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A New Catalyst for the Asymmetric Henry Reaction: Synthesis of β-Nitroethanols in High Enantiomeric Excess

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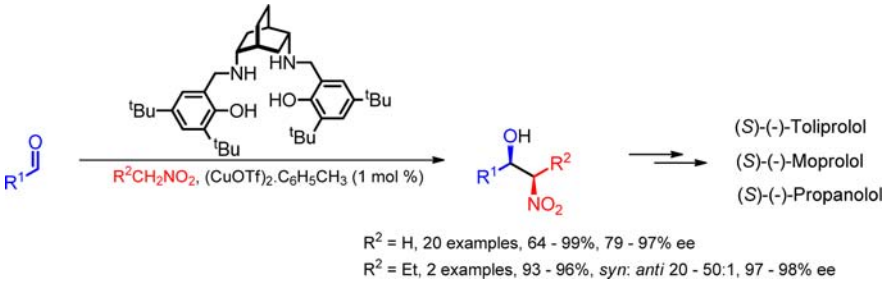
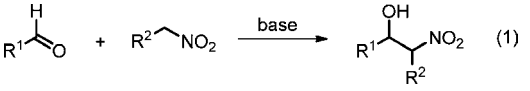
ABSTRACT



A new chiral tetrahydrosalen ligand has been designed and synthesized from *cis*-2,5-diaminobicyclo[2.2.2]octane. The complex generated in situ by the interaction of the ligand with $(CuOTf)_2 \cdot C_6H_5CH_3$ was an efficient catalyst for the asymmetric Henry reaction, producing nitroaldol products in high yield and good stereoselectivity. Henry reactions catalyzed by this tetrahydrosalen-Cu(I) complex led to syntheses of β-adrenergic blocking agents (*S*)-toliprolol, (*S*)-moprolol, and (*S*)-propanolol.

The base-catalyzed reaction of an aldehyde with a nitroalkane ("nitroaldol condensation") that was discovered by Henry more than a century ago[1] continues to attract synthetic interest for its versatility and operational simplicity.[2] In its general form (eq 1), the nitroaldol or Henry reaction positions hydroxyl and nitro groups in a vicinal relationship that provides a template for acquiring valued chemical entities including pharmaceuticals.[3]



Introduction of stereoselectivity into the Henry reaction has received much recent attention,[4] but there remains a need for efficient catalyst systems which deliver the nitroethanol product in high enantiomeric excess with certain substrate classes. We have previously reported the synthesis of a new salen ligand (**1**) based on the chiral scaffold *cis*-2,5-diaminobicyclo[2.2.2]octane (Figure 1), and we showed that the chromium(II) complex of **1** is an efficient catalyst for the hetero-Diels–Alder reaction of aldehydes with a Danishefsky diene and for the Nozaki–Hiyama–Kishi reaction of allyl bromide with aromatic aldehydes.[5]

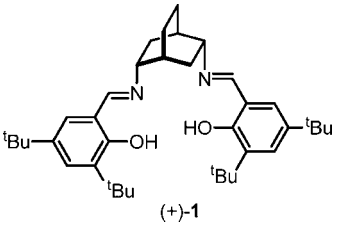


Figure 1. Salen ligand based on a *cis* 2,5-diaminobicyclo-[2.2.2]octane scaffold.

It is known that the Henry reaction can be catalyzed by copper(II) salts.[4g,h,p,x] The stable copper(II)-salen complex **2**,[5] prepared by treatment of **1** with copper(II) acetate in methanol (Scheme 1), was therefore investigated as a catalyst for the Henry reaction of *p*-nitrobenzaldehyde

(1) (a) Henry, L. *C.R. Acad. Sci. Ser. C* **1895**, 1265. (b) Henry, L. *Bull. Soc. Chim. Fr.* **1895**, *13*, 999.
(2) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915.
(3) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833.

