ORGANIC
LETTERS

2011
Vol. 13, No. 9
2488–2491

cis-2,5-Diaminobicyclo[2.2.2]octane, a New Scaffold for Asymmetric Catalysis via Salen–Metal Complexes

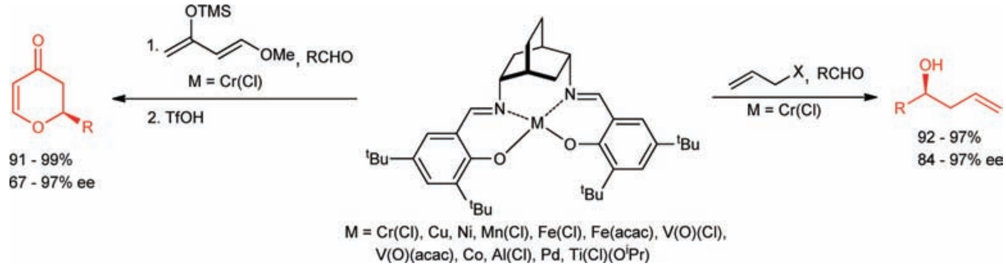
James D. White* and Subrata Shaw

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331, United States

James.white@oregonstate.edu

Received March 18, 2011

ABSTRACT



M = Cr(Cl), Cu, Ni, Mn(Cl), Fe(Cl), Fe(acac), V(O)(Cl), V(O)(acac), Co, Al(Cl), Pd, Ti(Cl)(O^{i}Pr)

A new C_2 symmetric salen scaffold based on *cis*-2,5-diaminobicyclo[2.2.2]octane has been synthesized that forms complexes with a wide range of metals. The chromium(III) complex is shown to catalyze the hetero-Diels–Alder reaction and the Nozaki–Hiyama–Kishi reaction with high efficiency and excellent stereoselectivity.

Chiral salen ligands in combination with certain metals have proven to be highly effective species for catalyzing a wide range of organic transformations with good to excellent levels of asymmetric induction.[1,2] Almost all ligands of this type are based on a chiral 1,2-diamine, e.g. *trans*-1,2-diaminocyclohexane (**1**), as the core scaffold.[3] Exceptions are Berkessel's salen ligand "DIANANE"[4] derived from *cis*-2,5-diaminobicyclo[2.2.1]heptane (**2**) and a 1,4-diamine derived from isophorone.[5] Although diamine **2** has been prepared in enantiopure form, only the Cr(III) complex of the salen derivative has been studied as an asymmetric catalyst. In our search for a chiral template that would have broad utility as a catalyst in asymmetric synthesis,[6] we have examined *cis*-2,5-diaminobicyclo[2.2.2]octane (**3**)[7] as a scaffold for salen–metal complexes. We have found that diamine **3** is not only easy to prepare in enantiopure form but that its salen derivative forms a large number of stable metal complexes. In this report, we show that the Cr(III) complex of this salen ligand catalyzes the hetero-Diels–Alder reaction[8,9] and the Nozaki–Hiyama–Kishi reaction[10,11] in high yield and with excellent levels of asymmetric induction.

---

(1) Larrow, J. F.; Jacobsen, E. N. *Top. Organomet. Chem.* **2004**, *4*, 123.

(2) Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85.

(3) Cozzi, P. G. *Chem. Soc. Rev.* **2004**, *33*, 410.

(4) Berkessel, A.; Schröder, M.; Sklorz, C. A.; Tabanella, S.; Vogl, N.; Lex, J.; Neudörfl, J. M. *J. Org. Chem.* **2004**, *69*, 3050.

(5) Berkessel, A.; Roland, K.; Schroder, M.; Neudorfl, J. M.; Lex, J. *J. Org. Chem.* **2006**, *71*, 9312.

(6) A structure meeting this qualification is defined as "privileged" (Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691).

(7) Aksani, R.; Eichenauer, H.; Kohler, J. *Chem. Ber.* **1982**, *115*, 751.

(8) For reviews of the hetero-Diels–Alder reaction, see: (a) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (b) Lin, L.; Liu., X.; Feng, X. *Synlett* **2007**, 2147.

