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A Novel Example of Chiral Counteranion Induced Enantioselective Metal Catalysis: The Importance of Ion-Pairing in Copper-Catalyzed Olefin Aziridination and Cyclopropanation

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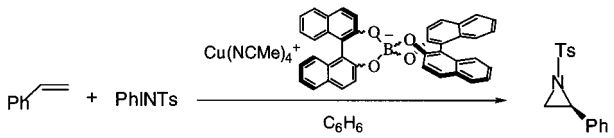
ABSTRACT



A new ion-pairing route to achieve asymmetric catalysis has been observed in the copper-catalyzed aziridination of styrene with a chiral counteranion. Structural studies suggest that enantioinduction occurs via ion-pairing of the cationic copper catalyst in the chiral pocket created by the anion. The degree of asymmetric induction can be tuned with features that affect ion-pairing, such as achiral and chiral ligands, temperature, and solvent polarity.

Asymmetric synthesis using chiral transition metal complexes represents one of the more important methods to generate optically active molecules.[1] Traditionally, chirality has been incorporated into metal catalysis through the design and synthesis of chiral or pro-chiral ligands and their coordination to the metal center.[2] However, asymmetric induction is an extremely sensitive phenomenon, with high enantioselectivities requiring only very small differences in transition state energies.[3] This implies that it may be possible to use more subtle features than metal−ligand interactions to effect chirality in metal-catalyzed reactions, such as fragments weakly associated outside the metal coordination sphere (Figure 1).[4−6] Formally nonbonding interactions provide an attractive potential source of asymmetry in catalysis since they can, in principle, incorporate chirality into active metal catalysts without significantly perturbing reactivity. In addition, weakly associated fragments are easily modified, allowing them to be readily scanned to achieve high levels of enantioselectivity.

Since many metal catalysts are cationic, the use of chiral counteranions may provide a method to effect asymmetric induction.[7,8] There is emerging evidence that noncoordinating or weakly coordinating counteranions can have dramatic

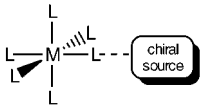


Figure 1. A nonbonding approach to chiral induction.

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(2) Seyden-Penne. *Chiral Auxilaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995.
(3) For example, 3 kcal/mol = ca. 95% ee at 25 °C.

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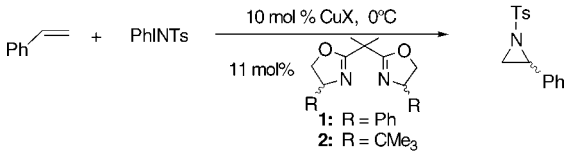
effects on selectivity in metal-catalyzed reactions.[9] While this suggests that significant ionic interactions can occur during catalysis, to our knowledge, the counteranion itself has never been used to achieve asymmetric induction.[10] We report below the first example of an enantioselective metal-catalyzed reaction where the sole source of asymmetry is a chiral counteranion. These results demonstrate that ionic interactions in metal catalysis are not only important but can be utilized to influence chirality in reaction products.

The systems examined for counteranion influence on chiral induction are copper-catalyzed nitrene[11] and carbene[12] transfer reactions to prochiral α-olefins. Prior to exploring the influence of chiral counteranions on these reactions, the degree of ion-pairing in Cu^+ X^- during catalysis was determined. As illustrated in Table 1, variation of the weakly

Table 1. Counteranion Influence on CuX-Catalyzed Styrene Aziridination[a]



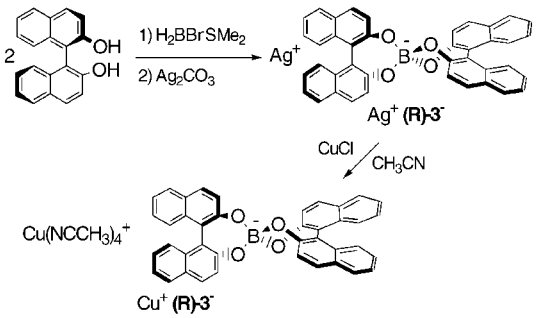
ligand	X	% ee (C_6H_6)[b]	% ee (MeCN)[b]
(*R*)-**1**	OTf	1 (*S*)	28 (*S*)
(*R*)-**1**	ClO_4	5 (*S*)	28 (*S*)
(*R*)-**1**	Cl	17 (*S*)	28 (*S*)
(*R*)-**1**	PF_6	33 (*S*)	28 (*S*)
(*S*)-**2**	OTf	66 (*R*)	2 (*R*)
(*S*)-**2**	ClO_4	57 (*R*)	2 (*R*)
(*S*)-**2**	Cl	26 (*R*)	2 (*R*)
(*S*)-**2**	PF_6	33 (*R*)	2 (*R*)

