Asymmetric Synthesis

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Highly Enantio- and Diastereoselective Reactions of γ-Substituted Butenolides Through Direct Vinylogous Conjugate Additions**

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The γ,γ-disubstituted butenolide unit, which bears a quaternary stereogenic center,[1] has been recognized as a crucial fragment in a number of natural products and medicinally important agents.[2] The stereocontrolled synthesis of γ,γ-disubstituted butenolide derivatives has thus been the subject of enormous interest in the past few decades. Protocols for asymmetric synthesis focused on utilizing Mukaiyama-type additions, which were limited to preformed silyloxyfurans.[3] With regard to atom economy and efficiency, natural non-activated γ-substituted butenolides gained attention because of their potential in the direct construction of γ,γ-disubstituted butenolides. The first breakthrough was reported by Chen and co-workers, who developed a highly enantio- and diastereoselective allylic alkylation of Morita-Baylis–Hillman carbonates with γ-aryl-substituted butenolides using $(DHQD)_2PYR$ as the Lewis base catalyst.[4] Subsequently, Alexakis and co-workers described the addition of γ-alkyl-substituted butenolides (α-angelica lactone) to enals using aminal–pyrrolidine (APY) as catalyst.[5] In both reactions, stereoselectivity was achieved through the formation of a covalent intermediate and/or transition state of the catalyst and the substrate.[6] Recently, Feng and co-workers presented the first Lewis acid catalyzed asymmetric vinylogous Mannich-type reaction of aldimines with γ-alkyl-substituted butenolides.[7] It is worth noting that reports on the use of hydrogen-bonding catalysis[8] to afford γ,γ-disubstituted butenolides are rare,[9] and reactions involving γ-aryl- and alkyl-substituted butenolides as nucleophiles have not yet been reported. Therefore, it is highly desirable to develop an efficient catalyst to allow easy access to diverse γ,γ-disubstituted butenolides from both γ-aryl- and alkyl-substituted butenolides.

Amides with α-stereogenic centers are useful building blocks for the synthesis of biologically active compounds.[10] Our groups have recently disclosed a wide range of asymmetric organocatalytic conjugate addition reactions that employ (*E*)-4-oxo-4-arylbutenamides as electrophiles.[11] In particular, the 2-oxazolidinone amide moiety allows the substrate to positively interact with bifunctional catalysts, such as C_2-symmetric bicyclic guanidine[11a,b,12] and *Cinchona* alkaloid thiourea,[8,11c] thus often resulting in much improved reactivity and stereoselectivity. Therefore we rationalized that direct vinylogous Michael addition of γ-substituted butenolides to (*E*)-4-oxo-4-arylbutenamides can be achieved with bifunctional catalysts.

We selected the addition of γ-phenyl-substituted butenolide **1a** to (*E*)-4-oxo-4-phenylbutenamide **2a** as the model reaction, and examined various bifunctional catalysts (Figure 1, Table 1). First, in the presence of C_2-symmetric bicyclic guanidine **A** (5 mol%), the reaction was completed in four hours, affording adduct **3a** in good yield, but poor enantioselectivity (19% *ee*; Table 1, entry 1). Subsequently, we screened chiral pyrrolidinyl sulfonamide (CPS) catalysts **B** and **C** (Table 1, entries 2 and 3), which were previously studied in our group to promote tandem conjugate addition–elimination reactions.[13] Product **3a** was obtained with promising 49% *ee* (entry 2), thus indicating that an L-amino acid is the preferred framework for a catalyst. In an attempt to improve the catalyst, we replaced the sulfonamide group with thiourea and prepared a series of amine–thiourea catalysts (**D**–**H**).[14] We anticipated an improvement to the enantioselectivity through additional H-bond interactions. The survey

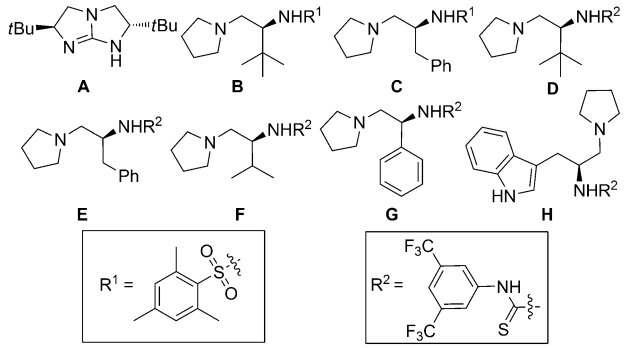

Figure 1. Catalyst structures.

