

Catalytic Asymmetric α -Iminol Rearrangement: New Chiral Platforms

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Supporting Information

ABSTRACT: A series of 19 different asymmetric catalysts were screened in an effort to identify the first chiral catalyst for the rearrangement of α -hydroxy imines to α -amino ketones involving a 1,2-carbon shift. Although aluminate complexes of VAPOL, VANOL, and 7,7'-^tBu₂VANOL were quite effective catalysts giving up to 88% ee, the new ultra catalyst for this reaction was found to be a zirconium complex of VANOL which gives 97 to >99% ee for the majority of the substrates examined. An X-ray diffraction study of the catalyst reveals that the zirconium exists as a homoleptic complex with three VANOL ligands and two protonated *N*-methyl imidazoles.

The first examples of the α -iminol rearrangement involving a 1,2-carbon shift were reported by Prins and Shoppee in 1943 (Scheme 1).¹ A review of the subsequent history appeared in 2003,² and there have been a number of examples since.³ Most often these reactions have been effected thermally (~150–200 °C) and several others with Brønsted acids (TsOH, HCO₂H, CH₃CO₂H, HCl, H₂SO₄),^{2,3} and in some cases alkoxide bases have been used.² The reaction can also be promoted by transition-metal Lewis acids including scandium, copper, and zinc triflates.^{3*f,j,r*} There has been only one report with a chiral catalyst. A nickel pybox complex and a number of chiral lanthanide complexes were found to facilitate the reaction, however, all gave racemic products.^{3*a*} There is one example of a catalytic asymmetric Amadori–Heyns rearrangement which involves a 1,2-hydrogen shift via an intermediary enol.^{3*t*}

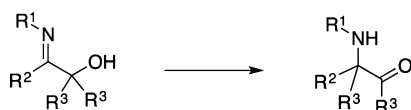
Our interest in the α -iminol rearrangement arose from our work with chiral catalysts for reactions of imines including aziridinations,⁴ aza-Cope rearrangements,⁵ heteroatom Diels–Alder reactions,⁶ and the Ugi reaction.⁷ These reactions involve a BOROX catalyst consisting of an ion-pair containing a boroxinate chiral anion with the gegen cation derived from a protonated substrate.⁸ We were thus disappointed to find that the VANOL and VAPOL BOROX catalysts **1** and **3** are essentially ineffectual for the α -iminol rearrangement of **22a** with the latter giving **23a** as a racemic product (Table 1, entries 4 and 7). The VANOL BOROX catalyst gives only 17% ee. There is not a significant background reaction since simply heating **22a** for 42

h at 80 °C gives <5% yield of the product (entry 1). However, the α -iminol rearrangement of **22a** does occur slowly at 150 °C providing racemic **23a** in 28% yield in 2 h with 79% conversion (entry 2). The induction can be increased to 62% ee if the VANOL BOROX catalyst is assembled from 2,4,6-tri-*t*-butyl phenol rather than phenol, however, the reaction is exceedingly slow even with 25 mol % catalyst (entry 6). The VANOL and VAPOL hydrogen phosphate catalysts and their derivatives have proven to be very effective chiral Brønsted acid catalysts for a number of reactions.^{9–19} A number of catalysts in this class were screened (4–9, Scheme 2), and it was found that they were not very effective (entries 8–13).

Given the fact that α -iminol rearrangement is known to be accelerated with either an acid or base,^{1,2} we decided to examine Shibasaki's amphoteric catalyst BINOL Al **10** (ALB) which is very effective in delivering high asymmetric induction in asymmetric Michael addition reactions.²⁰ The lithium/aluminum catalyst **10** prepared from BINOL only provided a very sluggish reaction. The corresponding aluminum catalysts prepared from VANOL and VAPOL have not been previously reported. These catalysts were generated according to Shibasaki's procedure from 2 equiv of the ligand and one of LiAlH₄ and were found to be very effective catalysts. Both the VANOL and VAPOL catalysts **11** and **13** gave quantitative yields of **23a**, and coincidentally, both gave 68% ee which was the highest induction that had observed up to this point. The induction could be increased to 88% ee with no loss in reactivity with the aluminate catalyst **12** derived from 7,7'-di-*t*-butyl VANOL (entry 17).²¹