[a] [styrene]/[PhINTs] = 5. [b] Major enantiomer in parentheses, determined by HPLC on a (*S,S*) Whelk-O 1 column (Regis).[11c]

coordinating counteranion (X = OTf, ClO_4, PF_6) in the CuX-catalyzed aziridination of styrene with PhINTs[13] in the presence of chiral bis(oxazoline) ligands **1** and **2** leads to changes in ee's of over 30% in benzene solvent. This anion influence on enantioselectivity displays no consistent trend with either the coordinating ability or size of the anion. In fact, the trend changes with each ligand employed. In addition, the ee's are independent of X^- in the more polar acetonitrile solvent. This demonstrates that strong ion-pairing does exist in Cu^+ X^- in nonpolar solvents, suggesting it would be a reasonable system to explore the effect of a chiral anion on enantioselectivity.

The chiral counteranion prepared, $\mathbf{3}^-$, contains two binaphthol units bound to a tetrahedral boron center (Scheme 1).[14] The chiral binaphthols generate a single C_2 symmetric

Scheme 1



enantiomer upon complexation to boron and therefore require no subsequent resolution. The silver salt of (*R*)-$\mathbf{3}^-$ can be readily generated by the reaction of 2 equiv of *R*-binaphthol with $H_2BBr{\cdot}SMe_2$[15] in dichloromethane followed by slow addition to Ag_2CO_3 in acetonitrile. Ag^+ (*R*)-$\mathbf{3}^-$ provides a useful precursor for incorporating $\mathbf{3}^-$ into metal halides. The reaction of Ag^+ (*R*)-$\mathbf{3}^-$ with CuCl in acetonitrile, followed by precipitation with diethyl ether, provides Cu^+ (*R*)-$\mathbf{3}^-{\cdot}$4NCMe as a white solid in 79% yield. The *S*-enantiomer, Cu^+ (*S*)-$\mathbf{3}^-$, can be similarly prepared from *S*-binaphthol.

The crystallization of Cu^+ (*R*)-$\mathbf{3}^-$ with four acetonitrile molecules suggests that the copper complex exists as the ionic 18-electron complex $Cu(NCMe)_4^+$ (*R*)-3^-. However, X-ray structural analysis reveals two isomeric complexes

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(5) Chiral phase transfer catalysts have been shown to induce high ee's: (a) Hiyama, T.; Mishima, T.; Sawada, H.; Nozaki, H. *J. Am. Chem. Soc.* **1975**, *97*, 1626−1627. (b) Hughes, D. L.; Dolling, U. H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745−4752.

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cocrystallizing in a 1:1 ratio: the tetrakis(acetonitrile) copper-(I) salt as well as a second isomer in which the anion, (*R*)-**3**$^-$, is coordinated through an oxygen atom to a Cu(NCMe)$_3^+$ fragment (Cu−O, 2.16 Å; Figure 2).[16] Nevertheless, the ^{1}H

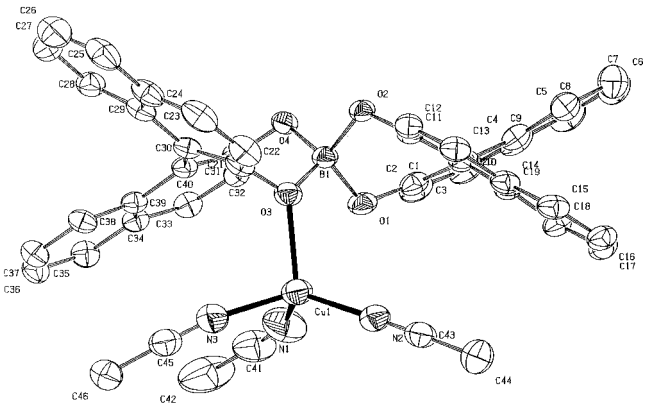
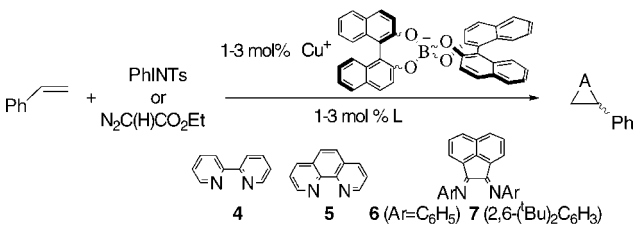


