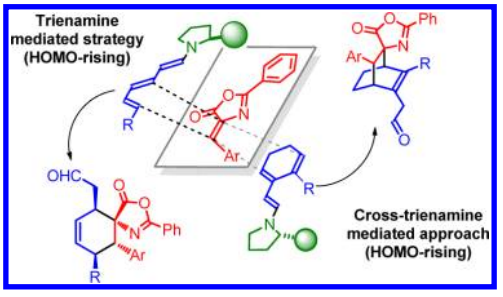


INTRODUCTION

The concept of vinylogy, originally introduced by Fuson,[1] has been applied to a wide range of reactions, such as the aldol, Mannich, and Michael reactions as well as Diels–Alder cycloadditions.[2] In the field of enantiocatalytic reactions significant advances have been made owing to the introduction of chiral metal complexes[3] and the availability of a large variety of silyl dienolates as stable vinylogous nucleophiles.[4] The attention has also recently been focused on the development of organocatalyzed vinylogous reactions.[5] In this area different catalytic strategies have been applied, such as chiral bases or acids,[6] and bifunctional, cinchona alkaloid-based, H-bond directing catalysts.[7]

Organocatalysts, such as primary or secondary amines, have been introduced as electrophilic enhancers or nucleophilic activators via iminum-ion or enamine formation, respectively.[8] The evolution of this concept has resulted in the development of dienamines,[8,9] trienamines,[8,10] and cross-trienamines[8,11] as vinylogous and hypervinylogous nucleophilic systems. Recently, it was demonstrated that *Z*-olefinic azlactones can react as dienophiles in a [4 + 2]-Diels–Alder-type cycloaddition either with trienamines or cross-trienamines via an interaction between the HOMO of these systems with the LUMO of the azlactones, in the presence of a silyl-protected diarylprolinol catalyst (Scheme 1).[10c,11]

Scheme 1. Previous HOMO-Rising Strategies Involving Olefinic Azlactones

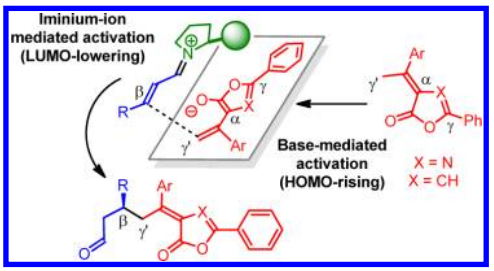


We envisioned the possibility to alter the classical reactivity of the olefinic system by introducing a methyl-substituent to the exocyclic double bond. It was anticipated that a reaction of such a system with a base might result in HOMO-rising, thereby promoting a reaction with the LUMO of an α,β-unsaturated aldehyde (enal), activated via iminium-ion formation. In this manner, it was assumed to reverse the previously reported reactivity patterns (Scheme 2). Furthermore, it was the goal that this concept could be further

Received: March 30, 2013

   dx.doi.org/10.1021/ja4029928 | J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Scheme 2. Novel Organocatalytic Vinylogous Michael-Type Reaction Between Enals and Olefinic Lactones

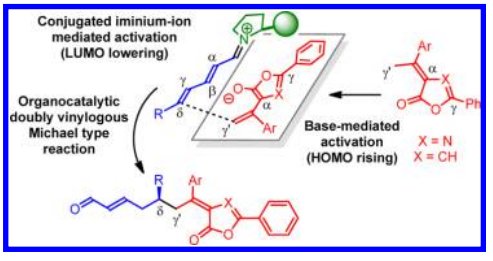


extended by replacing the nitrogen atom in the β-position of azlactone moiety with a carbon atom, thus obtaining a methyl-substituted olefinic butyrolactones as a new class of vinylogous pronucleophiles, potentially possessing the same vinylogous reactivity.

At this stage several challenges have to be addressed. First, the regioselectivity must be considered because of the polynucleophilic nature of the dienolates employed. It has been demostrated that α-substituted azlactones can react in the α-position with electrophilic reagents including enals[12] or in the γ-position with acyl phosphonates.[13] In a similar manner, γ-phenyl-substituted butenolides prefer to react at the γ-carbon atom with various Michael acceptors.[14] In the present case the vinylogous nucleophile can react at three different positions (α:γ:γ') thereby further increasing the complexity of the possible reaction pathways. Second, the configuration of the exocyclic double bond in the product has to be controlled. It should be noted that the geometry of the double bond in the starting compound is lost during the formation of the dienolate species. Moreover, with the azlactone nucleophiles, the starting material is an inseparable mixture of the *Z*- and *E*-isomers in various ratios.

Subsequently, an even more intriguing goal was envisioned, namely, the employment of 2,4-dienals rather than enals as the electrophilic counterpart which also adds further challenges. First, the competition between 1,4- (classical Michael) and 1,6-additions (vinylogous Michael) (Scheme 3). Typically, the 1,4-

Scheme 3. Unprecedented Organocatalytic Doubly Vinylogous Michael-Type Reaction Between 2,4-Dienals and Alkylidene Lactones



addition is favored over the 1,6-addition,[15] and only few examples of enantio- and regioselective 1,6-additions are known.[16] The 1,6-addition reaction of 2,4-dienals remains an important task and still is an unexplored field of research, particularly when stereoselective transformations are considered.[16e] Second, the enantiocontrol of the new δ-stereocenter which is six bonds away from the stereocenter of the catalyst is another important challenge that must be addressed. Finally, the geometry of the second conjugated double bond in the products must be controlled, as a mixture of *Z*- and *E*-isomers can potentially be formed.

