Chiral Amino Ether-Controlled Catalytic Enantioselective Arylthiol Conjugate Additions to α,β-Unsaturated Esters and Ketones: Scope, Structural Requirements, and Mechanistic Implications

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Asymmetric conjugate addition reaction of 2-trimethylsilylbenzenethiol with enoates and enones is catalyzed by a chiral amino ether−lithium thiolate complex and affords adducts with high enantioselectivity. Both the s-cis conformation and a steric wall at one side of the carbonyl group are structural requirements in substrates yielding adducts with high enantioselectivity. Reactions with *tert*-butyl enones gave addition products with high enantioselectivity. Construction of two contiguous chiral centers was possible by this addition−protonation sequence. Methyl tiglate was stereoselectively converted to a single syn-adduct of 95% enantiomeric excess (ee) bearing two contiguous chiral centers. Methyl 2-phenyl-2-butenoate was converted to a single syn-adduct of 95% ee, which was desulfurized to methyl 2-phenylbutanoate of 95% ee. These additions generate a transient lithium enolate that is protonated by a thiol anti to the C−S bond, giving the corresponding product having two adjacent stereocenters.

Introduction

Efficient catalytic asymmetric conjugate addition of achiral thiols to prochiral, activated olefins has been a long-standing challenge of asymmetric reactions.[1,2,3] Pioneering works by Wynberg and Mukaiyama revealed that some chiral amines were moderate activators as well as stereocontrollers of a thiol reaction with enones, yielding conjugate addition products with moderate enantioselectivity.[4] The unsatisfactory efficiency of these approaches is attributable to the imperfect reactivity of thiol activated by hydrogen bond formation with an amine, which renders insufficient nucleophilicity to a thiol to allow the reaction to proceed at lower temperatures. Recently developed successful methodologies are classified into two categories: nucleophilic activation of a thiol by metalation[5] and electrophilic activation of unsaturated carbonyl compounds with chirally modified Lewis acids.[6] Our methodology relies on nucleophilicity enhancement of a thiol through lithiation and subsequent chelate formation with an external chiral ligand.[7] An arylthiol is activated by way of lithiation−chelate formation with a chiral amino ether and can be used as a sulfur Michael donor in a catalytic asymmetric conjugate addition reaction with cyclic and acyclic enoates.[8] 2-Substituted benzenethiols were preferred nucleophiles for both their high reactivity and enantioselectivity, and 2-trimethylsilylbenzenethiol reacted with methyl crotonate in toluene−hexane at −78 °C, affording the corresponding sulfide with excellent enantioselectivity (up to 97% ee).[9] The conjugate addition chemistry of a thiol was extended to a catalytic enantioselective protonation reaction of a transient lithium ester enolate.[10,11] A transient lithium ester enolate was further shown to be trapped with aldehydes, yielding conjugate addition−aldol tandem products.[12,13] However, the range of enoates and thiols is not wide and is limited. The current report summarizes

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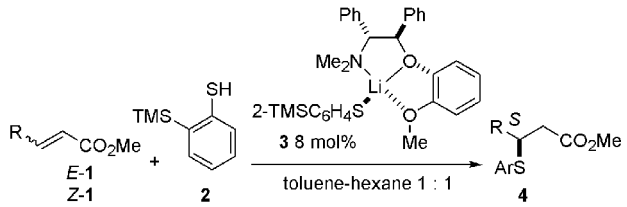
Table 1. Asymmetric Reaction with *E*- and *Z*-Enoates



entry	**1**	R	temp (°C)	time (h)	yield (%)	ee (%)	R/S
1	*E*	*i*-Bu	−60	30	93	94	*S*
2	*E*	Bn	−60	30	98	95	*S*
3	*Z*	*i*-Bu	−60/−40	48/24	48	57	*R*
4	*Z*	Bn	−60/−40	48/24	58[a]	54	*R*

[a] (*Z*)-**1** (R = Bn) 32% and (*E*)-**1** (R = Bn) 7% were recovered.

our efforts to address the relationship between enantioselectivity and reaction variables. One goal of the studies was to define the essential structural features of the α,β-unsaturated carbonyl compounds required for high enantioselectivity in 1,4-addition of arylthiols.

