Communications to the Editor

Enantioselective Addition of Hydrogen Cyanide to Imines Catalyzed by a Chiral (Salen)Al(III) Complex

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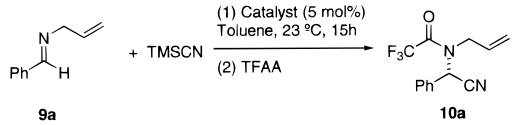
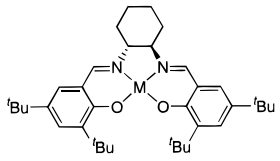
Received January 27, 1998

The addition of cyanide to imines (the Strecker reaction)[1] constitutes one of the most direct and viable strategies for the asymmetric synthesis of α-amino acid derivatives. Significant progress has been made in the development of stereoselective versions of this reaction using imines bearing covalently attached chiral auxiliaries.[2] However, despite the obvious practical potential of an enantioselective catalytic version of the Strecker reaction, only limited success has been attained to this end.[3] In this paper, we describe the first example of a metal catalyzed enantioselective Strecker reaction using a chiral (salen)Al(III) complex.

Chiral (salen)−metal complexes catalyze an array of asymmetric nucleophile−electrophile reactions including $TMSN_3$[4] and carboxylic acid additions to meso epoxides,[5] hetero Diels−Alder,[6] and TMSCN addition to aldehydes.[7] Also, (salen)Cr and (salen)-Co complexes have proven remarkably effective in the kinetic resolutions of terminal epoxides with $TMSN_3$[8] and H_2O.[9] Encouraged by the proven effectiveness of aldehydes and epoxides as electrophiles in (salen)-metal catalyzed enantioselective reactions, we evaluated the possibility of extending the scope of these catalysts to asymmetric transformations of imines. To this end, we screened a series of metal complexes of the readily available salen ligand **1** for catalysis of the addition of TMSCN to *N*-allyl benzaldimine (**9a**). Complexes of Ti, Cr, Mn, Co, Ru, and Al were all found to catalyze the reaction at room temperature with varying degrees of conversion and enantioselectivity.[10] The best



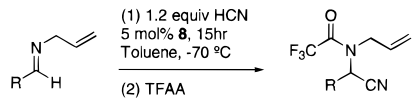
9a **10a**



M	ee	% Conv.
1: M = H, H		
2: M = Ti(IV)Cl_2	24	19
3: M = Cr(III)Cl	0	83
4: M = Mn(III)Cl	20	80
5: M = Ru(III)(NO)Cl	6	93
6: M = Co(II)	0	43
7: M = Co(III)OAc	6	65
8: M = Al(III)Cl	45	100

result obtained was with the Al complex **8**,[11,12] which led to complete substrate conversion and afforded product **10a** in 45% ee. Interestingly, no reaction was observed under strictly anhydrous conditions in the reaction catalyzed by **8**, suggesting that the reacting species is HCN rather than TMSCN. At room temperature, the uncatalyzed reaction between HCN and **9a** is quite rapid, but it is completely suppressed at −70 °C. At this lower temperature, the reaction of **9a** and HCN[13] (1.2 equiv) catalyzed by **8** was complete within 15 h and afforded **10a** in 91% isolated yield and 95% ee (Table 1, entry a).[14,15]

Table 1



9a-i **10a-i**

Entry		R	%yield[a]	%ee[b]
a	**9a**	Ph	91	95
b	**9b**	*p*-$CH_3OC_6H_4$	93	91
c	**9c**	*p*-$CH_3C_6H_4$	99	94
d	**9d**	*p*-ClC_6H_4	92	81
e	**9e**	*p*-BrC_6H_4	93	79
f	**9f**	1-Napthyl	95	93
g	**9g**	2-Napthyl	93(55)[c]	93(>99)[c]
h	**9h**	Cyclohexyl	77	57
i	**9i**	*t*-Butyl	69	37

[a] Isolated yield. Full characterization of compounds **10a**−**i** is provided in the Supporting Information. [b] All ee's were determined by GC or HPLC chromatography using commercial chiral columns. See Supporting Information. [c] After recrystallization from hexanes.

