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Catalytic enantioselective construction of quaternary stereocenters by direct vinylogous Michael addition of deconjugated butenolides to nitroolefins†

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A direct vinylogous Michael reaction of γ-substituted deconjugated butenolides with nitroolefins has been developed with the help of a newly identified quinine-derived bifunctional catalyst, allowing the synthesis of densely functionalized products with contiguous quaternary and tertiary stereocenters in excellent yield with perfect diastereoselectivity (>20 : 1 dr) and high enantioselectivity (up to 99 : 1 er).

The enantioselective construction of quaternary stereogenic centers has long been considered an important yet challenging task owing to the involved inherent steric repulsion.[1] Among different approaches towards this goal, the combination of trisubstituted carbon nucleophiles with an ensemble of electrophiles has particularly emerged as a very popular strategy.[1b] Inspired by the challenges associated with this task, we selected the direct coupling of a trisubstituted carbon nucleophile with an acceptor-activated olefin. Accordingly, γ-substituted deconjugated butenolides were selected as the nucleophilic component considering the wide abundance of the γ-butenolide moiety in bioactive natural products (Fig. 1). The silyl enol ether derivatives of γ-butenolide (silyloxy furans) have been heavily utilized in asymmetric vinylogous Mukaiyama-type aldol, Mannich and Michael reactions.[2] However, the application of butenolide itself in asymmetric synthesis remains relatively underexplored.[3] In the same context, the deconjugated 5-methyl butenolide (α-angelica lactone) started gaining attention only very recently due to its potential for the construction of a γ-quaternary stereocenter.[4,5] Asymmetric allylic alkylation[6] and vinylogous Mannich reaction[7] have been achieved under either metal or organocatalytic conditions. Direct Michael addition of angelica lactone to enals has been reported by Alexakis and co-workers during the course of our investigation.[8] However, despite the vast popularity of nitroolefins as a Michael acceptor, an asymmetric addition of angelica lactone to nitroolefin is yet to be achieved.

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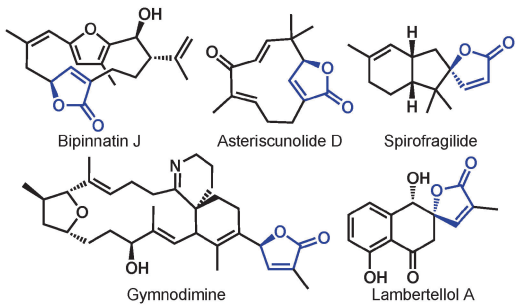
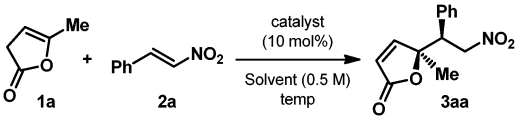


Fig. 1 Selected natural products containing the γ-butenolide moiety.

The purpose of this communication is to disclose our findings on the highly diastereo-and enantioselective Michael addition of several γ-substituted deconjugated butenolides to nitroolefins.

Our investigation was initiated with the goal of finding the best catalyst and optimal reaction conditions for the direct vinylogous Michael reaction between model substrates (angelica lactone) **1a** and ω-nitrostyrene **2a** (Table 1). The absence of any background reaction at rt (entry 1) allowed rapid screening of a selection of catalysts (Fig. 2) including several well-established bifunctional catalysts **I–VII**.[9] In most of these cases, complete conversion to the desired vinylogous Michael adduct **3aa** was observed with good to excellent diastereoselectivity within 30 min at rt. We were glad to find that the normal Michael adduct and the double Michael adduct were not observed in any of the above cases (see ESI† for details). While the widely popular Takemoto catalyst **I**[10] failed to induce any enantioselectivity to **3aa** (entry 2), low enantioselectivities were observed for reactions with the *Cinchona* alkaloids **II–V** (entries 3–6). Equally low level of enantioselectivity was also obtained with quinine and cinchonine-derived thiourea catalysts **VI** and **VII** (entries 7 and 8).[11] Following the work of Jacobsen and others,[12] we realized that introduction of a second element of chirality has the potential of improving the enantioselectivity. Indeed, replacing the aryl substituent of thiourea **VII** with a *tert*-leucine-derived chiral substituent resulted in thiourea **VIII**, which was found to be significantly superior and *ent*-**3aa** was obtained with improved enantioselectivity (entry 9). However, we were surprised to find that with **VIII**, the sense of stereoinduction is dictated by the *tert*-leucine segment of the catalyst (compare entries 8 and 9). With the corresponding

