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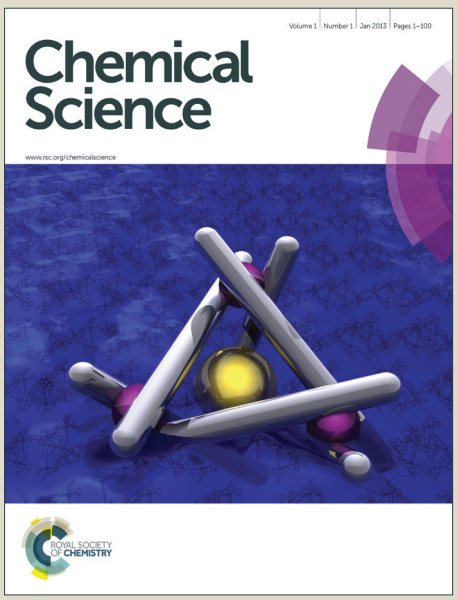

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EDGE ARTICLE

Iron Catalyzed Enantioselective Sulfa-Michael Addition: A Four-step Synthesis of the Anti-asthma Agent Montelukast

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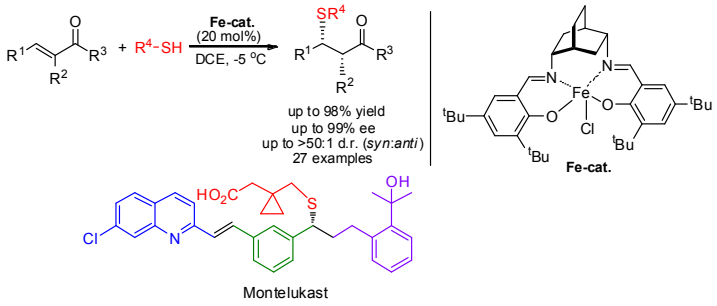
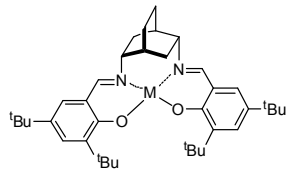


The asymmetric Michael reaction is one of the most powerful transformations in synthesis.[1] Among reactions of this class, conjugate addition of thiols to unsaturated carbonyl compounds (sulfa-Michael addition, SMA) is of special interest since it provides direct access to enantioenriched sulfides.[2] Although a diverse body of research has focused on catalytic asymmetric SMA, the Michael acceptors used in these reactions have been confined to nitroolefins,[3] α,β-unsaturated aldehydes,[4] carboxylic acid derivatives[5] and cyclic enones.[6] Acyclic α,β-unsaturated ketones as Michael acceptors in catalytic asymmetric SMA have received only limited attention[7] and diastereoselectivity associated with thiol addition to α-branched enones remains a significant challenge.[8] Thus, an efficient catalyst for asymmetric SMA of thiols to acyclic enones under mild conditions which affords adducts with good enantio- and diastereoselectivity is an important goal.

We have reported a new salen ligand (**1**) based on the chiral scaffold *cis*-2,5-diaminobicyclo[2.2.2]octane and we showed that the ligand forms stable, well characterized complexes (**2a-f**) with a variety of transition metals (Figure 1).[9] Certain of these chiral salen-metal complexes were found to possess significant catalytic activity.For example, chromium(III) complex **2c** was an efficient catalyst for the asymmetric hetero-Diels-Alder reaction and for the asymmetric Nozaki-Hiyama-Kishi reaction[9] while the copper(I) complex of the tetrahydrosalen ligand derived from reduction of **1** proved to be an excellent catalyst for the asymmetric Henry reaction.[10]