Results

s-Cis Conformation Is Not the Only Requirement of Enoates. The chiral amino ether−lithium thiolate complex **3**-catalyzed asymmetric conjugate addition reaction of 2-trimethylsilylbenzenethiol **2** took place on the *si*-face of acyclic *E*-enoates **1** (R = *i*-Bu, Bn) and gave the corresponding products **4** having the (*S*) absolute configuration in reasonably high enantioselectivity (94 and 95%, Table 1, entries 1 and 2).

On the other hand, the reaction with the corresponding *Z*-enoates **1** proceeded more slowly and gave (*R*)-**4** of the opposite absolute configuration in diminished enantioselectivity (57 and 54%, entries 3 and 4). Although the degree of enantioselectivity was not equivalent, the direction of the facial selectivity was the same regardless of which geometrical isomer was used. The thiolate attacks *E*- and *Z*-enoates **1** on the same face, giving the two enantiomers. This suggested that C=C and C=O double bonds of the enoates retain the same geometrical and positional relationships when the reaction takes place. The diminished enantioselectivity of the *Z*-enoate reaction is partially attributable to concomitant isomerization of the starting *Z*-**1** to the more stable *E*-**1** and its subsequent asymmetric conjugate addition. The isomerized *E*-enoate was isolated in 7% yield along with 32% recovery of the starting *Z*-enoate (entry 4). Regardless of the geometry of **1**, the same sense of enantiofacial selectivity suggested involvement of the same reaction mechanism. There are two possible conformations of acyclic enoate **1** with regard to rotational preference of a sigma bond connecting the C=C and C=O double bonds: the s-cis and s-trans forms (Figure 1). Molecular mechanics calculations on *E*- and *Z*-methyl crotonates indicated a preference for the s-trans over the s-cis conformation.

Since the s-trans conformation of *E*- as well as *Z*-enoates is generally more stable than the s-cis form, the present asymmetric reaction might be expected to proceed through the s-trans conformation. Chamberlin and Reich provided a precedent and successfully demonstrated that hydride reduction of enones resulted in stereoselective enolate formation with retention of the conformational preference of the starting s-cis and s-trans forms of enones.[14] Since the Curtin−Hammet principle is operative here,[15] it is important to examine reactions with enoates and enones having fixed s-trans and s-cis conformations.

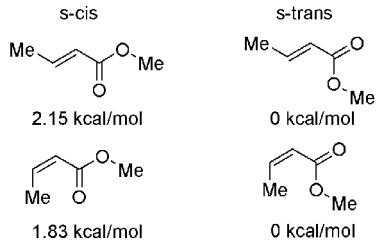
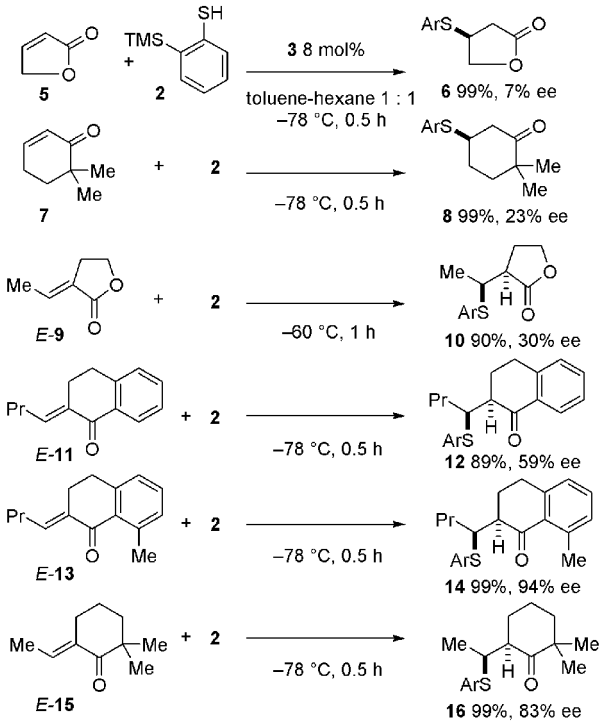


Figure 1. s-Cis and s-trans conformations of (*E*)- and (*Z*)-methyl crotonate and MM2 energy differences.

