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Catalytic Asymmetric Direct Vinylogous Michael Addition of Deconjugated Butenolides to Maleimides for the Construction of Quaternary Stereogenic Centers

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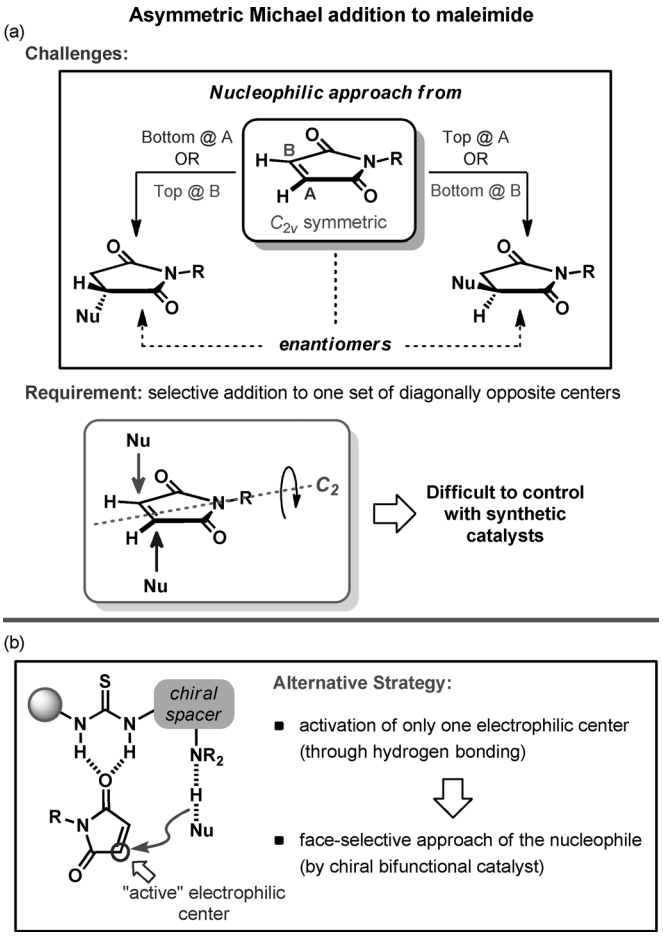
Dedicated to Professor Benjamin List on the occasion of his 45th birthday

Chiral succinimides and functionalized pyrrolidines are two synthetically and biologically important classes of structural motifs.[1] Conjugate addition of nucleophiles to maleimides constitutes the most straightforward route to chiral α-substituted succinimides. Despite such impetus, the application of maleimides in asymmetric synthesis has mostly been limited to various cycloaddition reactions.[2] The asymmetric Michael addition reaction to maleimides has remained largely overlooked except for a few sporadic examples.[3] The realization of the full potential of this powerful electrophile as Michael acceptor has only begun during the past decade. The initial reports came from Hayashi and coworkers when they disclosed a Rh-catalyzed 1,4-addition of boronic acids to maleimides.[4] The reason for this initial paucity of enantioselective conjugate addition reactions involving maleimides probably lies in their C_{2v} symmetry. Unlike Michael acceptors with only one prochiral electrophilic center (e.g., nitro-olefins, enals etc.), those containing C_{2v} symmetry (e.g., unsubstituted maleimides, 1,4-naphthoquinone etc.) pose additional challenges for developing an asymmetric Michael addition. Here, two chemically equivalent vicinal electrophilic centers are present and the diagonally opposite centers (related by a C_2 operation) are also stereochemically equivalent. Therefore, selective addition to only one set of diagonally opposite centers (for example, bottom@A or top@B, Scheme 1a) is the prerequisite for an enantioselective process.