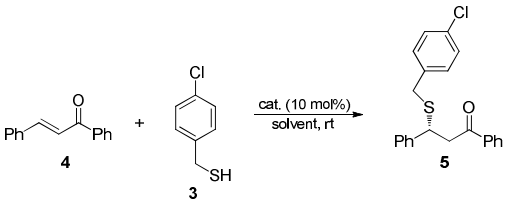


(+)-**1**: M = 2H
(+)-**2a**: M = Ti(Cl)(O*i*Pr)
(+)-**2b**: M = V(O)(Cl)
(+)-**2c**: M = Cr(Cl)
(+)-**2d**: M = Mn(Cl)
(+)-**2e**: M = Fe(Cl)
(+)-**2f** : M = Al(Cl)

Figure 1. Salen-ligand 1 and Metal Complexes 2a-f Based on a *cis*-2,5-Diaminobicyclo[2.2.2]octane Scaffold

Our initial studies on asymmetric SMA were carried out with metal-salen complexes **2a-f** using *p*-chlorobenzyl thiol (**3**) and *trans*-chalcone (**4**) as reactants in solvents of varying polarity. Results from this investigation indicated that iron(III)-salen complex (+)-**2e** was superior to other metal-salen complexes in delivering SMA product **5** with good enantioselectivity (Table 1, entries 5, 7-9). Non-polar chlorinated solvents as the reaction medium gave better results (Table 1, entries 8,9) than polar solvents (Table 1, entries 10-13). Further screening of reaction conditions with (+)-**2e** as catalyst established that optimum yield and enantioselectivity of **5** was achieved with 20 mol% catalyst loading at -5 °C in dichloroethane (DCE) as solvent (Table 2, entry 6) although good enantioselectivity was obtained with a catalyst loading as low as 4 mol%. Comparison of the optical rotation of **5** from this experiment with the literature value [7f] proved that **5** possessed (*R*) configuration.

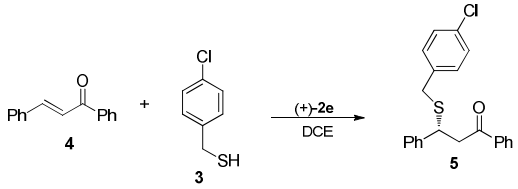
Table 1. Asymmetric Conjugate Addition of *p*-Chlorobenzyl Thiol (3) to *trans*-Chalcone (4) Catalyzed by Metal-salen Complexes 2a-f.[a]



entry	catalyst	solvent	t [h]	product 5 yield [%][b]	product 5 ee [%][c]
1	(+)-**2a**	PhMe	30	84	36
2	(+)-**2b**	PhMe	36	46	37
3	(+)-**2c**	PhMe	52	35	43
4	(+)-**2d**	PhMe	18	63	46
5	(+)-**2e**	PhMe	12	52	71
6	(+)-**2f**	PhMe	6	87	49
7	(+)-**2e**	$CHCl_3$	24	63	75
8	(+)-**2e**	CH_2Cl_2	36	68	84
9	(+)-**2e**	DCE	24	90	87
10	(+)-**2e**	THF	71	33	7
11	(+)-**2e**	$MeNO_2$	74	22	31
12	(+)-**2e**	MeCN	59	46	36
13	(+)-**2e**	MeOH	96	16	13

[a] The reaction between *trans*-chalcone (0.1 mmol) and 4-chlorobenzyl thiol (0.12 mmol) was carried out in 1 mL solvent in the presence of 10 mol% catalyst. [b] Yield of isolated product. [c] Determined by HPLC using a Chiralcel OD-H column.

Table 2. Asymmetric Sulfa-Michael Addition of 3 to 4 Catalyzed by (+)-2e. Effect of Catalyst Loading and Temperature.[a]

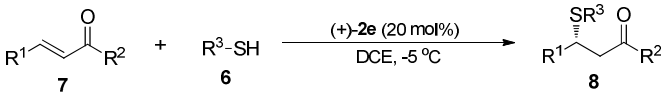


entry	catalyst loading (mol%)	temp	t [h]	product 5 yield [%][b]	product 5 ee [%][c]
1	10	12	32	84	91
2	10	0	47	79	95
3	10	-5	58	76	96
4	4	-5	63	82	86
5	15	-5	49	87	97
6	20	-5	36	94	98
7	20	-15	74	59	97

[a] The reaction between *trans*-chalcone (0.1 mmol) and 4-chlorobenzyl thiol (0.12 mmol) was carried out in 1 mL solvent. [b] Yield of isolated product. [c] Determined by HPLC using a Chiralcel OD-H column.