Herein, we present the first organocatalyzed vinylogous Michael-type addition of methyl-substituted olefinic azlactones and butyrolactones to aromatic and aliphatic enals. These additions proceed with full γ'-selectivity and very high double-bond configuration control and enantioselectivity. Moreover, we introduce a series of unprecedented examples of conjugated iminium-ion mediated 1,6-additions between methyl-substituted olefinic azlactones and butyrolactones and linear 2,4-dienals. Importantly, no substituents in the 2,4-dienals are required to guide the regioselectivity of the process to the remote electrophilic position and the reaction proceeds with virtually complete δ-selectivity. This enantioselective carbon−carbon bond forming reaction can be assumed as the first organocatalyzed doubly vinylogous Michael-type addition and the first direct enantioselective 1,6-addition to 2,4-dienals.

RESULTS AND DISCUSSION

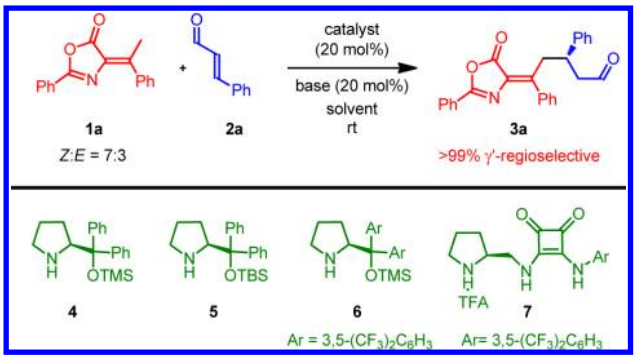
Michael-Type Addition of Vinylogous Olefinic Azlactone Nucleophiles to Enals. The 2-substituted oxazol-5-(4*H*)-ones, commonly known as azlactones, are useful reagents for the introduction of an amino acid moiety in molecules avoiding some of the drawbacks which can be caused by using classical peptide chemistry.[17] Furthermore, the azlactone is a flexible moiety in diversity oriented synthesis[18] due to the concomitant presence of two orthogonal reactive sites and for the easy accessibility from cheap and readily available compounds.[19] Therefore, the use of azlactones as building blocks in the field of organocatalysis constitutes an important tool in modern asymmetric synthesis.[17]

Studies were initiated by testing the feasibility of the olefinic azlactone **1a** with the methyl group attached to the olefinic moiety for nucleophilic attack to cinnamaldehyde **2a**. The addition was performed in the presence of 20 mol % of the TMS-protected diphenylprolinol catalyst **4** in CH_2Cl_2. Disappointingly, no reaction occurred, and complete recovery of the starting materials was observed (Table 1, entry 1). It was anticipated that the addition of a catalytic amount of base might facilitate the dienolate formation thereby enabling the novel reactivity pattern. Triethylamine was chosen as a base in the initial screening. Gratifyingly, the formation of the desired vinylogous adduct **3a** was achieved, albeit in a moderate yield (35%), 3:1 ratio between *Z*- and *E*-isomers and 70% ee for the major isomer (entry 2). In order to facilitate the catalyst turnover, 3 equiv of water were added. This turned out to be a useful solution, not only improving the yield of **3a** but also increasing the *Z*:*E* ratio to 4:1 and the enantioselectivity to 85% ee (entry 3). Employment of 1 equiv of the base instead of a catalytic amount resulted in better yield and *Z*:*E* selectivity although provided lower enantiocontrol (entry 4).

The screening of the catalysts revealed that only the diphenylprolinol catalysts **4** and **5** with different silyl protecting groups could be successfully employed in the transformation (entries 3, 5). In the presence of the TMS-protected diarylprolinol **6**, very poor yield of **3a** was obtained (entry 6), and the H-bond directing catalyst **7** proved to be unable to control the stereochemical outcome of the reaction (entry 7). By replacing the water with brine, the yield of **3a** was increased to 71% without alteration of the regio- and enantioselectivity (entry 8).[20] Changes in the solvents and bases did not improve the results in terms of yield and regioselectivity (entry 9−12). Interestingly, in the presence of stronger organic bases the

dx.doi.org/10.1021/ja4029928 | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. Michael-Type Addition of Vinylogous Olefinic Azlactone 1a to Cinnamaldehyde 2a Screening Results[a]



entry	cat	solvent	base	yield[b] (%)	Z:E[c]	ee[d] (%)
1	4	CH_2Cl_2	–	–	–	–
2	4	CH_2Cl_2	NEt_3	35	3:1	70
3[e]	4	CH_2Cl_2	NEt_3	55	4:1	85
4[e,f]	4	CH_2Cl_2	NEt_3	58	6:1	77
5[e]	5	CH_2Cl_2	NEt_3	58	5:1	95
6[e]	6	CH_2Cl_2	NEt_3	5	–	–
7[e]	7	CH_2Cl_2	NEt_3	73	3:1	−25
8[g]	**5**	**CH_2Cl_2**	**NEt_3**	**71**	**5:1**	**95**
9[g]	5	DCE	NEt_3	69	4:1	93
10[g]	5	THF	NEt_3	60	2:1	83
11[g]	5	CH_2Cl_2	DIPEA	50	3:1	97
12[g]	5	CH_2Cl_2	NaOAc	33	3:1	–