With the advent of organocatalysis, maleimides emerged as a very popular electrophile and a number of reports describing the asymmetric addition of a wide range of nucleophiles appeared within a rather short interval.[5] However, all these reports illustrate the addition of direct carbon-centered nucleophiles to maleimides and only one example of a vinylogous Michael addition.[6] In 2008, Loh et al. reported



Scheme 1. Enantioselective Michael addition to unsubstituted maleimides: challenges, requirements, and strategy.

modified cinchona alkaloids as catalysts for the addition of α,α-dicyanoolefins to *N*-phenyl and *N*-benzyl maleimides.[6]

We have recently reported a direct asymmetric vinylogous Michael addition of γ-substituted deconjugated butenolides to nitro-olefins for the construction of quaternary stereocenters.[7,8] With our continued interest in accessing compounds containing quaternary stereocenters,[9,10] we realized that the addition of the same nucleophile to unsubstituted maleimides would, once again, result in adjacent quaternary and tertiary stereocenters. In this communication, we report a

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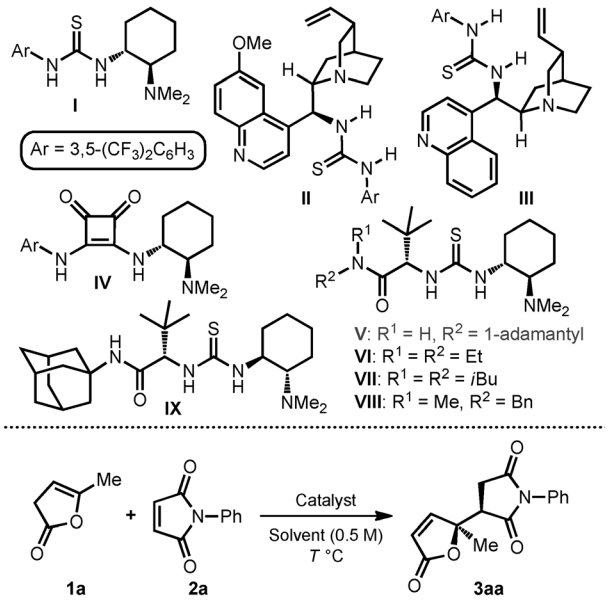
highly diastereo- and enantioselective direct vinylogous[11] Michael addition of γ-substituted deconjugated butenolides to unsubstituted maleimides.

We were aware of the potential difficulties associated with blocking of one set of diagonally opposite prochiral centers (Scheme 1a) and devised an alternative strategy (Scheme 1b). We realized that Brønsted acidic activation of the maleimide carbonyl would render only one (of the possible two) electrophilic centers "active" towards nucleophilic attack. Under this condition, merely a face-selective approach of the nucleophile would be sufficient to bring about enantioselective Michael addition. Such enantiofacial discrimination of maleimide was thought to be achieved by means of a chiral thiourea/tertiary-amine bifunctional catalyst.[12]

We began our investigation by studying the feasibility of the reaction between α-Angelica lactone (**1a**) and *N*-phenylmaleimide (**2a**; Table 1). As expected, no measurable product formation was detected in the absence of any catalyst even after 72 h when the reaction was conducted in chloroform at room temperature (Table 1, entry 1). However, upon exposure to 10 mol% of the Takemoto catalyst **I**,[13] complete conversion to the desired Michael adduct **3aa** was observed within one hour, albeit with only modest diastereo- and enantioselectivity (entry 2). Quinine- and cinchonine-derived thiourea derivatives **II** and **III**,[14] respectively, demonstrated good catalytic activity, but poor enantioselectivity (entries 3 and 4). Bifunctional squaramide derivative **IV**, introduced by Rawal and co-workers,[15] improved the enantioselectivity significantly while maintaining the catalytic activity (entry 5). Excellent enantioselectivity was obtained when the aryl moiety of the thiourea catalyst **I** was replaced with a *tert*-leucine-derived chiral substituent.[16] The resulting catalyst **V** afforded **3aa** with d.r. = 8:1 and e.r. = 97:3 (entry 6). Slight improvement in enantioselectivity was achieved when the reaction was conducted at 0 °C (entry 7). With a number of similar catalysts **VI**–**VIII**, containing various substituents on the amide nitrogen, product was obtained with diminished d.r. and e.r. (entries 8–10), and established secondary amide **V** as the optimum catalyst for this reaction. The corresponding diastereomeric catalyst **IX**, derived from (*S*,*S*)-1,2-diaminocyclohexane turned out to possess the "mismatched" combination, providing the product with lower d.r. and e.r. compared to **V** (entry 11 vs. 7). Interestingly, *ent*-**3aa** was obtained as the major enantiomer with catalyst **IX** and hence illustrates that the stereochemical outcome of this Michael reaction is dictated by the 1,2-diamine moiety and not by the chiral side chain. Lowering the reaction temperature to −36 °C further improved the enantioselectivity to e.r. = 98:2 without compromising the reaction rate too much (entry 12). A quick solvent screening revealed dichloromethane as the preferred solvent, providing the product with excellent d.r. (13:1) and outstanding e.r. (99:1) (entry 13). Under these reaction conditions, catalyst loading can be reduced to 5 mol% without any deleterious effect on the reaction selectivity (entry 16). A catalyst loading of 2 mol% provided the product with still useful level of enantioselectivity (e.r. = 96:4), but both the reaction rate and the diastereoselectivity were curtailed severely (entry 17). Therefore, 5 mol% of the catalyst **V** was used for all subsequent optimization studies. Diastereoselectivity was slightly improved to d.r. = 14:1 when the reaction concentration was reduced to 0.25 M (entry 19). However, no beneficial effect could be achieved by further diluting the reaction mixture

