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Intramolecular Sulfur Transfer in *N*-Enoyl Oxazolidine-2-thiones Promoted by Brønsted Acids. Practical Asymmetric Synthesis of β-Mercapto Carboxylic Acids and Mechanistic Insights

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Abstract: The ability of Brønsted acids alone to efficiently promote the sulfur transfer process in *N*-enoyl oxazolidine-2-thiones to give β-mercapto carbonyl derivatives is demonstrated. The reactions proceed with essentially perfect diastereocontrol for a range of alkyl-substituted *N*-enoyl oxazolidine-2-thiones (d.r. regularly above 98:2) and high selectivity for most aryl-substituted counterparts (d.r. typically above 92:8). Importantly, the reaction works remarkably well in β,β-disubstituted *N*-enoyl oxazolidine-2-thiones as well, giving rise to quaternary C−S stereocenters in selectivities usually above 95:5. The relative efficiency of a range of acids (trifluoroacetic, difluoroacetic, acetic, triflic) is assessed showing TFA and TfOH as the most efficient and acetic acid as a totally inefficient reaction promoter. The new procedure complements the Lewis acid promoted reaction previously described by our group in two aspects: First, stereodivergent results are obtained for the Lewis acid or Brønsted acid promoted reactions of β,β-disubstituted enoyl compounds. Second, while the Brønsted acid promoted reactions are stereospecific, providing a good correlation between the substrate *E*/*Z* configuration and products stereochemistry, the reactions mediated by Lewis acids (BF_3/OEt_2) provide invariant d.r. values regardless of the *E*/*Z* composition of the starting olefin. The synthetic value of the method is illustrated by (a) removal of the oxazolidinone moiety from the rearranged products under reducing conditions ($NaBH_4$, H_2O−THF) which yields β-mercapto alcohols and (b) treatment with $Sm(OTf)_3$ in MeOH which affords the corresponding β-mercapto carboxylic esters, both categories of compounds being isolated in up to 97% ee. Remarkably, the method constitutes the first general approach to highly enantioenriched building blocks bearing a quaternary C−S stereocenter. On the other hand, spectroscopic and inhibition experiments are carried out that demonstrate the participation of protons also in the Lewis acid promoted reactions. Finally, the computational studies carried out at the B3LYP/6-31G* level give support for an activation of the substrate enoyl by complexation with two molecules of either the Brønsted or Lewis acid and serve to explain the stereochemical outcome of the reactions.

Introduction

Among the existing methods for the synthesis of sulfur-containing molecules,[1] the Michael type addition of thiols to α,β-unsaturated carbonyls is of prime importance.[1,2] By this process, a new C−S bond is constructed at the β position of the carbonyl group, and further chemical manipulation of the latter opens the way to a range of structurally and functionally diverse sulfur-containing building blocks. Despite the interest of such building blocks as components of biologically active compounds, odorants,[3] and chiral ligands in catalysis, only a limited number of methods for the efficient asymmetric synthesis of β-thio carbonyls are available, in sharp contrast to the wealth of methods for accessing their β-oxy and β-amino congeners. The asymmetric Michael type addition of thiols to electron-deficient olefins is documented by using stoichiometric chiral auxiliaries[4] and reagents[5] or alternatively chiral catalysts,[6,7] including organocatalysts.[8] While the use of chiral catalysts is clearly more advanced, achieving high levels of reaction

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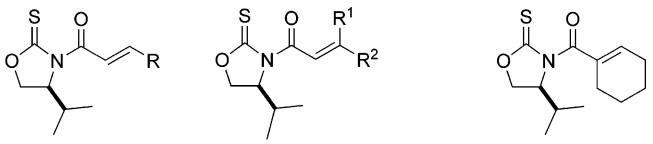
efficiency and selectivity under catalytic conditions is rather challenging, and methods that provide regularly high enantioselectivity (ee's above 90%) are scarce.[9] Moreover, the range of thiols well suited for both catalytic and stoichiometric methodologies is limited, being in most cases restricted to thiophenols.

Quite recently, we reported on a conceptually new approach to β-thio carbonyls, which relies on the Lewis acid promoted intramolecular sulfur transfer in *N*-enoyl oxazolidine-2-thiones (Chart 1).[10,11] Our method, Scheme 1, complements most of the existing ones in that it directly produces mercaptans instead of sulfides, a transformation that can be conceived as a formal conjugate addition of a "SH^-" anion. An additional strength of the method is the remarkably high stereoselectivity obtained with β,β-disubstituted enoyl acceptors (R^1, $R^2 \neq H$) to give quaternary C−S stereocenters. The overall process involves a dual function of the oxazolidine-2-thione auxiliary: as the controller of the reaction stereochemistry and as the sulfur transfer reagent.[12]

Herein we report full details of our work that demonstrates for the first time the validity of Brønsted acids as promoters of the sulfur migration process, which makes the method free from metal. New experimental and computational results toward getting some mechanistic insights of the reaction are also disclosed.

Chart 1. Survey of β-Mono- and β,β-Disubstituted *N*-Enoyl Oxazolidine-2-thiones Used Across This Study

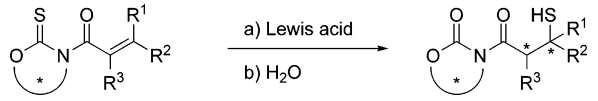


1a R: Me
1b R: Et
1c R: Pr
1d R: ^{i}Pr
1e R: Ph
1f R: 4-MeC_6H_4
1g R: 4-$MeOC_6H_4$
1h R: 4-ClC_6H_4
1i R: 3-BrC_6H_4
1j R: 2-$NO_2C_6H_4$

2a R_1: Me R_2: Ph
2b R_1: Me R_2: 4-MeC_6H_4
2c R_1: Me R_2: 4-$MeOC_6H_4$
2d R_1: Me R_2: 4-ClC_6H_4
2e R_1: Me R_2: 4-BrC_6H_4
2f R_1: Me R_2: 4-CNC_6H_4
2g R_1: nBu R_2: Ph

3

Scheme 1. General Pictogram of the Intramolecular Sulfur Transfer in *N*-Enoyl Cyclic Thiocarbamates (Oxazolidine-2-thiones) Promoted by Lewis Acids



Results and Discussion

Activation of the Michael Acceptor: Lewis Acid−Brønsted Acid Dichotomy. Prior reports from this laboratory have documented the efficiency of certain Lewis acids, particularly $SnCl_4$ and $BF_3{\cdot}Et_2O$,[13] in promoting the intramolecular sulfur transfer reaction shown in Scheme 1.[10,11] In the absence of the Lewis acid, no reaction is observed even at room temperature for prolonged reaction times. In subsequent, closely related work by Kataoka and co-workers, the tandem Michael−aldol reaction of *N*-enoyl oxazolidine-2-thiones with aldehydes or acetals was shown to proceed in the presence, again, of $BF_3{\cdot}Et_2O$ or $SnCl_4$ as the reaction promoters.[14] In general, Lewis acid assisted conjugate additions to enoyl systems are presumed to be accelerated via carbonyl−metal complexation which lowers the substrate LUMO energy. Nevertheless, for the Lewis acid mediated hetero-Michael addition reactions, Spencer and co-workers have recently revealed that protons, generated through hydrolysis of metal complexes, can be the true active catalysts.[15] We also found circumstantial evidence for the intervention of protons during the sulfur transfer process. Hence, pairs of reactions were carried out, respectively, in the presence or absence of 2,6-di-*tert*-butylpyridine, a base that binds to protons but is apparently unable to coordinate to metal ions,[16] and the

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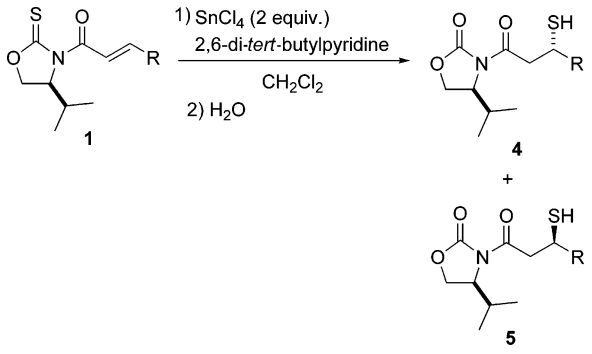
Table 1. Effect of 2,6-Di-*tert*-butylpyridine Additive on the Lewis Acid Promoted Sulfur Transfer Reaction in *N*-Enoyl Oxazolidine-2-thiones **1**[a]



compd	R	2,6-di-*tert*-butylpyridine (mol equiv)	*T* (°C)	*t* (h)	conv (%)
1a	Me		−78	2	95
	Me	2.5	−78	2	67
1b	Et		−78	3	>95
	Et	2.5	−78	3	20
1f	4-MeC_6H_4		rt	18	70
	4-MeC_6H_4	2.5	rt	18	0
1h	4-ClC_6H_4		rt	15	>90
	4-ClC_6H_4	2.5	rt	15	0