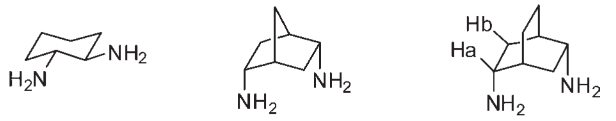
(9) For hetero-Diels–Alder reactions catalyzed by Cr(salen) complexes, see: (a) Schaus, S. E.; Branal, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. (b) Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, *57*, 845. (c) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Chem. Commun.* **2002**, 919. (d) Mellah, M.; Ansel, F.; Voituriez, A.; Schulz, E. *J. Mol. Catal.: Chem.* **2007**, *272*, 20. (e) Eno, S.; Egami, H.; Uchida, T.; Katsuki, T. *Chem. Lett.* **2008**, *37*, 632.

(10) For NHK reactions catalyzed by Cr(salen) complexes, see: (a) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3357. (b) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Polyhedron* **2000**, *19*, 537. (c) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew Chem. Int. Ed.* **2000**, *39*, 2327. (d) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Tetrahedron* **2001**, *57*, 835. (e) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Morganti, S.; Umani-Ronchi, A. *Org. Lett.* **2001**, *3*, 1153. (f) Berkessel, A.; Menche, D.; Sklorz, C. A.; Schroder, M.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*, 1032.

(11) For an asymmetric NHK reaction catalyzed by a chiral Cr(III)–sulfonamide complex, see: Choi, H.-W.; Nakajima, K.; Demeke, D.; Kang, F. A.; Jun, H. S.; Wan, Z. K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435.

10.1021/ol2007378

A structural feature of diamine **3** that is particularly attractive is the large separation of nitrogen atoms, as determined by X-ray crystallographic analysis, compared to **1** and **2** (Figure 1). This gives the salen ligand derived from **3** a broad "wingspan" that encloses a large volume of chiral space while preserving a rigid asymmetric environment. There is also a larger degree of "twist" around the C_2 axis of **3**, reflected in a H_a–C–C–H_b dihedral angle of 22°, than in the bicyclo[2.2.1]heptane frame of **2** where the corresponding dihedral is calculated to be 14°.



1	2	3
2.91	4.00	4.27

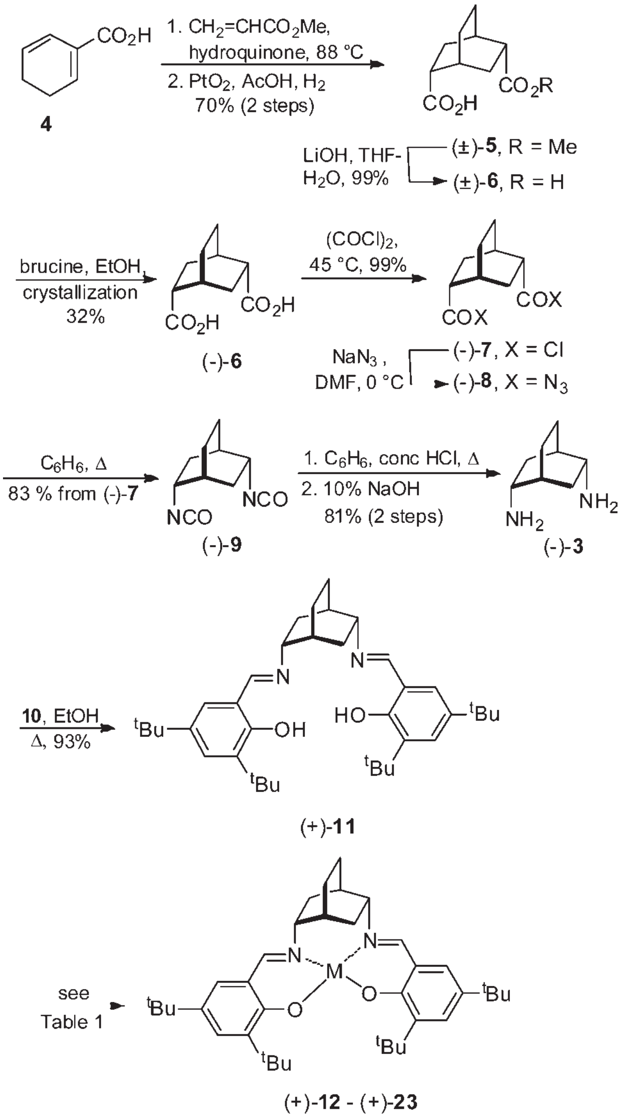
Figure 1. N–N distance (Å) in chiral diamine scaffolds for **1**–**3**.

