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Enantioselective Nitroaldol Reaction Catalyzed by Sterically Modified Salen−Chromium Complexes

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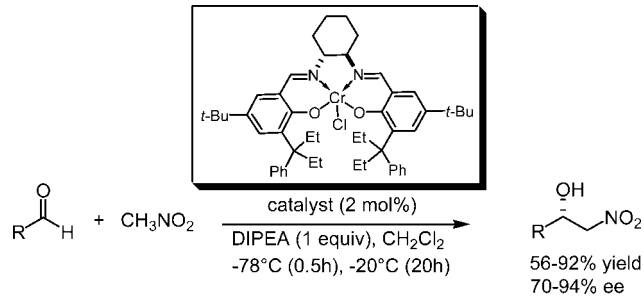

A group of modified (salen)Cr(III)Cl complexes with bulky benzylic substituents in the 3,3′-position of the salicylidene moiety have been successfully applied for the asymmetric nitroaldol reaction. The readily accessible complex bearing 3-phenylpent-3-yl groups (2 mol %) leads to β-nitro alcohols in up to 92% yield and 94% ee.

Introduction

The asymmetric nitroaldol (Henry) reaction provides direct access to chiral β-nitro alcohols, which are synthetic precursors of bioactive compounds.[1] Moreover, the nitro group opens the way for further modifications by reduction, Nef reaction, as well as displacement by the carbon, sulfur, and azide nucleophiles. Thus, the Henry reaction provides access to a large set of useful bifunctional compounds, particularly unusual amino alcohols with the stereogenic carbinol center not accessible by reduction of amino acids. When imine is applied, sequential aza-Henry reaction and reduction afford chiral diamines.[2] This powerful tool for creating at least one stereogenic center is therefore applicable to the synthesis of chiral ligands, pharmaceuticals, and natural compounds.

Bearing in mind its value, the asymmetric nitroaldol reactions have received increased attention from researchers, and numerous catalytic systems have been drawn up.[3] Among them, metal complexes based on lanthanum(III), zinc, cobalt(II), and copper(II) are widely exemplified. In spite of significant advances in this area, many of the reported catalytic systems required long reaction time, use of expensive catalyst or its high loading, and the need of dry solvents and molecular sieves.

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C_2-Symmetric metallosalen complexes proved to be useful catalysts for a wide range of reactions.[4] Moreover, usually salen ligands are easy to prepare[5] and their complexes with various metals have a benchtop stability. It is noteworthy that steric and electronic properties of salen complexes can be varied easily by simple modifications of salicylidene unit. Variations at the positions 3,3′ in close proximity to the metal center have been studied extensively,[6] also in our group.[7] It was proven that increasing of steric hindrance of substituents occupying the *ortho* position to the phenolic oxygen in salen ligand exerts a beneficial effect on enantioselectivity in various reactions. Enhancement in the effectiveness of branched ligands was rationalized to be of steric-based distortion of a nearly planar, flat salen framework.

Metallosalens were applied in various aldol-type reactions;[8] however, there are only a few successful examples for nitroaldol reaction, utilizing cobalt(II)[8a] and heterobimetallic Pd/La[8b] salen complexes. The first method with a classical cobalt complex[8a] requires long reaction time, and its applicability is limited mainly to halogenated aromatic aldehydes and nitromethane. In addition, reaction with benzaldehyde provided the respective nitro alcohol with low yield and moderate enantioselectivity (36% and 62% ee). Therefore, we decided to investigate this reaction with other metallosalen complexes, and we have recently found the commercially available, salen−chromium(III)[9] complex **1a** (Figure 1) to be a useful catalyst for the asymmetric Henry reaction.[10] The respective nitroaldols were achieved with moderate to good yields and enantioselectivities (up to 76% ee). In continuation of these studies, we attempted to optimize the salen−chromium(III) system via modifications of the ligand based on introduction of a more sterically demanding surround of the metal (Figure 1).[7]

