Enantioselectivity

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Reversal of Enantioselectivity between the Copper(I)- and Silver(I)-Catalyzed 1,3-Dipolar Cycloaddition Reactions Using a Brucine-Derived Amino Alcohol Ligand**

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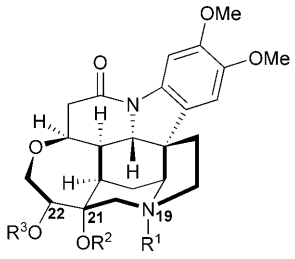
The development of asymmetric methods which lead to both enantioenriched products by using a single chiral source is a long-standing interest in organic chemistry.[1] This concept of asymmetric catalysis represents not only a highly attractive synthetic tool using readily available single enantiomeric natural products, but also provides valuable mechanistic information for reaction processes. Several notable methods have been reported to produce both enantiomerically enriched products by simply changing the reaction parameters (i.e., solvent, temperature, metal counterion, and additive) without employing the antipode of the chiral source. However, most of these reaction parameters are difficult to incorporate from the inception of catalysis design, and most often lack substrate generality. Whereas it is widely viewed that examination of diverse sets of metals in asymmetric catalysis leads to potential avenues for effective stereocontrol in an absolute sense,[2] a vast array of available metal sources together with potentially different catalytic cycles of varied metal oxidation states adds mulitple variables to the rational catalysis design. Recently, the structural modification of chiral sources has provided some significant breakthroughs, leading to a switch in the enantioselectivity of a reaction by using intricate hydrogen-bonding networks[3] and pseudoenantiomeric pairs of ligands.[4] Nevertheless, the design of effective catalytic asymmetric methods to induce a switch in the enantioselectivity of a reaction still remains a significant challenge.[1c]

Herein we present our efforts to design a new asymmetric approach to the reversal of enantioselectivity in a catalytic asymmetric 1,3-dipolar cycloaddition reaction. Our strategy for the development of catalytic systems to induce reversal of enantioselectivity was based on the premise that chiral amino alcohol ligands[5] should display different binding modes with different metals. Moreover, we envisioned that the various binding modes of amino alcohols to metal centers could be achieved by judicious choice of a metal having the appropriate ionic radius.[6]

For the generation of coordinationally stable metal–ligand complexes, the readily available strychnos-alkaloid-derived amino alcohol **1a** was utilized as a structurally rigid scaffold.[7]



1a: R^1 = lone pair, R^2 = H, R^3 = H
1b: R^1 = Bn, Br^-, R^2 = H, R^3 = H
1c: R^1 = lone pair, R^2 = H, R^3 = Ac
1d: R^1 = lone pair, R^2 = Ac, R^3 = Ac

Additionally, copper(I) and silver(I) sources were chosen as model catalysts because of their distinctive ionic radii and their impressive versatilities in catalytic asymmetric 1,3-dipolar cycloaddition reactions, which depends on their distinctive ionic radii.[8] To explore the possibility of the reversal of enantioselectivity, we selected the 1,3-dipolar cycloaddition of azomethine ylides[9] because of the biological significance of pyrrolidine derivatives, as well as their potential as organocatalysts (Table 1).[10] The attractive feature of our resulting pyrrolidines includes orthogonal reactivity of two ester groups, which allows selective synthetic manipulation.[11]

We first examined the copper(I)-catalyzed reaction of imine **2a** with 1.5 equivalents of *tert*-butyl acrylate (**3**) in the presence of 10 mol% brucine derivative **1a** at room temperature. Whereas the optimal copper(I) source and solvents were swiftly identified in our preliminary studies,[12] the observed reactivity as well as the enantioselectivity were highly sensitive to the nature of base employed (Table 1). For instance, aromatic bases displayed low enantioselectivities (Table 1, entries 1 and 2), but tertiary amine bases drastically improved the observed enantioselectivity to 75% (Table 1, entry 3). The yield and enantioselectivity of **4a** could be additionally improved to a 98% yield and 95% *ee*, respectively, by changing the solvent from CH_2Cl_2 to $CHCl_3$ (Table 1, entry 6). Although the catalyst loading could be lowered to 5 mol% without an appreciable drop in reactivity and enantioselectivity (Table 1, entry 7), the optimal reaction conditions were established using 10 mol% of CuI and **1a**.

