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Asymmetric Catalysis

Direct Catalytic Asymmetric Vinylogous Conjugate Addition of Unsaturated Butyrolactones to α,β-Unsaturated Thioamides**

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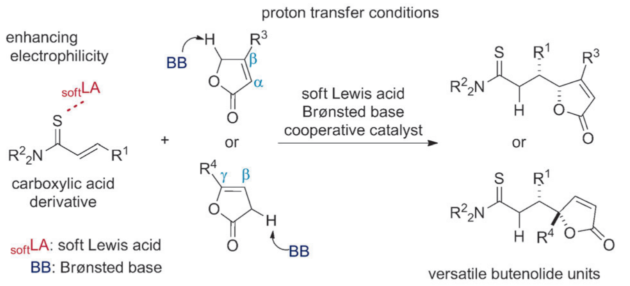
Abstract: *Soft Lewis acid/Brønsted base cooperative catalysts have enabled direct catalytic asymmetric vinylogous conjugate addition of α,β- and β,γ-unsaturated butyrolactones to α,β-unsaturated thioamides with perfect atom economy. When using α-angelica lactone and its derivatives as pronucleophiles, as little as 0.5 mol % catalyst loading was sufficient to complete the reaction necessary to construct consecutive tri- and tetrasubstituted stereogenic centers in a highly diastereo- and enantioselective fashion.*

Catalytic asymmetric conjugate additions are one of the most widely used methodologies in asymmetric carbon–carbon bond-forming reactions.[1] Compared with highly reactive enones, enals, and α,β-unsaturated nitroolefins, α,β-unsaturated carboxylic acid derivatives have been much less explored as Michael acceptors because of their inherently low electrophilicity. In the context of our continuing program of research in soft Lewis acid/hard Brønsted base cooperative catalysis,[2] specific activation of soft Lewis-basic α,β-unsaturated thioamides by a soft Lewis acid is key to compensating for the intrinsic low electrophilicity. Herein, we document the catalytic asymmetric vinylogous conjugate addition of α,β- and β,γ-unsaturated butyrolactones to α,β-unsaturated thioamides, a reaction allowing the generation of consecutive tri- and tetrasubstituted stereogenic centers.[3]

Butenolide units that feature a five-membered γ-lactone with unsaturation at α,β-carbon atoms occur in a wide range of natural products and biologically active compounds.[4] This ubiquitous nature of butenolides has attracted considerable attention regarding the development of a synthetic methodology for optically active butenolide-containing compounds.[5,6] The direct use of butenolides as pronucleophiles instead of 2-siloxyfurans[7–11] obviates undesired co-generation of silicon-derived by-products and the preactivation of butenolides, thus enabling an atom-economical entry into chiral building blocks bearing butenolide units.[12] The direct use of γ-butenolide in catalytic asymmetric conjugate addition was pioneered by Trost et al.,[13] and several reports from other groups demonstrated the synthetic utility of the direct conjugate addition.[14] However, the use of inherently less reactive α,β-unsaturated carboxylic acid derivatives as an electrophile has not been reported yet. In this context, we directed our efforts toward merging the specific activation of α,β-unsaturated thioamides and the utility of unsaturated butyrolactones as pronucleophiles in soft Lewis acid/Brønsted base cooperative catalysis (Scheme 1).[2]



Scheme 1. Direct catalytic asymmetric vinylogous conjugate addition of unsaturated butyrolactones to an α,β-unsaturated thioamide by a soft Lewis acid/Brønsted base cooperative catalysis.

We set out to identify the optimal combination of a soft Lewis acid and Brønsted base in the reaction of γ-crotonolactone (**1a**) with the α,β-unsaturated thioamide **2a** (Table 1). $[Cu(CH_3CN)_4]PF_6$/(*R*)-Segphos/$Li(OC_6H_4$-*p*-OMe) (5 mol %) produced the best reaction outcome, as it afforded **3a** with a yield of 84 % and 98 % *ee*, and the designated *syn* diastereomer was obtained exclusively.[15] The use of other soft Lewis acidic metal salts in combination with (*R*)-Segphos proved the superior catalytic efficiency of the copper(I) catalyst (entry 2 versus entries 7–9). Because $Li(OC_6H_4$-*p*-OMe) had to be prepared from *n*BuLi and HOC_6H_4-*p*-OMe just before use under anhydrous conditions, the alternative use of amine bases was advantageous for operational simplicity. DBU did not facilitate the reaction, but 50 mol % of either Et_3N or Cy_2NMe was effective in producing **3a** with comparable stereoselectivity (entries 10–12). Cy_2NMe afforded a slightly better yield and the catalyst loading could be further reduced to 2.5 mol % with Cy_2NMe (entry 13).