With optimized reaction conditions for asymmetric SMA of **3** and **4** settled, a broad portfolio of thiols **6** was examined in reaction with a variety of α,β-unsaturated ketones **7** using Fe(III)-salen complex (+)-**2e** as catalyst (Table 3). In every case, β-thioketone **8** was obtained in >90% enantiomeric excess and in high yield. Thiophenol (Table 3, entry 18) as well as aliphatic thiols and a hydroxyl substituted thiol (Table 3, entry 10) gave good results, and the reaction was found to tolerate a wide range of aromatic and alipatic substituents in the unsaturated ketone.

Table 3. Enantioselective Synthesis of β-Thioketones 8 from Thiols 6 and α,β-Unsaturated Ketones 7 Catalyzed by Metal-salen Complex (+)-2e[a]

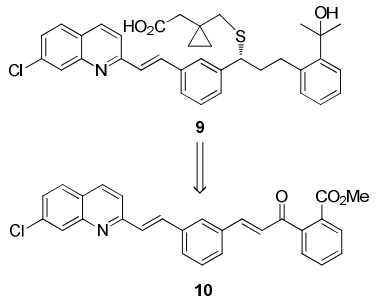


entry	R^1	R^2	R^3	t [h]	product	yield [%][b]	ee [%][c]
1	Ph	Ph	^iPr	41	**8a**	96	94
2	Ph	Ph	$C_6H_5CH_2$	36	**8b**	92	97
3	Ph	Me	^iPr	38	**8c**	89	96
4	Ph	Me	$C_6H_5CH_2$	31	**8d**	97	96
5	Ph	Me	4-Cl-$C_6H_4CH_2$	31	**8e**	93	97
6	3-$OMeC_6H_4$	Me	^iPr	36	**8f**	98	95
7	4-$OMeC_6H_4$	Me	^iPr	36	**8g**	89	92
8	4-$CF_3C_6H_4$	Me	cyclohexyl	36	**8h**	97	98
9	4-ClC_6H_4	Ph	^nBu	39	**8i**	98	93
10	4-ClC_6H_4	Ph	CH_2CH_2OH	20	**8j**	91	96
11	2,6-di-ClC_6H_3	Ph	^nBu	49	**8k**	98	96
12	2,4-di-$NO_2C_6H_3$	Me	^nBu	26	**8l**	98	95
13	4-(OH)-3-(OMe)-C_6H_3	Me	^iPr	38	**8m**	95	96
14	1-Naphthyl	2-furyl	^iPr	49	**8n**	94	97
15	1-Naphthyl	2-thiophenyl	^iPr	47	**8o**	96	94
16	Me	Me	$C_6H_5CH_2$	32	**8p**	97	95
17	Me	Me	4-Cl-$C_6H_4CH_2$	31	**8q**	95	93
18	Me	Me	Ph	34	**8r**	89	98
19	C_6H_{13}	Me	$C_6H_5CH_2$	48	**8s**	96	98

[a] The reaction between *trans*-enone (0.1 mmol) and thiol (0.12 mmol) was carried out in 1 mL solvent in the presence of 20 mol% catalyst. [b] Yield of isolated product. [c] Determined by HPLC using a Chiralcel OD, AD, OJ, OD-H or AS-H column.