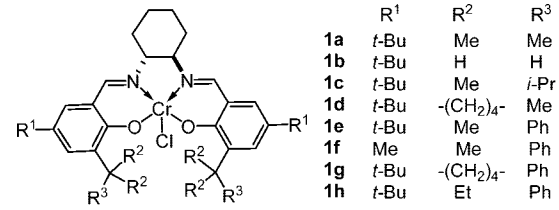
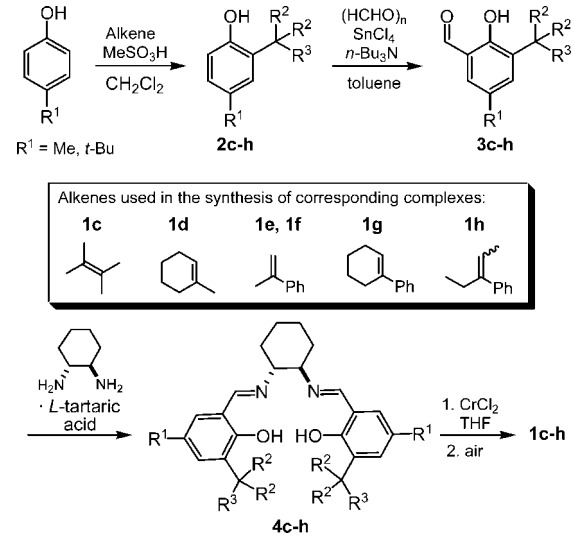


FIGURE 1. Salen−chromium(III) complexes **1a**−**h**.

SCHEME 1. General Synthesis of the Sterically Modified Catalysts



Results and Discussion

Applying the concept of steric modifications of salen complexes to nitroaldol reaction, several modified ligands were prepared in an easy manner from readily accessible and inexpensive materials (Scheme 1). Bulky subsitituents were introduced in the *ortho*-position via the acid-catalyzed alkylation of 4-*tert*-butyl- and 4-methylphenol by corresponding alkenes, leading to 2,4-disubstituted phenols **2c**−**h**. Salicylic aldehydes of type **3** were prepared from phenols **2** according to the Casiraghi[11] procedure and finally condensed with (*1R*,*2R*)-1,2-diaminocyclohexane tartrate to afford the crystalline salen ligands **4** (Scheme 1).[5] Chromium complexes **1a**−**h** were prepared using $CrCl_2$ according to the Jacobsen procedure.[12]

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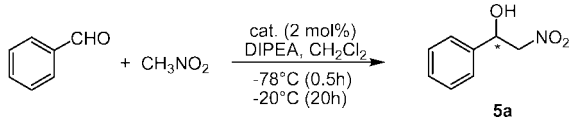
TABLE 1. Screening of the Catalyst in the Nitroaldol Reaction[a]



	catalyst					
entry	no.	R^1	R^2	R^3	yield[b] (%)	ee[c] (%)
1	**1a**	*t*-Bu	Me	Me	36	57 (*S*)
2	**1b**	*t*-Bu	H	H	16	19 (*R*)
3	**1c**	*t*-Bu	Me	*i*-Pr	70	76 (*S*)
4	**1d**	*t*-Bu	$-(CH_2)_4-$	Me	55	70 (*S*)
5	**1e**	*t*-Bu	Me	Ph	65	90 (*S*)
6	**1f**	Me	Me	Ph	77	79 (*S*)
7	**1g**	*t*-Bu	$-(CH_2)_4-$	Ph	78	89 (*S*)
8	**1h**	*t*-Bu	Et	Ph	62	93 (*S*)

[a] Reactions were performed on 0.5 mmol of benzaldehyde, 0.5 mmol of DIPEA, and 2.0 mL of nitromethane in 2.0 mL of CH_2Cl_2 applying 2 mol % of the respective (1*R*,2*R*)-salen−chromium(III) complex initially at −78 °C (0.5 h) and then at −20 °C (20 h). [b] Yields of isolated product by column chromatography on silica gel. [c] ee were determined by HPLC on chiral stationary phase (OD-H).

