Organic LETTERS

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Regioselective and Enantioselective Addition of Sulfur Nucleophiles to Acyclic α,β,γ,δ-Unsaturated Dienones Catalyzed by an Iron(III)−Salen Complex

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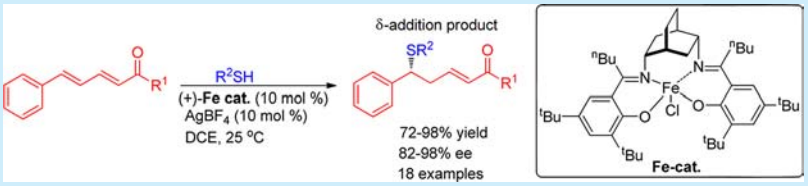
Supporting Information



ABSTRACT: The first regioselective, enantioselective conjugate addition of thiols to acyclic α,β,γ,δ-unsaturated dienones at the δ carbon is described. The reaction, catalyzed by a chiral iron(III)-salen complex derived from *cis*-2,5-diaminobicyclo[2.2.2]-octane as the scaffold, provides δ-thia-α,β-unsaturated ketones in high yield and enantioselectivity. The bicyclooctane scaffold of (2*R*,3*R*,5*R*,6*R*) configuration affords a δ-thia-α,β-unsaturated ketone of (*R*) configuration, indicating that the sulfur nucleophile is introduced at the *si* face of the γ,δ-double bond. A model providing an explanation for this regio- and stereoselection is proposed.

Asymmetric addition of sulfur nucleophiles to electron-deficient alkenes is a powerful method for constructing carbon−sulfur bonds in an enantioselective fashion from prochiral materials. With this objective in mind, several laboratories including our own[1] have explored methods based on asymmetric conjugate addition of sulfur nucleophiles to α,β-unsaturated carbonyl compounds (the "1,4-sulfa-Michael reaction").[2] Our contribution to this effort found that conjugate addition of sulfur nucleophiles to α,β-unsaturated ketones can be catalyzed with high enantioselectivity by iron(III)−salen complex **1** in which *cis*-2,5-diaminobicyclo[2.2.2]octane provides the chiral scaffold (Figure 1). Extension of the acceptor π-system,

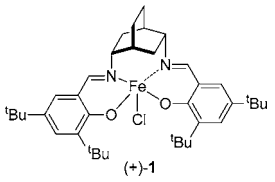


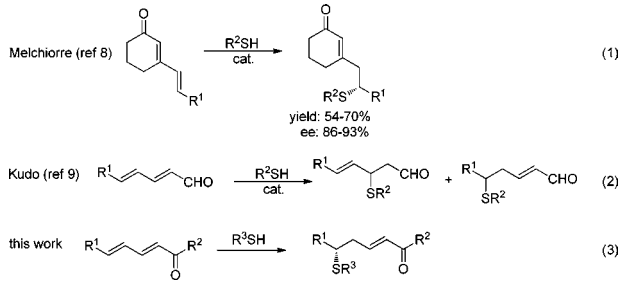
Figure 1. (2*R*,3*R*,5*R*,6*R*)-Iron(III)−salen complex (+)-**1** based on the chiral scaffold *cis*-2,5-diaminobicyclo[2.2.2]octane.

as in a α,β,γ,δ-unsaturated carbonyl substrate, creates the ambiguity of addition by the electron donor at either the β or δ carbon. The general observation is that the major product in this case results from 1,4-addition,[3] a result that can be rationalized computationally by the fact that both the π-orbital coefficient of the LUMO and the partial positive charge at the β-carbon of a conjugated dienone are larger than those at the δ-carbon.[4]

Attempts to reverse the intrinsic preference by nucleophiles for conjugate addition to the β carbon of α,β,γ,δ-unsaturated carbonyl compounds have met with limited success.[5] Tactics to circumvent the predilection toward nucleophilic attack at the β carbon over the δ carbon for this class of Michael acceptors have resorted to conjugated enynones as substrates (where the δ-carbon is sp-hybridized and therefore more electron-deficient)[6] or to substrates that bear a sterically blocking substituent at the β-carbon.[7] For sulfur nucleophiles in particular, the ability to direct enantioselective addition to the δ carbon site of an acyclic conjugated dienone remains an unsolved problem.