[a]Reactions were performed at 0.05 mmol scale in CH_2Cl_2 (0.2 M) using **1a** (1 equiv) and **3a** (3 equiv) (see Supporting Information). [b]Isolated yield. [c]Z:E ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Enantiomeric excess was determined by UPC.[2] [e]0.15 mmol of water was used. [f]1 equiv of NEt_3 was used. [g]0.15 mmol of brine was used.

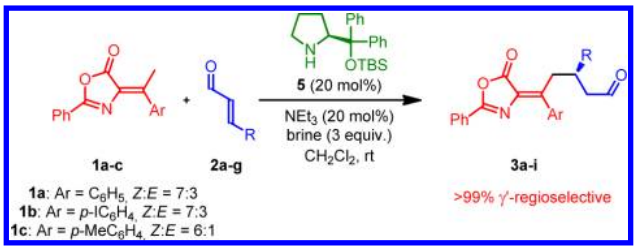
enantioselectivity was increased to 97% ee, albeit lower yield was observed (entry 11).[21]

With the optimized reaction conditions in hand, the generality of the vinylogous Michael addition with respect to both the olefinic substituents **1** and enals **2** was tested. In order to evaluate the disclosed methodology a higher scale was applied (0.2 mmol). Interestingly, better regio- and enatiocontrol were observed, and a slightly better yield was achieved when compared to the previous result (Table 1, entry 8 vs Table 2, entry 1).[22]

Both electron-donating and -withdrawing substituents in the *para*-position of the aromatic ring in the enals **2a**,**b** were well tolerated in the transformation providing the desired products **3b**,**c** with high regiocontrol and excellent enantioselectivity (Table 2, entries 2, 3). Moving the substituent to the *ortho*-position of the aromatic ring in the enal proved to be beneficial for the control of the geometry of the double bond in the product **3d**, and 97% ee was obtained (entry 4). Not only the presence of the phenyl rings afforded good results but also naphthyl and furyl substituents in the β-position of the enals were well tolerated (entries 5, 6). Even less reactive aliphatic aldehydes were successfully employed as demonstrated for the commercially available *trans*-2-octenal **2g**, which turned out fully compatible in the direct vinylogous Michael addition (entry 7).

With the positive results obtained for the enals **2** as the electrophilic system, the attention was turned to the reactivity of different nucleophiles.[23] Electron-donating and -withdrawing

Table 2. Scope of the Michael-Type Addition of Vinylogous Olefinic Azlactones 1 to Enals 2[a]



entry	1	R (2)	3	yield[b] (%)	Z:E[c]	ee[d] (%)
1	**1a**	C_6H_5 (**2a**)	**3a**	75	7:1	98
2	**1a**	*p*-$OMeC_6H_4$ (**2b**)	**3b**	62	6:1	96
3	**1a**	*p*-ClC_6H_4 (**2c**)	**3c**	58	5:1	93
4	**1a**	*o*-ClC_6H_4 (**2d**)	**3d**	66	11:1	97
5	**1a**	1-naphthyl (**2e**)	**3e**	63	5:1	93
6	**1a**	furyl (**2f**)	**3f**	60	5:1	90
7	**1a**	*n*-pentyl (**2g**)	**3g**	57	10:1	94
8	**1b**	**2a**	**3h**	72	5:1	92
9	**1c**	**2a**	**3i**	77	5:1	>99

[a]Reactions were performed at 0.2 mmol scale in CH_2Cl_2 (0.2 M) (see Supporting Information). [b]Isolated yield. [c]Z:E ratio as determined by ^{1}H NMR analysis of the crude reaction mixtures. [d]Enantiomeric excess was determined by UPC.[2]

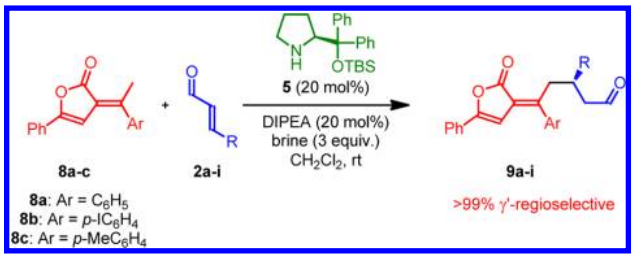
groups were introduced on the exocyclic aromatic ring in **1** to elucidate the role of the olefinic phenyl ring in this transformation. Methyl- and iodo-substituted aromatic systems gave analogous performance. In particular, in these cases very high levels of regio- and enantiocontrol were obtained (entries 8, 9).