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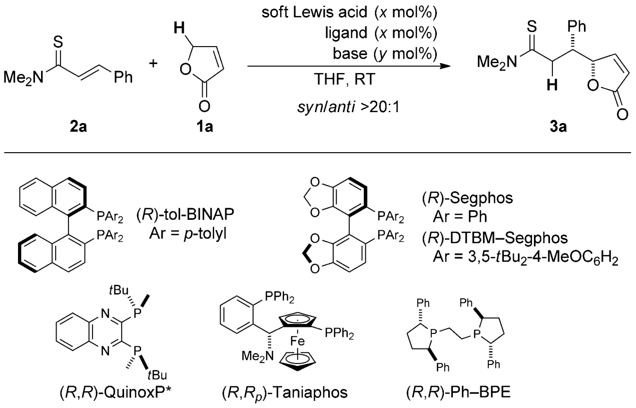
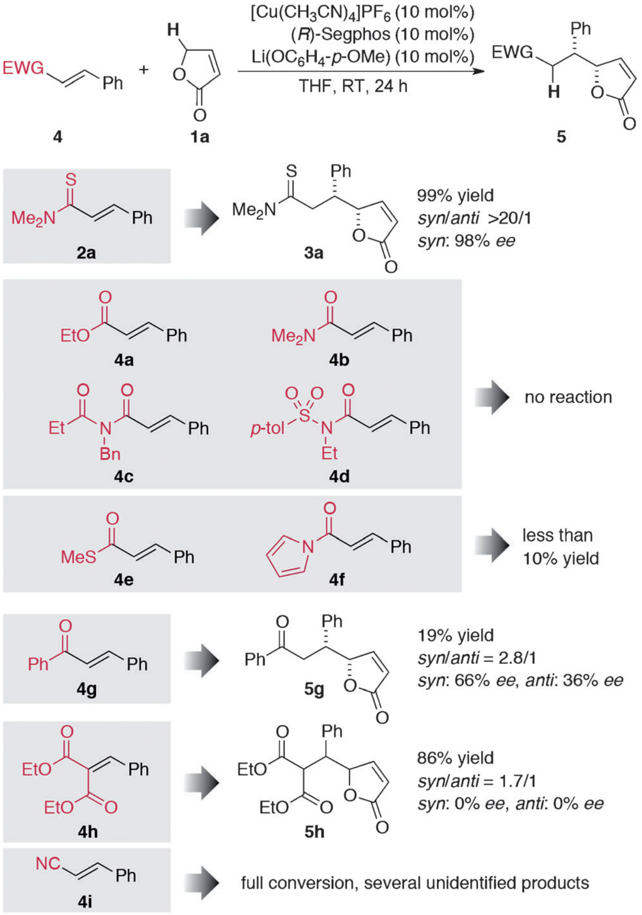
Table 1: Direct catalytic asymmetric vinylogous conjugate addition of γ-crotonolactone (**1a**) to the α,β-unsaturated thioamide **2a**.[a]



Entry	Soft Lewis acid	Ligand	x	Base	y	t [h]	Yield [%][b]	ee [%][c]
1	$CuPF_6$[d]	(*R*)-tol-BINAP	5	LiOAr[e]	5	24	56	96
2	$CuPF_6$[d]	(*R*)-Segphos	5	LiOAr[e]	5	24	84	98
3	$CuPF_6$[d]	(*R*)-DTBM-Segphos	5	LiOAr[e]	5	24	25	97
4	$CuPF_6$[d]	(*R*,*R*$_p$)-Taniaphos	5	LiOAr[e]	5	24	23	−56
5	$CuPF_6$[d]	(*R*,*R*)-QuinoxP*	5	LiOAr[e]	5	24	45	96
6	$CuPF_6$[d]	(*R*,*R*)-Ph-BPE	5	LiOAr[e]	5	24	72	−96
7	$AgPF_6$	(*R*)-Segphos	5	LiOAr[e]	5	24	12	80
8	$Pd(BF_4)_2$[d]	(*R*)-Segphos	5	LiOAr[e]	5	24	0	–
9	$Ni(OTf)_2$	(*R*)-Segphos	5	LiOAr[e]	5	24	trace	–
10	$CuPF_6$[d]	(*R*)-Segphos	5	DBU	50	24	trace	–
11	$CuPF_6$[d]	(*R*)-Segphos	5	Et_3N	50	24	88	98
12	$CuPF_6$[d]	(*R*)-Segphos	5	Cy_2NMe	50	24	99	98
13	$CuPF_6$[d]	(*R*)-Segphos	2.5	Cy_2NMe	50	72	95[f]	95