Melchiorre has reported that asymmetric δ-addition of alkyl thiols to β-substituted cyclohexenones can be catalyzed by a *Cinchona* alkaloid-derived primary amine[8] (Scheme 1, eq 1), but that work leaves open the more general question of whether similar regio- and enantioselectivity can be achieved with *unsubstituted acyclic* dienones. In fact, a publication by Kudo

Scheme 1. Addition of Sulfur Nucleophiles to Cyclic and Acyclic α,β,γ,δ-Unsaturated Carbonyl Compounds



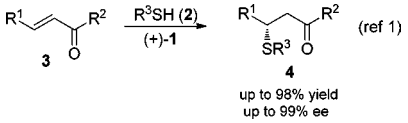
Received: August 6, 2015
Published: September 10, 2015

DOI: 10.1021/acs.orglett.5b02280
Org. Lett. 2015, 17, 4564−4567

concedes that addition of thiols to acyclic $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes catalyzed by a resin-based peptide leads to an equal mixture of β- and δ-addition products as well as to products resulting from bis-addition (Scheme 1, eq 2).[9] The important synthetic implications associated with efficient regioselective and asymmetric δ-addition of sulfur nucleophiles to acyclic conjugated dienones convinced us to extend our study that focused on α,β-unsaturated ketones[1] to this class of extended Michael acceptors (Scheme 1, eq 3). We now report the first catalytic asymmetric addition of thiols and thioacetic acid to acyclic $\alpha,\beta,\gamma,\delta$-unsaturated ketones and esters in which sulfur is incorporated selectively at the δ carbon in good yield and with high enantioselectivity.

Our previous investigation of the addition of thiols (**2**) to α,β-unsaturated ketones (**3**) using chiral metal−salen catalysts based on *cis*-2,5-diaminobicyclo[2.2.2]octane found that iron(III)−salen complex **1** was an especially efficient catalyst for the reaction, giving β-thiaketones (**4**) in high yield and with excellent enantioselectivity (Scheme 2).[1] Our initial studies of conjugate

Scheme 2. Asymmetric Sulfa-Michael Addition of Thiols (2) to α,β-Unsaturated Ketones (3) Catalyzed by Metal−Salen Complex (+)-1



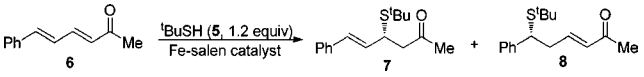
addition by thiols to $\alpha,\beta,\gamma,\delta$-unsaturated ketones as acceptors therefore focused on catalyst (+)-**1** to determine if this salen complex would direct regioselective addition of thiols to the δ carbon of this extended π-system with good enantioselectivity.

An investigation using 20 mol % of (+)-**1** as the catalyst in a mixture of *tert*-butylthiol (**5**) and (3*E*,5*E*)-6-phenylhexa-3,5-dien-2-one (**6**) under conditions which were successful for sulfa-Michael addition of thiols to α,β-unsaturated ketones gave disappointing results. In DCE and other nonpolar solvents at −5 °C, a mixture of regioisomeric thiaketones were obtained, β-addition product **7** being the major isomer (Table 1, entries 1−3). Increasing the solvent polarity decreased the proportion of δ-addition as well as the combined yield of products (Table 1, entries 4−6). On the other hand, raising the reaction temperature above −5 °C led to an increased ratio of δ-addition product **8** relative to **7** (Table 1, entries 7−9). Both **7** and **8** were stable under these reaction conditions, and we found no evidence to suggest they are interconvertible. Other metal−salen catalysts analogous to **1**, including previously synthesized chromium, manganese, aluminum, and oxovanadium complexes derived from *cis*-2,5-diaminobicyclo[2.2.2]octane,[10] led to mixtures that favored β-addition product **7**.