Michael-Type Addition of Vinylogous Olefinic Butyrolactones to Enals. The butenolide skeleton plays a prominent role in synthetic organic chemisty because of its presence as a pharmacophore in a number of natural products and synthetic or semisynthetic drugs.[24] The utilization of the butenolide moiety has been associated with the construction of the related silyl dienolate nucleophiles and their applications in vinylogous Mukaiyama addition reactions.[2,25] Importantly, in the past few years enantioselective versions of this reaction were successfully developed.[25c−g] Furthermore, γ-substituted butenolide units have also received considerable interest in organocatalysis, and a number of new methodologies were efficiently introduced.[2,5a] Usually, the *in situ* formed dienolate reacts with different electrophiles in the γ-position. In order to alter and expand the common reactivity profile of this important class of nucleophiles, we decided to apply the previously optimized conditions to the butyrolactone counterparts.

To our delight, the initial screening showed that the methyl-substituted olefinic butyrolactone **8a** was a promising candidate as a vinylogous nucleophile reacting in the γ'-position instead of the other electron-rich carbon atoms. Furthermore, compound **8a** proved to be more selective and reactive than the corresponding azlactone **1a**. Therefore, in order to improve the enantioselectivity we decided to employ a stronger base, such as DIPEA, which exhibited lower reactivity in the azlactone screening, although provided better enantiocontrol (see Table 1, entry 10). The reaction between cinnamaldehyde **2a** and **8a** afforded excellent results (Table 3, entry 1). All the positions in the aromatic ring were tested (entries 2−5), and the reactions proceeded with the formation of only one isomer

dx.doi.org/10.1021/ja4029928 | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 3. Scope of the Michael-Type Addition of Vinylogous Olefinic Butyrolactones 8 to Enals 2[a]



entry	8	R (2)	9	yield[b] (%)	E:Z[c]	ee[d] (%)
1	8a	C_6H_5 (2a)	9a	86	>20:1	98
2	8a	*p*-$OMeC_6H_4$ (2b)	9b	75	>20:1	90
3	8a	*p*-ClC_6H_4 (2c)	9c	86	>20:1	95
4	8a	*o*-ClC_6H_4 (2d)	9d	89	>20:1	95
5	8a	1-naphthyl (2e)	9e	91	>20:1	93
6	8a	furyl (2f)	9f	73	10:1	91
7	8a	*n*-pentyl (2g)	9g	25	>20:1	97
8	8b	2a	9h	63	>20:1	92
9	8c	2a	9i	77	>20:1	97

[a]Reactions were performed at 0.2 mmol scale in CH_2Cl_2 (0.2 M) (see Supporting Information). [b]Isolated yield. [c]*E*:*Z* ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Enantiomeric excess was determined by UPC.[2]

9 with excellent enantioselectivity (90–98% ee). The furyl-substituted enal **2f** also gave excellent results (entry 6). *trans*-2-Octenal **2g** was chosen as an aliphatic enal, and analogous results in terms of stereoselectivities were obtained; albeit lower yield of the addition product **9g** was obtained (entry 7) (*vide infra*).

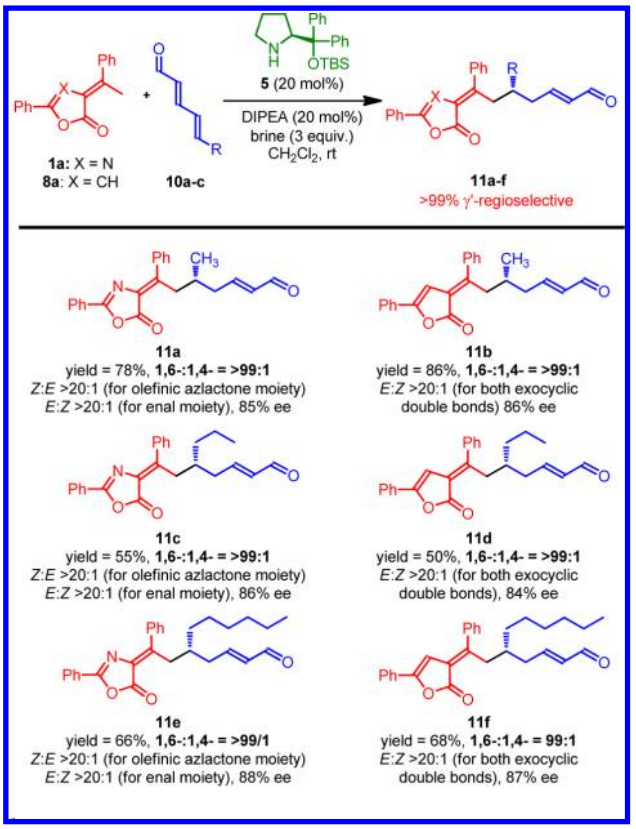
Further studies revealed that the presence of electron-donating and -withdrawing groups on the exocyclic aromatic ring in **8** were well tolerated in the reaction. With both substituents high level of regio- and enatiocontrol were achieved (Table 3, entries 8, 9).