Table 1. Catalyst evaluation and optimization of reaction conditions for direct vinylogous Michael reaction of α-Angelica lactone **1a** with *N*-phenylmaleimide **2a**.[a]



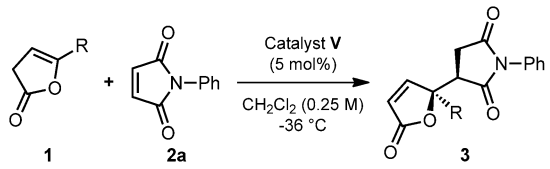
Entry	Cat. ([mol%])	Solvent	T [°C]	t [h][b]	d.r.[c]	e.r.[d]
1	–	$CHCl_3$	25	–[e]	–	–
2	**I** (10)	$CHCl_3$	25	<1	4:1	77:23
3	**II** (10)	$CHCl_3$	25	4	5:1	40:60
4	**III** (10)	$CHCl_3$	25	4	5:1	53:47
5	**IV** (10)	$CHCl_3$	25	5	6:1	92:8
6	**V** (10)	$CHCl_3$	25	<1	8:1	97:3
7	**V** (10)	$CHCl_3$	0	2	8:1	97.5:2.5
8	**VI** (10)	$CHCl_3$	0	2	5:1	92:8
9	**VII** (10)	$CHCl_3$	0	2	6:1	93.5:6.5
10	**VIII** (10)	$CHCl_3$	0	2	4:1	90:10
11	**IX** (10)	$CHCl_3$	0	3	7:1	5:95
12	**V** (10)	$CHCl_3$	−36	5	7:1	98:2
13	**V** (10)	CH_2Cl_2	−36	3	13:1	99:1
14	**V** (10)	toluene	−36	3	6:1	96.5:3.5
15	**V** (10)	TBME[f]	−36	6	11:1	98.5:1.5
16	**V** (5)	CH_2Cl_2	−36	6	13:1	99:1
17	**V** (2)	CH_2Cl_2	−36	44[g]	2:1	96:4
18[h]	**V** (5)	CH_2Cl_2	−36	8	11:1	99:1
19[h,i]	**V** (5)	CH_2Cl_2	−36	6	14:1	99:1
20[h,j]	**V** (5)	CH_2Cl_2	−36	11	9:1	99:1
21[h,k]	**V** (5)	CH_2Cl_2	−36	9	14:1	99:1

[a] Reactions were carried out using 1.0 equivalent of **1a** and 1.5 equivalents of **2a**. [b] Time required for complete conversion of **1a**. [c] Determined by ^{1}H NMR analysis of crude reaction mixture. [d] Determined by HPLC analysis using a stationary phase chiral column. Relative and absolute configuration of the product was determined by X-ray diffraction analysis. [e] No conversion after 72 h. [f] TBME: *tert*-Butyl methyl ether. [g] 85% conversion after 44 h. [h] 1.1 equivalents of **2a** was used. [i] Reaction concentration of 0.25 M. [j] Reaction concentration of 1.0 M. [k] Reaction concentration of 0.1 M.

to 0.1 M (entry 21). It must be noted that our optimized reaction conditions (entry 19) utilize only small excess (1.1 equiv) of maleimide **2a**.