The absolute configuration of **8** from the reaction of *tert*-butylthiol (**5**) with dienone **6** in the presence of catalyst (+)-**1** was established as (*R*) by the sequence shown in Scheme 3. Conjugate addition of **5** to cinnamaldehyde (**9**) catalyzed by (+)-**1** gave in high enantiomeric excess β-thiacarboxaldehyde **10** which was found to possess an (*R*) configuration by reduction to known alcohol **11**.[11] Wittig reaction of **10** with 1-(triphenylphosphoranylidene)-2-propanone (**12**) afforded **8** whose optical rotation matched that of the product obtained from **6**.

The disappointing δ/β regioselectivity observed in the conjugate addition of *tert*-butylthiol (**5**) to dienone **6** with (+)-**1** prompted a search for a catalyst that would increase the

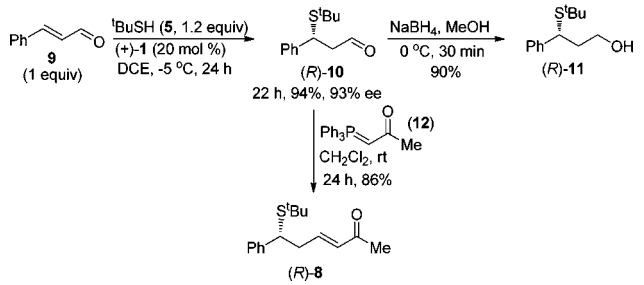
Table 1. Enantioselective Addition of *tert*-Butylthiol (5) to (3*E*,5*E*)-6-Phenylhexa-3,5-dien-2-one (6) Catalyzed by Iron(III)−Salen Complexes[a]



entry	catalyst	mol %	additive[b]	solvent	temp (°C)	*t* (h)	**8**/**7**[c]	**8** yield (%)[d]	**8** ee (%)[e]
1	(+)-**1**	20	-	DCE	-5	36	1:2	82	nd
2	(+)-**1**	20	-	$CHCl_3$	-5	32	1:2	88	nd
3	(+)-**1**	20	-	PhMe	-5	36	1:3	91	nd
4	(+)-**1**	20	-	THF	-5	48	1:2.5	36	nd
5	(+)-**1**	20	-	*t*-AmOH	-5	59	1:6	21	nd
6	(+)-**1**	20	-	MeOH	-5	76	1:8	14	nd
7	(+)-**1**	20	-	DCE	5	18	2:1	95	nd
8	(+)-**1**	20	-	DCE	15	40	2.7:1	89	72
9	(+)-**1**	20	-	DCE	25	40	3.1:1	92	80
10	(+)-**13**	20	-	DCE	25	20	5:1	87	89
11	(+)-**14**	20	-	DCE	25	29	7:1	95	95
12	(+)-**13**	20	$Ag(OCOCF_3)$	DCE	25	29	4:1	93	87
13	(+)-**14**	20	$Ag(OCOCF_3)$	DCE	25	28	7:1	90	95
14	(+)-**14**	20	$AgBF_4$	DCE	25	20	22:1	98	98
15	(+)-**14**	20	AgOAc	DCE	25	60	8:1	67	86
16	(+)-**14**	20	AgOTf	DCE	25	39	12:1	58	85
17	(+)-**14**	10	$AgBF_4$	DCE	25	27	20:1	96	98
18	(+)-**14**	6	$AgBF_4$	DCE	25	35	20:1	91	97
19	(+)-**14**	3	$AgBF_4$	DCE	25	56	13:1	58	84

[a]The reaction between dienone **6** (0.1 mmol) and *tert*-butylthiol (**5**, 0.12 mmol) was carried out in 1 mL of solvent. [b]The catalyst was stirred with the additive for 1 h before addition of **5** and **6**. [c]Determined by ^{1}H NMR analysis. [d]Isolated yields of **7** and **8** combined. [e]Determined by HPLC using a Chiralcel AS-H column.

