were performed by using the TEXSAN[13] crystallographic software package. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-153832. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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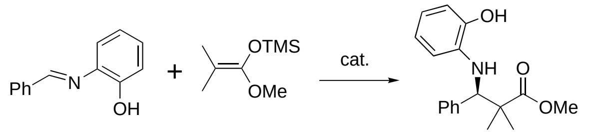
Active Site Design in a Chemzyme: Development of a Highly Asymmetric and Remarkably Temperature-Independent Catalyst for the Imino Aldol Reaction**

Song Xue, Su Yu, Yonghong Deng, and
William D. Wulff*

The asymmetric aldol reaction of an enolate or enolate equivalent with an imine is a reaction of established synthetic importance for the synthesis of chiral amines in general and β-amino esters in particular.[1] The development of chiral catalysts for this reaction has proven to be a difficult task and had eluded all attempts until recently when Kobayashi and co-workers examined imines derived from *o*-aminophenol.[2–4] Their method involves the catalysis of the reactions of these imines and ketene acetals with a catalyst generated from zirconium(IV) *tert*-butoxide and two equivalents of (*R*)-6,6′-dibromoBINOL (BINOL = 1,1′-binaphth-2-ol). Our interest in the synthesis of chiral amines led us to investigate the use of VAPOL-derived catalysts[5] (see Figure 1) for this reaction. Here we report the development of a remarkably temperature-independent and highly asymmetric method for this process that was guided by an analysis of models of intermediates that are suspected to be involved in the reaction.

A comparison of catalysts prepared from BINOL, 6,6′-dibromoBINOL and VAPOL ligands on the asymmetric induction in the reaction of the phenyl-substituted imine **1** and acetal **2** is summarized in Table 1. Following the Kobayashi protocol, the catalyst was prepared by reaction of the ligand with 0.5 equivalents of zirconium tetraalkoxide in the presence of 0.6 equivalents of *N*-methyl imidazole at room temperature for 1 h.[2] The VAPOL catalyst could be prepared in either methylene chloride or toluene, but for solubility reasons, the BINOL catalysts were prepared in methylene chloride. The VAPOL and Br_2BINOL catalysts were superior to the BINOL catalyst at −45 °C. The asymmetric induction dropped for the Br_2BINOL catalyst when the temperature was raised from −45 °C to room temperature, but curiously, the asymmetric induction for the VAPOL catalyst was essentially unchanged over this same temperature range. Only a small drop-off is noted (85 % *ee*) when the temperature is raised to 41 °C and the substrate-to-catalyst ratio is raised to 200:1 (entry 5). Both the *R* enantiomers of BINOL and Br_2BINOL ligands give the *R* enantiomer of the product **3**, whereas with the VAPOL ligand, it is the *S* enantiomer that gives the *R* product. This reversal is not unexpected given the structures of the ligands where the zirconium is in the minor groove of the BINOL ligands and in the major groove of the VAPOL ligand.[6, 7]

Table 1. Reactions of imine **1** with acetal **2** with various catalysts.[a]



1 **2** **3**

Entry	Ligand	mol % cat.	*T* [°C]	*t* [h]	Solvent	Yield **3** [%]	% *ee*
1	*S*-VAPOL	20	−45	10	CH_2Cl_2	50	80
2	*S*-VAPOL	20	−45	20	toluene	92	91
3	*S*-VAPOL	20	25	15	toluene[b]	94	89[c]
4	*S*-VAPOL	2	40	6	toluene[b]	100	86[d]
5	*S*-VAPOL	0.5	41	19	toluene	60	85
6	*R*-BINOL[e]	20	−45	19	CH_2Cl_2	80	36
7	*R*-BINOL[e]	20	25	4	CH_2Cl_2	100	28
8	*R*-Br_2BINOL[f]	10	−45	19	CH_2Cl_2	87	86
9	*R*-Br_2BINOL[f]	20	25	4	CH_2Cl_2	87	48
10	*R*-Br_2BINOL[f]	10	25	18	toluene	95	62