A variety of *N*-allyl imines were evaluated in the reaction catalyzed by **8** (Table 1). The products **10a**−**i** were isolated as the (*S*)-trifluoroacetamides in good yield and moderate-to-excellent enantioselectivity. Substituted aryl imines (**9a**−**g**) were clearly the best substrates, affording very high levels of enantioselectivity (entries a−g). In contrast, alkyl substituted imines underwent addition of HCN with considerably lower ee's (entries h−i).

With the hope of improving the results obtainable with alkyl substituted imines, we evaluated the effect of the catalyst structure and the imine nitrogen substituent on reaction enantioselectivity. Extensive variation of the steric and electronic properties of the (salen)AlCl ligand structure failed to yield any improvement in reaction enantioselectivity over that obtained with catalyst **8**. Several *N*-substituted imines of pivalaldehyde, an attractive starting material for the asymmetric synthesis of *tert*-leucine, were synthesized and screened (Table 2). Surprisingly, the *N*-substituent did not exert a very significant influence on the enantioselectivity of the reaction. Although only a marginal increase in ee was obtained with the *N*-benzyl derivative **11,** enhancement of the enantiomeric purity to 97.5% was achievable with reasonably good recovery by recrystallization of the corresponding product **14**.

The principal synthetic utility of the asymmetric Strecker reaction is for the preparation of enantiomerically enriched

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(5) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773.
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(8) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420.
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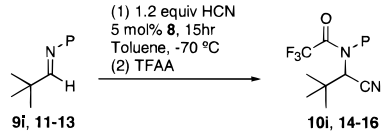
(10) The corresponding vanadyl, Fe(III), Ni(II), Cu(II), and Sn(IV) salen complexes were found to effect the reaction to less than 5% conversion.

S0002-7863(98)00299-6 CCC: $15.00
Published on Web 05/13/1998

Table 2

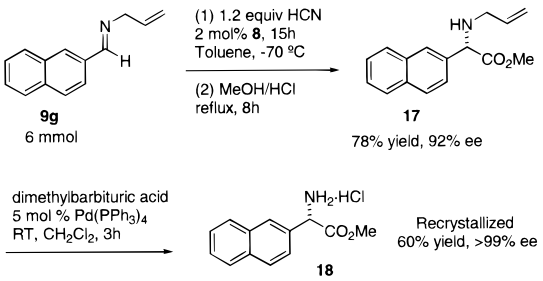


9i, **11-13** **10i**, **14-16**

	P	%yield	%ee
10i	Allyl	69	37
14	Benzyl	88(48)[a]	49(97.5)[a]
15	*p*-methoxybenzyl	67	44
16	*o*-$CH_3OC_6H_4$	74	40

[a] After recrystallization from 1:10 EtOAc:hexanes.

Scheme 1



α-amino acid derivatives. To illustrate the applicability of the present method, imine **9g** was converted on 6 mmol scale to the amino methyl ester HCl salt **18**, by means of a three-step sequence requiring no chromatography (Scheme 1). With a reduced catalyst loading of **8** (2 mol %), the corresponding amino nitrile was still obtained in high yield and in 92% ee within 15 h. Hydrolysis of the hydrocyanation adduct with methanolic HCl at reflux produced the allyl protected amino ester **17** in 78% yield over two steps with no racemization. Deprotection was achieved by Pd(0)-catalyzed deallylation using dimethylbarbituric acid as an allyl scavenger[16] followed by recrystallization to afford **18** in 60% yield and in enantiomerically pure form (>99% ee).

The asymmetric Strecker reaction catalyzed by **8** provides a straightforward entry into enantiomerically enriched α-amino acid derivatives using low catalyst loading from readily available substrate and catalyst precursors. The catalyst is easily prepared on a large scale and appears to have an indefinite "shelf life" even when stored under ambient conditions. To our knowledge, this is the first instance in which a main group (salen)metal complex has been identified as a highly effective asymmetric catalyst. Experiments are underway to elucidate the mechanism of this new enantioselective transformation and to establish to what extent this reaction is related mechanistically to other classes of (salen)metal catalyzed nucleophile−electrophile reactions.[17]

Acknowledgment. This work was supported by the NIH through GM-43214 and through a postdoctoral fellowship to M.S.S.