The absolute configuration of the stereocenter being formed was assigned to be (*S*) based on the X-ray structure of **15a** (*vide infra*). The absolute configuration of the other products were assigned by the analogy.[26]

Doubly Vinylogous Michael-Type Addition of Olefinic Az- And Butyrolactones to 2,4-dienals. The vinylogy concept is a milestone in modern organic chemistry.[1,2] However, its applicability can be a challenge, such as for the nucleophilic addition to the remote position when two or more double bonds are in conjugation with an electron-withdrawing group.[15] Nowadays, the vinylogous Michael reaction, or 1,6-addition to 2,4-dienals, still remains a challenging task in organocatalysis, and to the best of our knowledge, no examples of intermolecular enantioselective approaches have been reported.

In order to extend the generality and the potential of the disclosed methodology, we decided to apply the general conditions developed to linear 2,4-dienals. We initiated our investigation by applying the optimized conditions for the 1,4-addition to the reaction between the methyl-substitued olefinic azlactone **1a** and hexadienal **10a**. Remarkably, the 1,6-addition occurred exclusively and proceeded with a full δ-selectivity. Importantly, the nucleophile reacted also with complete regiocontrol from the γ'-position (Table 4). To our delight, high level of enantiocontrol was obtained, despite the long (six bonds) distance between the stereocenter of the catalyst and

Table 4. Scope of the Doubly Vinylogous Michael-Type Addition of Olefinic Lactones to 2,4-Dienals



[a]Reactions were performed at 0.1 mmol scale in CH_2Cl_2 (0.2 M) (see Supporting Information). [b]Isolated yield. [c]*Z*:*E* and *E*:*Z* ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Enantiomeric excess was determined by UPC.[2]

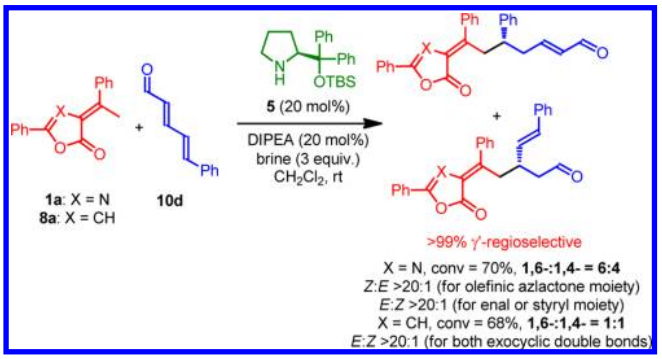
the newly generated δ-stereocenter in the vinylogous iminium-ion activated 2,4-dienal species. The reaction proceeded slower, but similar yields comparable to the 1,4-addition were obtained. Both methyl-substituted olefinic azlactones and butyrolactones were found to be useful substrates for the transformation, and different δ-substituted 2,4-dienals were evaluated to demonstrate the generality of the reaction. Methyl, propyl, and hexyl groups were found to be suitable as remote substituents. In all cases, high level of enantio- and regiocontrol were obtained (Table 4). The geometry of both exocyclic double bonds in the products **11** was fully controlled in all of the cases.

Interestingly, the 1,6-selectivity turned out to be dependent on the nature of the substituent in the 6-position of the 2,4-dienal. When a phenyl group was introduced in this position ((2*E*,4*E*)-5-phenylpenta-2,4-dienal **10d**), the reactions with the methyl-substituted olefinic azlactone **1a** and butyrolactone **8a** proceeded with low site-selectivity. In those cases a mixture of 1,4- and 1,6-addition products were obtained (Scheme 4) (for further discussion see Mechanistic Considerations below).

Mechanistic Considerations. The screening studies revealed that the presence of a base was crucial for the reaction (see Table 1 and Supporting Information). It is assumed that the base acts as a dual activator: First, it is involved in a classical acid–base reaction with the methyl-substituted olefinic azlactone **1** or butyrolactone **8**, which results in the *in situ* formation of the vinylogous dienolate species **12**. Together with the formation of **12**, the conjugated acid is formed, which is proposed to promote the condensation between catalyst **5**

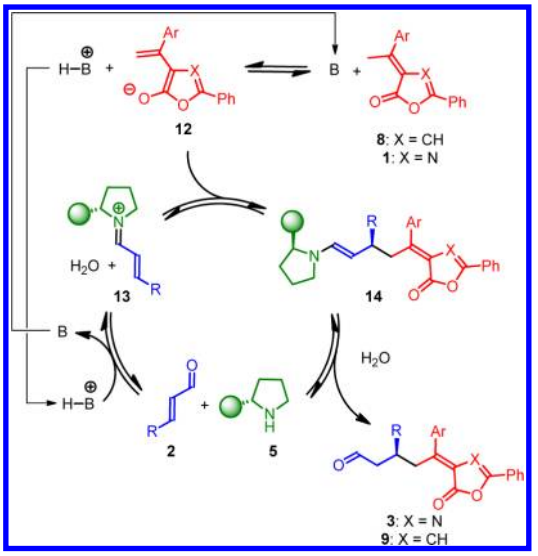
dx.doi.org/10.1021/ja4029928 | J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Scheme 4. 1,4- vs 1,6-Selectivity in the Reaction of (2*E*,4*E*)-5-Phenylpenta-2,4-dienal 10d with the Methyl-Substituted Olefinic Lactones



and enal **2** to give the iminium-ion intermediate **13** (Scheme 5). Based on these considerations, it is assumed that the