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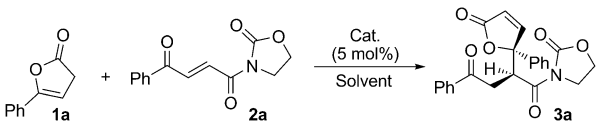
Table 1: Screening studies of direct vinylogous Michael addition of **1a** to **2a**.[a]



Entry	Cat.	Solvent	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	**A**	Et_2O	15	4	86	19	9:1
2	**B**	Et_2O	15	12	57	49	7:1
3	**C**	Et_2O	15	12	63	37	5:1
4	**D**	Et_2O	15	12	87	90	>99:1
5	**E**	Et_2O	15	12	78	85	>99:1
6	**F**	Et_2O	15	12	80	87	>99:1
7	**G**	Et_2O	15	12	93	30	>99:1
8	**H**	Et_2O	15	12	80	85	>99:1
9	**D**	Et_2O	0	24	63	83	>99:1
10	**D**	Et_2O	25	4	86	94	>99:1
11	**D**	toluene	25	48	77	86	>99:1
12	**D**	CH_2Cl_2	25	48	62	75	>99:1
13	**D**	THF	25	0.5	80	81	>99:1
14	**D**	MeCN	25	1	84	60	4:1
15	**D**	iPr_2O	25	4	51	91	24:1
16	**D**	MTBE	25	4	57	89	24:1
17[e]	**D**	Et_2O	25	2	89	94	>99:1
18[f]	**D**	Et_2O	25	5	88	94	>99:1
19[g]	**D**	Et_2O	25	10	80	90	>99:1

[a] Unless otherwise noted, reactions were performed with **1a** (0.11 mmol), **2a** (0.1 mmol), and catalyst (0.005 mmol) in solvent (1.0 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] 10 mol% **D** was used. [f] 1 mol% **D** was used. [g] 0.5 mol% **D** was used. MTBE = methyl *tert*-butyl ether.

showed that both enantio- and diastereoselectivity were improved dramatically in the presence of these catalysts with the exception of **G** (Table 1, entries 4–8). We then sought to improve the reaction by lowering the reaction temperature (Table 1, entries 9 and 10), but ambient temperature (25 °C) gave better enantioselectivity and reaction rate (entry 10). A screening of solvents showed that the best solvent is Et_2O (Table 1, entries 11–16). The catalyst loading could be reduced to 1.0 mol% and **3a** could be obtained in 88% yield without compromising the *ee* value and d.r. (Table 1, entry 17). Further reduction of the catalyst loading to 0.5 mol% resulted in a slight decrease in enantioselectivity of **3a** without a reduced yield (Table 1, entry 18).

Encouraged by the good enantioselectivities achieved with thiourea bifunctional catalysis using (*E*)-4-oxo-4-arylbutenamides that contain an oxazolidinone moiety,[11c] other analogs of (*E*)-4-oxo-4-arylbutenamides with pyrrolidine, morpholine, and pyrrolidinone units (**2b–d**) were also examined. In the cases of the addition of butenolide **1a** to **2b** and **2c**, adducts **3b** and **3c**, respectively, were obtained with significantly poorer diastereo- and enantioselectivities [Eq. (1)]. However, the pyrrolidinone group could still give adduct **3d** with a good enantioselectivity (90% *ee*), comparable to that of **3a**. These findings suggest that the carbonyl groups of the pyrrolidinone and oxazolidinone rings may play a crucial role in substrate–catalyst interactions.

With the favorable role of the oxazolidinone moiety and the optimal reaction conditions established, the direct vinylogous Michael addition was extended to a variety of γ-substituted butenolides and (*E*)-4-oxo-4-arylbutenamides (Table 2). The corresponding γ,γ-butenolide-substituted α-stereogenic amides were obtained in 71–93% yields with 90–96% *ee* and a d.r. of 16:1 to 99:1. Our results have shown that introducing various aryl substituents onto γ-aryl-substituted butenolides or (*E*)-4-oxo-4-arylbutenamides did not affect the *ee* value (Table 2, entries 1–16). High *ee* values could also be obtained when the phenyl group of (*E*)-4-oxo-4-arylbutenamide was replaced with another aromatic group, such as furan (Table 2, entry 17). Good yields and excellent enantio- and diastereoselectivities were observed for γ-alkyl-substituted butenolides, which gave corresponding adducts **3v** and **3w** (Table 2, entries 18 and 19).