We had previously found that a VAPOL zirconium catalyst was very effective in promoting the Mannich reaction of imines with ketene acetals.²² In the present investigation, these were found to be the optimal catalysts for the α -iminol rearrangement. The (*R*)-VANOL Zr catalyst **15** gives (*S*)-**23a** in 96% yield and 97% ee after 1 h at 80 °C (entry 20). The corresponding titanium catalyst **14** gives excellent asymmetric induction as well, but the turnover is much slower (entry 19). The corresponding VAPOL Zr catalyst **17** gives very poor asymmetric induction (entry 24). Unlike their corresponding aluminum catalysts, the VANOL and ^tBu₂VANOL zirconium catalysts **15** and **16** give the same degree of asymmetric induction, but the latter is a bit slower (entries 20 and 23 vs 16 and 17). The BINOL zirconium catalyst **19** is highly effective in the catalytic asymmetric Mannich reaction²³ but did not prove to be an effective catalyst for the α -iminol rearrangement (entry 26). The catalyst loading for the VANOL Zr catalyst **15** can be lowered to 0.5 mol % and gives

Scheme 1



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Table 1. Catalyst Screen for the α -Iminol Rearrangement of α -Hydroxy Imine **22a**^a

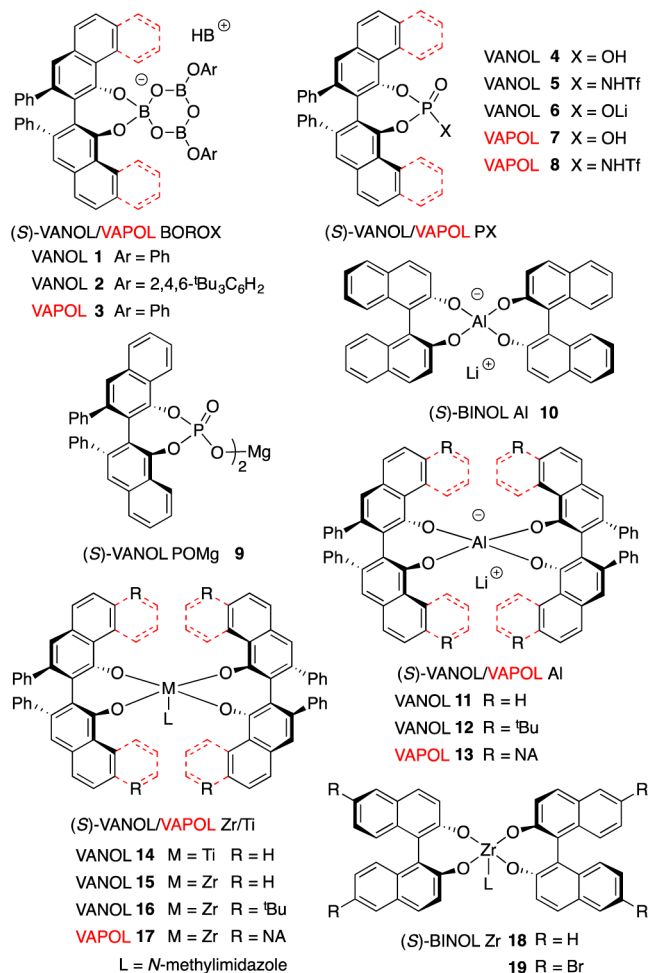
entry	catalyst	catalyst (mol %)	catalyst ^b	solvent	time (h)	temp (°C)	% yield 23a ^c	% ee 23a ^d
1	—	0	none	toluene	42	80	≤5	—
2	—	0	none	mesitylene	2	150	(28) ^e	—
3 ^f	—	0	none	mesitylene	5	150	(20) ^g	—
4	1	25	(S)-VANOL BOROX	toluene	42	75	60	-17
5 ^h	1	25	(S)-VANOL BOROX	toluene	25	75	75	-2
6	2	25	(S)-VANOL BOROX*	toluene	50	75	22	-62
7	3	25	(R)-VAPOL BOROX	toluene	20	75	73	0
8	4	25	(S)-VANOL POH	CH ₂ Cl ₂ /MeCN	15	55	89	-2
9	5	25	(S)-VANOL PNHTf	CCl ₄	36	60	100	-24
10	6	10	(S)-VANOL POLI	CCl ₄	24	100	30	-2
11	7	25	(S)-VAPOL POH	CCl ₄	14	60	100	-8
12	8	25	(S)-VAPOL PNHTf	CCl ₄	41	60	45	-24
13	9	10	(S)-VANOL POMg	CCl ₄	24	100	36	-8
14	10	10	(S)-BINOL Al	toluene	15	80	(11)	28
15	10	15	(S)-BINOL Al	THF	14	80	(28)	5
16	11	3	(R)-VANOL Al	toluene	8	70	100	68
17	12	3	(R)- ^t Bu ₂ VANOL Al	toluene	8	70	100	88
18	13	3	(S)-VAPOL Al	toluene	8	70	100	-68
19 ^f	14	5	(R)-VANOL Ti	toluene	14	80	89	92
20 ^f	15	5	(R)-VANOL Zr	toluene	1	80	96	97
21 ^f	15	0.5	(R)-VANOL Zr	toluene	1	80	96	95
22 ^{f,i}	15	2.5	(R)-VANOL Zr	mesitylene	0.008	160	95	89
23 ^f	16	5	(R)- ^t Bu ₂ VANOL Zr	toluene	3	80	64	97
24 ^f	17	5	(R)-VAPOL Zr	toluene	7	80	86	28
25 ^f	18	5	(S)-BINOL Zr	toluene	15	80	(66)	-10
26 ^f	19	5	(R)-Br ₂ BINOL Zr	toluene	2	80	(38)	5
27	20	5	Zr(O ⁱ Pr) ₄ (HO ⁱ Pr)	toluene	1	80	≤5	—
28 ^j	21	5	Zr(O ⁱ Pr) ₄ (HO ⁱ Pr)+NMI	toluene	1	80	12 ^k	—