[a] **1a** (0.6 mmol), **2a** (0.2 mmol). [b] Determined by ^1H NMR analysis of the crude reaction mixture using $(CHCl_2)_2$ as an internal standard. [c] Determined by HPLC analysis. [d] Tetrakis(acetonitrile) complex was used. [e] LiOAr = $Li(OC_6H_4$-*p*-OMe). [f] Yield of isolated products. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, THF = tetrahydrofuran.

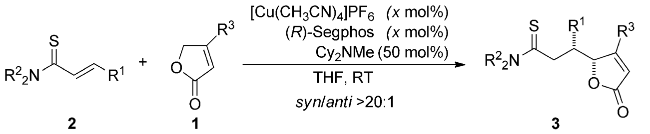


Scheme 2. Unsuccessful reactions using typical electron-deficient olefins as electrophiles.

In contrast with the smooth reaction using the α,β-unsaturated thioamide **2a**, which exhibited high stereoselectivity, the reaction of various typical electron-deficient olefins (**4**) resulted in no reaction when using 10 mol% of the cooperative catalyst consisting of $[Cu(CH_3CN)_4]PF_6$/(*R*)-Segphos/$Li(OC_6H_4$-*p*-OMe) (Scheme 2).[16] The electron-deficient olefins **4a**,**b** as well as the highly electron-deficient imide **4c** and the tosylated amide **4d**, resulted in complete recovery of the substrate.[17] Some conversion was detected in the reaction of the α,β-unsaturated thioester **4e** and the *N*-acylpyrrole **4f**. In the reaction of the α,β-unsaturated ketone **4g**, the desired conjugate addition proceeded partially (19% yield) to give **5g**, albeit with low diastereoselectivity (*syn*/*anti*: 2.8:1) and moderate enantioselectivity (*syn*: 66% *ee*, *anti*: 36% *ee*).[14a] The α-vinylidene malonate (**4h**) exhibited high reactivity, presumably because of its inherently high electrophilicity, to afford **5h** in 86% yield.[10f] The α,β-unsaturated nitrile **4i** was completely consumed under the present reaction conditions, however, the desired conjugate adduct was not detected. These collective unsuccessful reactions highlight the exclusive reactivity of the α,β-unsaturated thioamide **2a** in soft Lewis acid/Brønsted base cooperative catalysis, and further support the specific enhancement of electrophilicity through a soft–soft interaction. Indeed, NMR and mass spectroscopic analysis supported the formation of a ternary complex including (*R*)-Segphos/Cu^I/**2a**.[18]

The present catalytic asymmetric conjugate addition demonstrated wide substrate generality (Table 2). The reaction of β-aryl- or β-heteroaryl-substituted α,β-unsaturated thioamides proceeded smoothly with a 5 mol% catalyst loading, regardless of the electronic nature of the β-aryl or β-heteroaryl substituents (entries 1–10). *N*,*N*-Dibenzylthioamides could be employed as well as *N*,*N*-dimethylthioamide (entries 5, 7–9 and 13). A thioamide analogous to the Weinreb amide was also a suitable substrate (entry 11).[19] It is worth noting that high diastereo- and enantioselectivity was maintained for β-alkyl-substituted α,β-unsaturated thioamides. Although 10 mol% of catalyst was required to complete the reaction of β-Me and β-cyclohexyl thioamides, the corresponding conjugate addition products were obtained with high yield and stereoselectivity (entries 12 and 13). In particular, the reaction shown in entry 14 exemplified the exclusive 1,4-conjugate addition mode for α,β,γ,δ-unsaturated thioamides.