In order to illustrate the versatility of the protocol, we examined the vinylogous addition of γ-substituted butenolides **1** with (*E*)-oxazolidinone enoates **4**. The adducts of this reaction, γ,γ-butenolide-substituted β-stereogenic amide derivatives, have been recognized as useful precursors in the construction of biologically active compounds.[11d–e,15] To the best of our knowledge, there is no report on a direct

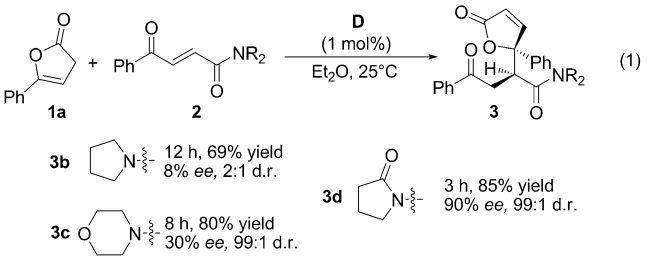
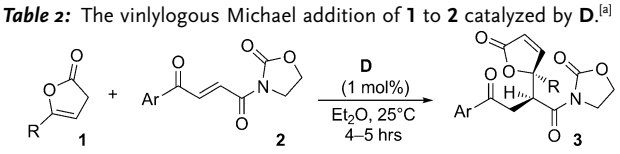


Table 2: The vinylogous Michael addition of **1** to **2** catalyzed by **D**.[a]

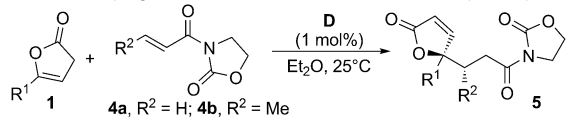


Entry	R/Ar (**3**)	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	4-FC_6H_4/C_6H_5 (**3e**)	80	95	49:1
2	4-ClC_6H_4/C_6H_5 (**3f**)	82	95	>99:1
3	4-BrC_6H_4/C_6H_5 (**3g**)	75	90	>99:1
4	3-BrC_6H_4/C_6H_5 (**3h**)	81	90	>99:1
5	2-naphthyl/C_6H_5 (**3i**)	77	95	>99:1
6	C_6H_5/4-$CF_3C_6H_4$ (**3j**)	85	96	>99:1
7	C_6H_5/4-FC_6H_4 (**3k**)	93	93	>99:1
8	C_6H_5/4-ClC_6H_4 (**3l**)	93	94	>99:1
9	C_6H_5/3-$NO_2C_6H_4$ (**3m**)	84	93	>99:1
10	C_6H_5/3-CNC_6H_4 (**3n**)	84	91	>99:1
11	C_6H_5/3,4-$Cl_2C_6H_3$ (**3o**)	89	95	>99:1
12	C_6H_5/3-BrC_6H_4 (**3p**)	88	91	49:1
13	C_6H_5/2-FC_6H_4 (**3q**)	86	94	>99:1
14	C_6H_5/4-PhC_6H_4 (**3r**)	88	95	20:1
15	C_6H_5/3-$MeOC_6H_4$ (**3s**)	86	91	>99:1
16	C_6H_5/2-naphthyl (**3t**)	84	95	>99:1
17	C_6H_5/2-furyl (**3u**)	71	90	33:1
18[e]	CH_3/4-ClC_6H_4 (**3v**)	75	91	16:1
19[e]	C_2H_5/3,4-$Cl_2C_6H_3$ (**3w**)	72	90	>99:1

[a] All reactions were performed with **1** (0.11 mmol), **2** (0.1 mmol), and **D** (0.001 mmol) in Et_2O (1.0 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis. [d] Determined by ^{1}H NMR analysis. [e] t = 7 h.

asymmetric variant of their syntheses.[16] We were delighted that under the established reaction conditions, the enantioselective synthesis of γ,γ-butenolide-substituted β-stereogenic amide derivatives **5** could be accomplished with yields of 75–90%, 92–99% *ee* and d.r. > 99:1 (Table 3). The substrate