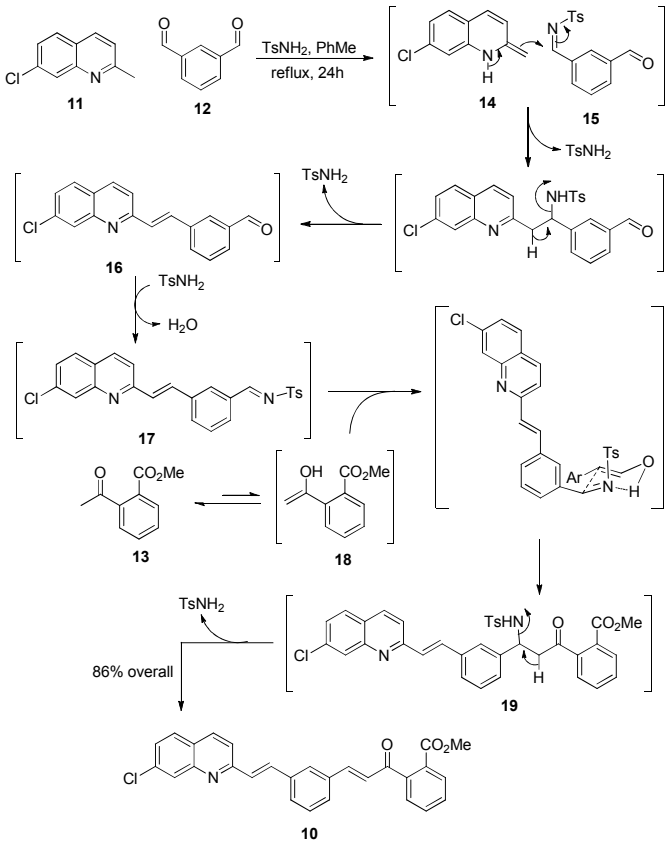
The utility of this enantioselective SMA was demonstrated in a synthesis of the leukotriene D_4 receptor antagonist (*R*)-Montelukast (**9**, Scheme 1).[11] Singulair® (MK-0476), the sodium salt of **9**, is an orally active drug used for treatment of asthma and other respiratory conditions;[12] it is currently synthesized in a multi-step process that introduces the (*R)* sulfur substituent indirectly by displacememt of a mesylate generated via an asymmetric ketone reduction.[13] We have found that the sulfur functionality in **9** can be inserted directly with excellent enantioselectivity using conjugated ketone **10** as the substrate in our asymmetric SMA methodology.

Scheme 1. Asymmetric SMA Route to the Anti-asthma Drug (*R*)-Montelukast (9)



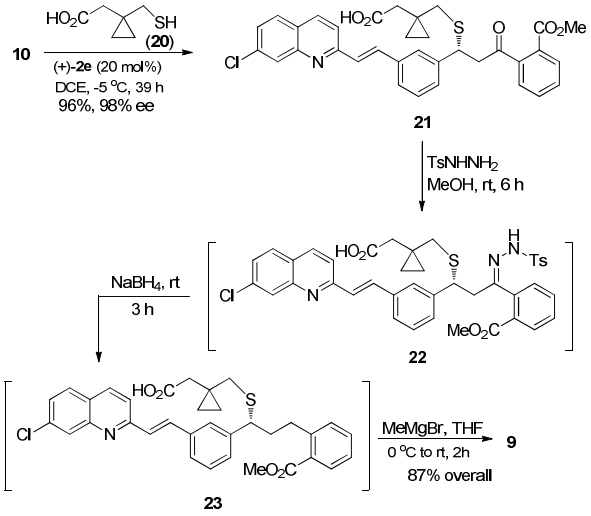
For the synthesis of **10** we devised a one-pot Mannich-aldol condensation employing 7-chloroquinaldine (**11**), 1,3-benzene dicarboxaldehyde (**12**) and methyl 2-acetylbenzoate (**13**). This three component reaction catalyzed by *p*-toluenesulfonamide gave α,β-unsaturated ketone **10** in high yield (Scheme 1). The reaction sequence is believed to be initiated by addition of enamine tautomer **14** of **11** to aldimine **15** and this is followed by elimination of *p*-toluenesulfonamide to generate aldehyde **16 (**Scheme 2). The latter condenses with the sulfonamide, forming a second aldimine **17** which reacts with enol **18** to produce **19**. Final elimination from **19** delivers **10** and regenerates *p*-toluenesulfonamide.