Table 2: Direct catalytic asymmetric vinylogous conjugate addition of the γ-butenolides **1** to α,β-unsaturated thioamides **2**.[a]



Entry	R^1	R^2		R^3		x	Product	t [h]	Yield [%][b]	ee [%][c]
1	Ph	Me	**2a**	H	**1a**	5	**3a**	12	96	98
2	2-MeC_6H_4	Me	**2b**	H	**1a**	5	**3b**	24	95	99
3	4-$MeOC_6H_4$	Me	**2c**	H	**1a**	5	**3c**	24	95	98
4	3-$MeOC_6H_4$	Me	**2d**	H	**1a**	5	**3d**	24	93	98
5	2-$MeOC_6H_4$	Bn	**2e**	H	**1a**	5	**3e**	12	98	97
6	4-$AcOC_6H_4$	Me	**2f**	H	**1a**	5	**3f**	24	94	94
7	4-FC_6H_4	Bn	**2g**	H	**1a**	5	**3g**	6	98	98
8[d]	4-BrC_6H_4	Bn	**2h**	H	**1a**	5	**3h**	6	94	98
9	3-pyridyl	Bn	**2i**	H	**1a**	5	**3i**	48	76	98
10	2-thienyl	Me	**2j**	H	**1a**	5	**3j**	12	97	98
11	Ph	Me, MeO	**2k**	H	**1a**	5	**3k**	24	94	98
12	Me	Me	**2l**	H	**1a**	10	**3l**	24	98[e]	96
13	cHex	Bn	**2m**	H	**1a**	10	**3m**	48	81	97
14	(E)-$CH_3CH{=}CH$	Me	**2n**	H	**1a**	5	**3n**	48	95	97
15	Ph	Me	**2a**	Me	**1b**	5	**3o**	48	78	98

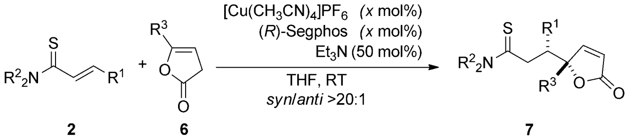
[a] **1** (0.6 mmol), **2** (0.2 mmol), 0.5 M in **2**. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] syn/anti = 14:1. [e] Based on the recovered starting material.

Next, we directed our efforts to apply this useful transformation to the construction of a tetrasubstituted stereogenic center. Recently, the utility of **6a** (for structure see Table 3) as a pronucleophile was explored in direct catalytic asymmetric alkylation,[20] vinylogous Mannich reaction,[21] and vinylogous conjugate addition.[14e] Specifically, conjugate addition was promoted through iminium catalysis and highly active enals were used as electrophiles. Although increasing steric constraint was anticipated at the transition state because of the methyl group located at the γ position of **6a**, we reasoned that the in situ generation of active nucleophiles and the subsequent conjugate addition would proceed in a similar manner. As expected, the optimized reaction conditions for the reaction using γ-crotonolactones (**1**) were applied successfully to the reaction of **6a**. The more common Et_3N was used to complete the reaction with a 0.5–2 mol% catalyst loading (Table 3, entries 1–11, 14, and 15).[22] Trends in substrate scope were similar to those listed in Table 2, and generally high diastereo- and enantioselectivity were observed for both β-aryl, β-heteroaryl, and β-alkyl (alkenyl) α,β-unsaturated thioamides. The reaction was conducted on a scale of more than 1 gram to show the robustness of the present catalysis (entry 4). The α-angelica lactone derivatives **6b** and **6c** were also used to afford the corresponding products with high stereoselectivity (entries 13 and 14).

Figure 1 delineates a plausible catalytic cycle. A vinylogous copper enolate is generated from either **1a** or **6a** by using a tertiary amine and the weak assistance of the Cu^I/(R)-Segphos complex. Subsequent coordination of **2a** to the tetracoordinate Cu^I center produces the transition-state **A**, in which one side of **2a** is shielded by a phenyl group of (R)-Segphos. By taking the identical stereochemical outcome from **1a** and **6a** into account, the enolates from **1a** and **6a** approach in a similar fashion, regardless of R^3 substituent, to preferentially produce a (3R,4S)-configured product.