The synthesis of **3** began with the Diels–Alder addition of neat methyl acrylate to 1,3-cyclohexadiene-2-carboxylic acid (**4**, Scheme 1).[12] The endo adduct was hydrogenated, and ester **5** was saponified to yield racemic dicarboxylic acid **6**.[13] The resolution of **6** was accomplished by treatment with (–)-brucine which afforded a crystalline salt amenable to X-ray analysis; acidic hydrolysis of this pure diastereomer gave (–)-**6** with (1*R*,2*R*,4*R*,5*R*) absolute configuration. Diacid (–)-**6** was advanced via the corresponding diacyl chloride **7** to diacyl azide **8** which underwent in situ double Curtius rearrangement upon heating to produce bis isocyanate (–)-**9**. Hydrolysis of **9** and concomitant decarboxylation of the biscarbamic acid gave diamine (–)-**3**. Condensation of (–)-**3** with 3,5-di-*tert*-butylsalicylaldehyde (**10**) furnished Schiff base (+)-**11** as a crystalline solid whose structure was confirmed by X-ray analysis.

Salen ligand (+)-**11** was reacted with the metal salts shown in Table 1 to give metal complexes **12**–**23** in near quantitative yield. The complexes are high-melting solids of various colors and crystallinity. The structures of Cu(II), Ni(II), and Pd(II) complexes, **13**, **14**, and **22** respectively, were confirmed by X-ray crystallographic analysis. The crystal structure including the absolute configuration of (+)-**22** is shown in Figure 2, confirming the absolute configuration of (–)-**6**. We were unable to prepare metal complexes of (+)-**11** with $Zn(OAc)_2$ and $Rh_2(OAc)_4$.

Our initial studies with metal complexes shown in Table 1 have focused on Cr(III) salen derivative (+)-**12** as a catalyst for the hetero-Diels–Alder cycloaddition of diene **24**[14] to aromatic aldehydes **25** (Table 2). Entries 1–9 in Table 2 establish that (+)-**12** is an efficient catalyst for this reaction, giving 5,6-dihydro-4- pyranones **26** in good yield and high enantioselectivity after hydrolysis of intermediate cycloadduct **27**. Enantioselectivity was modest for the reaction of **24** with furfural (entry 9) and with cyclohexanecarboxaldehyde (entry 11) although the yield of the cycloadduct was high in both cases. The absolute configuration of dihydropyranones **26** was established in all cases as (6*S*), except for entries 7 and 10, by comparison of the observed specific rotation with literature values.

Scheme 1. Synthesis of Diamine (–)-**3** and Its Salen–Metal Complexes



We next examined (+)-**12** as a catalyst for the Nozaki–Hiyama–Kishi (NHK) reaction of allyl halides with aromatic aldehydes **25** (Table 3). An efficient catalyzed asymmetric version of the NHK reaction has been a long sought goal, but a general solution to this problem has remained elusive.[15] The results in Table 3 show that homoallylic alcohols **28** are produced in high yield and with good enantioselectivity when allyl bromide reacts with an aryl aldehyde in the presence of 10 mol % of (+)-**12**.

---

(12) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911.

(13) Tichy, M.; Sicher, J. *Collect. Czech. Chem. Commun.* **1972**, *37*, 3106.

(14) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth.* **1990**, *61*, 147.