Scheme 2. One-pot Tandem Mannich-Aldol Sequence to Dienone 10



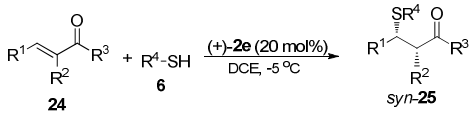
Conjugated ketone **10** underwent smooth SMA with 1-(mercaptomethyl)cyclopropyl]acetic acid (**20**) in the presence of catalytic (+)-**2e** to give β-thioketone **21** in high yield and enantioselectivity. Tosylhydrazone **22** from **21** was reduced with $NaBH_4$ in MeOH at room temperature[14] to yield sulfide **23** and addition of methylmagnesium bromide to this ester furnished (*R*)-Montelukast (**9**) (Scheme 3). The four step route to **9** proceeds in 72% overall yield based on **11**.

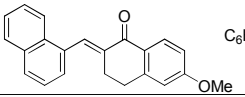
Scheme 3. Synthesis of (*R*)-Montelukast (9) from Enone 10



We next tested our asymmetric SMA methodology against α-substituted α,β-unsaturated ketones and found that thiols **6** underwent reaction with conjugated enones **24** in the presence of (+)-**2e** as catalyst to give SMA adducts in high yield and with a *syn*/*anti* ratio strongly favoring *syn* isomer **25** (Table 4). The *syn* adduct was produced in high enantiomeric excess from these reactions.

Table 4. Diastereoselectivity in Asymmetric Sulfa-Michael Addition of Thiols to α-Branched Enones Catalyzed by (+)-2e[a]



entry	R^1	R^2	R^3	R^4	t (h)	product	dr *syn*/*anti*[b]	yield [%][c]	ee [%][d]
1	Ph	Me	Me	$C_6H_5CH_2$	34	**25a**	>23:1	92	98
2	4-ClC_6H_4	Me	Me	$C_6H_5CH_2$	28	**25b**	>31:1	95	96
3	$(CH_3)_2CH$	n-Bu	Ph	Et	46	**25c**	>50:1	92	97
4	c-C_6H_{11}	n-Bu	Ph	$(CH_3)_2CH$	40	**25d**	>50:1	95	96
5	n-C_6H_{13}	n-Bu	Ph	$(CH_3)_3C$	46	**25e**	>50:1	90	95
6				$C_6H_5CH_2$	18	**25f**	>50:1	95	98

[a] The reaction between enone (0.1 mmol) and thiol (0.12 mmol) was carried out in 1 mL solvent in the presence of 20 mol% catalyst. [b] Determined by ^1H NMR analysis. [c] Combined yields of *syn* and *anti* isomers. [c] Determined by HPLC using a Chiralcel OD, AD, OD-H or AS-H column.

An attempt to give definition to the role of Fe-salen catalyst **2e** in asymmetric SMA led to an experiment in which 1-butanethiol was first incubated with the catalyst before Michael acceptor **26** was introduced. Formation of an initial Fe-thiol complex is supported by

the presence of a IR band centered at ca. 468 cm^{-1} consistent with a Fe-S stretching mode.[15] This precoordinated thiol may play a role in orienting or activating the enone acceptor within the Fe-salen complex through the known *trans* directing effect of sulfur ligands in metal complexes.[16-17]