[a] Catalyst generated from $Zr(OiPr)_4$/*i*PrOH, (*S*)-VAPOL (2.2 equiv) and 1.2 equiv *N*-methyl imidazole (NMI) in either CH_2Cl_2 or toluene at 25 °C for 1 h. Unless otherwise specified, all reactions were performed with 1.2 equiv of **2** and 0.125 M in imine. [b] 15:1 toluene:CH_2Cl_2. [c] 0.5 M in imine. [d] 1.0 M in imine. [e] Catalyst generated from $Zr(OiPr)_4$/*i*PrOH, *R*-BINOL (2.2 equiv) and 1.2 equiv NMI in CH_2Cl_2 at 25 °C for 1 h. [f] Catalyst generated from $Zr(OtBu)_4$, (*R*)-6,6′-dibromoBINOL (2.2 equiv) and 1.2 equiv NMI in CH_2Cl_2 at 25 °C for 1 h.

The mechanism that has been proposed for the catalytic cycle for the Br_2BINOL–zirconium-mediated reaction involves a catalyst bearing two Br_2BINOL ligands on one zirconium and the coordination of the *o*-hydroxyphenylimine to the zirconium as a bidentate ligand.[2g] It is clear from the examination of space-filling CPK models that it is possible to bind two VAPOL ligands to one zirconium atom but only with a facial arrangement of the four oxygen atoms as is illustratred by structure **6** in Scheme 1. This is supported by ^{1}H NMR experiments on a catalyst generated from zirconium tetraisopropoxide and VAPOL in the presence of two equivalents of *N*-methyl imidiazole. A clean spectrum is only observed with two equivalents of VAPOL relative to zirconium and the spectrum is consistent with a single C_2-symmetrical species

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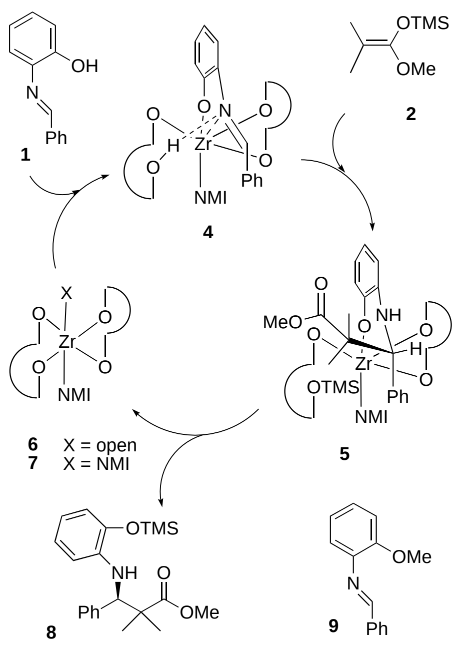


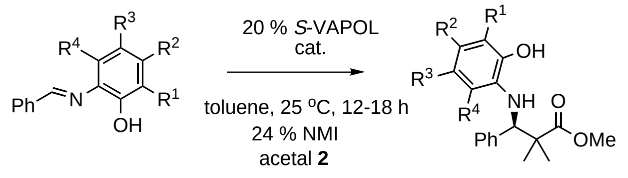
Scheme 1. Proposed mechanism for the reaction of imine **1** with acetal **2**.

which is tentatively identified as structure **7** bearing mutually *trans* NMI ligands bound to the zirconium.[8, 9] An approach of imine **1** to the open apical position in intermediate **6** is proposed to lead to intermediate **4** in which a phenol exchange has occurred. In support of this is the observation that the catalysis of the reaction of the O-methylated imine **9** with acetal **2** under the conditions in entry 3 in Table 2 gave **3** in 5% yield and 0% *ee*.[10] The requirement for NMI then can be explained as that of a monodentate ligand that binds to the other apical site and maintains an octahedral geometry. Reaction of species **4** with the ketene acetal would give intermediate **5** and then release of the product would regenerate the unsaturated species **6** and complete the cycle.