Table 3: The vinylogous Michael addition of **1** to **4** catalyzed by **D**.[a]



Entry	R^1/R^2 (**5**)	*t* [h]	Yield [%][b]	*ee* [%][c]
1	C_6H_5/H (**5a**)	80	87	99[d]
2	4-FC_6H_4/H (**5b**)	60	89	97
3	4-ClC_6H_4/H (**5c**)	80	83	97[e]
4	4-BrC_6H_4/H (**5d**)	40	85	96
5	4-MeC_6H_4/H (**5e**)	96	87	96[f]
6[g]	3-$NO_2C_6H_4$/H (**5f**)	18	90	97
7[i]	CH_3/H (**5g**)	84	90	96
8[h]	C_2H_5/H (**5h**)	96	75	92
9[h]	C_6H_5/CH_3 (**5i**)	168	77	93[j]

[a] Reactions were performed with **1** (0.11 mmol), **4** (0.1 mmol), and **D** (0.001 mmol) in Et_2O (1.0 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis. [d] 5 mol% **D**, 60 h, 86% yield, 99% *ee*; 10 mol% **D**, 24 h, 91% yield, 99% *ee*. [e] 10 mol% **D**, 12 h, 90% yield, 98% *ee*. [f] 10 mol% **D**, 60 h, 90% yield, 96% *ee*. [g] 5 mol% **D**. [h] 10 mol% **D**. [i] 20 mol% **D**. [j] d.r. = 99:1, determined by ^{1}H NMR analysis.

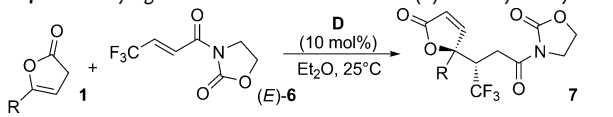
scope included γ-aryl- and alkyl-substituted butenolides, as well as β-alkyl-substituted and terminal oxazolidinone enoates. The reaction that was carried out on a gram scale gave product **5a** in good yield and excellent enantioselectivity after simple filtration [Eq. (2)]. Because all adducts, with the exception of **5h**, precipitated from the reaction mixture, this methodology would be suitable for large-scale production.

(2)

The presence of fluorine atom(s) in pharmaceutical compounds often enhances their pharmacological properties.[17] The stereospecific incorporation of the trifluoromethyl group into an organic compound is often an attractive strategy toward this goal.[18] The addition of a trifluoromethyl group to afford a tertiary chiral carbon center is thus a challenge, considering that there are only few related reports.[19] Consequently, we explored the asymmetric vinylogous addition of γ-substituted butenolides **1** to (*E*)-β-trifluoromethyl oxazolidinone enoates (*E*)-**6** (Table 4). The reaction proceeded smoothly with **D** (10 mol%) and provided adducts **7a–f** in high yields with excellent enantio- and diastereoselectivities (Table 4, entries 1–5). The reaction with γ-methyl-substituted butenolide also afforded **7f** with excellent diastereo- and enantioselectivity (Table 4, entry 6).

We have previously shown, through guanidine-catalyzed γ-selective allylic amination reaction, that enantiodivergent

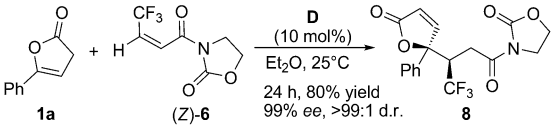
Table 4: The vinylogous Michael addition of **1** to (*E*)-**6** catalyzed by **D**.[a]



Entry	R (**7**)	*t* [h]	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	C_6H_5 (**7a**)	24	82	98	> 99:1
2	4-FC_6H_4 (**7b**)	24	78	97	> 99:1
3	4-ClC_6H_4 (**7c**)	24	83	97	> 99:1
4	4-BrC_6H_4 (**7d**)	24	86	98	> 99:1
5	4-$CH_3C_6H_4$ (**7e**)	24	88	98	> 99:1
6	CH_3 (**7f**)	72	77	98	> 99:1

[a] All reactions were performed with **1** (0.11 mmol), **6** (0.1 mmol), and **D** (0.01 mmol) in Et_2O (1.0 mL). [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Determined by ^{1}H NMR analysis.