Table 1 Catalyst optimization for the direct asymmetric vinylogous Michael reaction of angelica lactone **1a** with nitrostyrene **2a**[a]



Entry	Catalyst	Solvent	T/°C	t^b/h	dr[c]	er[d]
1	—	Toluene	25	[e]	—	—
2	**I**	Toluene	25	<0.5	12 : 1	50 : 50
3	**II**	Toluene	25	<0.5	15 : 1	40 : 60
4	**III**	Toluene	25	<0.5	14 : 1	41 : 59
5	**IV**	Toluene	25	1.5	10 : 1	65 : 35
6	**V**	Toluene	25	<0.5	12 : 1	58 : 42
7	**VI**	Toluene	25	<0.5	14 : 1	46 : 54
8	**VII**	Toluene	25	<0.5	13 : 1	61 : 39
9	**VIII**	Toluene	25	1.5	15 : 1	29 : 71
10	**IX**	Toluene	25	<0.5	>20 : 1	82.5 : 17.5
11	**IX**	Toluene	0	2	>20 : 1	86.5 : 13.5
12	**IX**	Toluene	−36	9	>20 : 1	91 : 9
13	**IX**	CH_2Cl_2	−36	11	>20 : 1	92 : 8
14	**IX**	CH_2Cl_2	−50	50	>20 : 1	92.5 : 7.5
15	**X**	CH_2Cl_2	−36	9	>20 : 1	91.5 : 8.5
16	**XI**	CH_2Cl_2	−36	14	>20 : 1	90.5 : 9.5
17	**XII**	Toluene	−36	24	>20 : 1	91 : 9
18	**XII**	CH_2Cl_2	−36	9	>20 : 1	88 : 12
19	***XII***	*$CHCl_3$*	*−36*	*34*	*>20 : 1*	*94.5 : 5.5*

[a] Reactions were carried out using 1.0 equiv. of **1a** and 1.5 equiv. of **2a**. Relative and absolute configuration of the product was determined by X-ray diffraction analysis (see ESI). [b] Time required for complete conversion of **1a**. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a stationary phase chiral column (see ESI). [e] No conversion after 72 h.

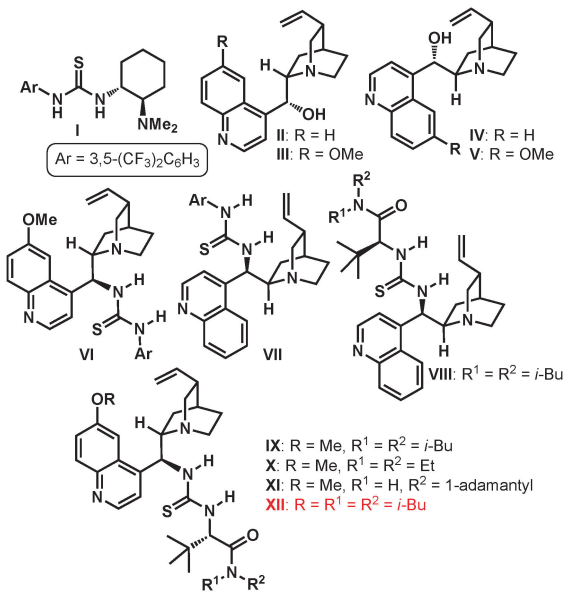
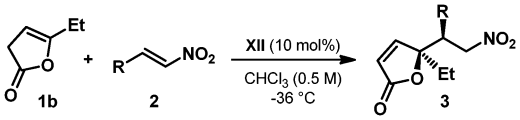


Fig. 2 A selection of catalysts screened for the vinylogous Michael reaction.

quinine-derived catalyst **IX**, the product was obtained essentially as a single diastereomer and with 82.5 : 17.5 er (entry 10). The same trend with the sense of stereoinduction was followed here as well (compare entries 7 and 10). Lowering the reaction temperature up to −36 °C and changing the reaction solvent to CH_2Cl_2 resulted in improved enantioselectivity, albeit at the expense of reaction rate (entries 12 and 13). Lowering the reaction temperature to −50 °C was not beneficial as the reaction rate reduced by several fold with little effect on the enantioselectivity (entry 14). The optimum catalyst was identified after steric tuning at the 6-position of quinoline: the tri-*iso*-butyl catalyst **XII** afforded **3aa** in 94.5 : 5.5 er when the reaction was conducted in $CHCl_3$ at −36 °C (entry 19). Catalyst loading could be reduced to 5 mol% without any deleterious effect on the product enantioselectivity (see ESI†).