To address the scope of reversal of enantioselectivity, we next explored Ag^I/**1a** catalytic system by examining different

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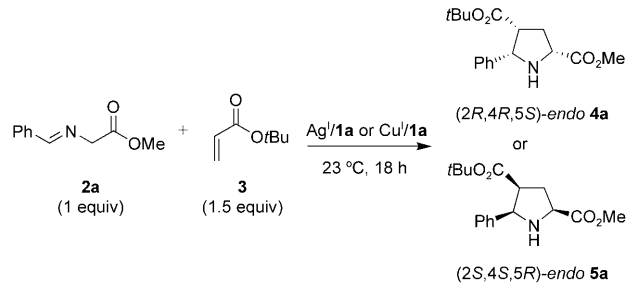
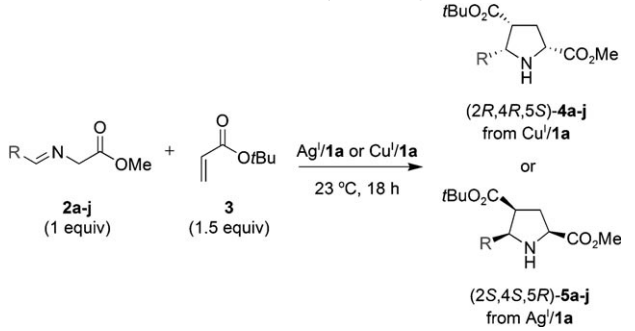
Table 1: Selected optimization conditions for the 1,3-dipolar cycloaddition.[a]



Entry	Metal	Additive	Solvent	Product	Yield [%][b]	*ee* [%][c]
1	CuI	pyridine	CH_2Cl_2	**4a**	10	40
2	CuI	DMAP	CH_2Cl_2	**4a**	95	0
3	CuI	*i*Pr_2EtN	CH_2Cl_2	**4a**	20	75
4	CuI	DBU	CH_2Cl_2	**4a**	30	34
5	CuI	DBU	$CHCl_3$	**4a**	46	94
6[d]	CuI	DBU	$CHCl_3$	**4a**	98	95
7[d,e]	CuI	DBU	$CHCl_3$	**4a**	88	92
8	AgOAc	DBU	$CHCl_3$	**5a**	90	4
9	AgOAc	*i*Pr_2EtN	$CHCl_3$	**5a**	10	58
10	AgOAc	–	$CHCl_3$	**5a**	18	75
11	AgOAc	4 Å M.S.	$CHCl_3$	**5a**	17	77
12[f]	AgOAc	4 Å M.S.	$CHCl_3$	**5a**	10	93
13	AgOAc	4 Å M.S.	CH_2Cl_2	**5a**	34	69
14	AgOAc	4 Å M.S.	$PhCH_3$	**5a**	67	65
15[g]	AgOAc	4 Å M.S.	$PhCH_3$	**5a**	79	74

[a] Reaction conditions: metal (10 mol%) and ligand **1a** (10 mol%) in solvent (0.16 M). [b] Yield of *endo* products isolated after column chromatography. [c] Determined by HPLC analysis (absolute configuration of products was determined by comparison of HPLC retention times with known data). [d] Concentrated conditions at 0.32 M. [e] CuI (5 mol%) and **1a** (5 mol%) were used. [f] Reaction at −15 °C. [g] **1a** (20 mol%) was used. DMAP = 4-(dimethylamino)pyridine, DBU = diazabicyclo[5,4,0]undec-7-ene.

Table 2: Reversal of enantioselectivity and scope of the iminoester **2**.



Entry	R	Metal	Yield [%][c]	*ee* [%][d]
1[a]	Ph (**4a**)	Cu^I	98	95
2[b]	Ph (**5a**)	Ag^I	79	74
3[a]	*p*-tolyl (**4b**)	Cu^I	75	96
4[b]	*p*-tolyl (**5b**)	Ag^I	75	75
5[a]	*p*-ClC_6H_4 (**4c**)	Cu^I	60	92
6[b]	*p*-ClC_6H_4 (**5c**)	Ag^I	94	82
7[a]	*p*-anisyl (**4d**)	Cu^I	82	96
8[b]	*p*-anisyl (**5d**)	Ag^I	72	75
9[a]	*o*-tolyl (**4e**)	Cu^I	70	85
10[b]	*o*-tolyl (**5e**)	Ag^I	81	80
11[a]	*m*-ClC_6H_4 (**4f**)	Cu^I	65	86
12[b]	*m*-ClC_6H_4 (**5f**)	Ag^I	65	78
13[a]	1-naphthyl (**4g**)	Cu^I	92	92
14[b]	1-naphthyl (**5g**)	Ag^I	86	90
15[a]	2-naphthyl (**4h**)	Cu^I	84	96
16[b]	2-naphthyl (**5h**)	Ag^I	77	96
17[a]	2-furyl (**4i**)	Cu^I	80	85
18[b]	2-furyl (**5i**)	Ag^I	71	77
19[a]	2-thienyl (**4j**)	Cu^I	64	88
20[b]	2-thienyl (**5j**)	Ag^I	74	83