Scheme 3. Determination of Absolute Configuration of δ-Sulfa-Michael Product 8

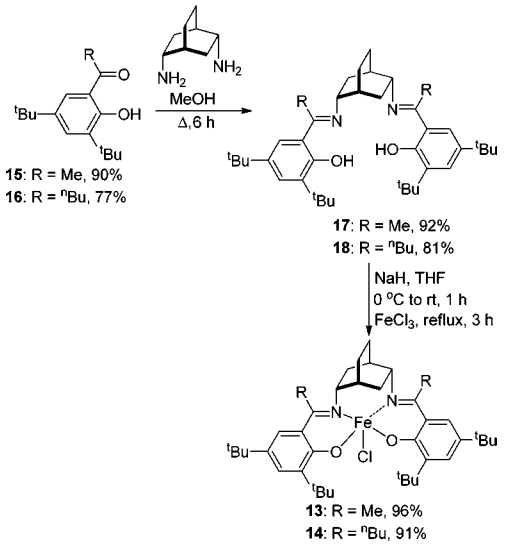


proportion of δ-addition product **8** from this reaction. Two structural changes to **1** involving replacement of hydrogen at the iminyl carbon of the salen ligand, in one case with a methyl group and in the other with a *n*-butyl substituent, were previously shown to catalyze highly enantioselective Conia-ene cyclization of acyclic alkynyl β-keto esters.[12] Second generation iron−salen complexes (+)-**13** and (+)-**14** were prepared from 3,5-di-*tert*-butyl-2-hydroxyacetophenone (**15**) and 3,5-di-*tert*-butyl-2-hydroxyvalerophenone (**16**), respectively, via their salen ligands **17** and **18** (Scheme 4) and were evaluated as catalysts for conjugate addition of thiol **5** to dienone **6**.

Exposure of dienone **6** to thiol **5** in the presence of 20 mol % of (+)-**13** in DCE at 25 °C resulted in an immediate increase in the proportion of δ-sulfa-Michael product **8** relative to β adduct **7** (Table 1, entry 10). Catalyst (+)-**14** further improved the **8**:**7** ratio (Table 1, entry 11), and when a silver salt was included in the reaction medium the proportion of the δ adduct increased still further (Table 1, entries 12−19). Silver tetrafluoroborate was found to be the most effective additive for this reaction (Table 1,

DOI: 10.1021/acs.orglett.5b02280
Org. Lett. 2015, 17, 4564−4567

Scheme 4. Synthesis of Second Generation Iron(III)−Salen Complexes (+)-13 and (+)-14



entries 14, 17, and 18). Optimized conditions for asymmetric δ-sulfa-Michael addition of *tert*-butylthiol (**5**) to dienone **6** were obtained with 10 mol % of (+)-**14** and silver tetrafluoroborate in DCE at 25 °C (Table 1, entry 17). Under these conditions, **8** was formed in excellent yield with >95% ee. Although it was possible to reduce the catalyst loading of **14** from 10 mol % to as low as 3 mol % and obtain a 13:1 ratio of **8**:**7**, both the yield of **8** and its enantiopurity decreased under those conditions (Table 1, entry 19).

With optimized conditions established for enantioselectve δ-addition of *tert*-butylthiol to dienone **6**, the scope of the reaction was investigated using a range of α,β,γ,δ-unsaturated ketones and several thiols. The results are shown in Figure 2. Methyl ketones, aryl ketones, and heteroaryl ketones as π-acceptors gave a good yield of the δ-sulfa-Michael product with both aliphatic thiols (**19**−**31**) and an aromatic thiol (**32**) as well as with thioacetic acid (**33**). Conjugate β-addition of a second molecule of thiol to the δ-adduct was not observed even with an excess of the thiol, but when ethane-1,2-dithiol was used as the nucleophile with **6**, *cis*-disubstituted dithiepane **31** was obtained. This result is consistent with initial addition of sulfur to the δ carbon of **6** followed by intramolecular addition of the second sulfur to the β carbon of the derived α,β-unsaturated ketone. Ethyl 5-phenyl-2,4-pentadienoate underwent conjugate addition with ethanethiol to give **34** in slightly lower yield and enantiomeric excess compared to the reaction with dienone acceptors.