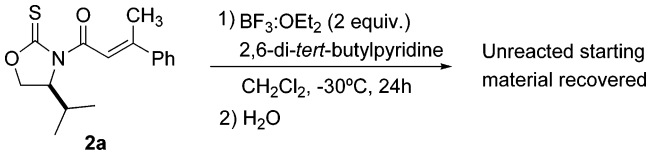
[a] Reactions were carried out at 0.2 mmol scale in 2 mL of dry CH_2Cl_2 under a nitrogen atmosphere. Diastereomeric ratio of the products not determined.

reaction conversions were measured. For instance, Table 1, the reaction of enoyl derivatives **1a** and **1b** with 2 mol equiv of $SnCl_4$ is clearly retarded in the presence of the pyridine base (conversion decay from 95% to 67% and from >95% to 20% after 2 and 3 h of reaction, respectively). This effect is even more drastic in the cases of β-aryl substituted substrates (**1f** and **1h**), wherein the reactions were essentially suppressed by the presence of the pyridine base, even at room temperature. As a matter of fact, in the context of the transformation considered here, β-aryl-substituted enoyl substrates, such as **1e**−**j** and **2** (Chart 1), proved to be substantially less reactive than the β-alkyl-substituted counterparts. This general trend justified the often different ranges of reaction temperature employed for both categories of compounds (see below).

Similarly, as shown in Scheme 2, $BF_3{\cdot}Et_2O$ was totally ineffective in promoting the reaction of β,β-disubstituted substrates in the presence of the pyridine base.

Given these preliminary results, and owing to the current interest in the development of metal-free synthetic methodologies,[17,18] we decided to investigate new conditions for triggering

Scheme 2. Inhibition of the $BF_3{\cdot}Et_2O$-Promoted Sulfur Transfer Reaction in β,β-Disubstituted Substrates by the Presence of 2,6-Di-*tert*-butylpyridine Base



the above sulfur transfer reaction that would require less of the metal promoter in the reaction. Accordingly, a set of experiments were carried out with substrates **1** using diverse combinations of Lewis acid ($SnCl_4$) and Brønsted acid (trifluoroacetic acid, TFA), Table 2. As the results show, the reaction of **1a** at −78 °C in the presence of 1 mol equiv of TFA worked with as little as 20 or even 10 mol % of the Lewis acid,[19] though considerably long reaction times were needed for optimal conversions. Shorter reaction times (15 h) were attainable by just increasing the loading of TFA up to 2 mol equiv (entries 2, 4). Under these conditions (200 mol % TFA), the transformation was essentially complete even in the total absence of the Lewis acid (entry 5) which rendered the method free from metal. Remarkably, the above conditions gave products with up to >98:2 diastereomeric purity in the cases studied.

Observations were somewhat different with the aryl-substituted substrate **1e**, which under substoichiometric quantities of $SnCl_4$ (50, 20, or 10 mol %, entries 6−8) led to diminished diastereoselectivities (from >95:5 to 85:15 using 10 mol % $SnCl_4$) and reaction rates (a poor 33% conversion was obtained after 48 h at −50 °C with only TFA, entry 9). These disadvantages could be circumvented by increasing the reaction temperature. Thus, after 48 h of reaction at −20 °C, in the total absence of $SnCl_4$ (entry 10), consumption of the substrate **1e** was complete and products **4e**/**5e** were formed in a 95:5 isomeric ratio and 80% isolated yield. While the reaction time could be further shortened by an additional increase of the temperature (2 h at 0/25 °C, entries 11, 12) with no apparent effect on the stereoselectivity, formation of side products became a problem.

Reaction Optimization and Scope for β-Monosubstituted Substrates. With these results in hand, which demonstrate the capability of TFA alone in promoting the reaction, further optimization of the reaction conditions and the scope with β-monosubstituted *N*-enoyl oxazolidine-2-thione substrates were investigated. First, the performance of several Brønsted acids other than TFA was surveyed, Table 3. A comparison of trifluoroacetic, difluoroacetic, acetic, and triflic acids showed good correlation between the strength of the acid and its performance. Thus acetic acid, the weakest acid, proved to be completely inefficient at transforming alkyl-substituted substrate **1a**, while triflic acid gave similar levels of chemical and stereochemical efficiency to those obtained with TFA. Difluoroacetic acid behaved as a borderline case, giving rise to comparable selectivity but slightly lower reactivity. For these reactions, temperatures in the range −78 °C/−20 °C could be used with little variation on yield and diastereoselectivity. Temperatures above −20 °C favored the formation of side-product **6** (Scheme 3), which was the almost exclusive product

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Table 2. Sulfur Transfer Reactions under Substoichiometric Loadings of $SnCl_4$ in the Presence of TFA[a]

entry	substrate, R	$SnCl_4$ (mol %)	TFA (mol equiv)	*T* (°C)	*t* (h)	conv (%)	ratio[b] **4:5**	yield (%)
1	**1a**, Me	20	1	−78	24	>95	98:2	n.d.
2	**1a**, Me	20	2	−78	15	>95	98:2	70
3	**1a**, Me	10	1	−78	40	75	98:2	n.d.
4	**1a**, Me	10	2	−78	15	>95	98:2	78
5	**1a**, Me	0	2	−78	24	95	98:2[c]	70
6	**1e**, Ph	50	2	−50	68	>95	>95:5	77
7	**1e**, Ph	20	2	−50	168	70	80:20	
8	**1e**, Ph	10	2	−50	60	50	85:15	
9	**1e**, Ph		2	−50	48	33	>95:5	
10	**1e**, Ph		2	−20	48	90	95:5	80[d]
11	**1e**, Ph		2	0	2	>95	95:5	n.d.
12	**1e**, Ph		2	rt	2	>95		mixtures

[a] All reactions were run at a 0.5 mmol scale in 10 mL of dry CH_2Cl_2 under a nitrogen atmosphere. [b] Determined by ^1H and ^{13}C NMR. [c] Determined by HPLC. [d] Reaction run at 1 mmol scale.

Scheme 3. Thermally Favored Formation of Side-Product **6** and Analogue **7** under Brønsted and Lewis Acid Conditions, Respectively, and a Plausible Interpretation of the Course of the Reaction

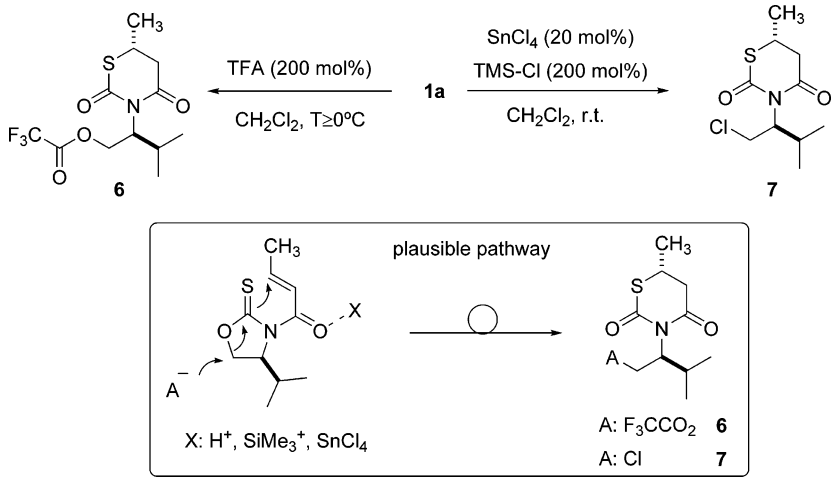
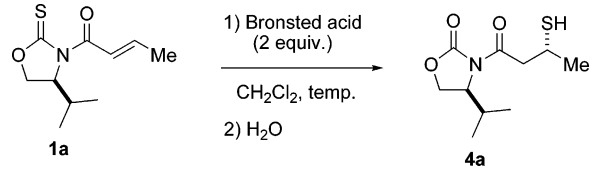


Table 3. Fitting the Best Brønsted Acid and Reaction Temperature[a]



Brønsted acid	*T* (°C)	*t* (h)	conversion (%)	d.r.[c] (**4a**)	yield (%)
CF_3CO_2H	−78	24	95	98:2	70
	−40	20	>95	96:4	n.d.
	−20	6	>95	94:6	75
	0	16[b]	>95	n.d.	82[d]
	rt	24[b]	>95	n.d.	80[e]
CF_2HCO_2H	−78	24	87	95:5	76
CH_3CO_2H	−78	20	0		
CF_3SO_3H	−78	20	>95	96:4	78

[a] All reactions were carried out at 0.5 mmol scale in 10 mL of dry CH_2Cl_2 under a nitrogen atmosphere. [b] Reaction time was not controlled. [c] Determined by HPLC. [d] Crude yield of a **4a**/**6** mixture of 65:35 ratio. [e] Crude yield of a **4a**/**6** mixture of 5:95 ratio.

