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

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James D. White* and Subrata Shaw

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

James.white@oregonstate.edu

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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*-1,2diaminocyclohexane (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

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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.

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⁽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.

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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°.



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 (1R, 2R, 4R, 5R) 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 Rh₂(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 24¹⁴ to aromatic aldehydes 25 (Table 2). Entries 1–9 in Table 2 establish that (+)-12 is an efficient catalyst for

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



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.

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.

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reagent	$\operatorname{solvent}$	temp	product	color brown	
$CrCl_2$, Et_3N , O_2	THF	ambient	$(+)-12, M = Cr(Cl)^{a}$		
$Cu(OAc)_2\!\cdot\!H_2O$	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	
$VOCl_3, Et_3N$	$\mathrm{CH}_{2}\mathrm{Cl}_{2}$	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	
${\rm Pd}({\rm OAc})_2$	MeOH	reflux	(+)- 22 , M = Pd	red	
TiCl(OiPr) ₃ , Et ₃ N	$\mathrm{CH}_{2}\mathrm{Cl}_{2}$	ambient	(+)- 23 , M = Ti(Cl)(O <i>i</i> Pr)	yellow	

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

^{*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.

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



		temp (°C)	<i>t</i> (h)	product 26	
entry	R			yield [%] ^b	ee [%] ^c
1	C_6H_5	-22	30	99	97
2	$2\text{-}\mathrm{CH}_3\mathrm{C}_6\mathrm{H}_4$	-22	24	98	92
3	$3-CH_3C_6H_4$	-22	24	99	92
4	$3-CH_3OC_6H_4$	-22	36	99	96
5	$4-ClC_6H_4$	-22	24	98	94
6	$4-O_2NC_6H_4$	-22	24	99	94
7	3,5-(CH ₃ O) ₂ C ₆ H 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	$c-C_6H_{11}$	-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*}



^{*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.

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

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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.



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.

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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.