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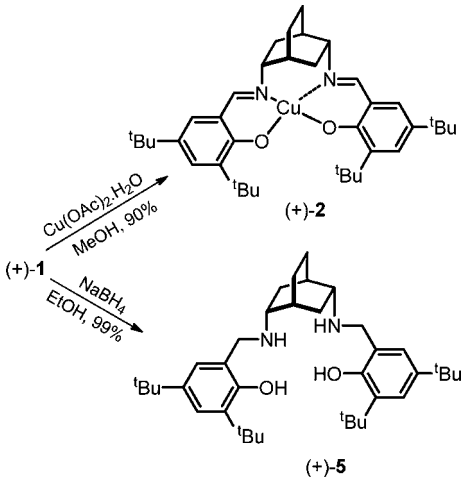
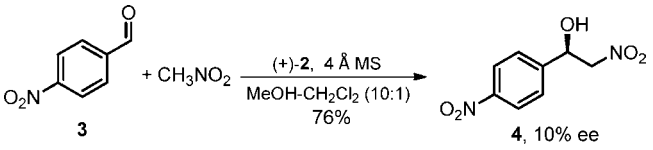
Scheme 1. Synthesis of Copper(II) Complex (+)-**2** and Tetrahydrosalen Ligand (+)-**5** From (+)-**1**



(**3**) with nitromethane under conditions that were intended to optimize chemical yield and enantioselectivity (Scheme 2). Initial results were not encouraging, however. Although 20 mol % of (*R*,*R*) complex **2** in a methanol/dichloromethane solvent pair at elevated temperature was found to give an acceptable yield of (*R*)-1-(4-nitrophenyl)-2-nitroethanol (**4**), the level of asymmetric induction was poor.

By contrast, reduction of (+)-**1** to diamine (+)-**5**, with sodium borohydride (Scheme 1), followed by complexation with copper(II) triflate led to a more promising outcome in the Henry reaction of aryl aldehydes with nitromethane. First results with *p*-nitrobenzaldehyde (**3**) and nitromethane using ligand (+)-**5** at 20 mol % and copper(II) triflate at 5 mol % as the metal source indicated that while the chemical yield of **4** was acceptable, the background

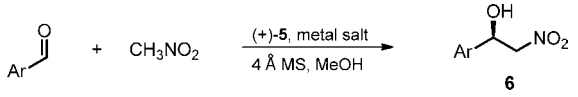
Scheme 2. Asymmetric Henry Reaction Catalyzed by Copper-(II)-Salen Complex (+)-**2**



reaction leading to racemic **4** overwhelmed asymmetric induction from (+)-**5** (Table 1, entry 1). However, when the toluene complex of copper(I) triflate[6] was used at 1 mol % with ligand (+)-**5** at 10 mol % in dry methanol (entry 5), a marked increase in the enantiomeric excess of (*R*)-**4** was observed. The optimum reaction temperature was found to be 40 °C. When the same conditions were applied to the Henry reaction of *p*-chlorobenzaldehyde with nitromethane an improved yield and enantiomeric excess of product **6** was observed (Table 1, entry 6); 2,6-dichlorobenzaldehyde as a substrate (entry 7) raised these figures further.

Guided by favorable results (entries 5−7) in Table 1, we next examined a broad portfolio of aromatic aldehydes (Table 2, entries 1−13) in their reaction with nitromethane catalyzed by the copper(I) complex of (+)-**5**. In every case, nitro alcohol **7** was obtained in >90% enantiomeric excess

Table 1. Asymmetric Henry Reaction of Aromatic Aldehydes with Nitromethane: Effect of Varying Metal Ion Source, Cu/(+)-**5** Ratio, Catalyst Loading, and Reaction Temperature[a]



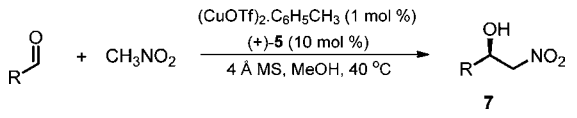
						product **4** or **6**	
entry	Ar	ligand loading (mol %)	metal salt (mol %)	temp (°C)	*t* (h)	yield [%][b]	ee [%][c]
1	4-$NO_2C_6H_4$	20	$Cu(OTf)_2$ (5)	20	30	**4**, 68	7
2	4-$NO_2C_6H_4$	10	$Cu(OTf)_2$ (2.5)	20	30	**4**, 55	28
3[d]	4-$NO_2C_6H_4$	10	$(CuOTf)_2{\cdot}C_6H_5CH_3$ (5)	20	24	**4**, 49	26
4	4-$NO_2C_6H_4$	10	$(CuOTf)_2{\cdot}C_6H_5CH_3$ (2.5)	40	15	**4**, 85	43
5	4-$NO_2C_6H_4$	10	$(CuOTf)_2{\cdot}C_6H_5CH_3$ (1)	40	20	**4**, 64	79
6	4-ClC_6H_4	10	$(CuOTf)_2{\cdot}C_6H_5CH_3$ (1)	40	16	**6a**, 76	83
7	2,6-$Cl_2C_6H_3$	10	$(CuOTf)_2{\cdot}C_6H_5CH_3$ (1)	40	20	**6b**, 89	94

[a] Reactions were carried out on 0.2 mmol scale with 0.6 mL of nitromethane. [b] Yield of isolated product. [c] Determined by HPLC using a Daicel Chiralcel AD or OD column. [d] No molecular sieves added.