Table 2 Catalytic asymmetric direct vinylogous Michael reaction of butenolide **1b** with various nitroolefins[a]



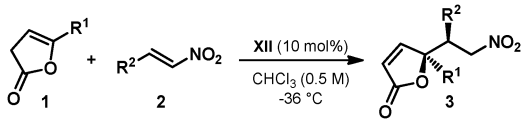
Entry	R	t/h	Product	Yield[b] (%)	dr[c]	er[d]
1	Ph (**2a**)	24	**3ba**	94	>20 : 1	95.5 : 4.5
2	4-ClC_6H_4 (**2b**)	48	**3bb**	94	>20 : 1	96 : 4
3	3-ClC_6H_4 (**2c**)	30	**3bc**	92	>20 : 1	95 : 5
4	4-FC_6H_4 (**2d**)	32	**3bd**	87	>20 : 1	95 : 5
5	4-BrC_6H_4 (**2e**)	69	**3be**	90	>20 : 1	94 : 6
6	4-$OMeC_6H_4$ (**2f**)	60	**3bf**	97	>20 : 1	96.5 : 3.5
7	4-MeC_6H_4 (**2g**)	60	**3bg**	91	>20 : 1	96 : 4
8	1-Naphthyl (**2h**)	44	**3bh**	90	>20 : 1	95 : 5
9	2-Naphthyl (**2i**)	50	**3bi**	96	>20 : 1	95.5 : 4.5
10	2-Furyl (**2j**)	60	**3bj**	97	>20 : 1	93.5 : 6.5
11	2-Thienyl (**2k**)	42	**3bk**	92	>20 : 1	96 : 4
12	2,4-$Cl_2C_6H_3$ (**2l**)	60	**3bl**	96	>20 : 1	97 : 3
13[e]	*i*-Bu (**2m**)	96	**3bm**	59	>20 : 1	95.5 : 4.5

[a] Reactions were carried out using 1.0 equiv. of **1** and 1.5 equiv. of **2** under an argon atmosphere. [b] Isolated yield of the products after column chromatography. [c] Determined by ^{1}H-NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a stationary phase chiral column (see ESI). [e] Reaction was conducted at −20 °C.

With the newly identified bifunctional catalyst **XII** and optimized reaction conditions in hand (Table 1, entry 19), we set out to elucidate the scope and limitations of this asymmetric vinylogous Michael reaction with respect to nitroolefins as well as butenolides. We first examined the viability of various nitroolefins with different steric and electronic properties using ethyl-substituted deconjugated butenolide **1b**. As can be seen from Table 2, the Michael adducts are generally obtained in excellent yield and with impeccable diastereoselectivity. The reaction rate and enantioselectivity seem to be dependent on the electronic nature of the nitroolefin. Nevertheless, both electron-rich and electron-poor aromatic groups on nitroolefin are well tolerated and adducts were obtained in high enantioselectivity (up to 97 : 3 er) within reasonable time scale. Heteroaromatic nitroolefins are also excellent substrates for this reaction (entries 10 and 11). When employing the more challenging and less reactive aliphatic nitroolefin **2m**, the Michael adduct **3bm** was acquired with high level of stereocontrol (95.5 : 4.5 er) but only in moderate yield after prolonged reaction time at slightly elevated temperature (entry 13). However, when this reaction was carried out at 0 °C (for 66 h) the product (**3bm**) was obtained in very good yield (87%) with only slightly reduced enantioselectivity (93 : 7 er).