Scheme 1. Asymmetric 1,4-Additions of a Thiol to Conjugated Esters and Enones with Fixed Conformations[a]



[a] In the reactions with *E*-**9**, *E*-**11**, and *E*-**13**, small amounts (less than 10%) of the diastereomers were formed.

The reaction of 2-TMS-benzenethiol **2** with 5*H*-furan-2-one **5** and 6,6-dimethylcyclohex-2-enone **7** of fixed s-trans conformation proceeded quite smoothly at −78 °C, but gave the adducts **6** and **8** with low enantioselectivities (7 and 23%, respectively; Scheme 1). These selectivities were lower than those of (*Z*)-**1** and (*Z*)-2,2-dimethylhex-4-en-3-one. The reaction of 4-*tert*-butylben-

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zenethiol with **7** proceeded under the same conditions and gave the adduct **8** (Ar = 4-*t*-BuC_6H_4) in a slightly better 40% ee. The reaction with cyclohex-2-enone was not efficient and afforded the addition product of low ee. The poor selectivity indicated that the more selective asymmetric 1,4-addition might proceed through the s-cis and not the s-trans conformation.

However, it was surprising to find that the reaction of 3-(*E*)-ethylidenedihydrofuran-2-one, the fixed s-cis compound **9**, gave the expected syn-product **10** in 90% yield, but in only 30% ee. Another fixed s-cis compound, 2-(*E*)-butylidene-3,4-dihydro-2*H*-naphthalen-1-one **11**, was converted to the syn-product **12** in 89% yield and 59% ee. The higher enantioselectivity observed in the latter reaction is attributable to the steric bulk around the carbonyl oxygen atom, especially at the side opposite to the olefin moiety. The greater steric hindrance of a methyl group in **13** instead of a proton in **11** markedly improved the enantioselectivity. Thus, the reaction of 2-(*E*)-butylidene-3,4-dihydro-8-methyl-2*H*-naphthalen-1-one **13** proceeded smoothly at −78 °C and gave the expected syn-product **14** of 94% ee in 99% yield. Similarly, the reaction of 6-(*E*)-ethylidene-2,2-dimethylcyclohexanone **15** bearing steric bulk at one side of the carbonyl group gave the syn-product **16** of 83% ee in 99% yield. The similar steric bulk in the s-trans enone **7** was not effective for increasing the enantioselectivity.

The dependence of enantioselectivity on the steric bulk of the s-cis α′-substituent indicated that the more selective asymmetric reaction proceeds through the s-cis conformation. Furthermore, steric hindrance around the carbonyl oxygen, especially at the side opposite to the reacting olefin moiety, is a critical requirement for high enantioselectivity. Lone pair-differentiating coordination of the carbonyl oxygen with the lithium cation of the reacting thiolate at the syn-site of the olefin is a mechanistic implication for high enantioselectivity. A methyl group locked in this position may provide such a steric wall for the carbonyl oxygen of crotonic methyl esters (Figure 1).[16]