at room temperature. Generation of compound **6** might imply nucleophilic opening of the oxazolidine ring with concomitant formation of the six-membered tiaazacycle. In fact, a similar compound **7**, whose structure was determined by X-ray crystallography,[20] is the major compound isolated upon treatment of **1a** with excess trimethylchlorosilane in the presence of $SnCl_4$ at room temperature, an observation that further stresses the necessity of subzero temperatures.[21]

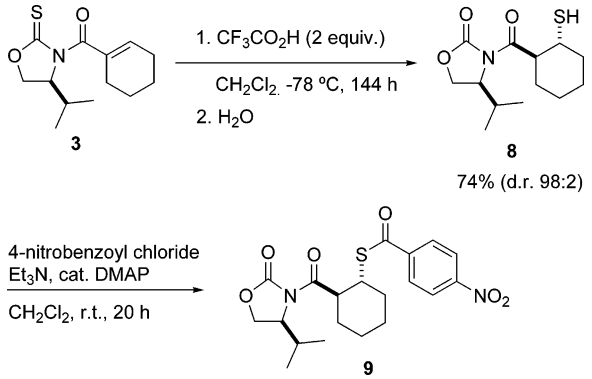
Table 4. Scope of the TFA-Promoted Sulfur Transfer Reaction in *β*-Monosubstituted *N*-Enoyl 4-Isopropyloxazolidine-2-thiones **1**[a]

compd **1**	R	*T*, °C	*t*, h	ratio **4:5**	yield,[b] %
a	Me	−78	24	98:2	70
b	Et	−78	24	98:2	72
c	Pr	−78	48	98:2	76
d	*i*Pr	−78	48	98:2	78
e	Ph	−20	48[c]	93:7[d]	80
f	4-Me−C_6H_4	−20	25	86:14[e]	75
g	4-MeO−C_6H_4	−20	168	70:30	40[f]
h	4-Cl−C_6H_4	−20	24	92:8[g]	80
i	3-Br−C_6H_4	−20	24	95:5	87
j	2-NO_2−C_6H_4	−20	96	98:2	88

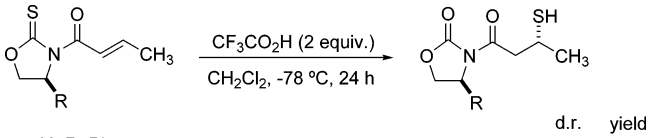
[a] Reactions conducted on a 0.5 mmol scale in 10 mL of dry CH_2Cl_2 under a nitrogen atmosphere. [b] Yield of isolated product after column chromatography. [c] Reaction run at 1 mmol scale. [d] Diastereoselectivity >98:2 after column chromatography. [e] The same d.r. was obtained when the reaction was run at −30 °C. [f] A subproduct appeared from the beginning of the reaction whose structure has not been elucidated yet. [g] Diastereoselectivity 98:2 after column chromatography.

Accordingly, conditions for the reaction of *β*-alkyl-substituted *N*-enoyl oxazolidine-2-thiones with TFA were set at −78 °C in dichloromethane as solvent,[22] while the temperature for the

Scheme 4. TFA-Promoted Sulfur Transfer Reaction in Cyclic α,β-Disubstituted Substrate Involving the Generation of Two Contiguous Stereocenters



Scheme 5. Testing the Efficacy of Other Oxazolidine-2-thione Auxiliaries



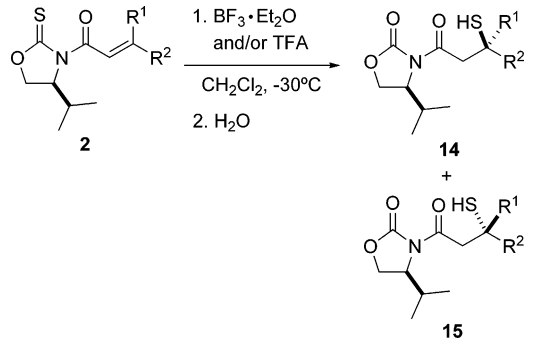
		d.r.	yield
10 R: Ph	**12** R: Ph	98:2	81%
11 R: Bn	**13** R: Bn	98.2	60%

β-aryl-substituted series was set at −20 °C (see Table 2). The results in Table 4 demonstrate the scope of the method. Substrates bearing linear as well as branched alkyl groups gave the corresponding β-mercapto adducts **4**/**5** in generally good yield and uniform diastereomeric ratio of about 98:2. The reactions involving substrates bearing aromatic R groups (Table 4, entries e−j) afforded isolated yields above 80% and diastereoreomeric ratios of 92:8 or higher when electron neutral (**1e**) or electron poor (**1h**−**j**) aromatic rings are involved. However, substrates **1f** and **1g**, which bear electron rich aromatic substituents, led to diminished selectivity and, in some cases, formation of undesired side products. The configuration of adducts **4a** and **4e** was established by X-ray crystal structure analysis and for the remaining adducts was assigned by assuming a uniform reaction mechanism which was supported by comparison with previously obtained chromatographic, spectroscopic, and crystallographic data.[20]

In addition to the above examples involving substrates bearing a single β-substituent group, cyclic enoyl substrates can be used successfully. In this instance, enoyl systems possessing substituents at both the α and β positions are involved thereby leading to products having two new contiguous stereocenters. For example, substrate **3** upon treatment with TFA in methylene chloride at −78 °C afforded **8** as the almost exclusive product out of the four possible diastereomers in 74% isolated yield (Scheme 4). Formation of the essentially pure trans product only, whose configuration was established by an X-ray crystal structure analysis of its *p*-nitrobenzoyl derivative **9**,[20] implies a highly biased α-protonation of the intermediate enolic species.

It is worth remarking that while we have systematically employed the chiral oxazolidine-2-thione auxiliary bearing the isopropyl R group, closely related auxiliaries such as those bearing phenyl or benzyl groups, Scheme 5, imparted the same level of stereocontrol, although the chemical yield may fluctuate.

Table 5. Sulfur Transfer Reaction of β,β-Disubstituted Substrates[a]



entry	compd	R^1	R^2	$BF_3{\cdot}Et_2O$ (equiv)	TFA (equiv)	*t* (h)	**14**:**15**[b]	yield[c] (%)
1	**2a**	Me	Ph	2		9	>99:1	80
2				0.2	2	24	25:75	n.d.
3					2	48	5:95	70
4	**2b**	Me	4-MeC_6H_4	2		7	>97:3	77
5					2	29	5:95	60
6	**2c**	Me	4-$MeOC_6H_4$	2		7	52:48	65
7					2	48	33:67	67
8	**2d**	Me	4-ClC_6H_4	2		9	92:8	72
9					2	60	3:97	59
10	**2e**	Me	4-BrC_6H_4	2		72	98:2	76
11					2	72	3:97	83
12	**2f**	Me	4-CNC_6H_4	2		36	92:8	73
13					2	140	1:99	69
14	**2g**	*n*Bu	Ph	2		15	96:4	68
15					2	36	4:96	65

[a] Reactions conducted at 0.5 mmol scale and 0.1 M substrate concentration. [b] Determined by ^1H and/or ^{13}C NMR. [c] Yield of isolated compound after column chromatography.

***β,β*-Disubstituted β-Mercapto Carboxylic Acid Derivatives.** In view of the results noted above, it was considered instructive to study the behavior of β,β-disubstituted Michael acceptors wherein the sulfur migration would generate a C−S bond with a quaternary carbon stereocenter,[23] an issue that remains essentially unexplored within the asymmetric endeavor.[24] Hence, the search for the optimum reaction conditions with β,β-disubstituted enoyl substrates was taken employing compounds **2a** and **2b** as a testing bench. As in the case of the monosubstituted substrates disclosed earlier, it was found that the reaction of **2** with 2 mol equiv of TFA proceeded satisfactorily, even in the absence of the Lewis acid (Table 5, entries 2, 3, 5). Reaction times with TFA were considerably longer than those using $BF_3{\cdot}Et_2O$, but the diastereomeric ratios were only slightly inferior. For example, for the reaction of substrate **2a**, the observed diastereoselectivity varied from >99:1 with $BF_3{\cdot}Et_2O$ to 5:95 with TFA (entries 1 and 3), and for the reaction of substrate **2b**, the variation was from >97:3 to 5:95 (entries 4 and 5). In some instances, the TFA-promoted reaction showed even superior stereoselectivity (compare entries 12 and 13). The TFA-promoted transformation involving β,β-disubstituted enoyl substrates appears to be quite general for a series of methyl-aryl substituted entries. It is worth noting that the

(20) See ref 10 and the Supporting Information for details.
(21) Formation of products structurally related to **6** and **7** in reactions assisted by excess $NbCl_5$ has been described recently. See: Hernández, H.; Bernès, S.; Quintero, L.; Sansinenea, E.; Ortiz, A. *Tetrahedron Lett.* **2006**, *47*, 1153−1156.
(22) The same reaction under otherwise identical conditions did not work at all in THF as solvent and led to only 25% conversion in Et_2O after 24 h.
(23) For recent reviews on quaternary carbon stereocenters, see: (a) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146. (b) *Quaternary Stereocenters*; Christoffers, J., Baro, A., Eds.; Wiley-VCH: 2005. (c) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473−1482.