Having optimized the catalyst structure and reaction conditions (Table 1, entry 19), we examined the influence of structural diversity of the deconjugated butenolide on the reaction outcome. The results are summarized in Table 2.

Table 2. Scope of deconjugated butenolides in the asymmetric vinylogous Michael reaction.[a]



Entry	R	t [h]	3	Yield [%][b]	d.r.[c]	e.r.[d]
1	Me (**1a**)	6	**3aa**	99	14:1	>99:1
2	Et (**1b**)	8	**3ba**	92	14:1	99.5:0.5
3	*n*Pr (**1c**)	5	**3ca**	96	14:1	98:2
4	*n*Pent (**1d**)	4	**3da**	96	13:1	98:2
5	*i*Bu (**1e**)	5	**3ea**	97	10:1	>99:1
6	*i*Pr (**1f**)	5	**3fa**	94	18:1	97.5:2.5
7	Bn (**1g**)	4	**3ga**	91	15:1	98.5:1.5

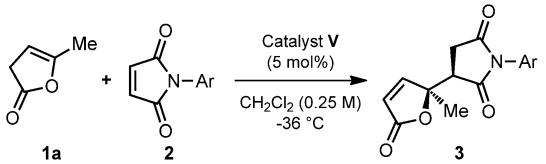
[a] Reactions were carried out using 1.0 equivalent of **1** and 1.1 equivalents of **2a** under an argon atmosphere. [b] Isolated yield of the products after column chromatography. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a stationary phase chiral column (see the Supporting Information).

We were delighted to find that the butenolide structure has little impact on the overall performance of this direct vinylogous Michael protocol. For butenolides with either linear alkyl chains (Me: **1a**, Et: **1b**, *n*Pr: **1c**, *n*Pent: **1d**; entries 1–4), branched alkyl groups (*i*Bu **1e**, *i*Pr **1f**; entries 5 and 6), or alkyl chain with an aromatic moiety (Bn **1g**; entry 7), products were obtained in uniformly high yield with excellent diastereoselectivity and outstanding enantioselectivity.

With the generality of the butenolide γ-substituent already established, we next turned our attention to the effect of maleimide N-substitution on the selectivity of the reaction. As can be seen from Table 3, a wide range of aromatic substituents are tolerated and the Michael adducts are generally obtained in excellent yield and enantioselectivity with high d.r. However, the substituents do influence the reaction rate depending on their electronic nature. The reactions are found to be slower for maleimides with electron-rich aromatic substituents (entries 5 and 8). Nevertheless, the level of diastereo- and enantioselectivity remained impervious to the electronic nature of the substituents. Our preliminary studies on maleimides with non-aromatic N-substituents showed a significant decrease in both reaction rate and selectivity, leaving room for future improvement.

Both the relative and absolute stereochemistry of **3ac** were determined by X-ray diffraction analysis (Figure 1).[17] The configuration of the other Michael adducts shown in Table 2 and 3 were tentatively assigned the same by assuming that a similar catalytic mechanism was followed.

Table 3. Scope of the maleimide N-substitution in the asymmetric vinylogous Michael reaction.[a]



Entry	Ar	t [h]	3	Yield [%][b]	d.r.[c]	e.r.[d]
1	4-BrC_6H_4 (**2b**)	6	**3ab**	93	5:1	98:2
2	4-ClC_6H_4 (**2c**)	4	**3ac**	95	6:1	98:2
3	4-$CF_3C_6H_4$ (**2d**)	5	**3ad**	90	10:1	96.5:3.5
4	4-MeC_6H_4 (**2e**)	4	**3ae**	93	18:1	>99:1
5	4-OMeC_6H_4 (**2f**)	12	**3af**	94	15:1	99:1
6	3-ClC_6H_4 (**2g**)	6	**3ag**	97	5:1	97.5:2.5
7	3-MeC_6H_4 (**2h**)	4	**3ah**	96	10:1	>99:1
8	2,4-$(OMe)_2C_6H_3$ (**2i**)	16	**3ai**	88	15:1	98:2

[a] Reactions were carried out using 1.0 equivalent of **1a** and 1.1 equivalents 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 the Supporting Information).