synthesis can be achieved using *E*/*Z* double bond geometry.[20] Similarly, diastereodivergent synthesis can be achieved with the same strategy. Under the same reaction conditions, γ-phenyl-substituted butenolide **1a** and (*Z*)-**6** gave adduct **8** with both a high *ee* value and d.r., but with opposite enantioselectivity with regard to its diastereomer **7a** [Eq. (3)]. This example also represents the first organocatalytic asymmetric reaction that utilizes β-trifluoromethyl oxazolidinone enoate **6** as the electrophile.[19,21]



(3)

In an effort to elucidate the role of the oxazolidinone group and the origin of stereoselectivity, density functional theory (DFT) calculations[22] were performed for the reaction between **1a** and **2a**, catalyzed by **D**. As there are three possible carbonyl groups in **2a**, which act as hydrogen bond acceptors, four binding models with a total number of 16 transition states (TSs) were located to identify the most plausible reaction profile (see the Supporting Information). Comparison of the relative free energies of all transition states suggested that the reaction via the *SS*-TS has the lowest activation free energy of 16.9 kcal mol^{-1}. The stereochemistry was consistent with experimental results and the X-ray solid-state structure of **3a**. Careful examination of the *SS*-TS geometry showed that the oxazolidinone C=O group has a considerable interaction with the α-H of the pendent pyrrolium moiety of the catalyst through a non-classical C-H···O hydrogen bonding with a bond distance of 2.397 Å (Figure 2).[23] The Mayer bond order[24] for this interaction was 0.031 and the AIM analysis[25] showed a bond critical point (BCP) between the carbonyl O and α-H with calculated electron density of 0.0095 au, thus confirming this weak yet important interaction. Moreover, among all the TS structures surveyed, *SS*-TS was the only one that showed such an interaction! Because employing **2b** [Eq. (1)] instead of **2a** as the electrophile in this conjugate addition reaction resulted in

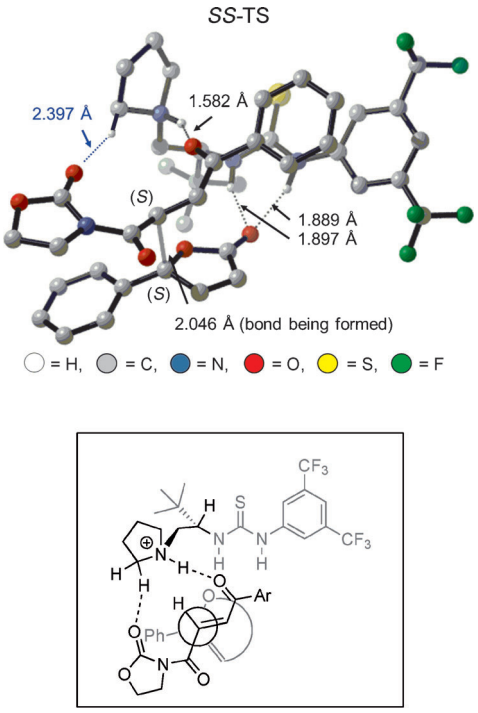
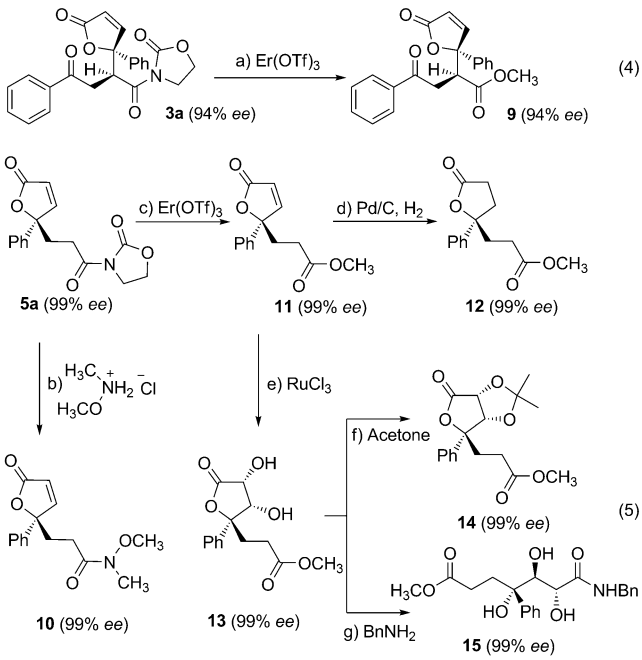


Figure 2. Transition-state geometry (B3LYP/6-31G**) leading to the (*S*,*S*) product.