^aAll reactions were carried out under nitrogen except where indicated. ^bFor protocols for the preparation of the various catalysts see the SI. ^cIsolated yield. Yields in parentheses are NMR yields with Ph₃CH as internal standard. ^dDetermined by HPLC. ^e71% of the starting material remains. ^fPerformed under air in a screw cap vial. ^g30% of the starting material remains and a side-product was formed in 50% yield that is tentatively identified as the imine resulting from oxidation of **23a**. ^h25 mol % PhCO₂H was added after the precatalyst was prepared. See ref 5. ⁱThe substrate was added to a solution of **15** in mesitylene that had been preheated to 160 °C. ^j5 mol % of a 1:1 mixture of Zr(OⁱPr)₄ + (HOⁱPr)₄ and *N*-methylimidazole. ^k79% of **22a** was unreacted.

23a in 96% yield with 95% ee in 60 min at 80 °C (entry 21). The most remarkable aspect of catalyst **15** is that its reactions can be carried out in the presence of air in a screw-cap vial (Table 1, entries 19–24). The reaction can even be carried out in the presence of air at 160 °C to give **23a** in 95% yield with 89% ee in 30 s. The catalyst is remarkably stable as a solution of **15** in toluene can be allowed to stand for more than 5 months in the presence of air at room temperature and will still give a 98% yield of **23a** in exactly the same asymmetric induction (97% ee) as freshly prepared catalyst (under the conditions in Table 2, entry 1).

The components of the catalyst are the ligand, Zr(OⁱPr)₄(HOⁱPr), and *N*-methylimidazole in a 2:1:1 ratio. Variations in the ratio of ligand to zirconium find that there is no change in induction when it is raised from 1:1 to 2:1 and to 3:1, but the yield does increase from 67 to 98% (see Supporting Information). However, the amount of *N*-methylimidazole has a

Scheme 2



dramatic effect on the rate of the reaction; without imidazole there is no reaction but with 1 equiv the reaction goes to completion in 1 h. Increasing the amount of *N*-methyl imidazole past 1 equiv slows down the reaction; the yield drops to 70% with 2 equiv and to 8% with 20 equiv.

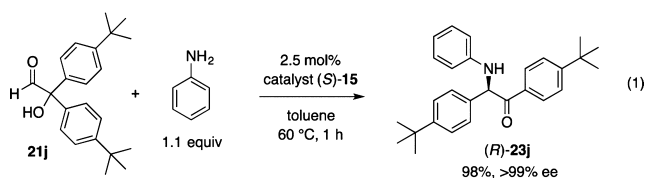
A survey of the scope of the α -iminol rearrangement is presented in Table 2. The imines **22** were prepared from the aldehydes **21** which in turn were prepared by Grignard or organolithium addition to the commercially available acetal **20**. Exceptionally high asymmetric inductions were observed over a broad range of substrates including aryl groups with both electron-rich and electron-poor substituents (i.e., entries 12 and 16). The only really problematic aryl substituent was the *para*-trifluoro-methyl group. This substrate reacted very slowly, and after 30% conversion the α -amino ketone **23n** was not detected. Instead the imine **24n**, resulting from oxidation of α -amino ketone **23n**, was isolated in 18% yield. All of the reactions of all of the substrates in Table 2 were carried out in the presence of air, but it was found that that the trifluoromethyl substituent **22n** required an inert atmosphere. When the reaction of **22n** was deoxygenated, the α -amino ketone **23n** could be isolated in 74% yield and 73% ee (70 °C, 10 mol % catalyst, 2.5 h), and the imine **24n** could not be detected. 1,2-Migrations of aliphatic groups were also highly efficient and stereoselective. Benzyl and cyclohexyl substituents gave >99 and 98% ee, respectively, while the rearrangement of **22p** with R = *n*-hexyl gave **23p** in 89% ee and 95% yield. The absolute configuration of **23a** was