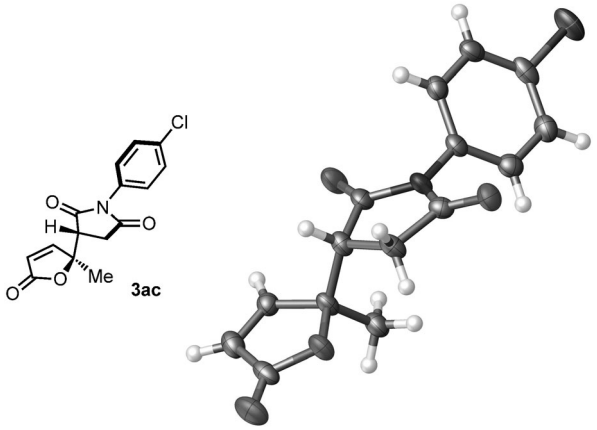
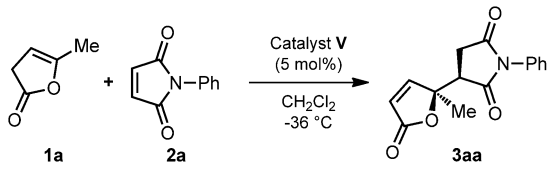


Figure 1. Relative and absolute stereochemistry of **3ac** and its X-ray structure.

The practicality of this protocol was demonstrated by a same-pot catalyst recycling experiment (Table 4) in which new batches of substrates (both **1a** and **2a**) were added once the reaction was judged complete by TLC without separation of the products formed. Each reaction cycle was conducted on a 0.25 mmol scale. It is clear from Table 4, that the d.r. and e.r. of the product remained consistent over three reaction cycles. The slight erosion of the overall product yield compared to a single catalytic experiment (Table 2, entry 1) and the longer reaction times for the second and third cycle are due to the loss of effective catalyst amount while extracting sample for analysis. In addition, a gradual decrease in reaction concentration with each cycle and competitive product inhibition of catalyst might also have contributed towards the attrition of the reaction rate.

Table 4. One-pot catalyst-recycling experiment.[a]

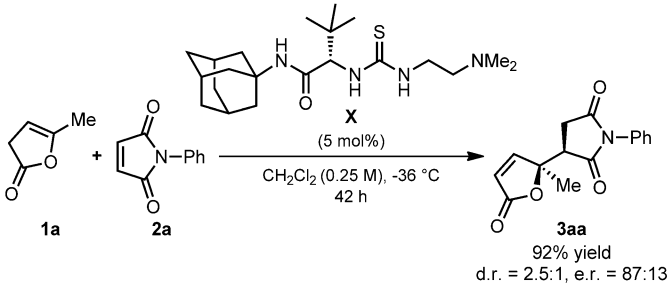


Cycles	Conc. of **1a** [M]	*t* [h]	d.r.[b]	e.r.[c]	Overall yield[d]
1st	0.25	6	14:1	99:1	
2nd	0.17	22	14:1	99:1	
3rd	0.12	50	14:1	99:1	84%

[a] Reactions were carried out using 1.0 equivalent of **1a** and 1.1 equivalents of **2a** under an argon atmosphere. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by HPLC analysis using a stationary phase chiral column (see the Supporting Information). [d] Isolated yield of the products after column chromatography.

Based on the observed stereochemistry of the Michael adduct (Figure 1) and the well-documented activation mode involving this type of bifunctional catalysts,[18] a plausible transition state model is proposed. As shown in Figure 2, nucleophilic addition of the butenolide occurs via its corresponding aromatic enol form, activated by the tertiary amine group of the catalyst by means of a general base catalysis. Dual hydrogen bonding from thiourea to the maleimide not only reduces its LUMO energy, but also orients the maleimide for a face-selective nucleophilic attack, a prime requirement for the development of asymmetric Michael reaction to maleimides (see Scheme 1). The X-ray structure of catalyst **V** (Figure 2)[17] supports the role of the bulky adamantyl group in the desired face selectivity.

