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A New Cobalt–Salen Catalyst for Asymmetric Cyclopropanation. Synthesis of the Serotonin–Norepinephrine Repuptake Inhibitor (+)-Synosutine

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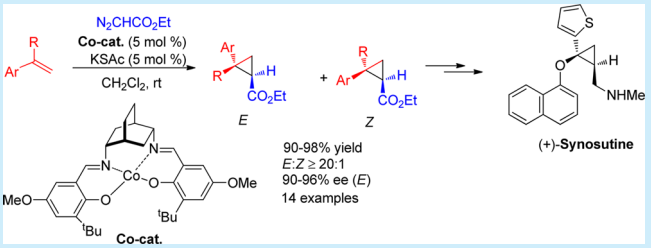
Supporting Information

ABSTRACT: A new C_2 symmetric cobalt(II)–salen catalyst based on *cis*-2,5-diaminobicyclo[2.2.2]octane as the chiral scaffold was prepared which, in the presence of potassium thioacetate as the promoter, catalyzed the formation of cyclopropanes from 1,1-disubstituted ethylenes and ethyl diazoacetate in high yield and with excellent diastereo- and enantioselectivity. Asymmetric cyclopropanation with the catalyst was used in a short, efficient synthesis of the dual serotonin–epinephrine reuptake inhibitor (+)-synosutine.



Chiral cyclopropanes represent an important class of carbocycles found in a wide range of naturally occurring structures.[1] Furthermore, the high degree of strain in a three-membered ring permits expansion, fragmentation, and rearrangement to other chiral cyclic and acyclic systems.[2] The most general method for enantioselective synthesis of substituted cyclopropanes is via addition of a carbene–transition metal complex (carbenoid) to an alkene where a chiral ligand surrounding the metal sets the stage for stereogenesis.[3] Catalytic methods based on this concept have employed chiral complexes of copper,[4] rhodium,[5] ruthenium,[6] and cobalt,[7] as well as species derived from late transition metals such as gold,[8] iron,[9] iridium,[10] and osmium.[11] Although some of these carbenoid complexes afford chiral cyclopropanes from alkenes and diazo compounds in highly enantio-enriched form, others are strongly substrate dependent and many give poor (*E*)/(*Z*) diastereoselectivity in trisubstituted cyclopropanes. In an effort to extend and improve existing methods for asymmetric synthesis of cyclopropanes, we have examined the reaction of ethyl diazoacetate with 1,1-disubstituted alkenes catalyzed by a new metal–salen complex in which *cis*-2,5-diaminobicyclo[2.2.2]octane (**1**) provides the chiral scaffold.[12]

Our previous studies with chiral metal-salen systems based on **1** found that chromium(II) complex **2** was an excellent catalyst for asymmetric hetero-Diels–Alder cycloaddition and for asymmetric Nozaki–Hiyama–Kishi addition of an allyl halide to aldehydes (Figure 1).[12] A copper(I) complex derived from a tetrahydro version of the same salen ligand was shown to be an efficient catalyst for the Henry reaction.[13] Recently, we found that iron(III) complex **3** catalyzed the highly enantioselective conjugate addition of thiols to α,β-unsaturated ketones (asymmetric sulfa-Michael reaction)[14] and we reasoned that a carbenoid unit embedded in a similar chiral architecture could be used to catalyze asymmetric cyclopropanation.

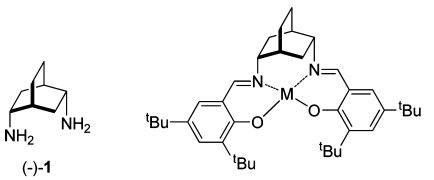


Figure 1. Diamine **1** and metal complexes **2**–**5** based on a *cis*-**2,5**-diaminobicyclo[2.2.2]octane scaffold.

