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Brucine-Derived Amino Alcohol Catalyzed Asymmetric Henry Reaction: An Orthogonal Enantioselectivity Approach

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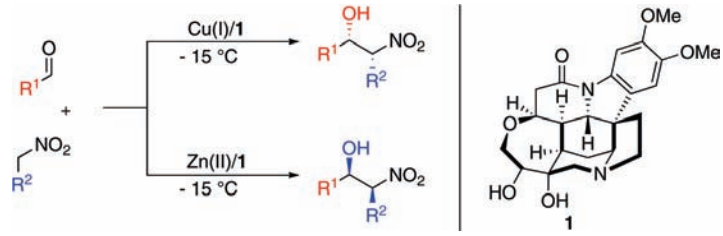
ABSTRACT



A new approach to both enantioenriched Henry products is developed by use of different molecularities of metal−ligand complexes generated from Cu(I) and Zn(II) metals with readily available chiral amino alcohol 1.

The control of absolute configuration of molecules is of paramount importance in modern asymmetric catalysis. While this is typically achieved by employment of chiral ligands in metal-catalyzed reactions, the syntheses of corresponding antipode ligands are sometimes not trivial since optical resolution and chiral pool synthesis are exclusively used to prepare "man-made" chiral ligands.[1] An alternative approach to the control of absolute configuration in asymmetric catalysis is the use of an enantiopure ligand in conjunction with different metals,[2] where two distinctive metal (**M**)−ligand (**L***) catalyst species could be generated. In fact, this orthogonal enantioselectivity has been *occasionally* observed in the asymmetric catalysis between rhodium (Rh^{I}) and iridium (Ir^{I}),[3] scandium (Sc^{III}) and yttrium (Y^{III}),[4] magnesium (Mg^{II}) and yttrium (Y^{III}),[5] or copper (Cu^{II})[6] in the presence of same chiral ligands. One particular drawback of this asymmetric approach is the lack of rational catalyst design methods because most of the C_2-symmetric chiral ligands employed in the past were not designed to generate the number of possible isomeric metal complexes. In the pioneering work of Shibasaki and co-workers in 2001,[7] it was found that different molecularities of the **M**−**L*** catalyst species between titanium (Ti^{IV}) and gadolinium (Gd^{III}) or samarium (Sm^{III}) were responsible for a highly orthogonal enantioselectivity in the silacyanation reaction of unsymmetric ketones. The formation of a 2:3 complex between a lanthanoid and a carbohydate-derived phosphine oxide ligand was postulated as the active catalyst species, in contrast to a 1:1 complex formation in the Ti^{IV}-catalyzed reaction.

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Previously, we exploited this concept of different catalyst molecularity in the asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides,[8] where two distinctive catalytically active species were postulated in the presence of brucine-derived amino alcohol **1** (Figure 1) and metals with different ionic radii: Cu(I)−L* and Ag(I)−$(L^*)_{2+n}$ complexes. Herein, we present a further extension of this orthogonal enantioselectivity approach in the context of catalytic asymmetric nitroaldol (Henry) reaction. Our strategy in the asymmetric Henry reaction was based on the possible orthogonal enantioselection of Cu(I)−L* and $(Zn(II))_{2+n}$−L* complexes.

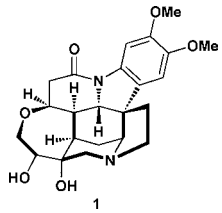

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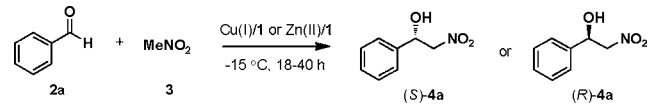
Figure 1. Brucine-derived amino alcohol **1**.