At this point we speculated that if this mechanistic model is operative, then a catalyst consisting of the *tert*-leucine-derived component as the sole chiral element should be able to promote a similar face-selective Michael addition. This assumption was indeed found to be true when **X** was used as the catalyst for reaction between **1a** and **2a** under our optimized reaction conditions. The same product stereoisomer **3aa** was obtained with rather impressive enantioselectivity (Scheme 2). This experiment provides strong evidence in support of our proposed stereochemical model.



Scheme 2. Asymmetric vinylogous Michael reaction between **1a** and **2a** using catalyst **X**.

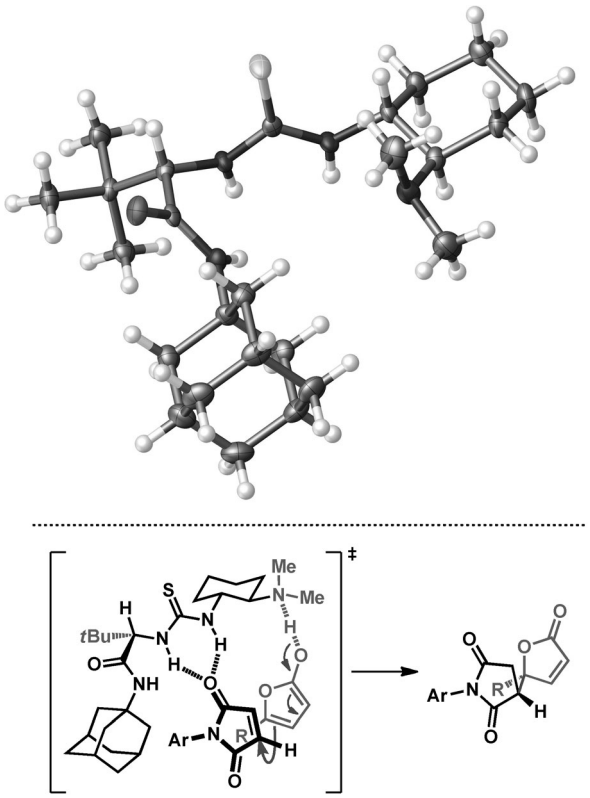


Figure 2. X-ray structure of the catalyst **V** and rationalization for the stereochemical outcome of the vinylogous Michael addition.

In conclusion, we have developed a highly diastereo- and enantioselective protocol for the direct vinylogous Michael addition of deconjugated butenolides to maleimides using a tertiary-amine/thiourea-based bifunctional catalyst. This operationally simple protocol should be synthetically useful due to the mild reaction conditions, low catalyst loading, and excellent level of product stereoselectivity. We are currently working on extending the scope of the reaction to include *N*-alkyl and substituted maleimides.

Experimental Section

Typical procedure for the direct asymmetric vinylogous Michael reaction between 1a and 2a: In an oven and vacuum dried Schlenk tube, *N*-phenylmaleimide **2a** (48.5 mg, 0.280 mmol; 1.1 equiv) and the catalyst **V** (5.7 mg, 0.012 mmol; 0.05 equiv) were taken under argon. Freshly distilled CH_2Cl_2 (0.5 mL) was added and the solution was cooled to −36 °C under a positive argon pressure. A solution of α-Angelica lactone **1a** (25.0 mg, 0.254 mmol; 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added and the resulting mixture was stirred at −36 °C until TLC (1:1 petroleum ether:CH_2Cl_2) revealed complete conversion of **1a**. The reaction mixture was then brought to room temperature, solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (100–200 mesh) using 1:1 EtOAc in petroleum ether to afford **3aa** as a colorless foam (68.1 mg, 0.251 mmol; 99%).

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Keywords: asymmetric catalysis · butyrolactone · maleimide · Michael addition · thiourea

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