Copper complexes have been widely employed as catalysts for asymmetric cyclopropanation since an initial report of this reaction by Noyori appeared in 1965,[4a] and we therefore assumed that copper(II)–salen complex **4** would be a good candidate for catalysis of cyclopropanation in our system. However, no cyclopropane formation was detected when α-methylstyrene (**6**) was exposed to ethyl diazoacetate in the presence of 20 mol % of **4** (Table 1, entry 1). On the other hand, the cobalt(II)–salen complex **5**[12] did produce trisubstituted cyclopropanes **7** and **8**, although in very low yield and with no (*E*)/(*Z*) selectivity (Table 1, entry 2). The presence of nucleophilic promoters has been shown by Katsuki to improve stereoselectivity in catalytic cyclopropanation,[7a−c,g] and addition of *N*-methylimidazole and 4-(dimethylamino)pyridine to the reaction of **6** with ethyl diazoacetate was found to increase the yield of **7** and **8** while decreasing the reaction time (Table 1, entries 3 and 4). Unfortunately, the stereoselectivity favoring (*E*)-cyclopropane **7** was low and a catalyst loading of at least 20 mol % of **5** was necessary for a practical preparation of this cyclopropane.

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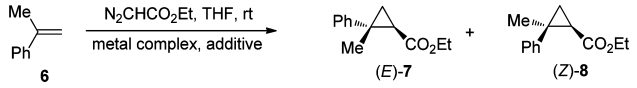
Table 1. Enantioselective Cyclopropanation of α-Methylstyrene (6) Catalyzed by Metal–Salen Complexes (+)-4 and (+)-5[a]

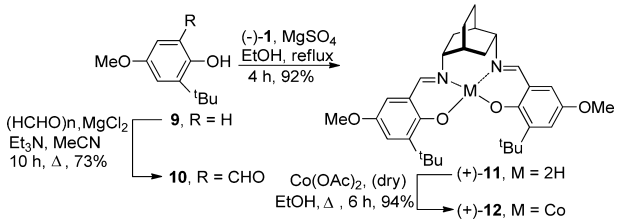


entry	metal complex[b]	additive	t (h)	dr E/Z[c]	yield [%][d]
1	(+)-**4**	–	48	–	nr
2	(+)-**5**	–	48	1:1	trace
3	(+)-**5**	NMI	18	1:1	52
4	(+)-**5**	DMAP	16	2:1	64

[a]The reactions were carried out on a 0.3 mmol scale in a 0.2 M solution with 1.5 equiv of **6** in the presence of 20 mol % catalyst. [b]The catalyst was stirred with the additive (20 mol %) for 1 h prior to the addition of **6**. [c]Determined by ^{1}H NMR analysis. [d]Isolated yields of *E* and Z isomers; nr = no reaction.

Katsuki has reported that the presence of an electron-donating substituent in the benzenoid rings of the salen framework of a metal complex can increase both the diastereo- and enantioselectivity of asymmetric cyclopropanation.[7a,b] This prompted us to modify our salen ligand in **5** by incorporating methoxy substituents at the C5 and C5′ positions of the benzenoid rings. Synthesis of our modified ligand began with formylation of 2-(*tert*-butyl)-4-methoxyphenol (**9**) with paraformaldehyde and triethylamine in the presence of magnesium chloride to give aldehyde **10** (Scheme 1).[15] Condensation of **10**

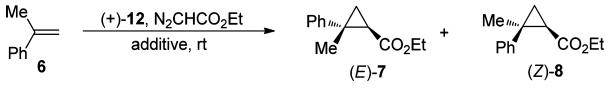
Scheme 1. Synthesis of the Second Generation Cobalt(II) Complex (+)-12



with (−)-diamine **1** using magnesium sulfate as the catalyst afforded salen ligand **11** which was reacted with rigorously dried cobalt(II) acetate in refluxing ethanol to furnish second generation cobalt–salen complex **12**.

The catalytic properties of **12** were first examined in the cyclopropanation of **6** with ethyl diazoacetate using 5 mol % of the catalyst in the presence of several additives (Table 2, entries 2–20). Without an additive, the reaction in THF produced cyclopropanes **7** and **8** in modest yield and with only 2:1 stereoselectivity favoring (*E*) isomer **7** (Table 2, entry 1) while certain additives (Table 2, entries 2–7) showed only a marginal gain in diastereoselectivity. However, the addition of DMF and DMSO to the reaction, each at 5 mol %, markedly improved the ratio of cyclopropanes in favor of **7** which exhibited a promising enantiomeric excess (Table 2, entries 8 and 9). After further experimentation with a series of electron-donor additives (Table 2, entries 10–20), it was found that cyclopropanation in a chlorinated solvent containing potassium thioacetate at 5 mol % gave **7** and **8** in >90% yield with a **7**:**8** ratio of *ca.* 30:1 (Table 2, entries 15–17). In chloroform or dichloromethane as solvent, the enantiomeric excess of **7** was >90% (Table 2, entries 16 and 17). The absolute configuration

