The Asymmetric Aldol Reaction of Tosylmethyl Isocyanide and Aldehydes Catalyzed by Chiral Silver(I) Complexes

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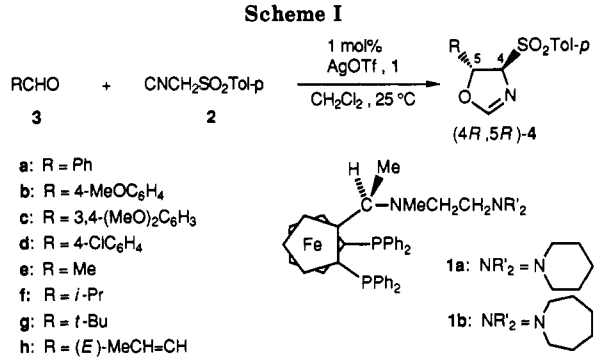
Summary: The asymmetric aldol reaction of tosylmethyl isocyanide and aldehydes in the presence of 1 mol % of chiral silver(I) catalysts gave optically active 5-alkyl-4-tosyl-2-oxazolines (up to 86% ee), which were converted to optically active α-alkyl-β-(*N*-methylamino)ethanols by $LiAlH_4$ reduction.

Earlier, we reported[1] that the asymmetric aldol reaction of methyl α-isocyano carboxylates (CNCHRCOOMe) and aldehydes proceeded with high stereoselectivity (up to 97% ee) when catalyzed by gold(I) complexes with a chiral *N,N,N',N'*-tetraalkylethylenediamino-substituted bis(diphenylphosphino)ferrocene ligand (**1**). The complexes were also efficient catalysts for the asymmetric aldol reactions of α-isocyano carboxamides ($CNCH_2CONR_2$)[1a,g,2] and (isocyanomethyl)phosphonates ($CNCH_2PO(OR)_2$).[1a,3]

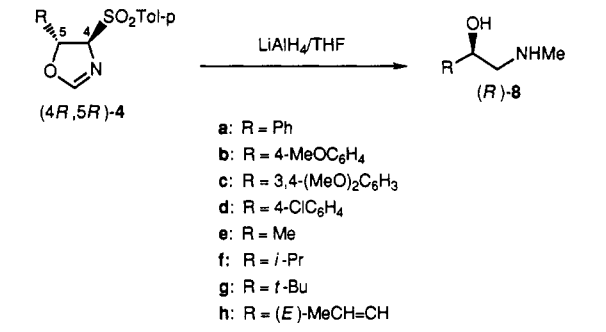
Now we report that the silver(I) analogues of such complexes are the chiral catalysts of choice for the stereoselective aldol reaction of tosylmethyl isocyanide (TosMIC) (**2**) and aldehydes. This reaction was also catalyzed by chiral gold(I) complexes, but the product *trans*-4-tosyl-2-oxazolines were formed with low stereoselectivity (ca. 20% ee).[4,5] The potentiality of the chiral silver(I) complexes as catalysts for the asymmetric aldol reaction was first revealed by NMR studies of the complexes in the presence of α-isocyanoacetate.[1a,6,7]

The reaction of TosMIC (**2**) with benzaldehyde (**3a**) was typical. To a solution of silver triflate (2.8 mg, 0.011 mmol), ligand **1b**[1a,c] (7.4 mg, 0.010 mmol), and **2** (195 mg, 1.00 mmol) in dry CH_2Cl_2 (5.0 mL) was added **3a** (160 mg, 1.5 mmol). The mixture was stirred under N_2 at 25 °C for 2 h. The catalyst was removed by passing the mixture through a bed of Florisil (17 mm × 30 mm, EtOAc), and MPLC purification (silica gel, CH_2Cl_2/EtOAc, 15:1) gave 288 mg (96%) of *trans*-5-phenyl-4-(*p*-tolylsulfonyl)-2-oxazoline[8] (**4a**), $[\alpha]^{20}_D$ +212°. An enantiomeric excess of 83% was found by HPLC analysis with a chiral stationary phase.[9]