Scheme 6. Diastereomeric Composition of the Sulfur Migration Product as a Function of the *E/Z* Composition of Substrate Olefin

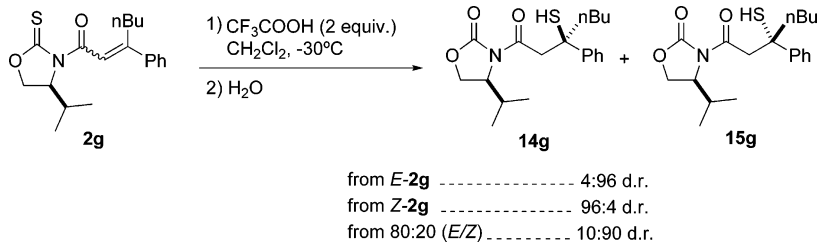
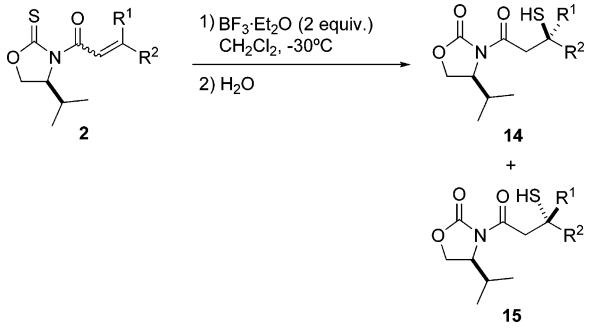


Table 6. $BF_3{\cdot}Et_2O$-Assisted Sulfur-Transfer Reaction in β,β-Disubstituted *N*-Enoyl Oxazolidine-2-thione of Variable *E*/*Z* Composition[a]



			substrate **2**	product **14**/**15**
compound	R^1	R^2	*E*/*Z* ratio[b]	dr[b]
e	Me	4-BrC_6H_4	100:0	92:8
			30:70	92:8
f	Me	4-CNC_6H_4	100:0	92:8
			83:13	92:8
g	*n*-Bu	Ph	100:0	96:4
			50:50	96:4
			0:100	96:4

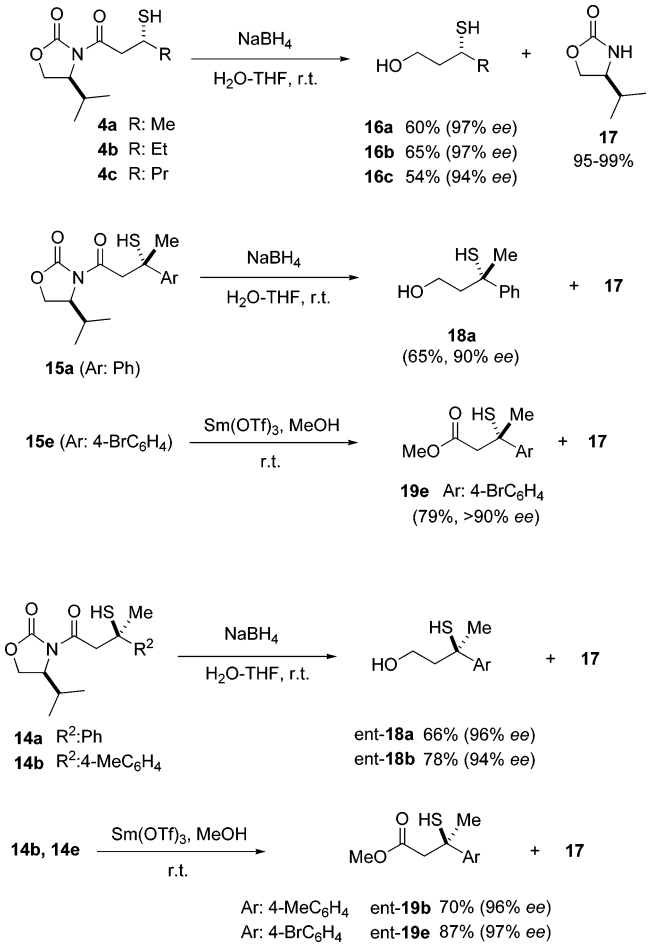
[a] Reactions conducted at 0.5 mmol scale and 0.1M substrate concentration. Ratio of **2**:$BF_3{\cdot}Et_2O$ 1:2. [b] Determined by 500 MHz ^1H NMR.

sense of the asymmetric induction in Lewis acid and Brønsted acid promoted reactions was opposite, and thus products of either configuration are easily accessible by the proper choice of the promoter employed, without the need for changing the source of chiral information. On the other hand, a similar trend is observed in both the TFA and $BF_3{\cdot}Et_2O$ series for the stereochemical efficiency as a function of the electronic nature of the aryl group. Thus, while substrates bearing electron rich aryl substituents behaved poorly under either reaction promoter (entries 6 and 7), substrates with electron neutral (entries 1−5) and especially electron poor (entries 8−13) aryl substituents behaved remarkably. In addition, the size of the "small" substituent at the β position does not influence selectivity very much in both promoted processes (entries 14, 15).

During the course of our investigation it was observed that the TFA-promoted transformation of β,β-disubstituted enoyl systems is a stereospecific process. Thus, as shown in Scheme 6, the *E*-configured substrate **2g** led to adduct **14g** as the major stereoisomer (96:4 isomeric ratio), while the *Z*-configured **2g** furnished **15g** as the major product (4:96 ratio). Also in accordance with these results, a product of lower diastereomeric purity was obtained when starting from configurationally nonhomogeneous **2g** (product of 10:90 d.r. obtained from an 80:20 *E*/*Z* isomeric mixture).

In striking contrast, the $BF_3{\cdot}Et_2O$-promoted transformation of β,β-disubstituted enoyl systems is not affected by the *E*/*Z* composition of the substrate employed. As results in Table 6 show, regardless of the *E*/*Z* composition of the substrate **2e**, **2f**, or **2g** employed, essentially the same ratio of isomers **14**/**15** is obtained in each case.

Scheme 7. Detachment of the Oxazolidinone Auxiliary Leading to Enantioenriched β-Mercapto Carboxylic Acid Esters and Alcohols



(24) α-Sulfenylation with moderate ee's: (a) Sobhani, S.; Fielenbach, D.; Marigo, M.; Wabnitz, T. C.; Jørgensen, K. A. *Chem.—Eur. J.* **2005**, *11*, 5689−5694. [2,3]-Sigmatropic rearrangement of sulfur ylide with double asymmetric induction: (b) Ma, M.; Peng, L.; Li, C.; Zhang, X. *J. Am. Chem. Soc.* **2005**, *127*, 15016−15017. Alkylation of optically active α-lithiated sulfides: (c) Marr, F.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **1999**, *1*, 2081−2083. (d) Stratmann, O.; Kaiser, B.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Chem.—Eur. J.* **2001**, *7*, 423−435. (e) Marr, F.; Hoppe, D. *Org. Lett.* **2002**, *4*, 4217−4220. α-Alkylation of thiolactone enolates: (f) Strijtveen, B.; Kellogg, R. M. *Tetrahedron* **1987**, *43*, 5039−5054. (g) McFadden, J. M.; Frehywot, G. L.; Townsend, C. A. *Org. Lett.* **2002**, *4*, 3859−2862. Mitsonobu type reaction of tertiary alcohols: (h) Ikegai, K.; Pluenpanupat, W.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006,** *79*, 780−790.

(25) Actually, during the preparation of the starting *N*-enoyl oxazolidine-2-thiones **2**, variable degrees of *E*/*Z* isomerization were observed in the intermediate acids, esters, and/or acid chlorides, likely facilitated by the basic or acid reaction conditions employed.