The knowledge that bicyclooctane complex (+)-**2e** with (*R,R*) absolute configuration produces sulfa-Michael adducts **8** of uniform (*R*) stereochemistry stipulates that thiol attack at the β-carbon of the enone occurs from the *si* face. A pathway accommodating this finding is proposed in Figure 2. This mechanism places the Fe-coordinated *s-trans* enone acceptor in the right front quadrant below the bicyclic scaffold and *anti* to the precomplexed thiol. Five coordinated atoms around the central Fe form a square pyramidal configuration with O^1, O^2, N^2 and S in the basal plane. Intermolecular approach by thiol to an enone complexed in this fashion should occur from the more accessible front face leading to *si* attack.[18] Subsequent protonation from the *re* face, perhaps assisted by intramolecular delivery from the free phenol, results in overall *syn* addition after detachment of the product from catalyst. A catalytic cycle that conforms to this proposed mechanism is shown in Scheme 4.

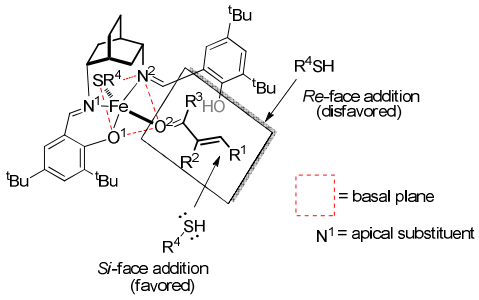
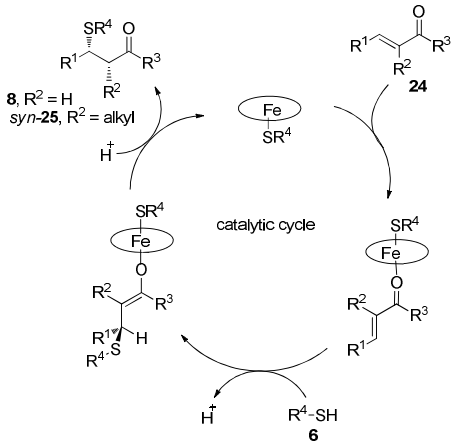


Figure 2. Proposed Mechanism for the Asymmetric Sulfa-Michael Addition of Thiols to α,β-Unsaturated Ketones Catalyzed by Fe(III)-salen complex (+)-2e

Scheme 4. Catalytic Cycle for the Formation of 8 and 25 via Asymmetric SMA in the Presence of (+)-2e



In summary, an iron(III)-salen catalyst **2e** based on a bicyclo[2.2.2]octane scaffold has been found to give products in high enantiomeric excess, diastereomeric ratio and yield in the sulfa-Michael addition of thiols to acyclic conjugated enones. β-Thioketones generated in this manner represent valuable entry points to important chiral sulfur-containing compounds as demonstrated by the synthesis of the drug (*R*)-Montelukast in four steps from commercially available materials. A key component of the synthesis route is a novel one-pot tandem Mannich-aldol sequence that links **11**, **12** and **13** in a catalyzed process leading to Michael acceptor **10**. Taken with the fact that **2e** is readily available in both enantiomeric forms through synthesis[9] and delivers products in higher enantiomeric excess than other catalyst systems, the method provides for efficient asymmetric incorporation of sulfur functions into conjugated acyclic enones in either absolute configuration.

Supporting Information

Experimental procedure and spectral data for all new compounds. This material is available free of charge via the internet at http://rsc.org.

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17 When a second thiol (mercaptoethanol) was introduced into the mixture containing **26** and the iron-salen-butanethiol complex, only the SMA product containing the second thiol was formed. This implies that the initially complexed thiol remains attached to the metal center and is NOT the Michael addend in SMA.

18 A 180^{o} rotation around the Fe-O^{2} bond creates a steric clash of R^{3} with the proximal *tert*-butyl group of the salen ligand.

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Asymmetric conjugate addition of thiols to acyclic α,β-unsaturated ketones catalyzed by an iron(III)-salen complex gives β-thioketones in high enantiomeric excess