The divergent transformation of the thioamide functionality of the conjugate adduct highlights the synthetic utility of the present process (Scheme 3). The thioamide moiety was transformed into amide, thioester, ketone, and aldehyde functionalities successfully. For the

Table 3: Direct catalytic asymmetric vinylogous conjugate addition of α-angelica lactone and its derivatives (**6**) to the α,β-unsaturated thioamides **2**.[a]



Entry	R^1	R^2		R^3		x	Product	t [h]	Yield [%][b]	ee [%][c]
1	Ph	Me	**2a**	Me	**6a**	1	**7a**	24	93	98
2	2-MeC_6H_4	Me	**2b**	Me	**6a**	1	**7b**	36	95	99
3	4-$MeOC_6H_4$	Me	**2c**	Me	**6a**	2	**7c**	24	96	99
4[d]	4-$MeOC_6H_4$	Me	**2c**	Me	**6a**	2	**7c**	24	93	99
5	3-$MeOC_6H_4$	Me	**2d**	Me	**6a**	2	**7d**	24	97	99
6	4-$AcOC_6H_4$	Me	**2f**	Me	**6a**	1	**7e**	36	88	98
7	4-FC_6H_4	Bn	**2g**	Me	**6a**	0.5	**7f**	24	92	97
8	4-BrC_6H_4	Bn	**2h**	Me	**6a**	1	**7g**	12	96	96
9	3-pyridyl	Bn	**2i**	Me	**6a**	2	**7h**	48	74	98
10	2-thienyl	Me	**2j**	Me	**6a**	0.5	**7i**	24	94	99
11	Ph	Me, MeO	**2k**	Me	**6a**	1	**7j**	24	91	99
12	cHex	Bn	**2m**	Me	**6a**	2	**7k**	72	51	98
13	Ph	Me	**2a**	Et	**6b**	1	**7l**	24	94	99
14	Ph	Me	**2a**	allyl	**6c**	2	**7m**	24	96	98
15	(E)-$CH_3CH{=}CH$	Me	**2n**	Me	**6a**	2	**7n**	48	83	98
16	EtO_2C	Me	**2o**	Me	**6a**	2	**7o**	12	94	96

[a] **6**: 0.6 mmol, **2**: 0.2 mmol, 0.5 M in **2**. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] 1.33 g of **2c** was used.

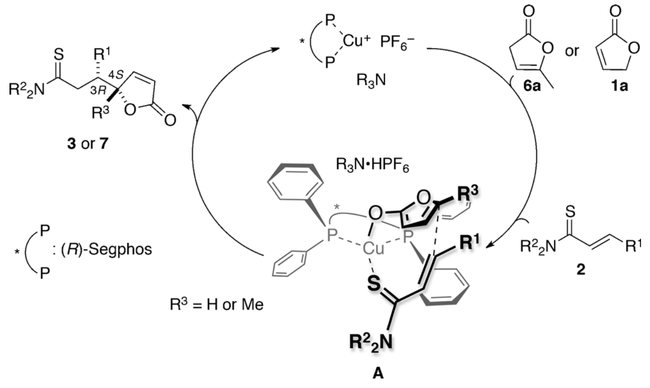
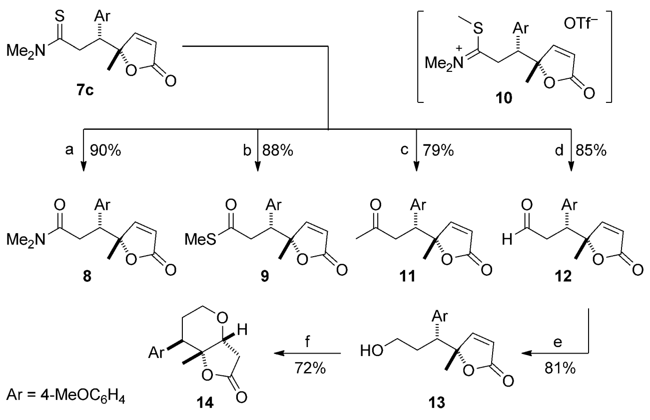


Figure 1. Plausible catalytic cycle.