(4) (a) Sasai, H.; S-uzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Sasai, H.; Tokunga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388. (c) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem.—Eur. J.* **1996**, *2*, 1368. (d) Davis, A. V.; Driffield, M.; Smith, D. K. *Org. Lett.* **2001**, *3*, 3075. (e) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621. (f) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861. (g) Risgard, T.; Gothelf, K. V.; Jorgensen, K. A. *Org. Biomol. Chem.* **2003**, *1*, 153. (h) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692. (i) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054. (j) Zhong, Y. W.; Tian, P.; Lin, G. Q. *Tetrahedron: Asymmetry* **2004**, *15*, 771. (k) Borah, J. C.; Gogoi, S.; Boruwa, J.; Kalita, B.; Barua, N. C. *Tetrahedron Lett.* **2004**, *45*, 3689. (l) Zubia, A.; Cossio, F. P.; Morao, L. A.; Rieumont, M.; Lopez, X. *J. Am. Chem. Soc.* **2004**, *126*, 5243. (m) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442. (n) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881. (o) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732. (p) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595. (q) Gruber-Khadjawi, M.; Purkharthofer, T.; Skranc, W.; Griengl, H. *Adv. Synth. Catal.* **2007**, *349*, 1445. (r) Handa, S.; Nagawa, S.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3230. (s) Toussaint, A.; Pfaltz, A. *Eur. J. Chem.* **2008**, 4591. (t) Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682. (u) Breuning, M.; Hein, D.; Steiner, M.; Gessner, V. H.; Strohmann, C. *Chem.—Eur. J.* **2009**, *15*, 12764. (v) Ji, Y. Q.; Qi, G.; Judeh, Z. M. A. *Eur. J. Org. Chem.* **2011**, 4892. (w) Jin, W.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 484. (x) Chougnet, A.; Zhang, G.; Liu, K.; Hausinger, D.; Kagi, A.; Allmendinger, T.; Woggon, W. D. *Adv. Synth. Catal.* **2011**, *353*, 1797.

(5) White, J. D.; Shaw, S. *Org. Lett.* **2011**, *13*, 2488.

Table 2. Asymmetric Synthesis of β-Nitro Alchohols under Optimized Conditions: Structural Effects on Yield and Enantioselectivity[a]



			product **7**	
entry	R	*t* (h)	yield [%][b]	ee [%][c]
1	Ph	20	**7a**, 90	92
2	3-$CH_3C_6H_4$	24	**7b**, 95	96
3	2-$MeOC_6H_4$	60	**7c**, 81	91
4	3-$MeOC_6H_4$	18	**7d**, 94	96
5	4-$CF_3C_6H_4$	24	**7e**, 96	96
6	2-$(OH)C_6H_4$	24	**7f**, 97	92
7	3,5-$(OMe)_2C_6H_3$	22	**7g**, 93	96
8	2,4-$(NO_2)_2C_6H_3$	12	**7h**, 93	95
9	3-(4-$MeOC_7H_6O$)-4-$(NO_2)C_6H_3$	24	**7i**, 99	95
10	2-(OH)-3-(Br)-5-$(Me_3C)C_6H_2$	24	**7j**, 87	98
11	1-naphthyl	18	**7k**, 98	93
12	2-furyl	24	**7l**, 87	94
13	3-furyl	20	**7m**, 98	95
14	cyclohexyl	42	**7n**, 90	94
15	Me_3C	51	**7o**, 89	95
16	$CH_3CH{=}C(CH_3)$ (*E*)	18	**7p**, 83	93
17	$PhCH{=}C(CH_3)$ (*E*)	48	**7q**, 95	97

[a] Reactions were carried out on 0.2 mmol scale with 0.6 mL of nitromethane. [b] Yield is based on allyl ethers **11**–**13**. [c] Determined by HPLC using a Daicel Chiralcel OD column.

and in good yield. Aliphatic aldehydes (entries 14–15) as well as α,β-unsaturated aldehydes (entries 16–17) also gave a high yield and enantiomeric excess of **7**.