Asymmetric Reaction with Acyclic Enones. The asymmetric addition reaction of 2-substituted benzenethiol with acyclic enones was examined as a touchstone to clarify the steric requirements for high enantioselectivity as described above. Four enones **17**−**20** bearing methyl, phenyl, trityl, and *tert*-butyl terminal groups attached at the carbonyl function were examined as substrates (Figure 2). Molecular mechanics calculations indicated that the s-trans form is more stable than the s-cis form by a factor of 0.43 kcal/mol in the case of **17**, while both forms were equally stable for **18** bearing a phenyl group. It is reasonable that the bulky trityl and *tert*-butyl substituents of **19** and **20** favored the s-cis conformation by over 1.4 kcal/mol because of steric repulsion of these groups with the β-vinylic proton. The analysis suggested that the *tert*-butyl enone **20** would be the best substrate for a highly enantioselective 1,4-addition because of the tendency to adopt the s-cis conformation and the effective blocking of one coordination site of the carbonyl oxygen lone pairs.

The reactions of 2-TMS-benzenethiol **2** with the four enones **17**−**20** proceeded smoothly at −78 °C and gave

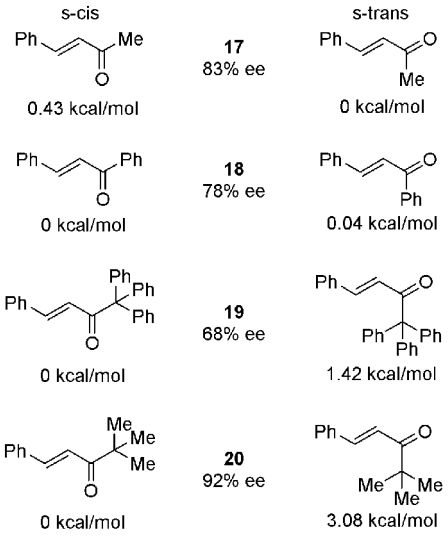

Figure 2. MM2 energy differences of enones and asymmetric addition of **2** to enones.

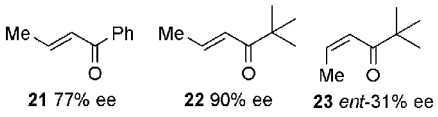

Figure 3. Asymmetric addition of **2** with enones.

the corresponding ketones quantitatively. The enantioselectivity varied in the range from 68 to 92%. The highest ee was obtained with *tert*-butyl enone **20**, as expected. In contrast, the trityl enone **19** showed the lowest (68%) selectivity, possibly because of the unfavorable steric hindrance by the large phenyl substituents to enantiofacial selection. The s-cis conformation, lone pair-differentiating coordination of the carbonyl oxygen, and appropriate bulkiness of the substituent attached to the carbonyl group emerged as crucial factors for high enantioselectivity in these 1,4-additions.

High selectivity of the *tert*-butyl enone **22** was also observed (90% ee) as compared with 77% ee for the phenyl enone **21** (Figure 3). However, the *Z*-enone **23** gave an adduct of only 31% ee, antipodal to the product obtained from **22**. The (*R*) absolute configuration of the product, (+)-(*R*)-**26**, obtained from enone **20** was correlated with the analogous 1,4-adduct (+)-**24** of methyl cinnamate.

Determination of the Absolute Stereochemistry of *tert*-Butyl Ketone. Reports on the synthesis and biological activity of carbonyl compounds bearing a C−S bond at the β position are widespread and testify to the increasing value of these subunits in organic synthesis.[17] The TMS grouping of (+)-**24**, obtained by reaction of **2** with methyl cinnamate in the presence of 8 mol % of **3**, was protodesilylated with triflic acid to give the product in 98% yield (Scheme 2). Treatment with ethanol−hydrochloric acid converted the methyl ester to the ethyl ester (+)-*R*-**25**, the absolute configuration of which has already been established.[18] The ester function of (+)-*R*-**24** was then reduced with DIBALH in toluene to an