Scheme I



Scheme II



The results summarized in Table I were obtained under similar conditions. The silver catalyst was effective with substituted aromatic (**3b–d**), saturated aliphatic (**3e–g**), and α,β-unsaturated aldehydes (**3h**). The oxazolines shown in Table I had 4*R*,5*R* absolute configuration, the same as observed in the gold-catalyzed asymmetric aldol reactions. Changing the alkyl groups on the terminal nitrogen atom of the *N,N,N',N'*-tetraalkylethylenediamino substituents of ligands **1** hardly affected the rate of reaction and produced only small changes in the enantiomeric excess of the products. The use of chiral ligand **5**, whose substituent is longer than that of **1** by one methylene unit, caused a dramatic decrease in the enantiomeric purity of oxazoline **4a** (to 44% ee), and also produced an inversion of configuration (4*R*,5*R* to 4*S*,5*S*). The same chain length effect was observed in the gold-catalyzed asymmetric aldol reactions. With chiral ligands **6** and **7**, which lack a terminal

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(4) For the base catalyzed aldol reaction, see: (a) Schöllkopf, U.; Schröder, R.; Blume, E. *Liebigs Ann. Chem.* **1972**, *766*, 130. (b) van Leusen, A. M. *Lect. Heterocycl. Chem.* **1980**, *5*, S111, and references cited therein.

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(7) Other isocyanides also underwent the silver-catalyzed aldol reaction with benzaldehyde with **1a** as the chiral ligand. The parent isocyanide, enantiomeric excess, configuration, and reaction temperature were as follows: $CNCH_2COOMe$, 13% ee, 4*S*,5*R*, 25 °C; $CNCH_2CONMe_2$, racemic, 25 °C; $CNCH_2PO(OPh)_2$, 56% ee, 4*R*,5*R*, 40 °C.

(8) The trans geometry was established by the value (6.0 Hz) of the coupling constant between the vicinal protons on the oxazoline ring. A small amount (trans:cis = 100:1) of cis isomer was detected by ^1H NMR. The cis isomer displayed a vicinal (H_4–H_5) coupling constant of 10.1 Hz. Trans-4,5-disubstituted 2-oxazolines always display smaller vicinal coupling constants than do cis isomers.

(9) To determine the enantiomeric excess, 50-μL aliquots of the reaction mixture were reduced with $LiAlH_4$. Hydrolysis, filtration, and evaporation gave crude **8a** (Scheme II). The crude amino alcohol was dissolved in $CHCl_3$ (0.5 mL) and was treated with α-naphthyl isocyanate (2 μL) at room temperature for 5 min. The solution was then passed through a short column of silica gel and was eluted with EtOAc (2 mL). The eluant containing the enantiomeric *N*-(2-hydroxy-2-phenylethyl)-*N*-methyl-*N'*-(1-naphthyl)urea was analyzed by HPLC with a chiral stationary phase (Sumitomo Chemical Co., Sumipax OA-2000; hexane/1,2-dichloroethane/EtOH, 15:5:1).

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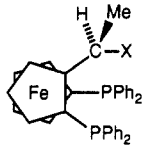
Table I. Aldol Reaction of TosMIC (2) and Aldehydes 3 Catalyzed by Chiral Silver Complexes[a] and Reduction of Oxazolines 4 with Lithium Aluminum Hydride To Produce α-Alkyl-β-(*N*-methylamino)ethanols 8

				4			8	
3	1	time,[b] h	ratio trans:cis (4)	yield,[c] %	% ee[d]	$[\alpha]^{20}_D$,[e] deg (% ee[f])	yield,[g] %	$[\alpha]^{20}_D$,[h] deg (configuration)
3a	**1a**	2	100:1	92	77 (4*R*,5*R*)[i]			
	1b	2	100:1	96	83 (4*R*,5*R*)[i]	+212 (86)	90	−35.6[k] (*R*)
3b	**1a**	2	100:1	96	74 (4*R*,5*R*)[j]			
	1b	2	60:1	95	77 (4*R*,5*R*)[j]	+239 (79)	82	−28.7 (*R*)
3c	**1a**	2	100:1	91	80 (4*R*,5*R*)[i]	+218 (77)	91	−15.8[l] (*R*)
	1b	2	100:1	97	73 (4*R*,5*R*)[i]			
3d	**1a**	1	100:1	94	73 (4*R*,5*R*)[j]			
	1b	1	100:1	94	77 (4*R*,5*R*)[j]	+200 (89)	89	−32.4 (*R*)
3e	**1a**	2	>20:1	94	83 (4*R*,5*R*)[i]	+300 (87)	71	−19.1[m] (*R*)
	1b	2	>20:1	93	75 (4*R*,5*R*)[i]			
3f	**1a**	2	100:1	94	86 (4*R*,5*R*)[j]	+341 (95)	68	−27.8 (*R*)
	1b	2	100:1	91	79 (4*R*,5*R*)[j]			
3g	**1a**	7	100:1	93	80 (4*R*,5*R*)[j]	+321 (86)	73	−37.7 (*R*)
	1b	7	100:1	97	85 (4*R*,5*R*)[j]			
3h	**1a**	9	30:1	96	85 (4*R*,5*R*)[j]	+296 (88)	70	−2.3 (*R*)
	1b	9	40:1	95	83 (4*R*,5*R*)[j]			