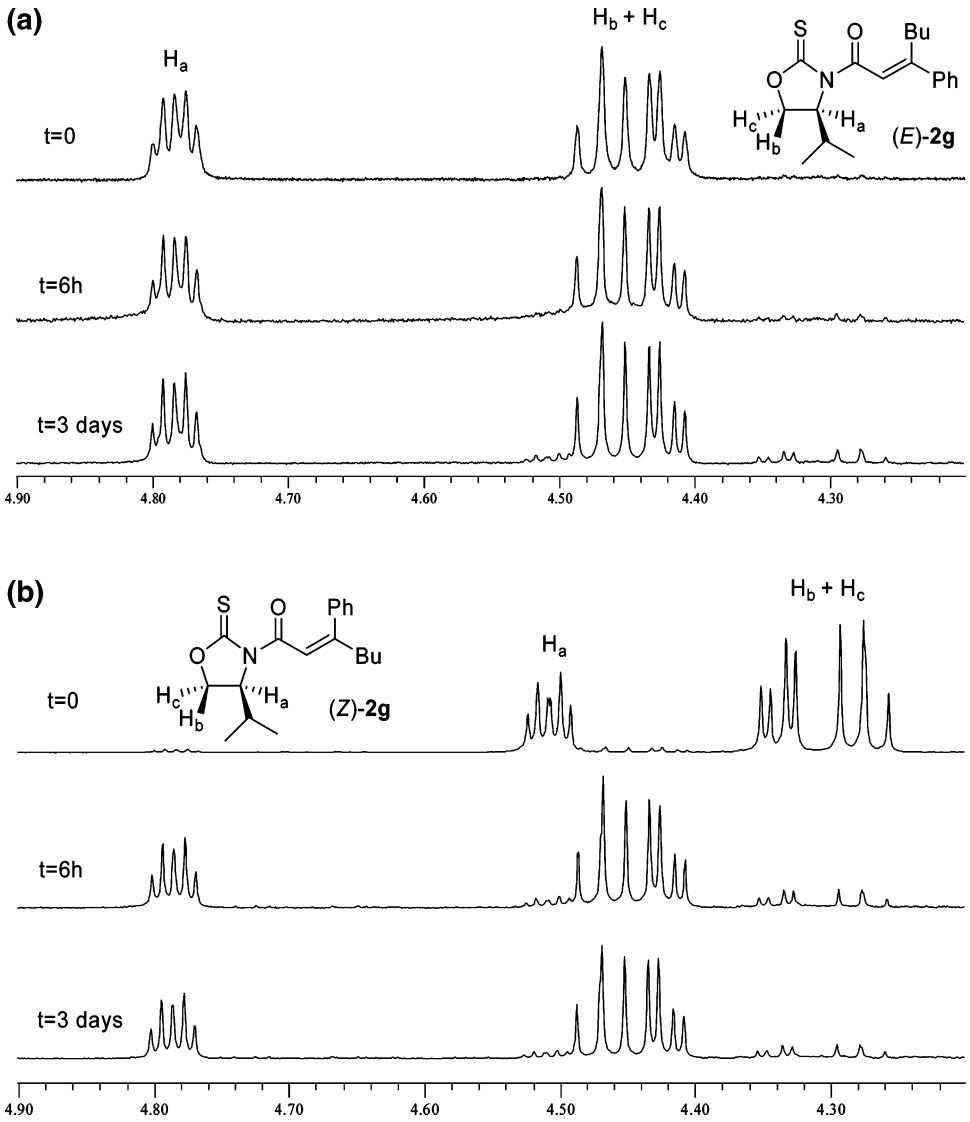
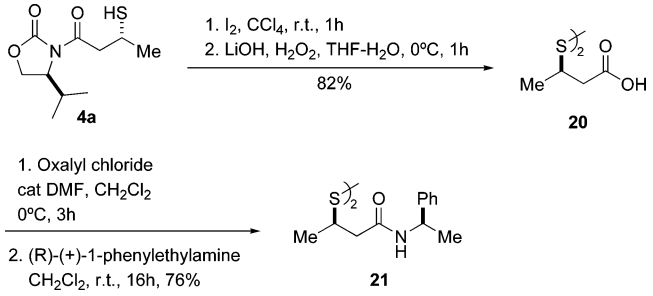


Figure 1. ^{1}H NMR plot inserts (4.20−4.90 ppm) corresponding to starting compound **2g** and aliquots taken at 6 h and 3 days from a solution of **2g**, BF_3OEt_2 (2 mol equiv), and 2,6-di-*tert*-butylpyridine (2.5 mol equiv) in CH_2Cl_2 at −30 °C: (a) starting from *E*-**2g**; (b) starting from *Z*-**2g**.

Scheme 8. Generation of Disulfide Species and Assessment of Enantiopurity



A plausible explanation of these observations would rely on a relatively fast *E*/*Z* isomerization of the substrate C−C double bond[25] on the time scale of the sulfur transfer reaction. Aimed at getting spectroscopic evidence of such an isomerization process, ^{1}H NMR monitoring of two sets of experiments was carried out. In the first set, a solution containing **2g**, 2 mol equiv of $BF_3{\cdot}Et_2O$, and 2.5 mol equiv of 2,6-di-*tert*-butylpyridine was stirred at −30 °C in CH_2Cl_2. As noted above, the presence of the pyridine base should inhibit the sulfur transfer process, and so, if operative, a clean *E*/*Z* isomerization event should be visible spectroscopically. In Figure 1, inserts of the ^{1}H NMR spectra region between 4.0 and 5.0 δ (ppm) are displayed, where protons at C_4 and C_5 of the oxazolidine-2-thione ring appear at a clearly distinguishable chemical shift for the *E* and the *Z* isomer, respectively. Inserts in Figure 1a correspond to starting material (*E*)-**2g**, the reacting mixture after 6 h, and the mixture after 3 days. As could be seen, (*E*)-**2g** is quite inert under these conditions, but after 3 days some appreciable quantity (around 5%) of the *Z* isomer is formed. Isomer *Z* in its turn (Figure 1b) isomerized to *E* much faster, and after 6 h most of the product is *E* (*Z*/*E* ratio around 5:95). It appears that this isomeric ratio no longer evolves, and thus it might correspond to an equilibrium composition of *E* and *Z* isomers at that temperature.

In a second set, compound **2g** was subjected to the standard reaction conditions (2 mol equiv of $BF_3{\cdot}Et_2O$ at −30 °C), in an NMR tube using CD_2Cl_2 as the solvent, and the same spectroscopic region was monitored at 2.5 h time intervals. When started from *E*-**2g** (Figure 2), a relatively slow consump-

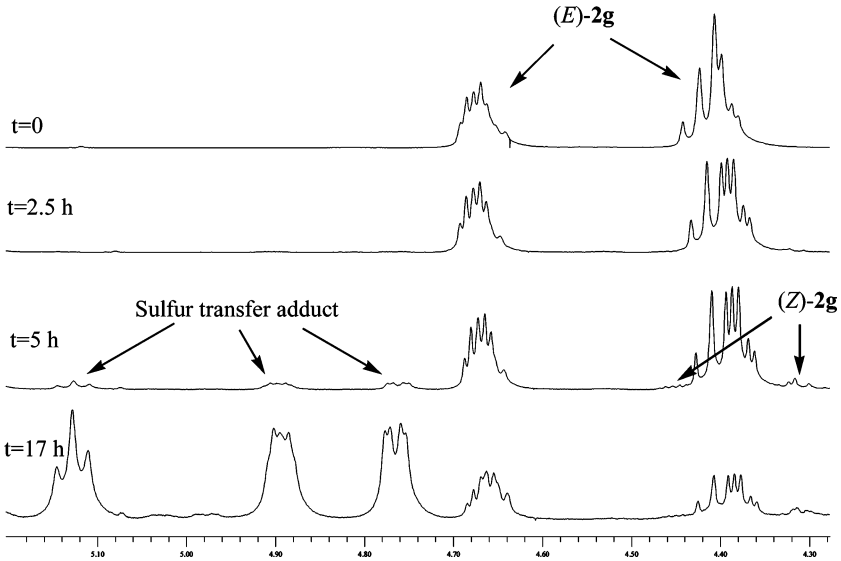


Figure 2. ^{1}H NMR plot inserts (4.32−5.32 ppm) at 0, 5, 10, and 17 h corresponding to a solution containing (*E*)-**2g** and BF_3•Et_2O (2 mol equivalents) in CD_2Cl_2 at −30 °C.