Since the seminal contribution of Shibasaki in 1992,[9] the catalytic asymmetric Henry reactions have received much attention from the synthetic community due to the versatile nature of the nitro group.[10] Although there was a decade long dormant period in its history, the subsequent development of catalytic asymmetric Henry reactions using metal catalysis (Zn,[11] Co,[12] Cu,[13] Mg,[14] and Cr[15]) and organocatalysis[16] has greatly expanded our understanding of the basis of reactivity and selectivity. One particular noteworthy aspect of the asymmetric Henry reaction is the possible involvement of **M**−**L*** complexes with a different molecularity; for example, the Cu-catalyzed reactions are known to proceed by a monometallic form of active species,[13] whereas there is strong evidence of multimetallic complexes as active species in the Zn-catalyzed reactions as proposed by Trost[11a] and Palomo.[11b] The recent mechanistic studies by Shibasaki indeed confirm that the preferential nucleation of ligands in his heterobimetallic catalyst systems were responsible for the prominent enantioamplification in the asymmetric Henry reaction.[17] In order to investigate the orthogonal enantioselectivity of **M**−**L*** complexes in catalytic asymmetric Henry reactions, we examined the role of copper and zinc metals in the presence of amino alcohol ligand **1**.[18]

Table 1. Selected Optimization Conditions[a]



entry	metal	additive	solvent	yield[b] (%)	ee[c] (%)/ config
1	CuOAc	Et_3N	CH_2Cl_2	50	59/*S*
2	CuOAc	Et_3N	2-MeTHF	50	76/*S*
3	CuOAc	*t*-BuOH	2-MeTHF	65	83/*S*
4[d]	CuOAc	*t*-BuOH	2-MeTHF	75	87/*S*
5[e]	CuOAc	*t*-BuOH	2-MeTHF	60	83/*S*
6[e]	CuOAc	*t*-BuOH	CH_2Cl_2	72	95/*S*
7[d]	$Zn(OTf)_2$	DBU	$PhCH_3$	95	3/*R*
8[d]	$Zn(OTf)_2$	*i*-Pr_2EtN	$PhCH_3$	95	46/*R*
9[d]	$Zn(OTf)_2$	Et_3N	$PhCH_3$	95	48/*R*
10[d]	$Zn(OTf)_2$	Et_3N	$CHCl_3$	45	19/*R*
11[d]	$Zn(OTf)_2$	Et_3N	Et_2O	60	2/*R*
12[d]	$Zn(OTf)_2$	Et_3N	2-MeTHF	80	40/*R*
13[d]	$Zn(OTf)_2$	Et_3N	THF	96	73/*R*
14[d,f]	$Zn(OTf)_2$	Et_3N	THF	95	75/*R*
15[e,f]	$Zn(OTf)_2$	Et_3N	THF	85	80/*R*

[a] Reaction with metal (10 mol %) and ligand **1** (10 mol %) in 0.16 M solvent. [b] Isolated yield of **4a** after column chromatography. [c] Determined by HPLC. [d] Reaction at 0 °C. [e] Reaction at −15 °C. [f] H_2O (30 mol %) was used.

We first examined the Cu(I)-catalyzed asymmetric Henry reaction of benzaldehyde **2a** in the presence of 10 mol % of amino alcohol ligand **1** at room temperature. Our brief test reactions swiftly led to the identification of optimal Cu(I) source;[19] therefore, we further optimized the reaction conditions using additives and temperature (Table 1). Initially, we employed 20 mol % base to improve the sluggish reaction

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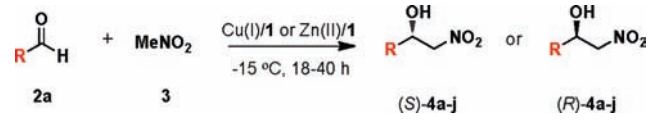
rate (Table 1, entries 1 and 2); however, we soon realized that acetate effectively plays the role of base in the presence of 30 mol % of *t*-BuOH. This experimental modification resulted in the improvement of both reaction rate and enantioselectivity (Table 1, entry 3). Next, we investigated the effect of reaction temperature. Although the observed reactivity and the enantioselectivity were further improved by conducting the reactions at lower temperature (Table 1, entries 4 and 5), the use of CH_2Cl_2 as solvent was crucial in the further optimization of CuOAc-catalyzed reaction to 72% yield and 95% ee (Table 1, entry 6).[20]