The asymmetric Henry reaction is well suited to preparation of the vicinal amino alcohol motif that characterizes blocking agents of the β-adrenergic receptor such as toliprolol (**8**),[7] moprolol (**9**),[8] and propanolol (**10**).[9] Each of these drugs features a 1-aryloxy-3-isopropylamino-2-propanol template with the active enantiomer having an (*S*) configuration (Figure 2).

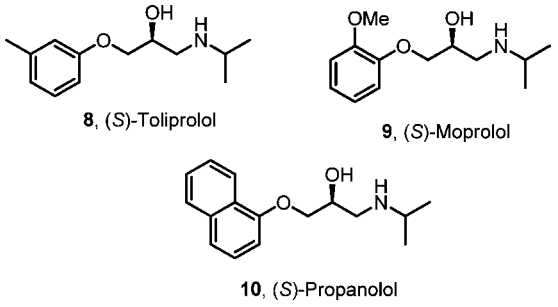


Figure 2. β-Adrenergic receptor blocking agents.

(6) Dines, M. B.; Bird, P. H. *J. Chem. Soc., Chem. Commun.* **1973**, 12.
(7) Howe, R.; Rao, B. S. *J. Med. Chem.* **1968**, *11*, 1118.

Access to these structures began with oxidative cleavage of allyl aryl ethers **11**–**13**[10] to give unstable aldehydes **14**–**16** which were reacted with nitromethane under the conditions specified in Table 2 (Scheme 3). The results of reactions of **14**–**16** with nitromethane are shown in Table 3 and confirm that ligand **5** is an efficient catalyst for conversion of these aldehydes to nitro alcohols. Catalytic hydrogenation of **17**–**19** led quantitatively to the corresponding amino alcohols which were condensed in situ with acetone. A second catalytic hydrogenation produced **8**, **9**, and **10**.[11] In this manner, a simple sequence in which the final three steps are carried out in a single pot leads from inexpensive starting materials (*m*-cresol, guaiacol, and 1-naphthol) to important commercial drugs in good overall yield and high enantiopurity.

Scheme 3. Syntheses of (*S*)-Toliprolol (**8**), (*S*)-Moprolol (**9**), and (*S*)-Propanolol (**10**)

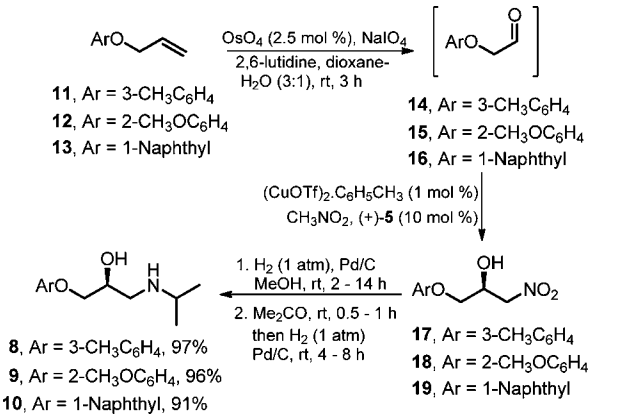


Table 3. Asymmetric Henry Reaction of Aldehydes **14**–**16** with Nitromethane Catalyzed by (+)-**5**[a]

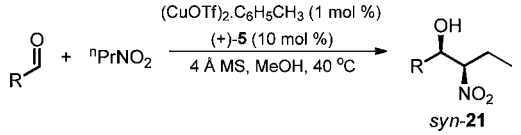
entry	aldehyde (Ar)	product	yield [%][b]	ee [%][c]
1	**14** (3-$CH_3C_6H_4$)	**17**	90	96
2	**15** (2-$CH_3OC_6H_4$)	**18**	93	94
3	**16** (1-naphthyl)	**19**	90	97

[a] Reactions were carried out on 0.2 mmol scale with 0.6 mL of nitromethane. [b] Yield is based on allyl ethers **11**–**13**. [c] Determined by HPLC using a Daicel Chiralcel OD column.