A space-filling CPK model of intermediate **6** is shown in Figure 1 and illustrates the binding cleft that is available for the docking with imine **1**. There are a number of possible orientations of **1** in the cleft of **6** and these are largely associated with changes in the Zr-O-C bond angle that has the effect of rocking the imine back and forth in the cleft. Rocking the imine down into the cleft should provide a conformation that provides a greater facial selectivity of attack on the imine since it should provide greater shielding of the *re*-face by the phenanthrene unit on the right side of the molecule as viewed in Figure 1. CPK models reveal that a methyl group on the imine *ortho* to the phenol function should be sufficient to push the imine down into the cleft. This methyl group is presented in red in the imine complex with intermediate **6**, and as illustrated in Figure 1 this methyl group makes close contacts with the floor of the cleft even when the imine is rotated down into the cleft and this results in greatly restricted movement about the Zr–O–C unit to the imine moiety. This model thus predicts that imines with a methyl substituent *ortho* to the phenol function in imine **1** should lead to increased asymmetric induction in the imino aldol reaction whereas methyl groups at postions *meta* and *para* to the phenol should not have any effect since they do not make close contacts with any part of the catalyst.

On the basis of the above predictions, a series of seven substituted imines were prepared; data from their reactions with ketene acetal **2** are summarized in Table 2. Indeed, of the four possible monomethyl-substituted imines, the highest induction was observed with a methyl group *ortho* to the

Table 2. Reactions of imines from substituted amino phenols.[a]



Imine	R1	R2	R3	R4	Product	Yield [%]	% *ee*
1	H	H	H	H	**3**	94[b]	89
11	Me	H	H	H	**17**	89	≥99
12	H	Me	H	H	**18**	87[c]	91
13	H	H	Me	H	**19**	93	95
14	H	H	H	Me	**20**	80[c]	36
15a	Me	H	Me	H	**21a**	100	≥98
16	H	H	Cl	H	**22**	78	60
15a	Me	H	Me	H	**21a**	93	47[d]

[a] See Table 1. [b] Reaction performed at 0.5 M imine in 15:1 toluene/CH_2Cl_2. [c] Reaction time of 2 h. [d] Catalyst (10 mol%) generated from (*R*)-6,6′-dibromoBINOL according to footnote [f] in Table 1.

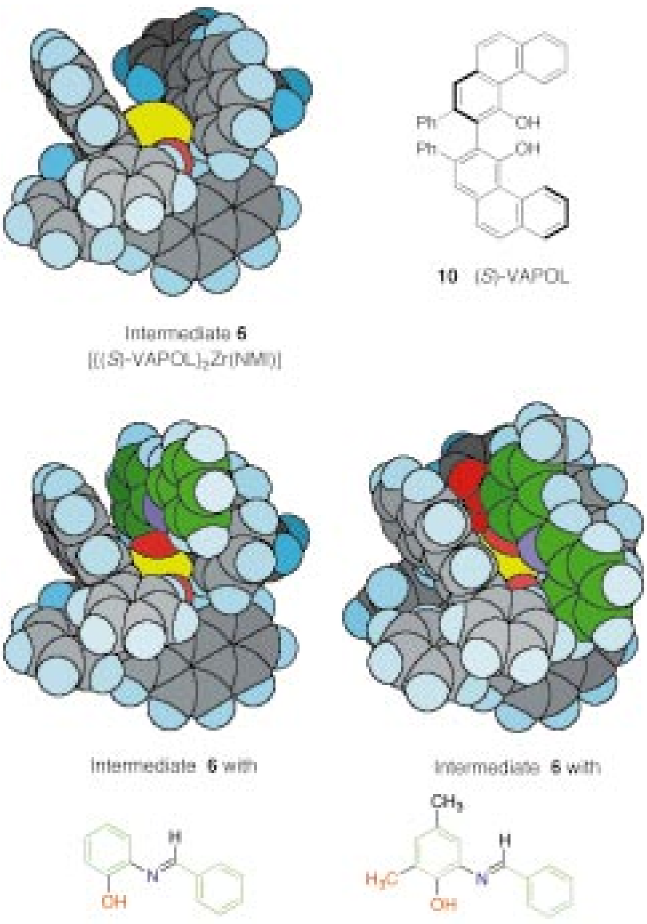
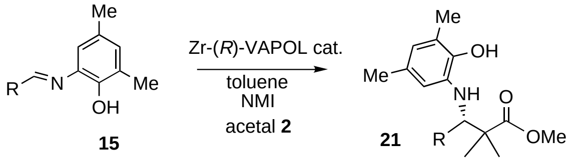


Figure 1. CPK models of intermediate **6** and of two imines complexed with intermediate **6**.