To investigate the scope of orthogonal enantioselectivity in the catalytic asymmetric Henry reaction, we next explored the Zn(II)/**1** catalytic system. $Zn(OTf)_2$ quickly emerged as the optimal source of Zn(II) source, outperforming $ZnMe_2$ and $ZnEt_2$,[21] but the reaction required a base to render an enhanced reactivity (Table 1, entries 7−9). In contrast to the marked increase in reactivity using bases, the observed enantioselectivity was highly sensitive to the nature of solvent employed (Table 1, entries 10−13). For instance, utilizing Et_2O as solvent resulted in the isolation of product (*R*)-**4a** in 60% yield and 2% ee, but otherwise identical reaction conditions in THF the Henry product was obtained in 95% yield and 73% ee (Table 1, entries 11 and 13). Upon observation of such a drastic solvent influence on the enantioselectivity, we next examined the effect of water.[22] To our delight, using 30 mol % of H_2O as additive at −15 °C the reaction was further improved to give enantiomerically enriched (*R*)-**4a** in 85% yield and 80% *ee* (Table 1, entry 15).

With our optimized conditions in hand, the reaction scope of aldehydes was investigated (Table 2). Excellent enantioselectivities (≥90% ee) were obtained with our Cu(I)/**1** catalytic system for aromatic aldehydes with different electronics (Table 2, entries 1−4) and for sterically demanding aromatic aldehydes (Table 2, entries 5−7). This trend of enantioselectivity continued for heteroaromatic (Table 2, entry 8) and aliphatic aldehydes (Table 2, entries 9 and 10). The corresponding antipodes, (*R*)-**4a**−**j**, were also obtained using the Zn(II)/**1** catalytic system with good to excellent enantioselectivities. Evidently, there exists some limitation with our Zn(II)/**1** catalytic system upon the use of sterically hindered aromatic aldehydes (Table 2, entries 5 and 6), where lower enantioselectivities were observed in the range of 67−76% ee. Consequently, the further extension of our Zn(II)/**1** catalytic system was significantly impaired in the cases of aliphatic aldehydes (Table 2, entries 9 and 10).

Table 2. Scope of Aldehydes



		CuOAc/**1**[a]		$Zn(OTf)_2$/**1**[b]	
entry	aldehydes **R**	yield[c] (%)	ee[d] (%) (*S*)-**4**	yield[c] (%)	ee[d] (%) (*R*)-**4**
1	Ph	72	95	85	80
2	*p*-toluyl	69	95	79	80
3	*p*-Cl-Ph	89	90	80	83
4	*p*-anisyl	67	95	70	88
5	*o*-toluyl	62	94	70	67
6	*m*-toluyl	71	94	72	76
7	2-naphthyl	82	90	75	80
8	2-furyl	80	97	88	90
9	*i*-Pr	70	96	30	42
10	*t*-Bu	63	97	<5	nd

[a] Reaction with CuOAc (10 mol %), **1** (10 mol %), and *t*-BuOH (30 mol %) in CH_2Cl_2 (0.16 M). [b] Reaction performed using $Zn(OTf)_2$ (10 mol %), **1** (10 mol %), Et_3N (20 mol %), and H_2O (30 mol %) in THF (0.16 M). [c] Isolated yields. [d] Determined by HPLC.