Table 2. Scope of the α -Iminol Rearrangement of α -Hydroxy Imines 22a–q^a

entry	series	R	% yield 21 ^b	% yield 22 ^b	% yield 23 ^b	% ee 23 ^c
1	a	C ₆ H ₅	80	89	94	97
2	b	2-MeC ₆ H ₄	83	88	88	84
3	c	2- ⁱ PrC ₆ H ₄	56	—	95	−54 ^d
4	d	3-MeC ₆ H ₄	77	84	96	98
5	e	3-ClC ₆ H ₄	67	100	92	−93 ^e
6	f	4-MeC ₆ H ₄	78	93	92	98
7	g	4- ⁿ BuC ₆ H ₄	73	93	95	99
8	h	4- ⁱ PrC ₆ H ₄	49	95	98	99
9	i	4-CyC ₆ H ₄	69	93	97	94
10	j	4- ^t BuC ₆ H ₄	61	98	100	>99
11	k	4-PhC ₆ H ₄	77	95	100	>99
12	l	4-MeOC ₆ H ₄	63	97	90	98
13	m	4-FC ₆ H ₄	99	95	97	>−99 ^d
14	n	4-CF ₃ C ₆ H ₄	53	90	≤5 ^f	—
15	n	4-CF ₃ C ₆ H ₄	53	90	74 ^{g,h}	73
16	o	4-MeC(O)C ₆ H ₄	55	88	100 ⁱ	97
17	p	<i>n</i> -hexyl	71	88	95	89
18	q	benzyl	46	100	98	>99
19	r	cyclohexyl	57	88	97	98

^aUnless otherwise specified, all reactions were run with 2.5 mol % (*R*)-**15** in toluene at 0.3 M in **22** (0.1 mmol) at 60 °C for 1 h under air and went to 100% completion. The catalyst was prepared by stirring a toluene solution of Zr(O^{*i*}Pr)₄{HO^{*i*}Pr} with 2 equiv of (*R*)-VANOL and 1 equiv of *N*-methylimidazole at 25 °C for 30 min. ^bIsolated yield. ^cDetermined by HPLC. Negative sign means that (*R*)-**23** is formed. ^d(*S*)-VANOL was used. ^eReaction at 70 °C for 6 h with 5 mol % of (*S*)-**15** under N₂. ^fThis reaction gives an 18% yield of imine **24n** after 19 h at 60 °C along with a 70% recovery of **22n**. ^gReaction at 70 °C for 2.5 h with 10 mol % catalyst. ^hThe reaction mixture was degassed by the freeze–thaw method. ⁱReaction at 0.1 M in **22** for 3 h.

determined by chemical correlation with the methyl ester of (*R*)-phenyl glycine, and the other products were assumed to be of the same antipode (see Supporting Information (SI)). It was also found that it was not necessary to carry out the reaction on the preformed imine. The reaction of aldehyde **21j** with aniline gives the rearranged product (*R*)-**23j** in the same yield and % ee as when starting with the preformed imine **22j** (eq 1).



A number of imines made from substituted anilines were also investigated with the conditions in Table 2 (Scheme 3).²⁴ The scale could be increased 40-fold over that used in Table 2 to give 1.22 g of α -amino ketone **23s** in 85% yield and 98% ee with 1.5 mol % catalyst at 80 °C in 2 h. The optical purity of a sample of **23s** that was 95% ee could be enhanced to $\geq 99\%$ ee by crystallization with 82% recovery. The synthetic utility of α -amino ketone **23s** was demonstrated in the synthesis of the amino alcohols **25**–**27** all of which are important as chiral ligands in asymmetric synthesis and catalysis.²⁵ Reduction of **23s** with super hydride gives the amino alcohol **25** with >50:1 selectivity for the *anti*-diastereomer. This compound was obtained in 92% ee, but this could be enhanced to >99% ee by crystallization with