Figure 2. Crystal structure of Cu(NCMe)$_3$((*R*)-**3**$^-$) (hydrogen atoms and Cu(NCMe)$_4^+$ (*R*)-**3**$^-$ omitted for clarity). Selected bond lengths [Å]: Cu(1)−O(3) 2.165(2), Cu(1)−N(1) 2.083(6), Cu(1)−N(2) 1.916(4), Cu(1)−N(3) 1.972(4).

NMR (CD_2Cl_2) of Cu$^+$ (*R*)-**3**$^-$ reveals that the weakly coordinating anion is completely ionized to form the tetrakis-(acetonitrile)copper salt in solution, with a single resonance for the four copper-bound CH_3CN molecules (δ 1.48) and equivalent binaphthol units within (*R*)-**3**$^-$.[17]

With the chiral copper salt in hand, the potential influence of the chiral counteranion on enantioselectivity was explored. Variation of (*R*)- or (*S*)-**3**$^-$ in the copper-catalyzed aziridination of styrene with chiral bis(oxazoline) ligands **1** and **2** at 0 °C reveals that the chirality of the counteranion has a minor influence on the enantioselectivity of the reaction (ca. 2%; Table 2, entries 1−4). This is despite the differences in both the solubility and color of these catalysts at the beginning of the reaction. On the other hand, the analogous cyclopropanation of styrene shows a dramatic anion influence on enantioinduction. The reaction of ethyldiazoacetate and styrene in the presence of Cu$^+$ (*R*)-**3**$^-$ or (*R*)-**3**$^-$ and ligand **1** at 0 °C leads to the formation of *trans*- and *cis*-cyclopropanes in a 1.4 and 2.2 *cis*/*trans* ratio, respectively (entries 5 and 6). Examination of the *cis*-isomer of the cyclopropane reveals that modification of the anion chirality from (*R*) to (*S*) not only influences enantioselectivity (28% to 6%) but actually changes the preferred enantiomer generated! The effect of ion-pairing in Cu$^+$ **3**$^-$ is very temperature sensitive, and performing the same reaction at 25 °C results in a complete loss of the anion's effect on ee's and catalyst activity (entries 7 and 8). This demonstrates that, under the correct conditions, the chirality of the counteranion can indeed influence the asymmetric environment about the metal−ligand complex.

Table 2: Aziridination and Cyclopropanation of Styrene with Cu$^+$ **3**$^-$ [a]



entry	L	X	A	solvent	% ee[b]	yield, %
1	(*R*)-**1**	(*S*)-**3**	NTs	C_6H_6	22 (*S*)	75
2	(*R*)-**1**	(*R*)-**3**	NTs	C_6H_6	24 (*S*)	85
3	(*S*)-**2**	(*S*)-**3**	NTs	C_6H_6	13 (*R*)	nd
4	(*S*)-**2**	(*R*)-**3**	NTs	C_6H_6	12 (*R*)	nd
5	(*S*)-**1**	(*S*)-**3**	$CHCO_2Et$	C_6H_6	6 (*R*)/21 (*R*)[c]	12
6	(*S*)-**1**	(*R*)-**3**	$CHCO_2Et$	C_6H_6	28 (*S*)/10 (*R*)[c]	20
7[d]	(*S*)-**1**	(*S*)-**3**	$CHCO_2Et$	C_6H_6	6 (*R*)/15 (*R*)[c]	34
8[d]	(*S*)-**1**	(*R*)-**3**	$CHCO_2Et$	C_6H_6	8 (*R*)/12 (*R*)[c]	34
9	none	(*R*)-**3**	NTs	C_6H_6	7 (*R*)	86
10	none	(*S*)-**3**	NTs	C_6H_6	7 (*S*)	88
11	none	(*R*)-**3**	NTs	CH_2Cl_2	4 (*R*)	97
12	none	(*R*)-**3**	NTs	CH_3CN	<1	87
13	**4**	(*R*)-**3**	NTs	C_6H_6	10 (*R*)	43
14	**5**	(*R*)-**3**	NTs	C_6H_6	10 (*R*)	41
15	**6**	(*R*)-**3**	NTs	C_6H_6	2 (*R*)	90
16	**7**	(*R*)-**3**	NTs	C_6H_6	<1	78