For the initial study, we employed the reaction of benzaldehyde with nitromethane in the presence of diisopropylethylamine (DIPEA) and 2 mol % of chromium complexes of type **1** (Figure 1, Table 1). The classical Jacobsen complex **1a** catalyzes the trial reaction with a moderate enantioselectivity (entry 1, Table 1); however, use of the complex **1b** with smaller methyl groups at the 3,3′-positions instead of *tert*-butyl resulted in dropping of both the yield and enantioselectivity (entry 2). Additionally, the direction of asymmetric induction was reversed. Simple expansion of bulkiness of the substituents by replacement of *tert*-butyl group in Jacobsen catalyst with 2,3-dimethylbut-2-yl (complex **1c**, entry 3) led to a substantial increase of the yield and enantioselectivity from 57 to 76% ee. A steady increase of ee's was noted as a result of further modifications of the substituent at 3,3′ position of salicylidene unit. Interestingly, introduction of the branched benzylic substituents had a beneficial effect on stereoselectivity as well as activity (entries 5−8) in each case compared to the classical salen−chromium **1a**[10] and cobalt(II)[8a] complexes. A simple replacement of one methyl in the 3,3′-*tert*-butyl groups in **1a** with phenyl (catalyst **1e**) resulted in a significant increase of enantioselectivity to 90% (entry 5). Bulky groups at the 5,5′-positions also have a beneficial effect on the selectivity in this reaction; the use of the corresponding complex with methyl instead of 5,5′-*tert*-butyl groups, **1f**, gave the product **5a** with lower enantioselectivity (79% ee, entry 6). Until now, the best result was obtained for the catalyst **1h** bearing a sterically demanding 3-phenylpent-3-yl group in the 3,3′-positions (93% ee, entry 8).

After screening of the most efficient ligand structure, we studied effects of temperature and concentration on enantioselectivity in the nitroaldol reaction with benzaldehyde catalyzed by complex **1h** (Table 2).

Our efforts revealed that increasing concentration and the reaction temperature from −78 to −20 °C led to the product in 77% yield and 93% ee (entry 6). Application of the more acidic chromium complex with ligand **4h** and the less coordinating counterion BF_4^- gave the product with a lower enantioselectivity (entry 4).

In order to evaluate the scope of the nitroaldol reaction catalyzed by complex **1h**, we applied the optimized procedure to various aldehydes (Table 3).

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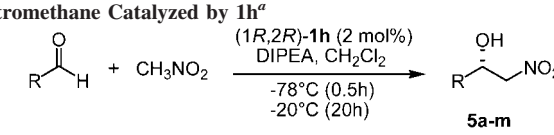
TABLE 2. Optimization of Reaction Conditions for the Complex 1h[a]

entry	*T* (°C)	nitromethane (equiv)	yield[b] (%)	ee[c] (%)
1	−78	74 (2 mL)	18	48
2	−78 (0.5 h) −20	74 (2 mL)	62	93
3	−78 (0.5 h) −20	10	51	87
4[d]	−78 (0.5 h) −20	10	58	82
5	−78 (0.5 h) −20	1.0	72	93
6[e]	−78 (0.5 h) −20	2.0	77	93

[a] Reactions were carried out using 2 mol % of catalyst **1h**, 0.5 mmol of benzaldehyde, and 0.5 mmol of DIPEA in 2.0 mL of CH_2Cl_2. [b] Yields of isolated product **5a** by column chromatography on silica gel. [c] ee were determined by HPLC on chiral stationary phase (OD-H). [d] (Salen)Cr(III)BF_4 was used. [e] The reaction was performed in 1.0 mL of CH_2Cl_2.

TABLE 3. Scope of Aldehydes in the Henry Reaction with Nitromethane Catalyzed by 1h[a]



	product			
entry	no.	R	yield[b] (%)	ee[c] (%) and configuration[d]
1	**5a**	Ph	77	93 (*S*)
2	**5b**	*p*Ph-C_6H_4	82	94 (*S*)
3	**5c**	*p*Cl-C_6H_4	76	85 (*S*)
4	**5d**	*p*Br-C_6H_4	68	85 (*S*)
5	**5e**	*p*CN-C_6H_4	65	80 (*S*)
6	**5f**	*m*Cl-C_6H_4	74	84 (*S*)
7	**5g**	*o*F-C_6H_4	84	83 (*S*)
8	**5h**	*o*MeO-C_6H_4	81	75 (*S*)
9	**5i**	2-naphthyl	92	91 (*S*)
10	**5j**	1-naphthyl	51	70 (*S*)
11	**5k**	2-furyl	56	86 (*R*)
12	**5l**	PhCH=CH	25	80 (*S*)
13[e]	**5l**	PhCH=CH	54	81 (*S*)
14	**5m**	cyclohexyl	38	90 (*S*)
15[e]	**5m**	cyclohexyl	61	83 (*S*)