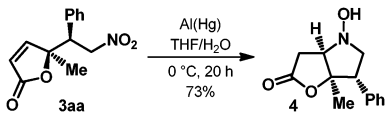
After demonstrating success with various nitroolefins and ethyl-substituted butenolide **1b**, we turned our attention

Table 3 Catalytic asymmetric direct vinylogous Michael reaction of various butenolides and nitroolefins[a]



Entry	R^1	R^2	t/h	Product	Yield[b] (%)	er[c]
1	Me (**1a**)	Ph (**2a**)	34	**3aa**	92	94.5 : 5.5[d]
2	Me (**1a**)	3-ClC_6H_4 (**2c**)	38	**3ac**	86	92 : 8
3	Me (**1a**)	4-$OMeC_6H_4$ (**2f**)	60	**3af**	94	95.5 : 4.5
4	Me (**1a**)	4-MeC_6H_4 (**2g**)	65	**3ag**	90	95 : 5
5	Me (**1a**)	4-$CF_3C_6H_4$ (**2n**)	30	**3an**	88	90 : 10
6	*n*-Pr (**1c**)	Ph (**2a**)	36	**3ca**	92	97 : 3
7	*n*-Pent (**1d**)	Ph (**2a**)	46	**3da**	91	97 : 3
8	*n*-Pent (**1d**)	4-MeC_6H_4 (**2g**)	48	**3dg**	95	96.5 : 3.5
9	*i*-Pr (**1e**)	Ph (**2a**)	60	**3ea**	90	98 : 2
10	*i*-Pr (**1e**)	4-MeC_6H_4 (**2g**)	96	**3eg**	92	98 : 2
11	*i*-Bu (**1f**)	Ph (**2a**)	24	**3fa**	93	97 : 3
12	*i*-Bu (**1f**)	4-MeC_6H_4 (**2g**)	24	**3fg**	96	97 : 3
13[e]	*i*-Bu (**1f**)	*i*-Bu (**2m**)	72	**3fm**	89	94 : 6
14	Bn (**1g**)	Ph (**2a**)	36	**3ga**	95	97 : 3
15	Bn (**1g**)	4-ClC_6H_4 (**2b**)	24	**3gb**	97	98 : 2[d]
16	Bn (**1g**)	4-BrC_6H_4 (**2e**)	22	**3ge**	98	97.5 : 2.5
17	Bn (**1g**)	2,4-$Cl_2C_6H_3$ (**2l**)	24	**3gl**	99	99 : 1

[a] Reactions were carried out using 1.0 equiv. of **1** and 1.5 equiv. of **2** under an argon atmosphere. [b] Isolated yield of the products after column chromatography. In all cases products were obtained with >20 : 1 dr. [c] Determined by HPLC analysis using a stationary phase chiral column (see ESI). [d] Products **3aa** and **3gb** were obtained with >99.5 : 0.5 er after a single recrystallization from EtOAc–PetEther. [e] Reaction was conducted at 0 °C.



Scheme 1 Synthetic utility of Michael adduct **3aa**.

to other butenolides, with the results summarized in Table 3. It is evident that the reaction conditions are tolerant to diverse substituents on either butenolide or nitroolefin. The products from angelica lactone **1a** were acquired with somewhat lower enantioselectivities (entries 1–5). However, an enantiopure product can be achieved after a single recrystallization as exemplified in the case of **3aa** (entry 1). For all other butenolides with either long alkyl chain substituents (*n*-Pr **1c**, *n*-Pent **1d**; entries 6–8), branched alkyl groups (*i*-Pr **1e**, *i*-Bu **1f**; entries 9–13) or alkyl chains with an aromatic moiety (Bn **1g**; entries 14–17), products were obtained with uniformly high enantioselectivity in very good yield. Once again, in all cases only a single diastereomer of the products could be detected by ^{1}H-NMR analysis.

The synthetic utility of our reaction products is illustrated by reductive aza-Michael cyclization of **3aa**, which afforded the bicyclic adduct **4** in reasonable yield (Scheme 1).

In summary, we have developed a quinine-derived thiourea-based bifunctional organocatalyst containing a second element of chirality for direct asymmetric vinylogous Michael addition of deconjugated butenolides to nitroolefins. Synthetically versatile highly functionalized γ-butenolides with contiguous quaternary and tertiary stereocenters were prepared stereoselectively. Efforts towards developing a more efficient catalyst to include less reactive butenolides and nitroolefins as well as models for stereoinduction are currently underway in our laboratory.

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