Scheme 5. Proposed Organocatalytic Cycle for the Vinylogous 1,4-Addition of Olefinic Azlactones or Butyrolactones to Enals



combination of the catalyst and base can efficiently cooperate, when the simultaneous *in situ* formation of the nucleophilic counterpart is necessary. With the formation of **13**, the products **3** or **9** are accessed via a classical iminium-ion-mediated catalytic cycle. This hypothesis was further proved by the fact that the reaction yield was improved by employing 1 equiv of the base (Table 1, entry 4).

The geometry of the double bond in the methyl-substituted olefinic azlactone **1** is lost during the formation of the vinylogous dienolate species **12**. Starting from a mixture of the *Z*- and *E*-isomers of **1**, a *Z*:*E*-ratio of up to 11:1 was obtained in product **3**. The configuration of the olefinic lactone moiety, both in the 1,4- and 1,6-addition products **3**, **9** and **11**, was unambiguously assigned by 2D-NOESY NMR experiments.

The configuration for the enal alkene moiety in the 1,6-addition product **11b** was determined to be *E* based on the coupling constants present in the ^{1}H NMR spectrum. Furthermore, the NOESY interactions confirmed this configuration.

Mechanistic aspects of the developed methodologies related to reactivity and regioselectivity of the processes are worth a special emphasis. Notably, calculations of the LUMO coefficients of the vinylogous iminium-ion intermediate can not be used to unambiguously rationalize the observed site selectivity. Therefore, it is postulated that an interaction between the negatively charged oxygen atom in the vinylogous dienolate species and the positively charged nitrogen atom of the iminium-ion intermediate is important for the outcome of the reaction. This interaction is proposed to be responsible for the proper alignment of the β-carbon atom of the iminium-ion intermediate with regard to the γ'-position of the dienolate intermediate and accounts for very high site-selectivity observed (Scheme 6, TS A). Furthermore, the π-stacking interaction between the β-aryl group of enal and β'-aryl moiety of dienolate is proposed to be an important factor, stabilizing the transition state of the 1,4-addition. However, in the case of alkyl substituted enals, the same alignment of the substrate results in a less-favorable interaction between the alkyl chain of the enal and the γ'-aryl moiety of the lactone counterpart. The reaction can proceed as proposed in Scheme 6, TS B, which accounts for the lower reactivity, especially pronounced in the case of the reaction of aliphatic enals and the butyrolactone-based substrate **8a** (Table 3, entry 7). The system can also, in order to avoid such adverse steric interaction, position the dienolate intermediate further away from the iminium-ion intermediate placing the reactive centers apart (Scheme 6, C). This alignment of reaction partners can also be accounted for the diminished reactivity of the aliphatic enal (Table 3, entry 7).

Interestingly, such a separating effect is beneficial for the developed 1,6-addition. In this case, it is proposed that the reaction proceeds via transition state D in Scheme 6 (with the alignment of reactants related to C rather than A/B) in order to avoid unfavorable steric interactions. In such a manner, the γ'-position of the dienolate species is situated in the spatial proximity to the δ-carbon atom of the vinylogous iminium-ion intermediate resulting in a regioselective 1,6-addition. In this context it is worth noticing that for the δ-phenyl substituted 2,4-dienal the π-stacking interaction can again be present, which places both reaction partners closer and forces the reaction to proceed through transition state E as outlined in Scheme 6. This merging interaction is proposed to be responsible for the low site-selectivity observed in that case as both β- and δ-carbon atoms of the vinylogous iminium-ion are positioned in a similar distance with regard to the γ'-position of the dienolate intermediate.

It is proposed that the stereochemical outcome of the vinylogous additions using both enals and 2,4-dienals is controlled by the shielding effect of the TBS-protected prolinol catalyst **5**. Therefore, the vinylogous methyl-substituted olefinic azlactone or butyrolactone nucleophiles attack from the side opposite to the steric bulk of the catalyst.

A final observation concerning the 1,6-addition of methyl-substituted olefinic lactones to 2,4-dienals was made. Interestingly, when the same conditions for the vinylogous 1,6-addition were applied to a nonvinylogous azlactone nucleophile, no reaction was observed, and complete recovery of the starting materials was achieved (Scheme 7). This behavior can be explained by different interactions between the nucleophile and the 2,4-dienal. In the vinylogous 1,6-addition a superimposition of the HOMO in the methyl-substituted olefinic azlactone or butyrolactone and the LUMO in the iminium-ion is achieved (see Scheme 3), whereas with a