[a] [styrene]/[PhINTs] = 5 at 0 °C. Aziridination: 3 mol % of Cu$^+$**3**$^-$, 3.1 mol % of L, analyzed by HPLC on an (*S*,*S*) Whelk-O 1 column (Regis). Cyclopropanation: 1 mol % of Cu$^+$ **3**$^-$, 1.1 mol % of L, analyzed by GC on a CP Chirasil-Dex column.[12b] [b] Major enantiomer at C1 in parentheses. [c] ee(*cis*)/ee(*trans*). [d] 25 °C.

The ability of the chiral counteranion by itself, without the need of a chiral ligand, to directly affect asymmetry in olefin aziridination is illustrated in the reaction of PhINTs and styrene with Cu$^+$ (*R*)-**3**$^-$ (entry 9). In contrast to other copper salts, analysis of the aziridine product shows that Cu$^+$-(*R*)-**3**$^-$, solely through the influence of ion-pairing interactions, produces aziridine in 7% enantiomeric excess. When the (*S*) enantiomer of counteranion **3**$^-$ is employed, the opposite enantiomer of the aziridine is obtained in 7% enantiomeric excess (entry 10). To our knowledge, this represents the first example of an enantioselective transition metal catalyzed reaction where the sole source of chirality is the counteranion.

As anticipated, the enantioinduction obtained from the chiral counteranion is very sensitive to factors which affect the degree and nature of ion-pairing during catalysis. Thus, changes in solvent polarity from benzene (ϵ = 2.3) to

(16) Crystallographic data for Cu$^+$ (*R*)-**3**$^-$: M_w = 1614.40, monoclinic, space group *P*2(1), a = 11.113(4), b = 25.109(7), c = 14.869(3), b = 104.84(3), V = 4011(2) Å^3, Z = 2, ρ_{calcd} = 1.337 mg m^{-3}, T = 293(2) K, m = 1.173 mm^{-1}; R (R_w) = 0.071 (0.1887). Crystallographic data for **8**: M_w = 1023.52, monoclinic, space group *P*2(1), a = 12.7853(3), b = 15.7945(3), c = 13.2045(2), b = 101.9080(10), V = 2609.10(9) Å^3, Z = 2, ρ_{calcd} = 1.318 mg m^{-3}, T = 293(2), m = 2.164 mm^{-1}; R (R_w) = 0.0968 (0.2461). Full details of the crystallographic analysis are described in the Supporting Information.

(17) The symmetry in (*R*)-**3**$^-$ could also arise from an equilibrium coordination to copper. However, the addition of 10 equiv of CH_3CN, or 2 equiv of ligand **1**, which would perturb any coordination, has almost no effect upon the ^{1}H NMR of (*R*)-**3**$^-$.

methylene chloride ($\epsilon = 9.1$) to acetonitrile ($\epsilon = 38.8$) results in a gradual diminishment of ee's (entries 9−12), consistent with their effect on ion-pairing.[18] The cation/anion interactions can be further tuned by changes in the copper coordination sphere. The addition of 2,2′-bipyridine (**4**) or 1,10-phenanthroline (**5**) results in an actual enhancement of enantioselectivity to 10% (entries 13 and 14). This increase in % ee upon addition of a bidentate ligand argues against the coordination of (*R*)-**3**$^-$ to the copper center during catalysis (vide infra) and instead likely arises from ligand coordination changing the preferred orientation of (*R*)-**3**$^-$ about the metal center. Increasing the steric bulk of the ligand (entries 15 and 16) appears to inhibit tight ion-pairing and leads to an almost complete loss of chiral induction from the counteranion.