Scheme 3

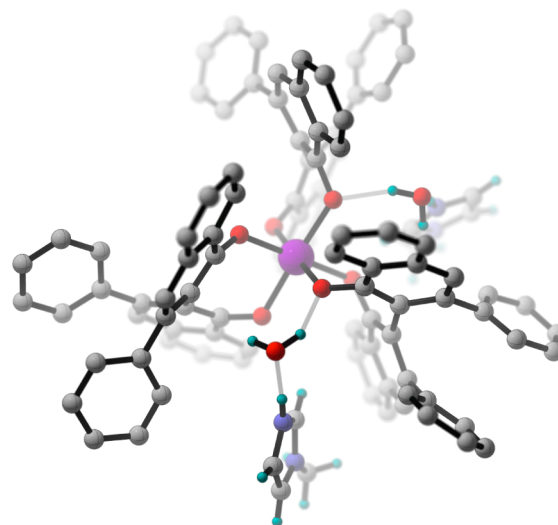
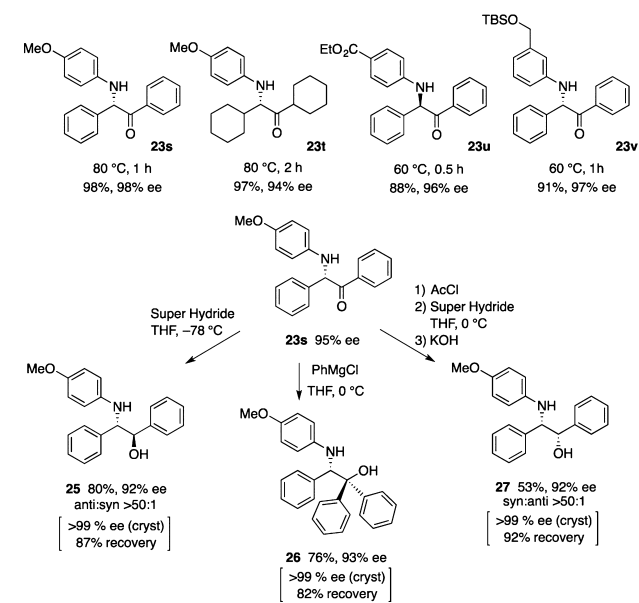
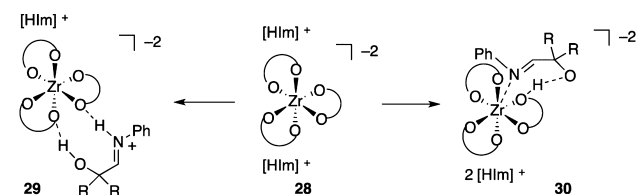


Figure 1. Structure of Zr((*S*)-VANOL)₃(NMI)₂ **28** (hydrogens and bromobenzene not shown).

83% recovery. The reduction of **23s** with super hydride could also be used to deliver the *syn*-diastereomer **27** with >50:1 stereoselectivity if the amino group was first converted to an acetamide.^{26,27} Finally, Grignard addition of a phenyl group to **23s** can be used to gain facile access to the triphenyl amino alcohol **26**.

A sample of the catalyst prepared from a ratio of VANOL:Zr:Im = 2:1:1 was grown from bromobenzene, and single crystals were obtained and characterized by X-ray diffraction as the complex **28** in Figure 1. The solid-state structure revealed that the zirconium exists as a six-coordinate homoleptic complex with three VANOL ligands and is charge balanced with two protonated *N*-methyl imidazoles. The protonated imidazoles are not H-bonded to the dianionic core but rather are H-bonded to water molecules which in turn are H-bonded to the oxy-zirconium core. The imidazolium hydrogen was located, but the protons on water were not. The N–O distance for the H-bond of the protonated imidazole in the foreground is 2.701 Å, and the O–O distance for the H-bond for

Scheme 4



the associated water molecule to the anionic core is 2.689 Å. The same solid-state structure was observed for crystals grown from a 3:1:2 mixture of VANOL:Zr:Im. Each unit cell contains two zirconium centers. A number of structures of rare earth complexes have been reported with three BINOL ligands but not for zirconium.^{20,28} This is the first homoleptic complex of zirconium derived from three bis-phenol ligands.

Crystals of zirconium complex **28** (2.5 mol %) were found to catalyze the α -iminol rearrangement of **22a** to give the amino ketone **23a** in 96% yield and 98% ee under the conditions in Table 2, entry 1. Whether complex **28** (Scheme 4) is the actual catalyst in solution remains to be determined as does the mechanism for this reaction. Possibilities to be considered are (1) the activation of the imine and the alcohol by hydrogen-bond interactions after proton exchange between the α -iminol and an imidazole and (2) the Lewis acid/Bronsted acid activation of the imine by the zirconium and the alcohol by an alkoxide ligand of the zirconium.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds and X-ray data and pdb file for **28**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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(24) The imine **23w** from benzylamine and aldehyde **21a** does not rearrange after 19 h at 80 °C. Rearrangement does occur after 2 h at 120 °C to give **23w** in 95% yield and 10% ee (see SI).

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