Table 2. Enantioselective Cyclopropanation of α-Methylstyrene (6) Catalyzed by Cobalt–Salen Complex (+)-12[a]



entry	(+)-**12**[b] (mol %)	additive (mol %)	solvent	t (h)	dr E/Z[c]	yield [%][d]	ee [%][e]
1	5	–	THF	48	2:1	63	nd
2	5	NMI (5)	THF	30	3:1	82	nd
3	5	DMAP (5)	THF	36	3:1	91	nd
4	5	pyridine (5)	THF	48	2:1	46	nd
5	5	2,6-lutidine (5)	THF	50	4:1	51	nd
6	5	Ph_3P (5)	THF	39	4:1	39	nd
7	5	Ph_3As (5)	THF	39	3:1	95	nd
8	5	DMF (5)	THF	40	9:1	89	72
9	5	DMSO (5)	THF	40	12:1	68	68
10	5	NaOAc (5)	THF	36	3:1	49	nd
11	5	KSAc (5)	THF	36	21:1	97	73
12	5	HMPA (5)	THF	27	6:1	56	54
13	5	DMPU (5)	THF	27	6:1	53	59
14	5	Br_2 (5)	THF	20	9:1	87	67
15	5	KSAc (5)	DCE	29	28:1	95	84
16	5	KSAc (5)	CH_2Cl_2	29	31:1	93	93
17	5	KSAc (5)	$CHCl_3$	28	30:1	90	91
18	5	KSAc (5)	PhMe	48	17:1	77	86
19	2.5	KSAc (2.5)	CH_2Cl_2	60	22:1	67	88
20	1	KSAc (1)	CH_2Cl_2	60	17:1	58	85

[a]The reactions were carried out on a 0.3 mmol scale in a 0.2 M solution with 1.5 equiv of **6** in the presence of catalyst and additive. [b]The catalyst was stirred with the additive for 1 h prior to the addition of **6**. [c]Determined by ^{1}H NMR analysis. [d]Isolated yields of (*E*) and (*Z*) isomers. [e]Determined by HPLC using a Chiralcel OD-H column.

of **7** was shown to be (1*R*,2*R*) by comparison of its optical rotation with the literature value.[6a,d]

The optimized conditions developed for asymmetric cyclopropanation of **6** were tested on a range of 1,1-disubstituted ethylenes (Table 3). 1-Alkyl-1-aryl ethylenes (**13**, Table 3, entries 1–13) afforded (*E*) cyclopropanes **14**–**26** in 89–97% yield and >20:1 diastereoselectivity. The enantiomeric excess of the major cyclopropane from these reactions was 90–98%. A 1,1-dialkyl ethylene gave (*E*) cyclopropane **27** in good yield but with lower stereoselectivity (Table 3, entry 14), and a thioenol ether also led to a cyclopropane (**28**) with diminished stereoselectivity (Table 3, entry 15). These results are consistent with a mechanistic model for cyclopropanation with **12** where stereoelectronic effects play a prominent role (*vide infra*).

A practical application of asymmetric cyclopropanation with **12** was demonstrated in a synthesis of (+)-synosutine (**29**), a cyclopropyl homologue of the commercial antidepressant duloxetine (Cymbalta) and itself a powerful dual inhibitor (1–2 nM) of serotonin and norepinephrine reuptake (Figure 2).[16] A previous synthesis of **29** installed the cyclopropane core via Charette asymmetric cyclopropanation[17] of an allylic alcohol using a chiral boronate catalyst in a process that required separation of (*E*) and (*Z*) allylic alcohols and was expensive to scale up.