Chart 2. Relative Energies (kcal/mol) for the Hydrogen-Bonded Reactant and the Two Plausible Intermediates of the Reaction Promoted by a Single Molecule of CF_3CO_2H

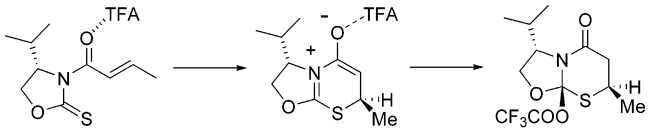
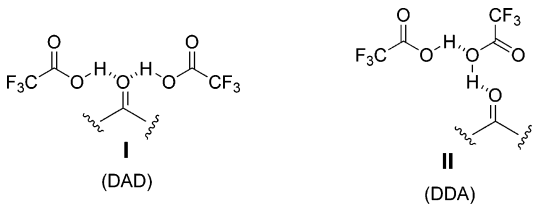


Chart 3. Different Modes of Activation of the Acceptor Carbonyl (A) by Hydrogen Bonding Involving Two Molecules of Donor (D) CF_3CO_2H



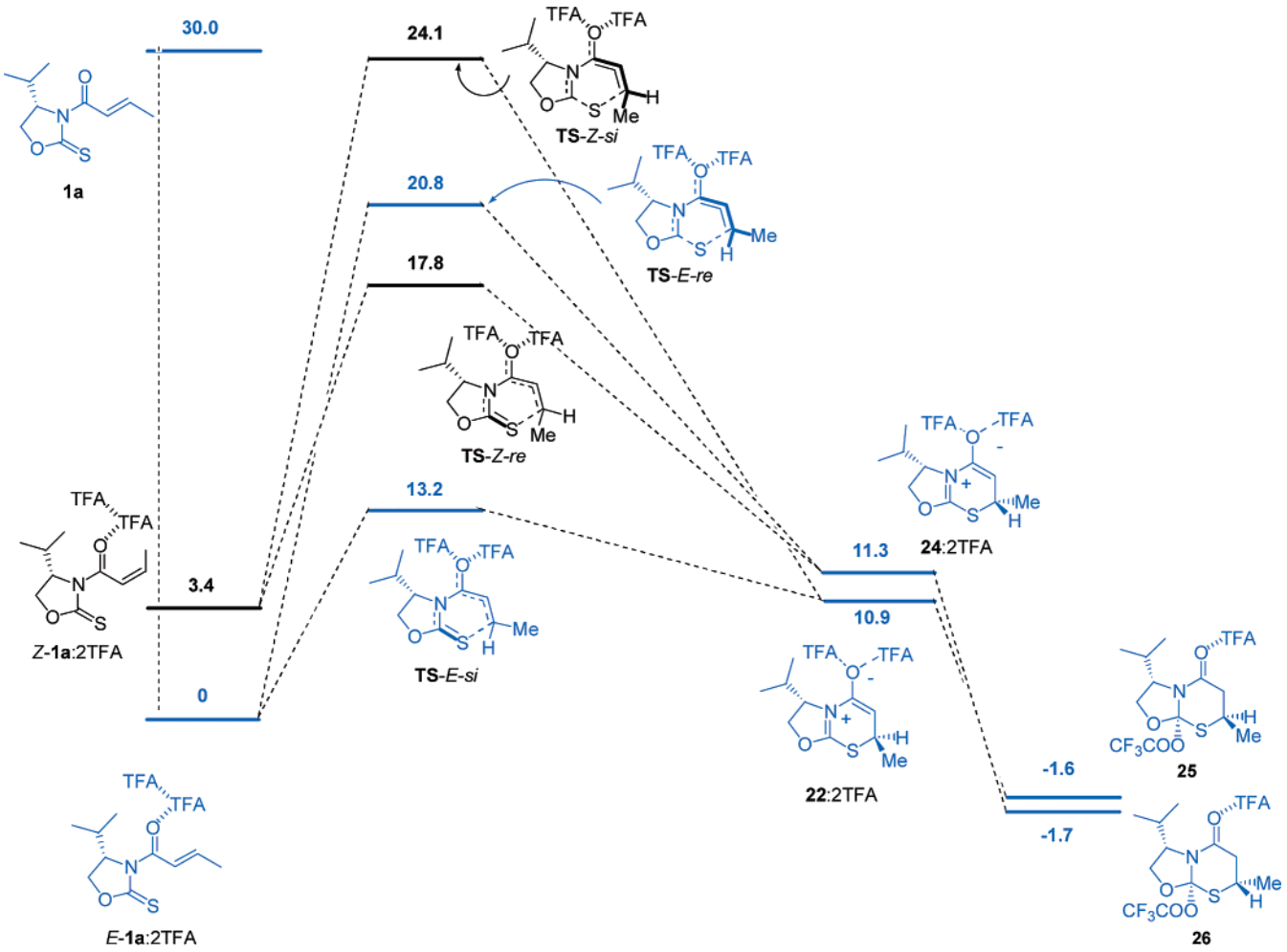
tion of starting material was observed (at 2.5 h reaction time, more than 95% of the starting material remained unaltered) to produce the sulfur transfer adduct (three peaks at 4.88, 5.00, and 5.25 ppm). What is significant is that peaks of the *Z* isomer, visible at the 4.40 ppm edge, appeared from the earliest stages and were maintained at a stationary low concentration level over elapsed time. In a similar experiment, but starting from the *Z* isomer,[26] a fast consumption of starting material was observed (more than half *Z*-**2g** consumed after 2.5 h), along with concurrent formation of *E*-**2g** and sulfur transfer adduct. These experiments clearly demonstrate that, under the presence of the Lewis acid, *E*/*Z* isomerization of the substrate compound is viable and thus the actual composition of *E* and *Z* isomers reacting at any given time might be a little dependent on the initial composition.

Chemical Elaboration of Adducts. Preparation of β-Mercapto Carboxylic Acids and Alcohols. Detachment of the oxazolidinone moiety from the adducts would liberate the corresponding β-mercapto carboxylic acids and derivatives in an enantiomerically enriched form. From the very beginning, however, we realized that the reaction conditions for the cleavage of the C−N bond might have to be selected carefully in order to avoid deleterious results. Initial failures were explained on the basis of the reactive profile of the SH group against either basic or oxidative reaction conditions needed for the cleavage. Thus, the lithium peroxide assisted hydrolysis, effectively employed for the cleavage of *N*-acyl oxazolidinones,[27] was not applicable in our case because of the complex mixture of the oxidized products formed. Typical saponification conditions, like those using KOH, were unfruitful as well, because formal elimination of H_2S with concurrent formation of the corresponding unsaturated product took place instead. Fortunately, conditions were found to overcome these problems: on one hand, treatment of adducts **4** with sodium borohydride in a mixture of THF−H_2O[28] gave rise to oxazolidinone **17** in isolated yields within the 95−99% range, along with the respective mercapto alcohols **16** in 54−65% yields after chromatography, Scheme 7. Likewise, treatment of **15a** led to the corresponding 1,3-hydroxymercaptan **18a**. The enantiomeric purity of the mercapto alcohols was determined by HPLC analysis and comparison with racemic samples.[29] Alternatively, treatment of adducts with $Sm(OTf)_3$ in MeOH[30] afforded the corresponding β-mercapto carboxylic ester. For instance, starting from adduct **15e**, ester **19e** was obtained in 79% yield and >90% ee. Parallel transformations starting from the corresponding diastereomeric adducts **14** afforded the enantiomeric products **18** and **19** in an equally effective manner. From these experiments, β-functionalized C−S quaternary mercaptans are available in high ee. It should be noted that no general method is

(26) See the SI for the corresponding plot of the NMR spectra.

(27) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. J. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049.
(28) Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067−7070.
(29) For an efficient HPLC detection, adducts **16a**−**c** as well as the corresponding racemic samples were derivatized to their dibenzoyl esters prior to analysis (for details, see Supporting Information).
(30) (a) Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K. *J. Am. Chem. Soc.* **2001**, *123*, 10131−10132. (b) Reference 11a.

Chart 4. Potential Energy Profile of the Cyclization of **1a** Promoted by 2 TFA mol equiv[a]



[a] Energy values in kcal/mol, relative to **1a** + 2TFA, refer to B3LYP/6-31G*//B3LYP/6-31G* computations.

currently known for accessing quaternary SH-bearing stereocenters in high selectivity.[23,24]

Alternatively, before detachment of the oxazolidinone moiety, the mercaptan can be oxidized to the corresponding disulfide dimer, which was found to be more stable toward base-promoted elimination, thereby allowing for standard basic hydrolysis of the imide system. For instance, Scheme 8, a two-step process relying on the initial smooth oxidation to the corresponding mercaptan to disulfide followed by lithium peroxide assisted hydrolysis led to dimeric dicarboxylic acid **20** as a glassy solid. Coupling of **20** with (*R*)-(+)-α-methylbenzylamine gave rise to the symmetrical diamide **21** as the only diastereomer detected.

In each of the cleavage processes above, oxazolidinone **17** is produced in nearly quantitative yield. Subsequent regeneration of oxazolidine-2-thione from recovered **17** was achieved by treatment with Lawesson's reagent.[31] In not fully optimized runs, we found that treatment of oxazolidinone **17** with Lawesson's reagent in dioxane at reflux for 7 h gave rise to a complete reaction conversion. Under these conditions, the corresponding pure oxazolidine-2-thione could be isolated with yields in the range 75−80%.

Reaction Mechanism. Given the apparent diversity of the results, it seemed unlikely that the whole body of observed results could be rationalized on the basis of a simple model. The most striking aspects of the present reaction system are as follows: (i) the requirement of an overstoichiometric quantity of the acid promoter for achieving practical reaction times/conversions; (ii) the divergent stereochemical behavior of β,β-disubstituted substrates depending on whether the promoter is a Lewis acid (BF_3·Et_2O) or a Brønsted acid (TFA); (iii) in close connection to the latter aspect, the fact that TFA-promoted reactions show stereospecificity with regard to the enoyl double bond *E*/*Z* configuration and *R*/*S* configuration of the newly forming C−S stereocenter, whereas the BF_3·Et_2O-promoted reaction did not. In an attempt to get some insights regarding the above questions, we set out to study these reactions computationally.