phenol function ($R^1 = Me$). The asymmetric induction increases from 89% *ee* with imine **1** to >99% *ee* with imine **11** (entries 1 and 2). The induction significantly drops with imine **14** with a methyl group *ortho* to the imine which may be a result of twisting of the imine to expose the *re*-face. The introduction of a methyl group at R^2 has very little effect and the slight increase in induction for the methyl group at R^3 may indicate an electronic effect that results in a shortening of the zirconium–oxygen distance. This is corroborated with the decrease in induction observed for the imine **16** with a chloro substituent at R^3. The catalyst generated from Br_2BINOL has a completely different response to substituents on the imine; the induction drops with introduction of a methyl group *ortho* to the phenol. The catalyst prepared from this ligand gives an enantiomeric excess of 62% with imine **1** (Table 1, entry 10) and 47% with the dimethyl-substituted imine **15a** (Table 2, entry 8).

The rate of the reaction of imines with ketene acetals with the VAPOL catalyst is slower with imines generated from substituted aminophenols, however, as indicated in Table 3, this effect can be offset by performing the reaction at higher temperature where greater turnover numbers are observed. It was quite striking to observe that the induction with imine **15a** shows absolutely no temperature dependence over the range of 25 to 100 °C.[11] Furthermore, the reaction at 100 °C can be performed with an order of magnitude change in catalyst loading with no loss in induction. The turnover numbers have not yet been measured, as the minimum time for these reactions was not investigated. The electronic nature of the imine has a small effect on the induction at this temperature with a slight increase noted for a *p*-methoxy substituent and slight decrease for a *p*-chloro substituent.

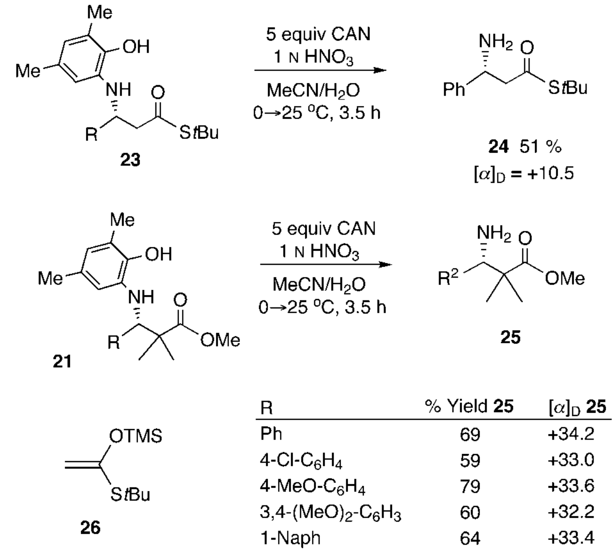
Table 3. Temperature dependence of the asymmetric induction in **21**.[a]



Series	R	mol% cat.	T [°C]	Yield **21** [%]	% *ee* **21**
a	Ph	20	25	100[b]	98.0
		20	65	93[c]	98.4
		20	85	94[c]	98.5
		20	100	91[c]	98.5
		5	100	90[c]	98.4
		2	100	95[d]	98.5
b	4-Cl-C_6H_4	2	100	90[e]	95.4
c	4-MeO-C_6H_4	2	100	85[e]	99.8
d	3,4-$(MeO)_2$-C_6H_3	2	100	85[e]	96.4
e	1-Naph	2	100	83[e]	93.0

[a] See Table 1; reaction time 2–3 h. [b] Reaction time 15 h. [c] (*S*)-VAPOL used. [d] Reaction time 5 h. [e] Reaction time 24 h.

The reactions of the imines **15** with the ketene acetal **26** mediated by the VAPOL–zirconium catalyst are slower than those involving the ketene acetal **2** and do not display the same temperature independence. The reaction of imine **15e** with **26** gives **23e** in 91% enantiomeric excess at 25 °C (20 mol% catalyst) and in 76% enantiomeric excess at 100 °C (5 mol% catalyst). Similarly, the reaction of imine **15a** with **26** gives **23a** in 71% *ee* at 25 °C (20 mol% catalyst) and 60% *ee* at 100 °C (2 mol% catalyst). The deprotection of the amine function in the adduct **23a** can be accomplished by direct treatment with 5 equivalents of ceric ammonium nitrate at 0 °C and then warming to room temperature over 3.5 h. The deprotection of the methyl esters **21a–e** were accomplished with the same conditions in 60–79% chemical yield (Scheme 2).