The development of catalytic asymmetric Henry reactions of nitroalkanes other than nitromethane has been a notoriously challenging task, presumably due to the presence of two distinctive mechanistic models: a chelation model for *syn*-selectivity and a nonchelation model for *anti*-selectivity.[23] Although we were mindful of the necessity of further reaction optimizations with our Cu(I)- and Zn(II)-catalyzed Henry reactions in this direction, we briefly examined the feasibility of our orthogonal enantioselectivity approach in the context of asymmetric Henry reactions using nitroethane (Figure 2). Gratifyingly, an excellent orthogonal enantioselectivity was observed with 2-furaldehyde, leading to Henry products **5a** with 94 and 96% ee's using the Cu(I)/**1** system, while the corresponding antipodes **6a** were obtained in 60

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(18) Using α-keto esters and nitromethane, Henry products with less than 60% ee were obtained from Cu(II)/bis(thiazoline) catalysis; see: (a) Lu, S.-F.; Du, D.-M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433. Enantiomeric Henry products were observed in the Et_2Zn catalysis in the range of 13−85% ee; see: (b) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712. Using aldehydes and nitromethane, Henry products with 75−95% ee were obtained in the presence of 3 equiv of Et_2Zn and 8 mol % of chiral bisoxazolidine; see: (c) ref 11c. Reversal of enantioselectivity was observed in the Cu(I) catalysis in the range of 74−97% ee; see: (d) Spangler, K. Y.; Wolf, C. *Org. Lett.* **2009**, *11*, 4724.

(19) Other copper salts were also screened in the presence of 20 mol % of Et_3N in CH_2Cl_2/CuCl (53% ee), CuI (24% ee), CuCN (16% ee), $Cu(NCCH_3)_4PF_6$ (40% ee), and $CuCl_2$ (0% ee).

(20) Use of 2-Me-THF at −15 °C resulted in the partial suspension of CuOAc/**1** catalyst. Use of 5 mol % of catalyst loading gave (*S*)-**4a** in 75% yield and 83% ee.

(21) Use of 10 mol % of Et_2Zn and Me_2Zn in toluene at 0 °C gave 40% ee and 54% ee, respectively.

(22) The potential role of H_2O was previously discussed; see: (a) Sasai, H.; Suzuki, T.; Itoh, N.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 851. (b) See also ref 17c.

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and 92% ee's with the Zn(II)/**1** system. The high level of reversal of enantioselectivity with *syn*-stereoisomers was also observed with benzaldehyde (92% ee using Cu(I)/**1** and 76% ee using Zn(II)/**1**) and cyclohexanecarbaldehyde (98% ee using Cu(I)/**1** and 52% ee using Zn(II)/**1**). Interestingly, our Cu(I)-catalyzed asymmetric Henry reaction also delivered *anti*-Henry products with good to excellent enantioselectivites, whereas modest results were observed with our Zn(II)-catalyzed system. Notably, an enhanced diastereoselectivity was obtained with cyclohexanecarbaldehyde, preferring *syn*-Henry products. In particular, the Zn(II)/**1** system improved its reactivity (69% yield) with cyclohexanecarbaldehyde, but no reversal of enantioselectivity was realized with the minor *anti*-Henry product.

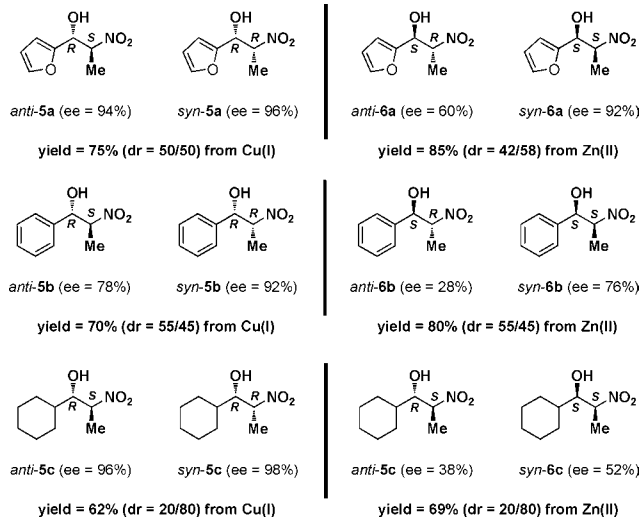

Figure 2. Asymmetric Henry reactions using nitroethane.