[a] Reaction conditions: CuI (10 mol%) and **1a** (10 mol%) in $CHCl_3$ (0.32 M). [b] Reaction conditions: AgOAc (10 mol%) and **1a** (20 mol%) in the presence of 4 Å M.S. in $PhCH_3$ (0.16 M). [c] Yield of isolated product after column chromatography. [d] Determined by HPLC analysis (see the Supporting Information).

silver sources and solvents. To our delight, the formation of **5a**, having the opposite configuration relative to **4a**, was obtained albeit in low yields. In contrast to the copper(I)-catalyzed system, the reaction did not require a base, thereby implying that acetate possibly plays the role of a base (Table 1, entries 8–10).[13] Additional optimization conditions were investigated using 4 Å molecular sieves (M.S.) since it has been suggested that molecular sieves facilitate the catalytic efficiency.[14] Although the enantioselectivity could be as high as 93% in the presence of 4 Å M.S. in $CHCl_3$ at −15 °C (Table 1, entries 10–12), the reaction conversion remained low. Finally, using other non-coordinating solvents in conjunction with a 1:2 ratio of Ag^I/**1a**, the yield and enantioselectivity were improved to 79% yield and 74% *ee*, respectively (Table 1, entries 13–15).[15]

Having optimized conditions in hand, the reaction scope of reversal of enantioselectivity was investigated using various iminoesters (Table 2). A wide range of azomethine ylides, derived from electron-rich or electron-poor, and sterically diverse aromatic aldehydes (Table 2, entries 1–16), as well as heteroaromatic aldehydes (Table 2, entries 17–20),[16] provided the desired (2*R*,4*R*,5*S*)-**4a–j** in good to high yields with excellent enantioselectivities using the Cu^I/**1a** catalytic system; and the corresponding antipodes, (2*S*,4*S*,5*R*)-**5a–j**, were obtained with good to excellent enantioselectivities, reaching over 90% *ee* using naphthyl iminoesters (Table 2, entries 13–16) and the Ag^I/**1a** catalytic system. Extension of the substrate scope was examined using iminoesters derived from aminoesters other than glycinate as well as different dipolarophiles (Figure 1). Good to excellent reversal of enantioselectivity was observed with the iminoesters derived from alanine and phenylalanine, leading to 94 and 85% *ee* using the Cu^I/**1a** system (**4k–l**), whereas the corresponding pyrrolidines **5k–l** with a quaternary center at the 2-position were obtained in 79 and 80% *ee* using the Ag^I/**1a** system. Although the asymmetric reactions utilizing substituted *tert*-butyl acrylates proceeded sluggishly,[17] pyrrolidines from methyl methacrylate and methyl crotonate were obtained with extremely high enantioselectivities using the Cu^I/**1a** system (**4m–n**). In contrast, pyrrolidines with lower enantioselectivities were obtained using the Ag^I/**1a** system (**5m–n**). Notably, the exclusive formation of *endo* products has been observed in all cases.

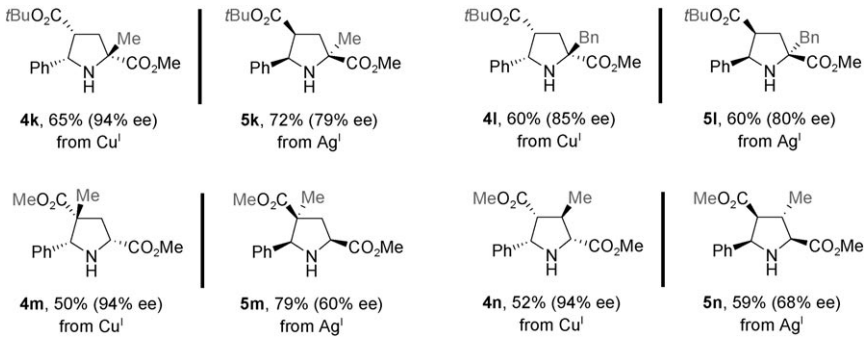


Figure 1. Scope of reversal of enantioselectivity.