[a] Reactions were performed using 2 mol % of catalyst **1h**, 1.0 mmol of aldehyde, 1.0 mmol of DIPEA, and 2.0 mmol of nitromethane in 1.0 mL of CH_2Cl_2 initially at −78 °C (0.5 h) and then at −20 °C (20 h). [b] Yields of isolated product by column chromatography on silica gel. [c] ee were determined by HPLC on chiral stationary phases (OD-H, AD-H). [d] Absolute configuration assigned by measurement of optical rotation and comparison with the literature data. [e] Reactions were performed 0.5 h at −78 °C and then 20 h at −4 °C.

The reaction works well for aromatic aldehydes with enantioselectivities usually over 80% up to 94% ee (entries 1−11). The highest enantiomeric excesses (over 90%) were observed for benzaldehyde, *p*-biphenylcarbaldehyde, and 2-naphthaldehyde (entries 1, 2, and 9). Benzaldehydes bearing an electron-withdrawing group (Cl, Br, CN) at the *para* (entries 3, 4 and 5) and *meta* (entry 6) positions gave the respective nitro alcohols with slightly diminished ee (80−86%). Interestingly, for the aromatic aldehydes with substituents at the *ortho* position, e.g., 2-methoxybenzaldehyde and 1-naphthaldehyde, the ee was below 80% (entries 8 and 10), with the exception for small substituents, e.g., fluorine (83% ee, entry 7). This implies that the geometry of the substrate has a detrimental effect on the enantioselectivity.

Heteroaromatic (furfural, entry 11), α,β-unsaturated (cinnamaldehyde, entry 12), and aliphatic aldehydes (cyclohexylcarbaldehyde, entry 14) were also possible partners in the nitroaldol reaction affording the respective nitroalcohols in up to 90% ee. Low conversions of some substrates were overcame by increasing the reaction temperature with slight or no lowering of the ee (entries 13 and 15).

Salen−chromium complexes with (1*R*,2*R*) configuration led to formation of nitroalcohols **5** with (*S*)-configuration ((*R*) in the case of furfural), as a consequence of nitronate approach at the *Re* face of the aldehyde. This direction of asymmetric induction is in a good agreement with the results observed in other reactions of aldehydes catalyzed by salen−chromium complexes and the proposed stereochemical model.[7b]

Conclusion

We have shown that the easily accessible (salen)Cr(III)Cl complex **1h** with bulky substituents at the 3,3′-positions catalyzes the asymmetric nitroaldol reaction with enantioselectivities usually over 80% up to 94% ee, significantly higher than the classical Jacobsen complex. Although a dozen protocols have been reported to provide nitro alcohols of type **5** with ees reaching 90%,[3d−j,m,o,q−t] we believe that application of modified salen−chromium complexes demonstrates a promising alternative approach to these products. Moreover, the advantage of our catalytic system is low loading of **1h** (2 mol %), relatively short reaction time, and mild conditions, with no need for anhydrous solvents or an inert atmosphere.

Experimental Section

General Procedure for Catalyst Screening in the Nitroaldol Reaction of Benzaldehyde with Nitromethane (Table 1). Salen−chromium(III) complex **1a**−**h** (0.01 mmol, 2 mol%) was placed in a 10 mL reaction vessel and dissolved in dichloromethane (0.5 mL). After the complex was cooled to −78 °C (acetone−dry ice bath), benzaldehyde (53 mg, 51 μL, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) followed by nitromethane (2.0 mL) and solution of DIPEA (86 μL, 1.0 equiv) in CH_2Cl_2 (1.0 mL) were added at 5 min intervals. The resulting solution was stirred for 0.5 h at −78 °C, then put into the freezer (−20 °C) for 20 h, and finally diluted with *n*-hexane (5 mL). Purification by flash chromatography on silica gel (gradient *n*-hexane/AcOEt 9:1−7:3, v/v) afforded the desired nitro alcohol **5a**.