Although the lack of structural information on the catalytically active species enforces further studies, the key to our success in the Zn(II)-catalyzed Henry reactions could be attributed to the generation of multimetallic complexes as shown in Figure 3. Whereas the Cu(I)-catalyzed asymmetric Henry reactions are known to generate monometallic catalysts from a 1:1 metal and chiral ligand mixture, a high order molecularity of catalytically active species has been suggested using the Zn(II) species with chiral ligands due to the oxophilic nature of zinc metals.[11a,b] The tertiary amine moiety (N_{19}) and the C_{21}-OH group are expected to participate in the formation of monometallic complex (Figure 3a),[24] where a *Re*-face attack of the nitronate anion to the aldehyde occurs through a chairlike transition state. We believe that the C_{22}-OH group does not act as a H-bond donor in our Cu(I)-catalyzed Henry reaction since a varied amount of *t*-BuOH did not affect either yield or ee value.[25] As for the Zn(II)-catalyzed reaction, we propose a dinuclear zinc species (Figure 3b), where the neighboring C_{22}-OH group now participates in the creation of secondary Zn(II) metal site for the *Si*-face attack, which is in turn coordinated to the primary Zn(II) metal site. It is not possible to speculate on the exact stereochemical environments of those two Zn(II) metal sites, but our preliminary studies using a varied ratio of Zn(II) and **1** or additives suggest that the ligand sites (L and L* in Figure 3b) might not be saturated by **1**.[26] Nevertheless, further mechanistic investigation is required to understand the origin of enantioselectivity in the Zn(II)-catalyzed reaction.

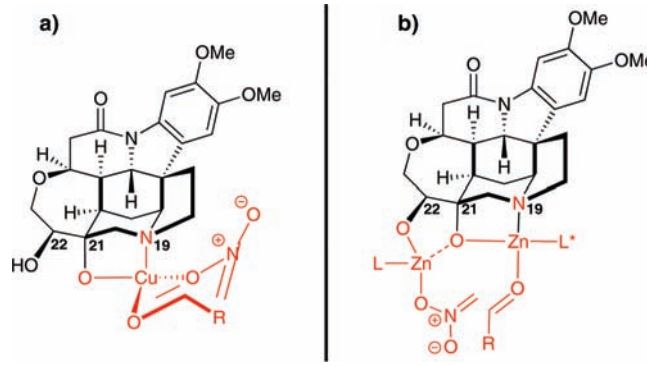

Figure 3. Working models for catalytic systems.

In summary, we have presented a new rational design method for orthogonal enantioselectivity approach in the catalytic asymmetric Henry reactions. Our two catalyst systems are highly stereoselective with a wide range of aldehydes and nitroalkanes,[27] providing a novel way of absolute stereochemical control in the catalytic asymmetric C−C bond formation. Further investigations into the full reaction scope and the asymmetric origin of our catalysts are currently ongoing.

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

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(24) Upon using the modified ligands (having either the nitrogen atom or the C_{21}-OH group protected), significantly lower ee's were observed (0% ee and 23% ee).

(25) No significant change in ee was observed with varying amounts of *t*-BuOH, 15 mol % (74% ee), 30 mol % (79% ee), 50 mol % (76% ee), and with different alcohols, 30 mol % of *i*-PrOH (73% ee), CF_3CH_2OH (72% ee), PhOH (70% ee).

(26) The reaction is extremely sensitive to the ratio of $Zn(OTf)_2$ and **1**; for instance, use of 20 mol % of $Zn(OTf)_2$ resulted in 11% ee while 20 mol % of **1**, ethylene glycol, or ethanolamine gave products with 40−50% ee.

(27) Employment of 1-nitropropane gave results similar to those of nitroethane, but the chiral HPLC separations for these products are not fully resolved using AS-H, AD-H, and OD-H columns. Our full account for these cases will be reported elsewhere.