An experiment to determine if δ-sulfa-Michael addition by thiols to α,β,γ,δ-unsaturated ketones was reversible was conducted with ethanethiol adduct **20** (Scheme 5). Exposure of **20** to benzylthiol and catalyst (+)-**14** under the optimized conditions of Table 1, entry 17, for as long as 72 h, gave no trace of crossover product **35**. Furthermore, no product **36** resulting from β-addition of benzylthiol to **20** was observed from the reaction. These results are consistent with a mechanism for δ-sulfa-Michael addition to a conjugated dienone that is irreversible. They also imply that a second conjugate addition is prohibited after a δ substituent is in place.

A second experiment with dienone **6** using catalyst (+)-**14** and *S*-deuterio *tert*-butylthiol (**37**) yielded a surprising result in the form of deuterated α,β-unsaturated ketone **38** (Scheme 6). The ^{1}H NMR spectrum of **38** (Table 2) displayed a clean set of four

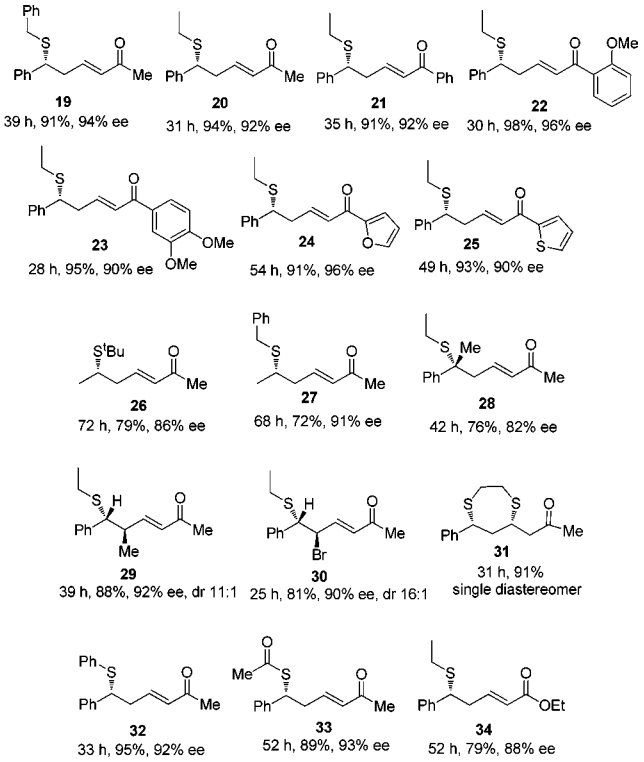
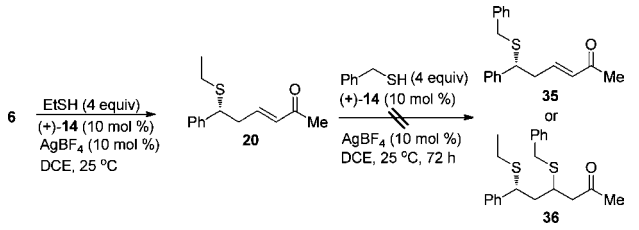


Figure 2. Substrate Scope in Asymmetric δ-Sulfa-Michael Addition of Thiols to α,β,γ,δ-Unsaturated Dienones Catalyzed by (+)-**14**.