Scheme 3. Transformation of the conjugate adduct. Reagents and conditions: a) TFAA, CH_2Cl_2, RT, 3 h, then $NaHCO_3$ aq, 90%. b) MeI, TFA, THF/H_2O (1:1), RT, 12 h, 88%. c) MeOTf, THF/Et_2O (1:1), RT, 10 min; then MeLi, −78 °C, 30 min, 79%. d) MeOTf, THF/Et_2O (1:1), RT, 10 min; then LiAlH(O*t*Bu)$_3$, −78 °C, 12 h, 85%. e) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 30 min, 81%. f) NaHMDS, THF, 0 °C, 1 h, 72%. HMDS = hexamethyldisilazide, TFAA = trifluoroacetic anhydride, TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl.

transformation into ketone and aldehydes, electrophilic activation of thioamide to give the iminothioether **10** was key. Intriguingly, Luche reduction of the aldehyde **12** gave the primary alcohol **13**,[23] which was transformed into the bicyclic compound **14** by intramolecular oxa-Michael reaction.[24]

In conclusion, a direct catalytic asymmetric vinylogous conjugate addition of γ-crotonolactone, α-angelica lactone, and their derivatives to α,β-unsaturated thioamides was developed. The cooperative action of a soft Lewis acid and a Brønsted base is crucial to promoting this reaction with high stereoselectivity. The use of related electron-deficient olefins as electrophiles failed to give the conjugate adduct because of the lack of a soft–soft interaction. The catalyst was readily prepared from a commercial source, and the reaction was conducted on a scale of more than 1 gram at room temperature, thus allowing the production of enantioenriched dicarbonyl compounds bearing consecutive stereogenic centers through an operationally simple protocol. The thioamide functionality was advantageous not only for specific activation by a cooperative catalyst, but also for divergent functional-group transformation, thus highlighting the synthetic utility of the present catalysis.

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[1] For reviews on catalytic asymmetric conjugate addition: a) D. Almaşi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; b) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; c) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123; d) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065; e) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279.

[2] For recent reviews of soft Lewis acid/hard Brønsted base cooperative catalysis, see: a) N. Kumagai, M. Shibasaki, *Angew. Chem.* **2011**, *123*, 4856; *Angew. Chem. Int. Ed.* **2011**, *50*, 4760; b) N. Kumagai, M. Shibasaki, *Isr. J. Chem.* **2012**, *52*, 604.

[3] For the concept of vinylogy, see: a) R. C. Fuson, *Chem. Rev.* **1935**, *16*, 1; b) S. Krishnamurthy, *J. Chem. Educ.* **1982**, *59*, 543.

[4] For reviews of natural products containing butenolides, see: a) A. Bermejo, B. Figadére, M. Zafra-Polo, I. Barrachina, E. Estornell, D. Cortes, *Nat. Prod. Rep.* **2005**, *22*, 269; b) J. D. Sellars, P. G. Steel, *Eur. J. Org. Chem.* **2007**, 3815; c) I. Prassas, E. P. Diamandis, *Nat. Rev. Drug Discovery* **2008**, *7*, 926; d) P. A. Roethle, D. Trauner, *Nat. Prod. Rep.* **2008**, *25*, 298.

[5] a) G. Casiraghi, F. Zanardi, L. Battistini, G. Rassu, *Synlett* **2009**, 1525; b) G. Casiraghi, L. Battistini, C. Curti, G. Rassu, F. Zanardi, *Chem. Rev.* **2011**, *111*, 3076.

[6] Q. Zhang, X. Liu, X. Feng, *Curr. Org. Synth.* **2013**, *10*, 764.

[7] For a newer review, see: G. Rassu, F. Zanardi, L. Battistini, G. Casiraghi, *Synlett* **1999**, 1333.

[8] For recent examples for catalytic asymmetric aldol reactions using 2-siloxyfurans, see: a) L. Palombi, M. R. Acocella, N. Celenta, A. Massa, R. Villano, A. Scettri, *Tetrahedron: Asymmetry* **2006**, *17*, 3300; b) K. D. Sarma, J. Zhang, T. T. Curran, *J. Org. Chem.* **2007**, *72*, 3311; c) M. J. Fabra, J. M. Fraile, C. I. Herrerías, F. J. Lahoz, J. A. Mayoral, I. Pérez, *Chem. Commun.* **2008**, 5402; d) M. Frings, I. Atodiresei, J. Runsink, G. Raabe, C. Bolm, *Chem. Eur. J.* **2009**, *15*, 1566; e) R. P. Singh, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2010**, *132*, 9558.