(*S*)-1-Phenyl-2-nitroethanol (5a):[13] 77% yield; $[\alpha]^{22}_D = +41.7$ (*c* 0.28, CH_2Cl_2), 93% ee by HPLC analysis (Chiracel OD-H column, 1.0 mL/min, *n*-hexane/*i*-PrOH 90:10, $\lambda = 206$ nm), (*R*)-isomer $t_R = 13.33$ min and (*S*)-isomer $t_R = 16.19$ min; ^{1}HNMR ($CDCl_3$, 500 MHz) δ 7.35−7.41 (m, 5H), 5.46 (dd, $J = 9.6$, 2.9 Hz, 1H), 4.61 (dd, $J = 13.4$, 9.6 Hz, 1H), 4.52 (dd, $J = 13.4$, 3.0 Hz, 1H), 2.82 (bs, 1H); ^{13}CNMR ($CDCl_3$, 125 MHz) δ 138.1, 129.0, 128.9, 125.9, 81.2, 71.0.

General Procedure for the Optimized Nitroaldol Reaction Catalyzed by Complex 1h (Table 3). Complex **1h**(8.2 mg, 0.02 mmol, 2 mol %) was dissolved in dichloromethane (0.5 mL) in a 5 mL reaction vessel stoppered with a rubber septum. The resulted brown solution was cooled to −78 °C, and a solution of the respective aldehyde (1.0 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) was added via syringe. After 5 min, nitromethane (100 μL, 2.0 mmol, 2.0 equiv) followed by DIPEA (172 μL, 1.0 mmol, 1.0 equiv) were infused. The reaction mixture was stirred 0.5 h at −78 °C and then left at −20 °C in the refrigerator for 20 h. Dilution by *n*-hexane and purification by flash chromatography on silica gel (gradient *n*-hexane/AcOEt 9:1−7:3, v/v) afforded the desired products **5a**−**m**. Ee's were determined by HPLC on chiral columns (Chiralcel OD-H or Chiralpak AD-H).

Catalyst 1h. Prepared according to the Jacobsen procedure.[12] (1*R*,2*R*)-**1h**: $[\alpha]_D = -1420.0$ (*c* 0.01 $CHCl_3$); IR (KBr) ν 3429, 2961, 1622 ($\nu_{C=N}$), 1533, 1437, 1258, 700, 546 cm^{-1}; HRMS calcd for $C_{50}H_{64}N_2O_2Cr$ (ESI $[M - Cl]^+$) 776.4373, found 776.4392. Anal. Calcd for $C_{50}H_{64}N_2O_2CrCl$: C, 73.91; H, 7.94; N, 3.45; Cl, 4.36. Found: C, 73.76; H, 8.10; N, 3.17; Cl, 4.35.

(13) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, W. H.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693.

Precursors of Catalyst 1h. 4-*tert*-Butyl-2-(3-phenylpent-3-yl)phenol (2h). To stirred solution of *p*-*tert*-butylphenol (6.0 g, 40.0 mmol) and 3-phenylpent-2-ene (9.76 g, 60 mmol, 1.5 equiv) in 20 mL of CH_2Cl_2 was added methanosulfonic or sulfuric acid (2 mL) dropwise at 0 °C. The resulting solution was stirred overnight at room temperature. Then water (30 mL) and CH_2Cl_2 (30 mL) were added, and the organic phase was separated, washed with saturated $NaHCO_3$, dried with $MgSO_4$, and concentrated. The resulting crude reaction mixture was dissolved in a minimum volume of hot EtOH and crystallized giving the product with 52% yield as a colorless crystals: mp = 120−122 °C; IR (film) ν 3504, 2965, 2950, 2877, 1494, 1209, 824, 764, 704 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43 (d, *J*=2.4 Hz, 1H), 7.38−7.19 (m, 5H), 7.16 (dd, $J = 8.4$, 2.4 Hz, 1H), 6.65 (d, $J = 8.4$ Hz, 1H), 3.81 (bs, 1H), 2.30−1.95 (m, 4H), 1.35 (s, 9H), 0.60 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 151.5, 146.4, 142.3, 132.1, 128.9, 127.4, 126.9, 125.2, 124.3, 117.0, 48.4, 34.3, 31.7, 27.4, 8.3; HRMS calcd for $C_{21}H_{28}ONa$ (ESI, $[M + Na]^+$) 319.2032, found 319.2040.