The new route to **29** began with acylation of 1-naphthol (**30**) with thiophen-2-carbonyl chloride (**31**) to give ester **32** which after Tebbe methylenation[18] afforded enol ether **33** (Scheme

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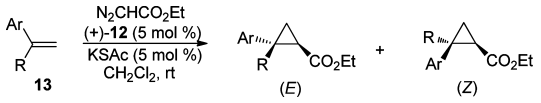
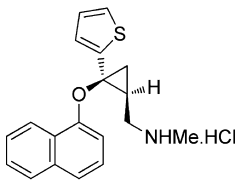
Table 3. Asymmetric Cyclopropanation of 1,1-Disubstituted Ethylenes (13) Catalyzed by (+)-12[a,b]



entry	Ar	R	t (h)	product[c]	dr E/Z[d]	yield [%][e]	ee [%][f]
1	Ph	Et	32	**14**	26:1	94	92
2	Ph	^{n}Bu	32	**15**	23:1	91	90
3	2-OMeC$_6$H$_4$	Me	26	**16**	30:1	90	96
4	2-furyl	Me	36	**17**	23:1	89	92
5	Ph	CH_2CO_2Et	28	**18**	25:1	91	91
6	(2-CO$_2$Me)-C$_6$H$_4$	Me	19	**19**	30:1	92	95
7	3,4-Di-OMeC$_6$H$_3$	Me	22	**20**	32:1	96	94
8	2-thiophenyl	Me	33	**21**	25:1	93	90
9	1-naphthyl	Me	26	**22**	33:1	97	96
10	4-MeC$_6$H$_4$	$(CH_2)_2CO_2Me$	28	**23**	27:1	96	94
11	3-(CO$_2$Et)-5-C$_6$H$_5$-2-furyl	Me	39	**24**	26:1	92	97
12	4-CF$_3$C$_6$H$_4$	^{n}Pr	26	**25**	21:1	95	92
13	4-OMeC$_6$H$_3$	$(CH_2)_3$-	20	**26**	>50:1	90	98
14	CH_2-(1-naphthyl)	Me	36	**27**	18:1	95	83
15	SC$_6$H$_5$	^{n}Pr	48	**28**	16:1	87	88

[a]The reactions were carried out on a 0.3 mmol scale in a 0.2 M solution with 1.5 equiv of **13** in the presence of (+)-**12** and KSAc each at 5 mol %. [b]Catalyst (+)-**12** was stirred with KSAc for 1 h prior to the addition of **13**. [c]See Supporting Information. [d]Determined by ^{1}H NMR analysis. [e]Isolated yields of (*E*) and (*Z*) isomers. [f]Determined by HPLC using a Chiralcel OD, AD, OD-H or AS-H column.



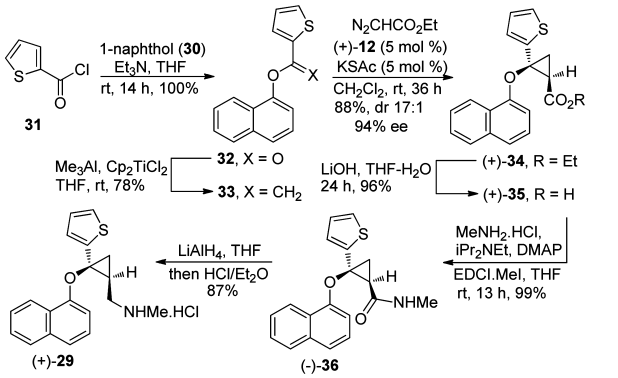
(+)-**29**

Figure 2. Synosutine, a balanced dual inhibitor of serotonin and norepinephrine reuptake.

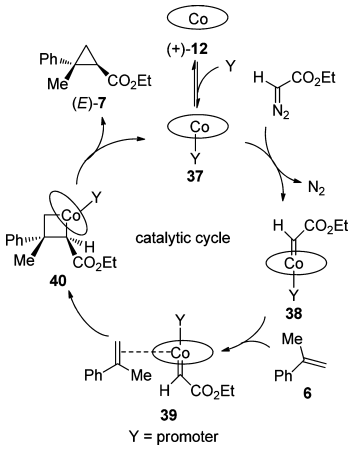
2). Exposure of **33** to ethyl diazoacetate in the presence of **12** (5 mol %) and potassium thioacetate (5 mol %) in dichloromethane at room temperature resulted in smooth cyclopropanation to furnish (*Z*) ester **34** with a (*Z*)/(*E*) ratio 17:1. The major (*Z*) isomer **34** was formed in 94% enantiomeric excess. Saponification of **34** produced the known (1*R*,2*S*) carboxylic acid **35**[16] which was condensed with methylamine to give amide **36**. Final reduction of **36** with lithium aluminum hydride led to (+)-synosutine (**29**) in a five-step sequence from commercial materials. This route shortens our previous synthesis of **29** by four steps and circumvents the separation of (*E*) and (*Z*) allylic alcohols required for Charette cyclopropanation.