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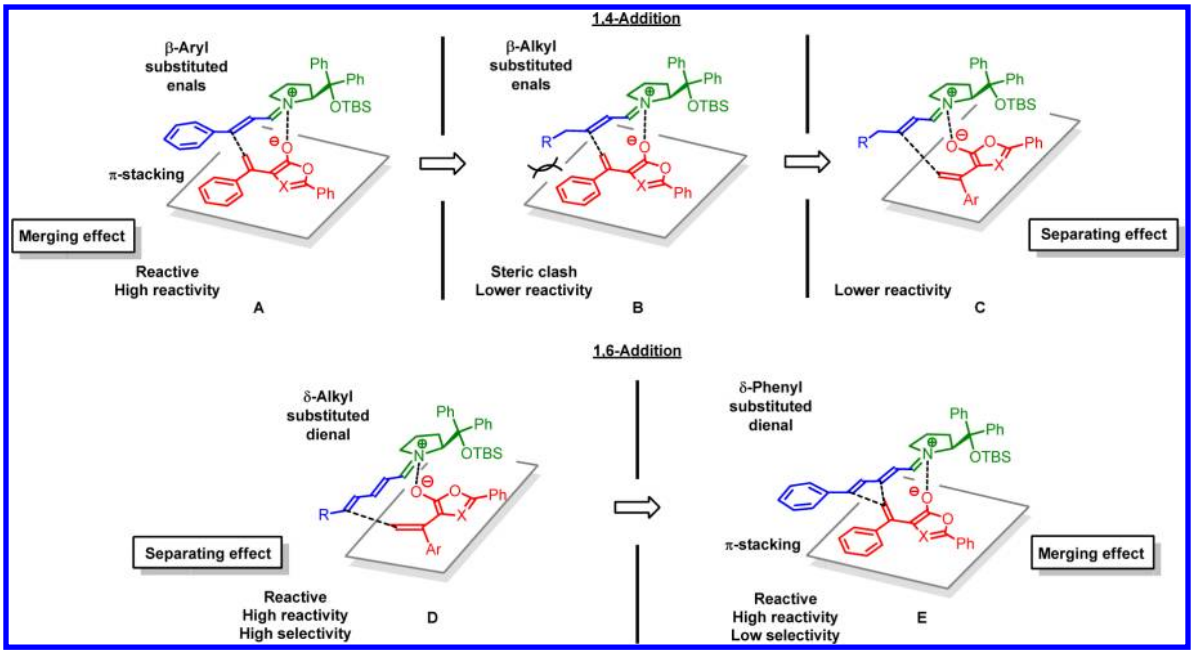
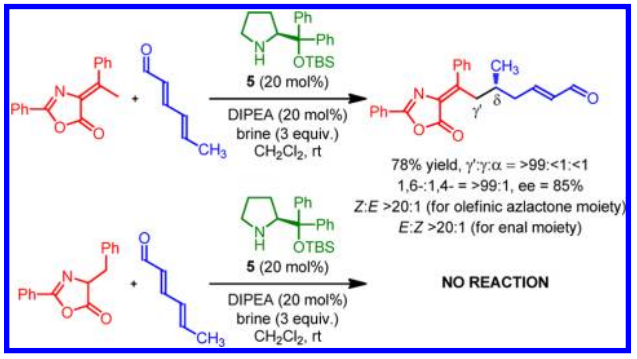
Scheme 6. Rationalizations for the Observed Reactivity and Site-Selectivity Patterns



Scheme 7. Comparison Between the Vinylogous 1,6-Addition of Olefinic Azlactone and the Nonvinylogous 1,6-Addition of Alkyl Azlactone

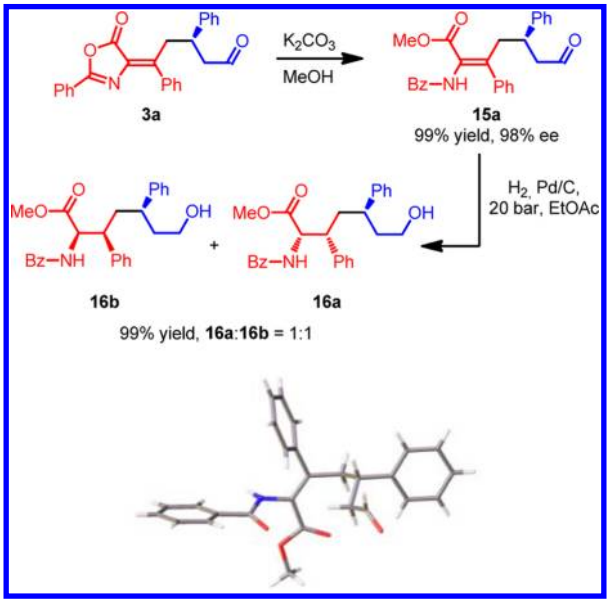


nonvinylogous nucleophile this favorable interaction is not possible.

Product Manipulations. In order to prove the synthetic potential of the disclosed methodology and versatility of the optically active products obtained, we envisioned different manipulations for both the 1,4- and 1,6-addition products.