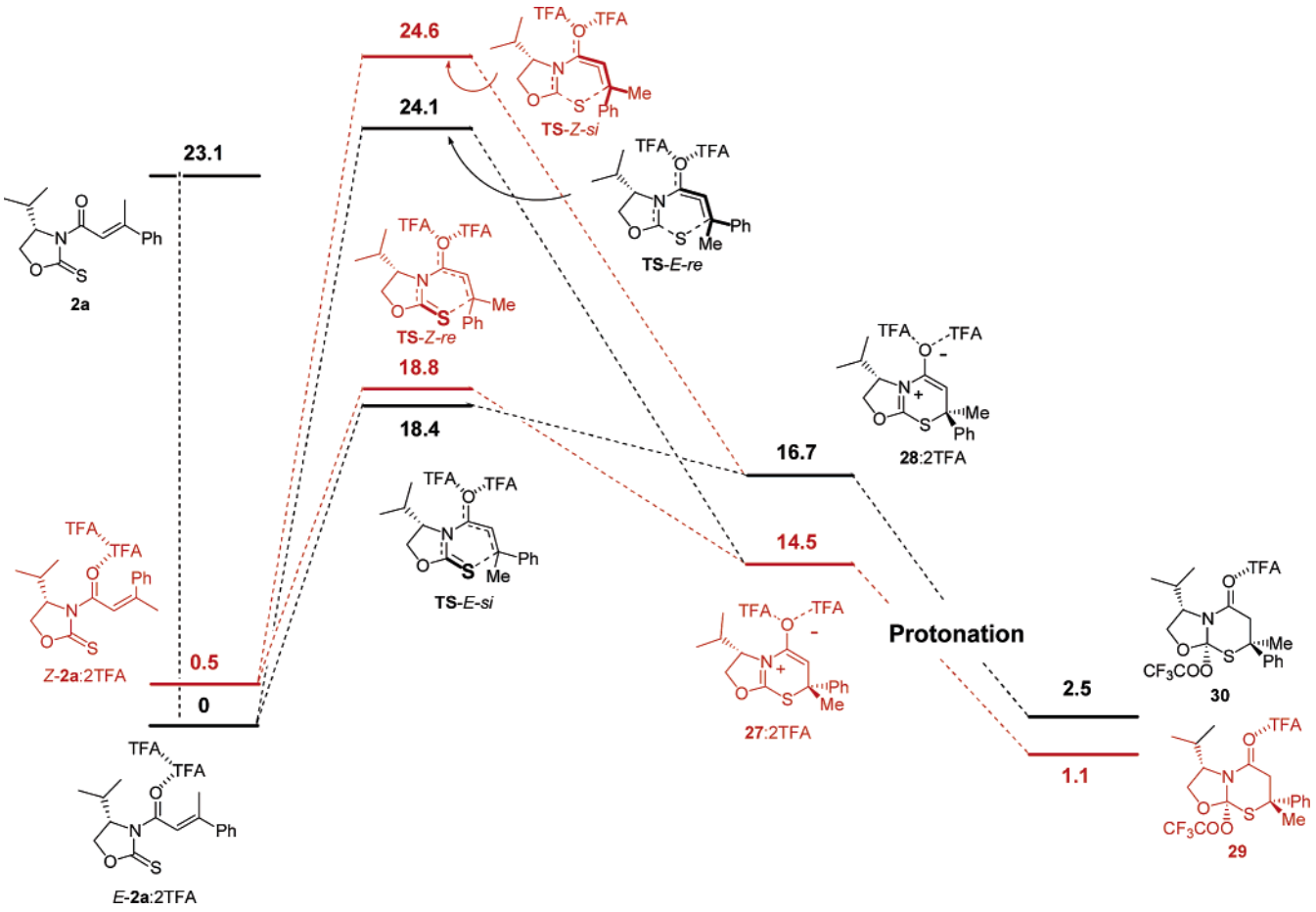
(a) Brønsted Acid Triggered Reaction of Monosubstituted Substrates 1. We studied computationally the sulfur transfer in **1a** by DFT[32] at the B3LYP/6-31G* level.[33] Despite certain limitations, DFT calculations using B3LYP are a well-established, accurate method for application to many chemical problems.[34] For this purpose we used a direct approach; i.e.,

(31) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. O., Ed.; John Wiley: Chichester, 1995; Vol. 1, p 530.

(32) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.

(33) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (d) Kohn, W.; Mecke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974.

Chart 5. Potential Energy Profile of the Cyclization of **2a** Promoted by 2 TFA mol equiv[a]



[a] Energy values in kcal/mol, relative to **2a** + 2TFA, refer to B3LYP/6-31G*//B3LYP/6-31G* computations.

no model but the real system was examined, as illustrated below. Initially we assumed that the reaction could occur through intramolecular Michael addition of the thione sulfur to the s-trans enoyl system with formation of zwitterionic species **22**. Eventually, **22** might undergo subsequent quenching by a protonating agent prior to the aqueous workup, thus leading to the isolated β-mercapto acyloxazolidinones.

The possibility of activation by a single molecule of TFA was considered first, and therefore the free energies of the hydrogen-bonded complexes **1a**/TFA and **22**/TFA were computed (Chart 2). Calculation showed that the zwitterionic intermediate **22**/TFA is actually higher in energy than the starting complex (+4.3 kcal/mol), which indicates an energetically unfavored reaction profile. Internal protonation of **22**/TFA to **23** was thought to be the driving force for the reaction. However, the high energy of this intermediate (+2.2 kcal/mol higher than **1a**/TFA) again indicated that the reaction cannot proceed with the activation by a single TFA molecule.

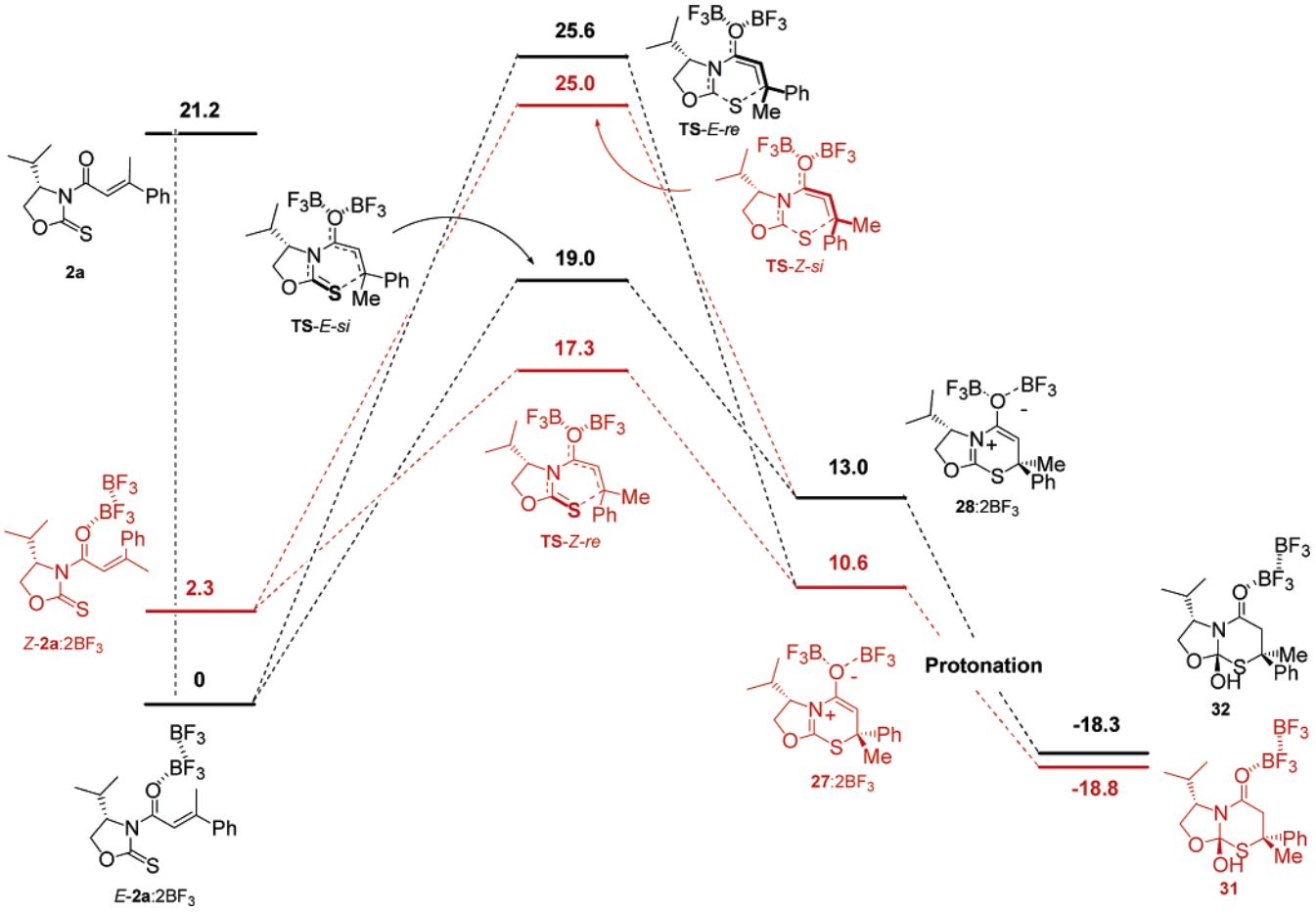
Considering that extra hydrogen bond stabilization could bring the reaction to completion, the participation of two molecules of CF_3CO_2H was studied. While computing the formation of hydrogen bonds between the imide carbonyl group of **1a**[35] and two molecules of CF_3CO_2H, two logical activation models came under consideration (Chart 3). In model **I**, the carbonyl oxygen forms two hydrogen bonds of similar strength with participation of the two lone pairs at its sp^2 orbitals. Both molecules of acid act as simple hydrogen donors (D) with the substrate carbonyl as the acceptor (A), and a donor−acceptor−donor (DAD) type assembly prevails.[36] In model **II**, the substrate carbonyl (A) participates in a single hydrogen bond with one acid molecule (D), whose donor capacity has been enhanced by additional hydrogen bonding to the second acid molecule (DDA type assembly).