Table 1. Complexes Formed by (+)-**11** with Metal Salts

reagent	solvent	temp	product	color
$CrCl_2$, Et_3N, O_2	THF	ambient	(+)-**12**, M = Cr(Cl)^a	brown
$Cu(OAc)_2 \cdot H_2O$	MeOH	reflux	(+)-**13**, M = Cu	black
$Ni(OAc)_2 \cdot 4H_2O$	MeOH	reflux	(+)-**14**, M = Ni	red-orange
$Mn(OAc)_2 \cdot 4H_2O$, O_2, NaCl	MeOH	reflux	(+)-**15**, M = Mn(Cl)^{a,b}	brown
$FeCl_3$, NaH	THF	reflux	(+)-**16**, M = Fe(Cl)	brown
$Fe(acac)_3$	MeOH	reflux	(+)-**17**, M = Fe(acac)	violet
$VOCl_3$, Et_3N	CH_2Cl_2	ambient	(+)-**18**, M = V(O)(Cl)	green
$VO(acac)_2$	MeOH	reflux	(+)-**19**, M = V(O)(acac)	green
$CoBr_2$, NaH	THF	reflux	(+)-**20**, M = Co	orrange
$AlCl_3$, NaH	THF	reflux	(+)-**21**, M = Al(Cl)	pale yellow
$Pd(OAc)_2$	MeOH	reflux	(+)-**22**, M = Pd	red
$TiCl(O\textit{i}Pr)_3$, Et_3N	CH_2Cl_2	ambient	(+)-**23**, M = Ti(Cl)(O*i*Pr)	yellow

[a] The flask was opened to air after the initial reaction. [b] The reaction mixture was washed with brine during workup.

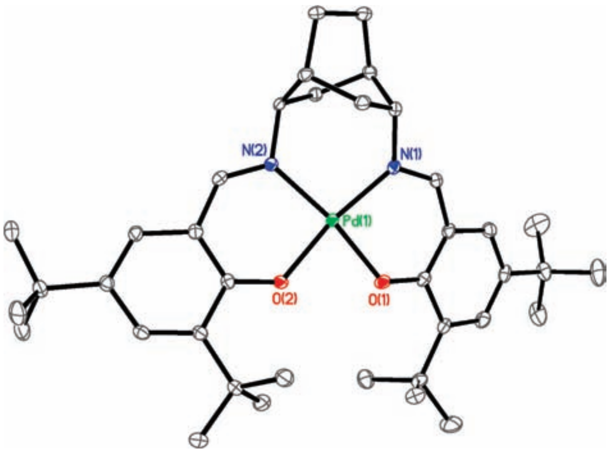
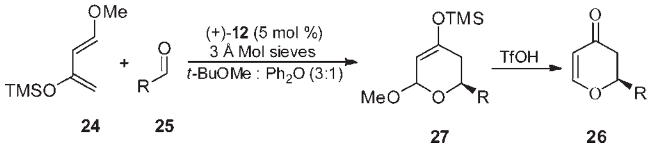


Figure 2. Crystal structure of Pd–salen complex (+)-**22**.

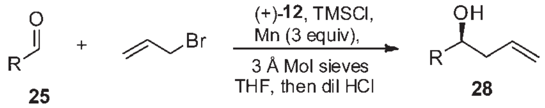
Table 2. Asymmetric Hetero-Diels–Alder Reactions Catalyzed by Chromium(III)–Salen Complex (+)-**12**^{a}



				product **26**	
entry	R	temp (°C)	*t* (h)	yield [%]^b	ee [%]^c
1	C_6H_5	−22	30	99	97
2	$2\text{-}CH_3C_6H_4$	−22	24	98	92
3	$3\text{-}CH_3C_6H_4$	−22	24	99	92
4	$3\text{-}CH_3OC_6H_4$	−22	36	99	96
5	$4\text{-}ClC_6H_4$	−22	24	98	94
6	$4\text{-}O_2NC_6H_4$	−22	24	99	94
7	$3,5\text{-}(CH_3O)_2C_6H_3$	−30	48	97	94^d
8	1-naphthyl	−30	40	96	94
9	2-furyl	−22	18	99	67
10	3-furyl	−30	42	97	94^d
11	$c\text{-}C_6H_{11}$	−22	36	91	68

[a] Reactions were carried out on 0.25 mmol scale with 1.2 equiv of **24**. [b] Yield of isolated product. [c] Determined by HPLC using a Daicel Chiralcel OD column. [d] The absolute configuration was not determined.