R	% Yield **25**	$[\alpha]_D$ **25**
Ph	69	+34.2
4-Cl-C_6H_4	59	+33.0
4-MeO-C_6H_4	79	+33.6
3,4-$(MeO)_2$-C_6H_3	60	+32.2
1-Naph	64	+33.4

Scheme 2. Products, yields, and optical rotations of the reactions of imine **15** with the ketene acetal **26** and deprotection of **21** and **23**.

The VAPOL–zirconium catalyst described herein is unusually robust providing very high asymmetric inductions in the Mukaiyama type condensation of ketene acetals with imines. We will report in due course on continuing studies directed toward experimentally probing the mechanism of this reaction as well as further development of the scope and synthetic potential of these reactions.

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[8] The reaction of VAPOL with 0.5 equivalents of zirconium tetraisopropoxide in the presence of two equivalents of NMI produces the clean formation of a single C_2-symmetrical species which is tentatively assigned by ^{1}H NMR spectroscopy as **7**: ^{1}H NMR ($C_6D_5CD_3$): $\delta = 1.60$ (brs, 6H), 4.37 (brs, 2H), 5.57 (brs, 2H), 5.87 (brs, 2H), 6.79–6.84 (m, 12H), 6.98–7.01 (m, 8H), 7.05 (s, 4H), 7.14 (d, 4H, $J = 8.7$ Hz), 7.19 (d, 4H, $J = 8.7$ Hz), 7.22 (td, 4H, $J = 8.1$, 1.1 Hz), 7.41 (dd, 4H, $J = 8.1$, 1.2 Hz), 7.84 (td, 4H, $J = 8.1$, 1.5 Hz), 11.33 (d, 4H, $J = 8.4$ Hz). The ^{1}H NMR spectrum shows that a number of species are generated when a 1:1 stoichiometry of VAPOL to zirconium is employed.

[9] As reported with the BINOL–Zr catalyst,[2a] the induction falls off with a catalyst prepared with a 1:1 stoichiometry of zirconium to VAPOL (to 60% *ee* for the reaction indicated in entry 3 in Table 1).

[10] A similar observation has been made for the Br_2BINOL catalyst where this imine gave a good yield but only 5% *ee*.[2a]

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Cu^{2+} Inhibits the Aggregation of Amyloid β-Peptide(1–42) in vitro[**]

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Alzheimer's disease (AD) is the most frequent cause of late-life dementia, with pathological characteristics of extracellular aggregation of amyloid β-peptides (Aβs) with 39–43 amino acids, which are proteolytically derived from the transmembrane amyloid precursor protein (APP).[1] Recent studies indicate that the amyloid β-peptide(1–42) (Aβ(42)) plays a central role in the formation of the β-amyloid fibril (fAβ) in vivo among the different coexisting Aβ species.[2] Further elucidation of the mechanism of Aβ(42) aggregation, and the effect of extrinsic or environmental factors such as pH, metal ions, ionic strength, membrane-like surfaces, and solvent hydrophobicity on the aggregation is useful for our understanding of the pathophysiology and treatment of Alzheimer's disease and other similar neurodegenerative diseases.

Some metal ions such as Zn^{2+}, Cu^{2+}, etc., are essential in trace amounts with important fundamental roles in the biochemistry of human life.[3] It was recently reported that Cu^{2+}, Zn^{2+}, and Fe^{3+} are concentrated in the normal neocortex. The concentrations of these cations are more than doubled in the cerebral amyloid deposits of AD brains compared with the neuropil of normal age-matched brains.[4] However, the role of Cu^{2+} in neurodegenerative diseases such as Alzheimer's disease is still not clear, although the effect of Zn^{2+} on the aggregation of Aβs has been demonstrated by several groups in recent years.[5] Our recent study indicated that the complexation of peptides with Cu^{2+} is responsible for inducing and enhancing the formation of the α-helix conformation of the alanine-based peptides with a Trp/His pair in different geometrical spacings and positions.[6] Herein we describe the aggregation of Aβ(42) and demonstrate for the first time that Cu^{2+} inhibits the aggregation of Aβ(42) with both thioflavin T (ThT) fluorescence assay and atomic force microscopy (AFM) in vitro.

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