Supporting Information Available: Characterization and ee analysis of compounds **10a**−**j** and **14**−**16** and experimental details on the synthesis of **17** and **18** (18 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(11) **Catalyst Preparation (8):** In a flamed dried 100 mL round-bottom flask equipped with a stir bar were combined and stirred 1.52 g (2.78 mmol) of (*R*,*R*)−(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine and 20 mL of CH_2Cl_2 (freshly distilled fromCaH_2). At ambient temperature, 1.54 mL of diethyl aluminum chloride (1.8 M solution in toluene, 2.78 mmol) was added slowly to the stirring solution. After stirring for 2 h, the solvents were removed in vacuo and the resulting yellow solid was rinsed with 50 mL of hexanes. The solid was dried in vacuo to yield **8** (1.59 g, 95% yield) as a yellow solid. mp >350 °C (dec); IR (KBr) 2966, 2953, 2867, 1640, 1544, 848 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.84 (s, 2H), 7.77 (s, 2H), 7.61 (s, 2H), 3.51 (m, 2H), 1.91 (s, 18H), 1.39 (s, 18H) 1.36 (m, 4H), 0.59 (m, 4H);^{13}C NMR {^1H} (100 MHz, CD_2Cl_2) δ 162.7, 141.2, 139.3, 131.4, 128.7, 128.4, 118.7, 64.6 (broad), 35.9, 34.4, 31.6, 30.0, 28.2, 24.1. Anal. Calcd for $C_{36}H_{52}AlClN_2O_2$: C, 71.20; H, 8.42; Al, 4.44; Cl, 5.84; N, 4.61. Found: C, 71.05; H, 8.63; Al, 4.49; Cl, 5.73; N, 4.56.

(12) For the synthesis of (salen)Al complexes, see: (a) Dzugan, S. J.; Goedken, V. L. *Inorg. Chem.* **1986**, *25*, 2858. (b) Gurian, P. L.; Cheatham, L. K.; Ziller, J. W.; Barron, A. R. *J. Chem Soc., Dalton Trans.* **1991**, 1449. (c) Atwood, D. A.; Jegier, J. A.; Rutherford, D. *Inorg. Chem.* **1996**, *35*, 63.

(13) Ziegler, K. In *Organic Syntheses*; Gilman, H., Blatt, A. H., Eds.; Wiley: New York, 1932; Collect. Vol. 1, p 314. CAUTION! Hydrogen cyanide is a highly toxic and volatile compound that should be handled carefully to avoid inhalation.

(14) The direct product of HCN addition was observed to undergo racemization upon exposure to silica gel. The corresponding triflouroacetamde derivatives were found to be stable, so all yield and ee determinations were carried out on these derivatives.

(15) **Representative Procedure: Synthesis of Compound 10a.** In a flame-dried 5 mL round-bottom flask equipped with a stir bar, 12 mg of **8** (5 mol %, 0.02 mmol) and 1.4 mL of toluene were combined. The reaction was stirred at ambient temperature until the catalyst had completely dissolved. The reaction flask was cooled to −70 °C by means of a constant-temperature bath, and 1.2 equiv of HCN was added (0.59 mmol, 690 μL of a 0.85 M solution in toluene). After 5 min, 71 mg (0.49 mmol) of **9a** was added in one portion via syringe. After 15 h, the reaction was quenched with 103 μL of trifluoroacetic anhydride (0.73 mmol, 1.5 equiv) and allowed to warm to ambient temperature. The solvents were removed in vacuo, and the resulting residue was purified by flash chromatography (3:2 hexanes:CH_2Cl_2) to afford **10a** as a clear oil (119 mg, 91% yield).

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