Table 3. Asymmetric Nozaki–Hiyama–Kishi Reactions Catalyzed by Chromium(III)–Salen Complex (+)-**12**^{a}



					product **28**	
entry	R	cat. load (mol %)	temp (°C)	*t* (h)	yield [%]^b	ee [%]^c
1	C_6H_5	10	20	8	97	69
2	C_6H_5	20	−10	15	92	89
3	$2\text{-}CH_3C_6H_4$	10	10	6.5	92	92
4	$4\text{-}CH_3C_6H_4$	10	10	6.5	97	95
5	$3\text{-}CH_3OC_6H_4$	10	10	6	96	89
6	$4\text{-}ClC_6H_4$	10	20	5	96	96
7	$3,5\text{-}(CH_3O)_2C_6H_3$	10	10	8	95	93^d
8	$2,6\text{-}Cl_2C_6H_3$	10	20	7	92	84
9	1-napthyl	10	20	4	97	97
10	3-furyl^e	10	10	3	93	85

[a] Reactions were carried out on 0.125 mmol scale with 1.5 equiv of allyl halide. [b] Yield of isolated product. [c] Determined by HPLC using a Daicel Chiralcel OD column. [d] The absolute configuration was not determined. [e] Allyl chloride was used.

The configuration of **28** was found to be (*S*) in all cases except entry 7 where it was not determined. Our results compare favorably with those obtained recently on the asymmetric NHK reaction using catalysts that employ both salen[10f] and other chiral scaffolds.[16]

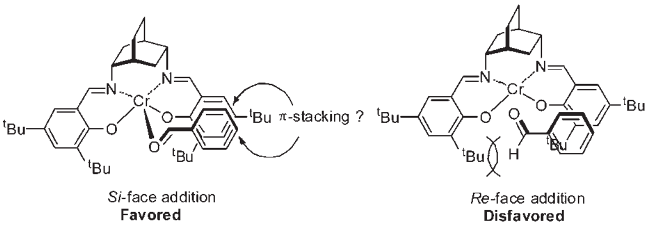
A proposed model for coordination of an aryl aldehyde with chromium–salen catalyst (+)-**12** is shown in Figure 3. With the aldehyde positioned in an open quadrant below

---

(15) For an account of earlier efforts directed towards the NHK reaction, both stoichiometric and catalytic, see: Furstner, A. *Chem. Rev.* **1999**, *99*, 991.

(16) For NHK reactions catalyzed by a Cr(III) complex of other chiral scaffolds, see: (a) McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Adv. Synth. Catal.* **2006**, *348*, 551. (b) Hargaden, G. C.; McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Org. Biomol. Chem.* **2007**, *5*, 763. (c) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140. (d) Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252. (e) Lee, J. Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837. (f) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554.

the bicyclo[2.2.2]octane scaffold and the carbonyl oriented to avoid a steric interaction between its hydrogen atom and a neighboring *tert*-butyl substituent, the *re* face of the carbonyl group is blocked by an opposing aryl ring of the salen residue whereas the *si* face is accessible. The addition of diene **24** or allyl bromide to the *si* face of aldehyde **25** leads to an (*S*) configuration of **26** and **28** as observed. It is likely that a π-stacking interaction contributes to stabilization of the coordination complex with aryl aldehydes, a factor that could explain the lower enantioselectivity observed with cyclohexanecarboxaldehyde.



Si-face addition
Favored

Re-face addition
Disfavored

Figure 3. Proposed model for coordination of an aryl aldehyde with Cr–salen catalyst (+)-**12**.

In summary, we have prepared a new salen ligand based on a chiral diaminobicyclo[2.2.2]octane. The ligand shows strong affinity for transition metals as well as certain other metals with which it forms stable well-characterized complexes. The Cr(III) complex of this salen ligand possesses excellent catalytic activity in the hetero-Diels–Alder reaction and the Nozaki–Hiyama–Kishi reaction of aromatic aldehydes, giving products in high enantiomeric excess in most cases.

Acknowledgment. We are grateful to Dr. Lev Zakharov, University of Oregon, for X-ray crystal structure determination of (+)-**11**, (+)-**13**, (+)-**14**, (+)-**22**, and the brucine salt of (−)-**6**. Financial support was provided by the National Science Foundation (CHE0834862). Support for the Oregon State University NMR facility through grants from the Murdock Charitable Trust (Grant 2005265) and from the National Science Foundation (CHE-0722319) is gratefully acknowledged.

Supporting Information Available. Experimental procedures and characterization data for new compounds; X-ray crystallographic data for five compounds. This material is available free of charge via the Internet at http://pubs.acs.org.