Scheme 5. Exchange Experiment with 20 and Benzylthiol



Scheme 6. Conjugate Addition of *S*-Deuterio-*tert*-butylthiol (37) to Dienone 6

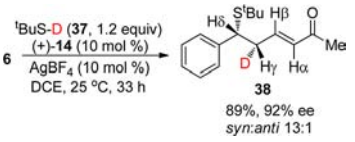


Table 2. Selected ^{1}H NMR Data for 38

proton	chemical shift (δ)	coupling (Hz)
Hα	6.08	d, *J* = 15.3
Hβ	6.84	dd, *J* = 15.3, 6.1
Hγ	2.94	dd, *J* = 9.2, 6.1
Hδ	3.95	d, *J* = 9.2

one-proton signals for the acyclic portion of the structure which revealed that a label had been incorporated exclusively at C5. The residual proton H_γ at C5 showed coupling to H_δ (9.2 Hz) typical of a *syn* relationship of acyclic vicinal hydrogens (~8.5−9.5 Hz).[13] Incorporation of deuterium solely at C5 of **6** in this experiment is inconsistent with a mechanism for conjugate addition by the thiol that proceeds via an iron-enolate

DOI: 10.1021/acs.orglett.5b02280
Org. Lett. 2015, 17, 4564−4567

intermediate since some fraction of label should be seen at C3 of **38** in that case. Furthermore, a *syn* relationship between H_γ and H_δ requires that both the sulfur substituent and deuterium label are introduced at the same (*si*) face of the γ,δ double bond of **6**, the labeled carbon C5 consequently having an (*S*) configuration. This result stands in contrast to conjugate addition of thiols to α,β-unsaturated ketones catalyzed by (+)-**1** (Scheme 2) where it was found that the sulfur substituent and the hydrogen atom were added at opposite faces of the double bond.[1]

Our previous study of asymmetric conjugate addition of sulfur nucleophiles to α,β-unsaturated ketones[1] found spectroscopic evidence for formation of a precomplex from catalyst **1** in which a thiol unit occupies a vacant coordination site on the Fe(III) core.[14] The resulting *trans* directing effect from sulfur coordination[15] places the Fe-complexed enone that is located in the right front quadrant below the chiral scaffold in an orientation which permits attack by an external nucleophilic sulfur only from the *si* face of the double bond, with approach to the *re* face being blocked by an aryl residue of the salen ligand. Extrapolation of this model to dienone **6** would account for the regioselective formation of δ-thiacarbonyl products of (*R*) configuration if additional steric bulk around the iron center of the catalyst created by the *n*-butyl substituents of **14** obstructs approach by the sulfur nucleophile to the β carbon of the dienone (Figure 3). A similar rationale could explain the stereoselective introduction of the label at C5 of **38** with catalyst (+)-**14**.

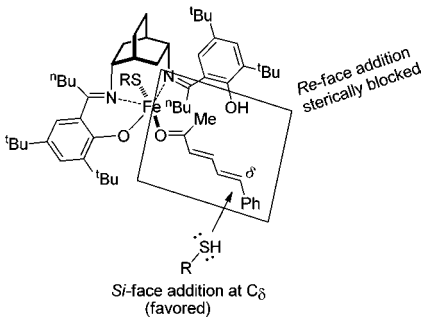


Figure 3. Proposed model for enantioselective δ-addition of a thiol to an $\alpha,\beta,\gamma,\delta$-unsaturated dienone catalyzed by (+)-**14**.

In summary, we have demonstrated the first catalytic enantioselective δ-addition of thiols and thioacetic acid to acyclic $\alpha,\beta,\gamma,\delta$-unsaturated ketones. High regioselectivity for δ-addition over β-addition can be achieved with this method without a "blocking" substituent at the β-carbon. The chiral iron−salen complexes employed in this study exhibit high stability and can be obtained pure in either enantiomeric form. Importantly, catalysts **13** and **14** employ environmentally benign iron(III) as the reactive metal center. Our method thus provides a practical tool for installing a stereogenic carbon−sulfur bond in an achiral substrate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02280.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by the National Science Foundation (CHE-0834862). Support for the Oregon State University NMR facility used in this work was provided by the National Science Foundation (CHE-0722319) and by the M. J. Murdock Charitable Trust (Grant 2005265).

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DOI: 10.1021/acs.orglett.5b02280
Org. Lett. 2015, 17, 4564−4567