Diastereoselectivity associated with higher order nitroalkanes in the asymmetric Henry reaction has been studied by Shibasaki[4b,r] and by Jorgensen.[4g] In our hands, reaction of benzaldehyde and 1-naphthaldehyde with nitropropane in the presence of (+)-**5** and a copper(I) triflate toluene

(8) Lunsford, C. D.; Mays, R. P.; Richman, J. A.; Murphey, R. S. *J. Am. Chem. Soc.* **1960**, *82*, 1166.
(9) Dukes, M.; Smith, L. H. *J. Med. Chem.* **1971**, *14*, 326.
(10) Allyl ethers **11**–**13** were obtained by reaction of the parent phenol with allyl bromide and potassium carbonate in acetone at rt.
(11) Sasai, H.; Itoh, N.; Suzuki, T.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 855.

Table 4. Asymmetric Addition of 1-Nitropropane to Benzaldehyde and 1-Naphthaldehyde Catalyzed by (+)-**5**/$(CuOTf)_2 \cdot C_6H_5CH_3$[a]



			product **21**		
entry	R	*t* (h)	dr *syn*/*anti*[b]	yield [%][c]	ee [%][d]
1	Ph	24	>20:1	**21a**, 96	97
2	1-naphthyl	28	>50:1	**21b**, 93	98

[a] Reactions were carried out on 0.2 mmol scale with 0.6 mL of nitropropane. [b] Determined by ^{1}H NMR analysis. [c] Combined yields of *syn* and *anti* isomers. [d] Determined by HPLC using a Daicel Chiralcel OD-H or AS-H column.

complex under the conditions specified in Table 2 gave a *syn*/*anti* ratio strongly favoring the *syn* product **21** which was formed in high enantiomeric excess (Table 4).

It is clear from the results in Tables 2 and 3 that there is a strong preference for (1*R*,2*R*,4*R*,5*R*) ligand (+)-**5** to give nitroaldol products **7** of an (*R*) configuration in the reaction of aldehydes with nitromethane. This stipulates that attack by nitromethane occurs predominantly at the *si* face of the carbonyl group; a transition state rationalizing this outcome is proposed in Figure 3. In this model, reactants are coordinated to copper(I) complex **20** in a quadrant under the bicyclic scaffold (right, front) with C−C bond formation taking place from the less sterically encumbered direction.[12] It is likely that organization of transition state **20** is assisted by a N−H hydrogen bond with the nitronate since complex (+)-**2** in which this hydrogen bond is absent leads to lower enantioselectivity. The results in Table 4 imply that the copper complexed nitronate of nitropropane in transition state **22** has a (*Z*) configuration with attack occurring at the *si* face of the aldehyde carbonyl as shown in Figure 3.

A catalytic cycle that would incorporate transition states **20** and **22** is proposed in Scheme 4. Initial ligand exchange of tetrahydrosalen (+)-**5** for toluene would give copper(I) triflate complex **23**. Progression of **23** via copper(I) complexes **24** and **25** would complete the catalytic cycle while generating **7** or **21**.

(12) A 180° rotation of the aldehyde in **20** (which would lead to an *re* face attack by nitromethane) is disfavored by a steric clash of the aldehyde hydrogen with a *tert*-butyl substituent on the opposing benzenoid ring of the salen ligand.

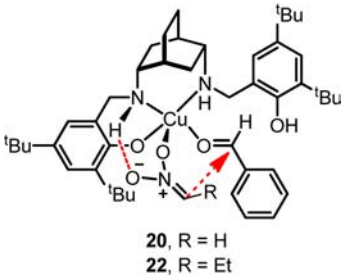
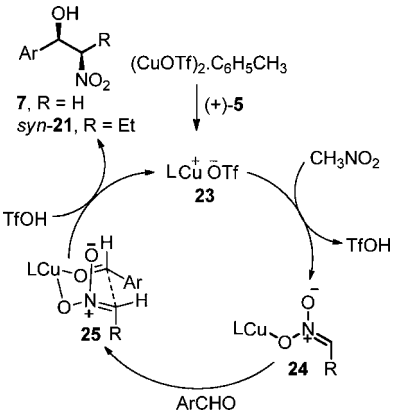


Figure 3. Proposed transition state for the asymmetric henry reaction of aldehydes with nitromethane and 1-nitropropane catalyzed by a (+)-**5**/$(CuOTf)_2 \cdot C_6H_5CH_3$ complex.

Scheme 4. Proposed Catalytic Cycle for the Formation of **7** and **21**



In summary, an efficient catalyst based on a copper(I) complex of tetrahydrosalen (+)-**5** has been developed for the asymmetric Henry reaction. It was shown that high yields, diastereoselectivity, and enantioselectivity of β-nitro alcohols can be obtained with this catalyst.

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

The authors declare no competing financial interest.