[a] The reaction was performed in CH_2Cl_2 at 25 °C; 2:3:catalyst = 1:1.5:0.01. [b] Reaction time for the aldol reaction. [c] Yield of product isolated by MPLC. [d] Enantiomeric excess as determined by HPLC analysis of the enantiomeric α-naphthylurea derivatives of amino alcohols 8. [e] *c* 1.0–1.1 (tetrahydrofuran). [f] Enantiomeric excess of the isolated product. [g] Yield obtained after bulb-to-bulb distillation. [h] *c* 1.0–1.5 (ethanol), unless otherwise noted. [i] Configuration determined by converting oxazoline 4 into α-alkyl-β-(*N*-methylamino)ethanol 8 of known absolute configuration. [j] Configuration assigned by similarity of optical rotations of 4 and 8. [k] The reported specific rotation is $[\alpha]^{20}_D$ −40.7° (*c* 1.3, ethanol). See: Ito, Y.; Amino, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1983**, *105*, 1586. [l] Specific rotation at 28 °C. The reported specific rotation for (*S*)-**5c** is $[\alpha]^{28}_D$ +23.48° (*c* 0.0921, ethanol). See: Brown, S. D.; Hodgkins, J. E.; Reinecke, M. G. *J. Org. Chem.* **1972**, *37*, 773. [m] Specific rotation at 25 °C. The reported specific rotation for (*S*)-**5e** is $[\alpha]^{25}_D$ +25.551° (*c* 10.794, ethanol). See: Koepke, S. R.; Kupper, R.; Michejda, C. J. *J. Org. Chem.* **1979**, *44*, 2718.

nitrogen atom, no oxazoline **4a** was produced after 3 h at 25 °C.



5: X = $NMeCH_2CH_2CH_2NMe_2$
6: X = $NMeCH_2CH_2OH$
7: X = NMe_2

The optically active oxazolines (**4a–h**) were converted to optically active α-alkyl-β-(*N*-methylamino)ethanols (**8a–h**) in good to excellent yield by reduction with $LiAlH_4$ in THF at room temperature.

The elucidation of the mechanistic differences between gold and silver catalysts in the asymmetric aldol reaction remains incomplete.

Supplementary Material Available: Melting points and ^1H NMR, ^{13}C NMR, and infrared spectra for *trans*-**4b–e,g,h** and **5f–h** and analytical data (or high-resolution mass spectra) for new compounds (2 pages). Ordering information is given on any current masthead page.

The Photochemistry of Pyran-4-ones: Intramolecular Trapping of the Zwitterionic Intermediate with Pendant Hydroxyl Groups

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Summary: Pyran-4-ones **5–11** bearing hydroxyalkyl side chains underwent efficient photocyclization to bicyclic oxyallyl zwitterions, and subsequent intramolecular nucleophilic trapping gave bicyclic cyclopentenone ethers **12–18** in good to excellent yield.

Pioneering studies by Barltrop[1] and Pavlik[2] have implicated bicyclic zwitterionic intermediates in the photorearrangement of pyran-4-ones to pyran-2-ones. The relative locations of substituents in starting materials vs products as well as the obvious analogy to the extensively studied cyclohexadienone series[3-5] support the intermediacy of a transient species such as **1** (eq 1). Even more compelling is the formation of adducts such as **2** when photolysis is carried out in hydroxylic solvents. Beyond the intrinsic mechanistic interest of this transformation, we were struck by its potential synthetic utility (i.e., formation of functionalized cyclopentenones of defined stereochemistry from planar heterocyclic precursors, and a possibly general entry into systems displaying enolonium-type reactivity).

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