Starting from the 1,4-addition product **3a**, the opening of the azlactone moiety was attempted, thus affording access to the protected amino acids. The ring-opening reaction was performed by treating **3a** with MeOH under basic conditions. The reaction furnished the desired product **15a** in quantitative yield, while the enantiomeric excess was maintained. Subsequently, **15a** was subjected to a reduction catalyzed by Pd/C under H_2 atmosphere (20 bar) to afford two protected amino acids **16a** and **16b** in excellent yield.[27] Interestingly, after the reduction of the tetrasubstituted double bond, the aldehyde moiety was also reduced to the corresponding alcohol. The possibility to form three different non-natural amino acids of which the first (**15a**) contained a conjugated double bond, and the other two (**16a**,**b**) possessed three stereocenters, in a simple two-step sequence, starting from compound **3a**, highlights the synthetic relevance of the olefinic azlactone 1,4-addition products (Scheme 8). Furthermore, only in the presented organocatalyzed vinylogous addition to enals is it possible to

Scheme 8. Transformations of the 1,4-Addition Product 3a to Olefinic α-Amino Acid 15a and its X-ray structure (bottom) and α-Amino Acids 16a,b



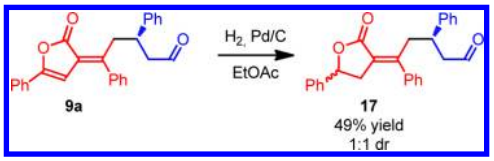
reach the formation of two new stereocenters starting from the amino acid **15a** originating from the exocyclic double bond in the corresponding azlactone.

The butyrolactone addition product **9a** was subjected to reduction of the endocyclic double bond under H_2 atmosphere in the presence of a catalytic amount of Pd/C to afford the desired compound **17** with concomitant introduction of one new stereocenter (Scheme 9).[28]

Finally, a transformation of the 1,6-addition products was attempted. It was imagined to highlight the importance of these compounds by utilizing the existing enal moiety. Therefore, the

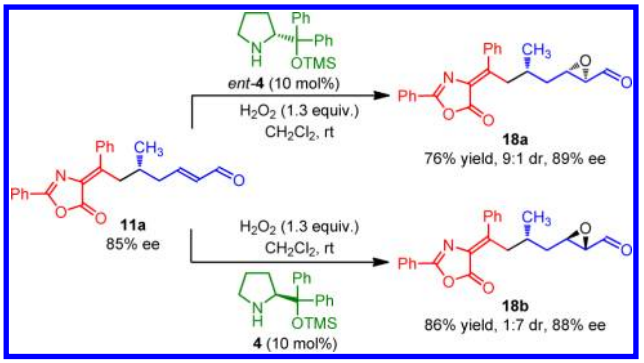
dx.doi.org/10.1021/ja4029928 | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Scheme 9. Transformations of the 1,4-Addition Product 9a into Olefinic Lactone 17



adduct **11a** was subjected to an organocatalyzed epoxidation. Initially, with the (*R*)-configured TMS-protected diphenylprolinol catalyst *ent*-**4** was employed. The epoxide **18a** was obtained in good yield and diastereoselectivity. Interestingly, a slightly improved enantioselectivity compared to the starting material **11a** was achieved (Scheme 10).

Scheme 10. Transformations of the 1,6-Addition Product 11a to Epoxides 18a,b



The use of the (*S*)-configured diphenylprolinol catalyst **4** gave comparable results. As expected a different diastereoisomer was obtained with excellent yield, enantioselectivity, and good diastereoselectivity (Scheme 8). As a result, it was found that the diastereo- and enantioselectivity of the process is virtually controlled by the shielding effect exerted by the organocatalyst. Thus, the exisiting δ-stereocenter does not influence the stereochemical outcome of the reaction.

The absolute and relative configuration of the epoxides **18a,b** was assigned by analogy to the previous results[29] and confirmed by 2D-NOESY NMR experiments (See Supporting Information for details).

CONCLUSION

In summary, we have demonstrated the possibility to alter the reactivity patterns of selected electrophiles, reversing the LUMO-lowering activation into the HOMO-rising activation by the application of organocatalysis. Both methyl-substituted olefinic azlactones and butyrolactones showed complete regiocontrol for the remote nucleophilic position. Very high levels of site-selectivity, enantioselectivity, and good to excellent control of double-bond configurations in the developed vinylogous Michael additions to enals and in the doubly vinylogous Michael additions to 2,4-dienals were achieved. Moreover, full site-selectivity was obtained in the conjugate addition to the distal δ-position with 2,4-dienals. The nonvinylogous nucleophile did not show the same reactivity in this transformation. This reveals the need of the peculiar vinylogous characteristics in the nucleophile counterpart to reach a perfect HOMO−LUMO interaction with the 2,4-dienal electrophiles.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data and NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was made possible by grants from Aarhus University, Carlsberg Foundation, and FNU. Thanks are also expressed to The Dell'Amico and Calendi Foundation for supporting the stay of L.D.A. T.N. thanks South African National Research Foundation and Oppenheimer Memorial Trust for financial support. Thanks are also expressed to Dr. Jacob Overgaard for X-ray analysis.

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(27) No attempts to optimize the diastereoselectivity of this reaction were made as the products could easily be separated by column chromatography.

(28) No attempts to optimize the diastereoselectivity of this reaction were made. The absolute configuration of the new stereocenter formed has not been assigned.

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