Scheme 1. Several examples of transformation of the corresponding Michael adducts. Reagents and conditions: a) $Er(OTf)_3$ (1.0 equiv), CH_3OH/CH_2Cl_2 (1:1, *v*/*v*), 60 °C, 24 h, 85 % yield; b) $CH_3(CH_3O)NH{\cdot}HCl$ (5.0 equiv), $AlMe_3$ (6.0 equiv), CH_2Cl_2, 0 °C, 4 h, 73 % yield; c) $Er(OTf)_3$ (0.5 equiv), CH_3OH/CH_2Cl_2 (1:1, v/v), 25 °C, 3 h, 87 % yield; d) Pd/C, H_2, EtOAc, 25 °C, 12 h, 61 % yield; e) $RuCl_3{\cdot}H_2O$ (0.07 equiv), $NaIO_4$ (2.0 equiv), CH_3CN/H_2O (7:1, v/v), 5 min, 65 % yield; f) TsOH (0.1 equiv), acetone, RT., 24 h, 92 % yield; g) $BnNH_2$ (1.2 equiv), PhCl, −10 °C, 8 h, 92 % yield; h) $BnNH_2$ (1.2 equiv), PhCl, 60 °C, 24 h, 95 % yield. Bn = benzyl, Tf = trifluoromethanesulfonyl, TsOH = *p*-toluenesulfonic acid.

a poorer yield and selectivity, calculations with a removed carbonyl group were also conducted. Indeed, the corresponding *SS*-TS transition state was located with a much higher activation barrier (28.5 kcal mol^{-1}), thus suggesting a less favorable catalytic process.

To demonstrate the synthetic value and versatility of this work, we explored various important transformations to give key intermediates (Scheme 1). The 2-oxazolidinone group of **3a** could be converted to a methyl ester with $Er(OTf)_3$ in $MeOH/CH_2Cl_2$ (1:1) at 60 °C to afford the corresponding α-stereogenic ester **9** [Scheme 1, Eq. (4)]. Similarly, a β-substituted stereogenic Weinreb amide derivative **10** could be prepared from **5a** in the presence of $AlMe_3$ and $MeONHMe{\cdot}HCl$ [Scheme 1, Eq. (5)]. Compound **5a** can then be converted to alkene **11** in presence of $Er(OTf)_3$. Reduction of alkene **11** with hydrogen gas on Pd/C afforded 5,5-disubstituted dihydrofuran-2(3*H*)-one **12**.[26] Alternatively, a highly stereoselective dihydroxylation of **11** furnished compound **13** using $RuCl_3{\cdot}H_2O$ and $NaIO_4$. The acetonide **14** was obtained from **13** with 92 % yield using 10 mol % TsOH in acetone. A glycerol derivative **15**, which bears a tertiary hydroxy group, was obtained after reacting **13** with benzylamine; these analogues have exhibited significant biological activities[27] and are highly valued by synthetic organic chemists.[14,28]

In summary, we have successively developed the direct asymmetric vinylogous conjugate additions of γ-aryl- and alkyl-substituted butenolides. Suitable electrophiles include (*E*)-4-oxo-4-arylbutenamides with oxazolidinone motif, (*E*)-oxazolidinone enoates, and (*E*)-/(*Z*)-β-trifluoromethyl oxazolidinone enoate. Various γ,γ-butenolide-substituted α- and β-stereogenic amides that contain a quaternary chiral center were obtained in good to excellent yields with excellent enantio- and diastereoselectivities (up to 93 % yield, 99 % *ee*, and d.r. > 99:1). According to experimental observations and DFT calculations, the carbonyl group of oxazolidinone is responsible for interaction with the catalyst through weak nonbonding interactions. L-*tert*-Leucine-derived amine–thiourea could be easily prepared and was identified as the best catalyst with low catalyst loading needed. The enantiopure adducts serve as important synthetic fragments and allow access to biologically important γ,γ-disubstituted butenolides. Further investigations, which involve the application of this catalytic approach, are ongoing and will be reported in due course.

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