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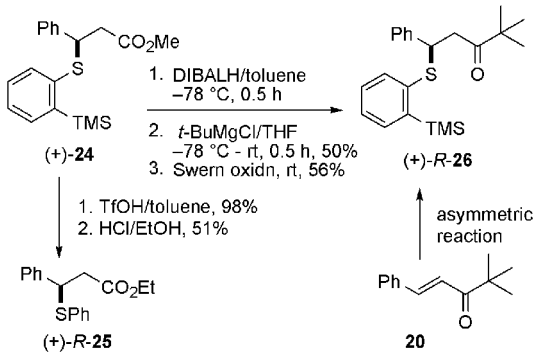
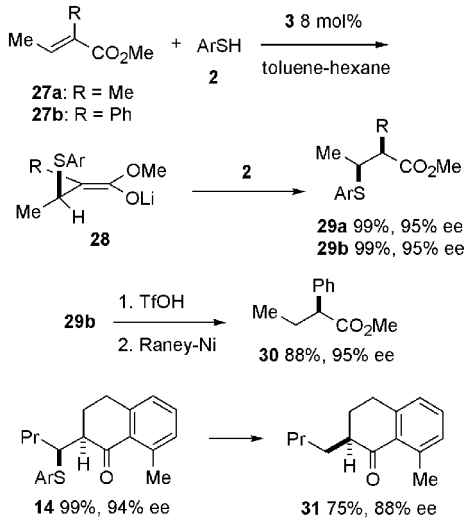
Scheme 2. Determination of the Absolute Configuration by Chemical Correlation



Scheme 3. Asymmetric 1,4-Addition Reaction



aldehyde, which was then *tert*-butylated with *tert*-butylmagnesium chloride in THF to afford a mixture of two diastereomeric alcohols. Oxidation with DMSO−oxalyl chloride gave a ketone (+)-**26** without any loss of enantioselectivity. The asymmetric 1,4-addition of 2-TMS-benzenethiol **2** to enone **20** gave (+)-**26** of 92% ee, the absolute configuration of which was thus correlated with the ester (+)-*R*-**25**. The absolute configurations of the other esters and ketones were analogously assigned.

Asymmetric 1,4-Additions to α,β-Disubstituted Enoates. The chiral ligand−lithium thiolate complex **3**-catalyzed 1,4-addition of thiol **2** to enones *E*-**13** and **15** enantio- and diastereoselectively produced **14** and **16** bearing two contiguous chiral carbons (Scheme 1). A high level of stereocontrol is operative in this addition−protonation sequence not only for cyclic enones but also for acyclic enoates. Thus, reaction with methyl tiglate **27a** proceeded at −20 °C giving **29a** of 95% ee as the sole product and in quantitative yield after 20 h (Scheme 3).

The absolute and relative configurations were confirmed by reduction with lithium aluminum hydride in THF to an alcohol of established stereochemistry.[19] Similarly, reaction with **27b** quantitatively gave **29b** of 95% ee, after 33 h at −78 °C. Desulfurization[20] of **29b** gave methyl (*S*)-2-phenylbutanoate **30**[21] in 95% ee and 88% yield. The relative configuration of **29b** was determined by oxidation and subsequent thermal elimination of the sulfoxide.[22] Desulfurization of **14** gave ketone **31** of 88% ee, the absolute configuration of which was established by circular dichroism.

Thiolate addition to **27** produced the transient lithium enolate **28**, which was protonated by thiol **2** in a mode anti to the C−S bond giving **29**.[23] The anti-protonation is mainly governed by the conformation **28** of the enolate, not by the chiral amino ether ligand.[22,24] In the absence of the chiral ligand at −60 °C in THF, **27b** was converted to racemic **29b** as the sole product in 94% yield. The sense of asymmetric induction in the protonation step was predicted to proceed anti to the newly generated C−SAr bond of the stable conformation **28**.

Conclusion

Asymmetric conjugate addition reactions of thiols with an activated olefin are catalyzed by a chiral amino ether−lithium thiolate to afford the corresponding adducts with high enantioselectivity. A lone pair-differentiating coordination has emerged as an important mechanistic consideration on the basis of conformational and steric requirements of the activated olefin.

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Supporting Information Available: General experimental procedure and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org/.

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