A catalytic cycle that rationalizes the formation of cyclopropane **7** from **6** and ethyl diazoacetate in the presence of cobalt complex **12** and a promoter (Y) is shown in Scheme 3. As noted previously with iron−salen complex **3** which

Scheme 2. Enantioselective Synthesis of Synosutine (29)



Scheme 3. Catalytic Cycle for the Formation of (*E*)-7 via Asymmetric Cyclopropanation of 6 in the Presence of (+)-12



undergoes prior activation by a thiol before catalyzing the asymmetric sulfa-Michael reaction,[14] the nucleophilic promoter potassium thioacetate is believed to activate the cobalt complex by reacting with **12** to produce the new complex **37**. This activated complex[19] then reacts with ethyl diazoacetate to generate cobalt carbenoid **38** which undergoes stereoselective cycloaddition with **6** to furnish transiently four-membered cobaltocycle **40**. The formation of cobaltocycles of this type is well documented, as is their collapse to cyclopropanes by stereospecific extrusion of the complexed cobalt species.[20]

The relative and absolute configuration of the trisubstituted cyclopropane **7** generated in this process can be explained by the approach of the alkene toward the cobalt carbenoid **38** along the trajectory shown in Figure 3. With the carbenoid ligand situated in the more open lower right quadrant under the

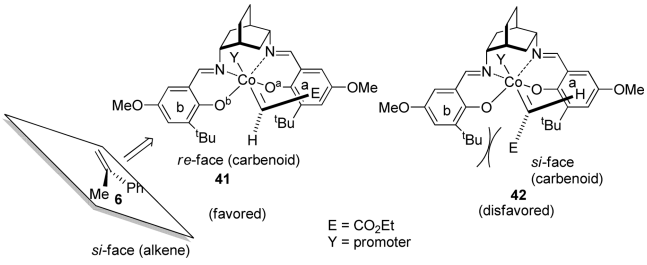


Figure 3. Proposed transition state for the enantioselective cyclopropanation of α-methylstyrene (**6**) with ethyl diazoacetate catalyzed by cobalt(II)−salen complex (+)-**12**.

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bicyclic scaffold of **12** and with the ester oriented to minimize steric interaction with a neighboring *tert*-butyl group of the salen framework, the *si* face of the carbenoid is obstructed by benzenoid ring "a" whereas the *re* face is exposed to attack by the alkene π system. Approach to this cobalt carbenoid by the *si* face of α-methylstyrene is dictated by steric bulk around the cobalt, which determines the regioselectivity of cycloaddition, and by the geometry of the carbenoid, which aligns the ester group with the smaller methyl substituent of **6**. This leads to (*E*) cobaltocycle **40**. When the steric size of substituents in a 1,1-disubstituted ethylene is more closely matched, diminished (*E*/(*Z*) stereoselectivity of cyclopropane formation, as in **27** and **34**, is to be expected with this model.

In summary, a new cobalt−salen complex **12** based on a chiral *cis*-2,5-diaminobicyclo[2.2.2]octane scaffold has been prepared in which the salen ligand is modified by incorporating an electron-donating methoxy substituent in each benzenoid ring. In the presence of the additive potassium thioacetate, **12** was found to catalyze the reaction of α-methylstyrene and other 1,1-disubstituted ethylenes with ethyl diazoacetate to give trisubstituted cyclopropanes with high diastereo- and enantioselectivity. The reaction was applied to a 1,1-disubstituted enol ether to produce a cyclopropane that was carried forward to (+)-synosutine, a dual inhibitor of serotonin and norepinephrine reuptake in five steps with 57% overall yield. A rationale for the stereochemical outcome of cyclopropanation with (1*R*,2*R*,4*R*,5*R*)-**12** is proposed in which an initially formed activated cobalt carbenoid undergoes *re* face cycloaddition with the alkene at its *si* face to generate a four-membered cobaltocycle regio- and stereoselectively. Cobalt is extruded stereospecifically from the metallocycle to furnish a cyclopropane and regenerate the catalyst.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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