All experimental evidence suggests that ion-pairing between Cu^+ and **3**$^-$ is the source of enantioselectivity.[19] To obtain further insight into the nature of this cation/anion interaction, the structure of complex Cu^+ (*R*)-**3**$^-$ was examined under the actual catalysis conditions. The addition of Cu^+ (*R*)-**3**$^-$ to bipyridine and 5 equiv of styrene in CH_2Cl_2, which models the conditions employed above for styrene aziridination, followed by the slow diffusion of pentane results in the crystallization of the copper salt as a yellow solid. X-ray structural analysis of this complex reveals it to be (bipy)Cu($H_2C{=}CHC_6H_5$)$^+$ (*R*)-**3**$^-$ (**8**) (Figure 3).[16] This

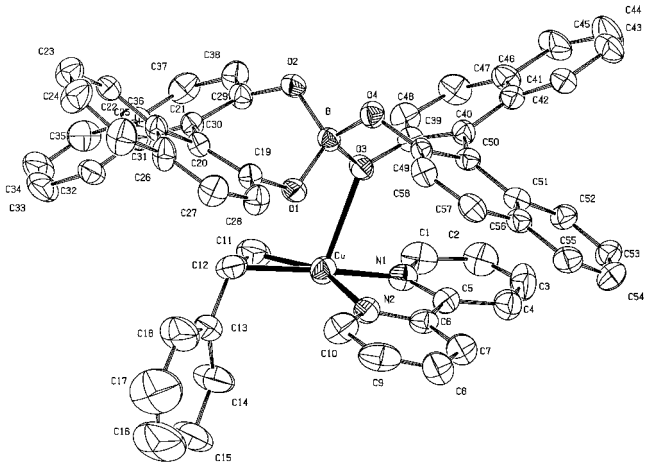


Figure 3. Crystal structure of **8** (hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [deg]: Cu−O(3) 2.546(5), Cu−C(11) 2.022(10), Cu−C(12) 2.021(9); N(1)−Cu-O(3) 84.0(2), N(2)−Cu-O(3) 91.3(2), C(11)−Cu-O(3) 105.5 (3), C(12)−Cu-O(3) 108.2(3).

structure clearly shows that, under the conditions employed for catalysis, the borate counteranion **3**$^-$ cannot compete with the bidentate ligand and styrene for coordination to the copper center. Interestingly, the counteranion does appear to have a long-range ion-pairing interaction through one oxygen of the binaphthol fragment (Cu−O, 2.55 Å in **8**, compared to 2.16 Å in Cu^+ (*R*)-**3**$^-$). The net effect of this interaction is to place the copper cation within a chiral pocket created by two separate binaphthol fragments on the boron center. This ion-pairing induces the coordination of only a single styrene enantioface in **8**, in which the phenyl group is directed away from the bulky binaphthol rings. While a direct extrapolation of this solid state structure to the catalytically active species in solution cannot be made, this does suggest that strong ion-pairing in Cu^+ (*R*)-**3**$^-$ can lead to a preferred orientation of the catalyst in the chiral environment of the counteranion.

In conclusion, a new method to induce asymmetry into metal catalysis has been observed via the use a chiral counteranion with an achiral metal complex. This illustrates that weak forces such as ion-pairing can indeed be employed to affect enantioselectivity in catalysis. The significant influence observed with the chiral counteranion in concert with chiral ligands suggests that the further design of these anions can lead to even higher levels of ion-pairing induced enantioinduction. Considering the flexibility in counteranion structures, the tunability of their influence on the metal center (i.e., solvent polarity, temperature, and ligand effects), and their ease of incorporation into catalysts, such cation/anion interactions would appear prime candidates for exploration in the future development of enantioselective metal-catalyzed processes. Efforts in these directions are currently under investigation in our laboratory.

Acknowledgment. We thank Dr. Anne-Marie Lebuis for determination of the crystal structures of Cu^+ (*R*)-**3**$^-$ and **8** and NSERC (Canada) and FCAR (Quebec) for their financial support of this research. D.B.L. thanks NSERC for a graduate fellowship.

Supporting Information Available: Synthesis and spectroscopic and X-ray structural data on complexes Cu^+ (*R*)-**3**$^-$ and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Control experiments demonstrate that enantioselectivity remains continuous throughout catalysis, while ^{11}B NMR analysis shows that (*R*)-**3**$^-$ decomposes slowly and only at the end of the reaction, demonstrating that asymmetric induction is due to an intact (*R*)-**3**$^-$. We thank the reviews for this suggestion.