Although a detailed mechanistic explanation awaits further studies,[18] the pronounced difference in ionic radii of copper(I) and silver(I) may be interpreted on the basis of the positions of two hydroxy groups proximal to tertiary amine moiety (N_{19}).[19] The hydroxy group on C_{21} is expected to stabilize smaller Cu^I–N_{19} complex (Figure 2a), leaving the

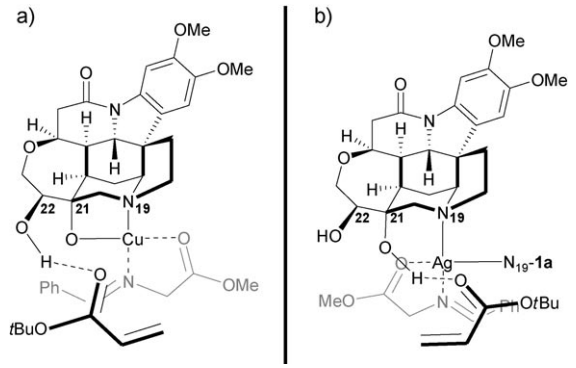


Figure 2. Working models for catalytic systems. a) Binding mode I for the smaller Cu metal center. b) Binding mode II for the smaller Ag metal center.

OH group at C_{22} available for hydrogen-bonding interactions to dictate the approach of acrylates.[20] Not surprisingly, the effect of the OH group on C_{21} is less evident with the Ag^I–N_{19} complex, therefore the initial 1:1 Ag^I/**1a** complex undergoes a conformational change to allow another **1a** molecule to participate in the formation of a new 1:2 Ag^I/**1a** complex (Figure 2b).[21] Our preliminary mechanistic studies support the necessity of the tertiary amine moiety and the possible roles of two hydroxy groups. Thus, upon using the modified ligands **1b**, **1c**, and **1d** (having either the nitrogen atom or the hydroxy groups protected) in the copper(I)-catalyzed reactions, racemic *endo* products were obtained in 50, 70, and 65% yields, respectively. However, analogous reactions under the silver(I)-catalyzed conditions were found to be less sensitive to the modification of OH group on C_{22} in **1c**, resulting in the formation of *endo*-**5a** in 60% yield with 64% *ee*. Interestingly, no reversal of enantioselectivity was observed upon using **1d** (both OH groups protected), thereby resulting in *endo*-**4a** (95% yield, 33% *ee*) with the same sense of absolute stereochemistry as the Cu^I/**1a** system.[22] Clearly, further mechanistic investigation will be required to understand the origin of enantioselectivity in the silver(I)-catalyzed reaction.[23]

In summary, we have presented a new rational design of asymmetric catalysts to induce reversal of enantioselectivity. Our underlying concept was based on the introduction of different metal binding modes of structurally rigid ligand **1a** in the presence of metals with different ionic radii. Our two catalyst systems have proven to be highly stereoselective with a wide range of dipolarophiles and iminoesters, culminating in the catalytic asymmetric synthesis of pyrrolidines with a quaternary center at the 2-position or 4-position as well as all-carbon-substituted pyrrolidines. Additional investigations into the full reaction scope and the asymmetric origin of our catalysts are currently ongoing.

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[15] No beneficial effect was observed in the presence of ratios ranging from 1:3 to 1:10 of Ag^I/**1a**; instead the decomposition of acrylate was observed with excess of **1a**.
[16] Employment of *iso*-propyl iminoester led to both pyrrolidines with reversal of enantioselectivity; 54% yield with 90% *ee* (Cu^I/**1a**) and 40% yield with 30% *ee* (Ag^I/**1a**), despite the fact that alkyl-substituted imino esters under our optimized conditions are unstable.
[17] Although good to excellent reversal of enantioselectivity was obtained, reaction yields remained low (< 25%) upon using *tert*-butyl methacrylate (Cu^I: 97% *ee*, Ag^I: 78% *ee*) and *tert*-butyl cinnamate (Cu^I: 95% *ee*, Ag^I: 74% *ee*).
[18] So far we have not been able to isolate single crystals of metal/**1a**, our effort in this direction will be reported in the near future.
[19] Typical ionic radius for Cu^I with a coordination number four is 0.60 Å, whereas that of Ag^I is around 1.00 Å; see: *Handbook of Chemistry and Physics*, 87th ed., CRC, Boca Raton, FL, **2006**, pp. 12–11.
[20] Use of one equivalent of protic additives or three to five equivalents of *tert*-butyl acrylate lowers the observed *ee* values to between 40 and 60% in both the Cu^I- and Ag^I-catalyzed reactions.
[21] Optimal use of 1:2 ratio of Ag^I/**1a** complex supports this speculation, however our initial ^{15}N NMR study was inconclusive. Presently, the formation of a 1:(2+*n*) ratio of Ag^I/**1a** complexes cannot be completely ruled out.
[22] Selective modification of the C_{21}-OH has not been successful.
[23] Effect of different counter ions in our systems appears to be minimal; **4a** was obtained in 78–90% *ee* using other Cu salts (CuCl, CuBr, CuOAc).