The results of our computations using B3LYP/6-31G* showed that complex **1a**/2TFA belongs to the DDA activation model **II**, which is about 2.0 kcal/mol more stable than its DAD counterpart (Chart 4). Actually, upon complexation with acid, the starting reactant **1a** yields **1a**/2TFA (**I**) and **1a**/2TFA (**II**) located 27.9 and 30.0 kcal/mol lower in energy, respectively. Surprisingly, the hydrogen bonding of transition structures and intermediates with CF_3CO_2H follows the DAD activation mode **I**. Although both activation models **I** and **II** were computed for all stationary points, Chart 4 only shows those corresponding to model **I**, with the exception made for species **1a**/2TFA which corresponds to model **II**.

Activation by two Brønsted acid molecules brings the reaction

(34) Kock, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*; Wiley-VCH: Weinheim, 2001.
(35) The calculated energy for **1a** adopting a s-cis conformation instead was 5.3 kcal/mol higher. For a discussion on the energy preferences of different conformations of *N*-enoyl oxazolidinones, see: Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063−3064 and references therein.
(36) For examples of carbonyl activation through hydrogen bonding that follows a DAD model, see: (a) Reference 17b. (b) Reference 17c. (c) Tonoi, T.; Mikami, K. *Tetrahedron Lett.* **2005**, *46*, 6355−6358. For an example where a DDA activation model is proposed, see: (d) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336−1337.

Chart 6. Potential Energy Profile of the Cyclization of **2a** Promoted by 2 mol equiv of $BF_3{\cdot}Et_2O$[a]



[a] Energy values in kcal/mol, relative to **2a** + 2TFA, refer to B3LYP/6-31G*//B3LYP/6-31G* computations.

to work; i.e., it is thermodynamically favored by 1.7 kcal/mol, as illustrated in Chart 4. In fact, the whole process from the free enoyl **1a** to the final cyclized complex (*S*)-**26** is exothermic by 31.7 kcal/mol. Again, the zwitterionic species **22**/2TFA was found to be lying 10.9 kcal/mol higher in energy than starting complex **1a**/2TFA, thereby showing that the reaction will only take place after internal protonation and trapping have occurred.

In accordance with our initial hypothesis, the reaction occurs through a cyclic transition state (i.e., it is not a [3,3] sigmatropic process), involving sulfur attack on either diastereotopic face of the enoyl C−C double bond disposed in the s-trans conformation. The bond forming distances are very similar in both cases, namely 2.25 Å for the **TS**-*E*-*si* and 2.24 Å for **TS**-*Z*-*re*. Also, the computed hydrogen bonds show length values within a narrow range for all compounds, between 1.6 and 1.7 Å. Nevertheless, the so-called **TS**-*E*-*si* was found to lie at a significantly lower energy value than **TS**-*Z*-*re* possibly as a consequence of severe distortion of the π system.

These calculations allow us to explain the reason for the high diastereoselectivity found experimentally. The energy difference between the two diastereomeric transition states **TS**-*E*-*si* and **TS**-*E*-*re* is sufficiently high, more than 7.6 kcal/mol, to ensure the observed levels of diastereoselectivity for a kinetically controlled reaction. The activation energy for the experimentally found (*S*,*R*) diastereomer is +13.2 kcal/mol, whereas that for the (*S*,*S*) species is +20.8 kcal/mol. In contrast, the difference in energy between diastereomeric intermediates **24**/2TFA and **22**/2TFA is much smaller (0.4 kcal/mol), and the isomeric final products after protonation have almost the same energy, **26** being slightly more stable than **25**. These data clearly support the idea of a kinetically controlled reaction, where the selectivity depends only on the energy difference between transition states; otherwise the reaction would be completely nonselective. In addition, the energy profile confirms the necessity of 2 equiv at least of CF_3CO_2H for completion of the reaction, as only under these conditions is the Brønsted acid promoted cyclization thermodynamically allowed.

(b) Reaction of Disubstituted Substrates 2. (i) Brønsted Acid Triggered Reactions. Calculations were next performed for the reaction of disubstituted substrate **2a** with 2 equiv of TFA. As for the monosubstituted case, complexation of the substrates and the intermediates with two molecules of TFA was considered, as well as a final protonation of the zwitterionic intermediate. The relative energies of the two diastereomeric TSs were calculated for each *E*- and *Z*-configured starting olefin, and the values are shown in Chart 5. As could be anticipated, the energies of the *E*- and *Z*-configured complexes **2a**/2TFA lie now closer to one another (only 0.5 kcal/mol gap), which reflects the enhanced similarity of the *E* and *Z* isomers as dissimilarity of the two substituents at β decreases from H/alkyl or H/aryl pairs to an alkyl/aryl pair. Also, calculated values for the most favorable TS from both *E*-**2a** (*si* face attack) and *Z*-**2a** (*re* face attack) are close in energy (18.4 and 18.8 kcal/mol,

respectively). Significantly, however, the energies for the less favorable TS in each case lie 5.8 and 5.7 kcal/mol higher, respectively, which is in agreement with the sense and the high degree of diastereoselection observed in these reactions. The corresponding cyclic zwitterionic intermediates **27**/2TFA and **28**/2TFA are, again, too high in energy and a final protonation step is required for the full reaction to be energetically viable.

(ii) Lewis Acid Triggered Reactions. When moving from the TFA- to the BF_3·Et_2O-promoted process, calculated energies show two major distinguishable features (compare energy profiles in Charts 5 and 6). One is the considerably high energy difference (2.3 kcal/mol) between the most stable *E*-**2a**/2BF_3 complex and the *Z*-**2a**/2BF_3 complex. The second is the remarkably low activation barrier for the most favorable *re* attack in the *Z* isomer (15.0 kcal/mol) as compared with the most favorable *si* attack in the *E* isomer (19.0 kcal/mol). The latter is in good agreement with the shorter reaction times observed experimentally for the *Z* isomer (vide supra). In addition, the high energy barrier calculated for the sulfur transfer process in isomer *E* gives chances for an alternative reaction path, which would involve prior *E*-to-*Z* isomerization and subsequent (fast) reaction of the *Z* compound. In this way, final compound **14** would be the major reaction product regardless of the *E*/*Z* composition of the starting material. On the other hand, the high relative stability calculated for *E*-**2a**/2BF_3 (2.3 kcal/mol more stable than the *Z* complex) correlates well with the virtual composition of the two isomers at "equilibrium", found spectroscopically to be around 95:5 in favor of *E*.

Conclusions

A new asymmetric synthesis of β-mercapto carboxylic acids and derivatives therefrom has been realized through efficient acid-promoted intramolecular sulfur transfer reactions in *N*-enoyl oxazolidine-2-thiones. This model reaction, which is very simple in execution, holds several interesting features: (1) the reaction can be triggered by either metal-containing Lewis acids or simple Brønsted acids, such as trifluoroacetic acid, and thus metal-free reaction conditions are practicable; (2) high chemical and stereochemical efficiency is generally attained; (3) the chiral reagent that controls the reaction stereochemistry can be easily recovered; and (4) β,β-disubstituted products of either handness are available in high stereoselectivity from the same starting chiral material by just shifting from Lewis acids to Brønsted acid reagents. Finally, computational calculations at the DFT B3LYP/6-31G* level of theory in combination with designed experiments allow for a reaction model proposal that accounts for the requirement of at least 2 mol equiv of the acid promoter as well as the stereochemical outcome of the reaction.

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Supporting Information Available: Experimental details, analytical data, and stereochemical proofs for all new compounds (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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