[9] For recent examples for catalytic asymmetric Mannich reactions using 2-siloxyfurans, see: a) E. I. Carswell, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **2006**, *118*, 7388; *Angew. Chem. Int. Ed.* **2006**, *45*, 7230; b) H. Mandai, K. Mandai, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, *130*, 17961; c) L. C. Wieland, E. M. Vieira, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 570; d) A. S. González, R. G. Arrayás, M. R. Rivero, J. C. Carretero, *Org. Lett.* **2008**, *10*, 4335; e) Z.-L. Yuan, J.-J. Jiang, M. Shi, *Tetrahedron* **2009**, *65*, 6001; f) H.-P. Deng, Y. Wei, M. Shi, *Adv. Synth. Catal.* **2009**, *351*, 2897; g) T. Akiyama, Y. Honma, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2008**, *350*, 399.

[10] For recent examples for catalytic asymmetric conjugate addition using 2-siloxyfurans, see: a) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051; b) J. S. Yadav, B. V. S. Reddy, G. Narasimhulu, G. Satheesh, *Tetrahedron Lett.* **2008**, *49*, 5683; c) H. Yang, S. Kim, *Synlett* **2008**, 555; d) H. Suga, T. Kitamura, A. Kakehi, T. Baba, *Chem. Commun.* **2004**, 1414; e) Q. Zhang, X. Xiao, L. Lin, X. Liu, X. Feng, *Org. Biomol. Chem.* **2011**, *9*, 5748; f) J. M. Fraile, N. García, C. I. Herrerías, *ACS Catal.* **2013**, *3*, 2710.

[11] Other recent example of catalytic asymmetric C–C bond-forming reactions using 2-siloxyfurans, see: Y.-Q. Jiang, Y.-L. Shi, M. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 7202.

[12] B. M. Trost, *Science* **1992**, *254*, 1471.

[13] B. M. Trost, J. Hitce, *J. Am. Chem. Soc.* **2009**, *131*, 4572.

[14] a) Y. Zhang, C. Yu, Y. Ji, W. Wang, *Chem. Asian J.* **2010**, *5*, 1303; b) N. E. Shepherd, H. Tanabe, Y. Xu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, *132*, 3666; c) J. Wang, C. Qi, Z. Ge, T. Cheng, R. Li, *Chem. Commun.* **2010**, *46*, 2124; d) H. Huang, F. Yu, Z. Jin, W. Li, W. Wu, X. Liang, J. Ye, *Chem. Commun.* **2010**, *46*, 5957; e) A. Quintard, A. Lefranc, A. Alexakis, *Org. Lett.* **2011**, *13*, 1540; f) M. Terada, K. Ando, *Org. Lett.* **2011**, *13*, 2026; g) Addition to α,β-unsaturated imides, see: W. Zhang, D. Tan, R. Lee, G. Tong, W. Chen, B. Qi, K.-W. Huang, C.-H. Tan, Z. Jiang, *Angew. Chem.* **2012**, *124*, 10216; *Angew. Chem. Int. Ed.* **2012**, *51*, 10069.

[15] Relative and absolute configuration of **3a** was determined after converting the thioamide moiety into a phenyl ketone. See the Supporting Information.

[16] Li(OC$_6$H$_4$-*p*-OMe) was selected as a Brønsted base because the lithium cation may have a beneficial effect on the electrophilic activation of carbonyl-type electrophiles. The application of the optimized reaction conditions for the reaction of the α,β-unsaturated thioamide **2a** with the electrophiles **4a–i** yielded nearly identical reaction outcomes.

[17] The reaction using dicarbonyl compounds for example, methyl furanoate and its half amide also did not react under identical reaction conditions.

[18] See the Supporting Information.

[19] For the utility of Weinreb amide, see: a) S. Balasubramaniam, S. Aidhen, *Synthesis* **2008**, 3707; b) S. G. Davies, A. M. Fletcher, J. E. Thomson, *Chem. Commun.* **2013**, *49*, 8586.

[20] H.-L. Cui, J.-R. Huang, J. Lei, Z.-F. Wang, S. Chen, L. Wu, Y.-C. Chen, *Org. Lett.* **2010**, *12*, 720.

[21] L. Zhou, L. Lin, J. Ji, M. Xie, X. Liu, X. Feng, *Org. Lett.* **2011**, *13*, 3056.

[22] Relative and absolute configuration of **7a** was determined by X-ray crystallographic analysis.987259 contains the supplementary crystallographic data for **7a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[23] a) J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226; b) A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454.

[24] Stereochemistry was confirmed by an NOE experiment. See the Supporting Information.