5-*tert*-Butyl-2-hydroxy-3-(3-phenylpent-3-yl)benzaldehyde (3h). Prepared according to the Casiraghi procedure:[11] yield 70%, light yellow crystals; mp = 96−97 °C, crystallized from MeOH; IR (KBr) ν 3059, 2961, 2875, 1644, 1611, 1446, 1259, 1210, 761, 698, 545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (d, $J = 0.6$ Hz, 1H), 9.79 (s, 1H), 7.77 (d, $J = 2.4$ Hz, 1H), 7.37 (d, $J = 2.4$ Hz, 1H), 7.24−7.20 (m, 2H), 7.14−7.12 (m, 3H), 2.41 (dt, $J = 7.3$ Hz, 2H), 2.04 (dt, $J = 7.3$ Hz, 2H), 1.38 (s, 9H), 0.60 (t, $J = 7.4$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 158.4, 147.7, 141.1, 135.1, 133.9, 127.8, 127.4, 126.9, 125.1, 119.9, 48.7, 34.2, 31.3, 26.9, 8.5; HRMS calcd for $C_{22}H_{28}O_2Na$ (ESI $[M + Na]^+$) 347.1982, found 347.1998.

(1*R*,2*R*)-*N*,*N*′-Bis[5-*tert*-butyl-3-(3-phenylpent-3-yl)salicylidene]-1,2-cyclohexanediamine (4h). Prepared according tothe Jacobsen procedure.[5] A round-bottom, 150 mL flask was charged with (1*R*,2*R*)-cyclohexanediamine L-tartrate salt (2.65 g, 10 mmol, 1.0 equiv), K_2CO_3 (3.1 g, 22 mmol), and water (12 mL). The resulted mixture was stirred for 10 min followed by addition of ethanol (96%, 50 mL) and heated to 60−70 °C for 0.5 h. The temperature was maintained, and aldehyde **3h** (6.82 g, 21 mmol) was added in one portion. The mixture was vigorously stirred and refluxed for 3 h. Ligand **4h** oiled out from the reaction mixture. The mixture was concentrated to ca. 1/4 of its initial volume, dissolved in CH_2Cl_2 (75 mL), and washed with water (2 × 50 mL). The organic phase was dried and concentrated to give a yellow solid which was dissolved in 25 mL of hot ethanol. The resulting solution was cooled to ambient temperature, and 10 mL of 50% aqueous ethanol was added to produce yellow precipitate that was collected with 81% yield: yellow crystals; mp = 92−94 °C; $[\alpha]_D$= +325.6 (*c* 0.53, $CHCl_3$); IR (KBr) ν. 2963, 2875, 1628 ($\nu_{C=N}$), 1597, 1445, 1263, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.10 (s, 2H), 7.98 (s, 2H), 7.43 (d, $J = 2.4$ Hz, 2H), 7.08−7.20 (m, 10H), 6.89 (d, $J = 2.4$ Hz, 2H), 3.02−3.07 (m, 2H), 2.28−2.44 (m, 4H), 1.98−2.07 (m, 4H), 1.70−1.80 (m, 4H), 1.49−1.59 (m, 2H), 1.29−1.32 (m, 2H), 1.28 (s, 18H), 0.57 (t, $J = 7.3$ Hz, 6H), 0.51 (t, $J = 7.3$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 157.5, 148.6, 139.2, 133.2, 129.2, 127.2, 127.0, 125.9, 124.7, 117.6, 72.3, 49.0, 34.0, 32.9, 31.4, 28.1, 27.2, 24.2; HRMS calcd for $C_{50}H_{66}N_2O_2Na$ (ESI $[M + Na]^+$) 749.5022, found 749.5021. Anal. Calcd for $C_{50}H_{66}N_2O_2$: C, 82.60; H, 9.15; N, 3.85. Found: C, 82.55; H, 9.23; N, 3.83.

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Supporting Information Available: Experimental procedures, analytical data for (salen)Cr(III)Cl complexes **1** and their precursors (**2**−**4**), as well as reprints of NMR spectra for nitroaldol products **5a**−**m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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