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A Redox-Reconfigurable, Ambidextrous Asymmetric Catalyst

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Supporting Information

ABSTRACT: A redox-reconfigurable catalyst derived from L-methionine and incorporating catalytic urea groups has been synthesized. This copper complex catalyzes the enantioselective addition of diethyl malonate to *trans*-β-nitrostyrene. Either enantiomer of the product can be predetermined by selection of the oxidation state of the copper ion. Enantiomeric excesses of up to 72% (S) and 70% (R) were obtained in acetonitrile. The ability of the catalyst to invert enantiomeric preference was reproduced with several different solvents and bases. Facile interconversion between the Cu^{2+} and Cu^{+} redox states allowed easy access to both active helical forms of the complex and, therefore, dial-in enantioselectivity.

Inversion of helicity has long intrigued investigators in a number of fields.[1] In synthetic chemistry, interesting studies have included the employment of single enantiomer ligands with different solvents,[3] counterions,[4] metals,[5] and temperatures[6] in an attempt to toggle the enantioselectivity of a reaction, which has enjoyed varying degrees of success.[7] Most such systems reported to date have been discovered by serendipity, and rational design of catalysts with ready triggers to modulate or invert enantioselectivity have been elusive. Recently, the Feringa group designed a thiourea organocatalyst employing a phototriggered, helically chiral molecular rotor scaffold.[8] In this system, photoswitching produced thermally interconverting atropisomers that catalyzed the formation of enantiomeric products of the addition of a thiophenol to cyclohexenone. Redox-modulated catalysts have been reported that provide elements of allosteric reactivity control, but no redox-based system has been shown to control enantioselectivity.[9]

Previous studies from this laboratory described redox-responsive coordination complexes capable of helical inversion.[10,11] Complexes derived from methionine or cysteine were shown to undergo inner sphere ligand rearrangement upon one-electron oxidation or reduction of copper. The rearrangement was coupled to the orientation of two quinoline rings and affording right (**Δ**, Cu^{2+})- or left (**Λ**, Cu^{+})-handed orientations as evidenced in solution by exciton-coupled circular dichroism.[12] In this study, we examine the attachment of catalytic moieties to the quinoline units of tripodal ligands derived from L-methioninol for asymmetric catalysis. In such a system, the copper ion inner coordination sphere would not be involved in catalysis but would serve to modulate the asymmetric orientation of the catalytic groups, which in turn could potentially catalyze organic reactions in both oxidation states to produce either enantiomer product from a single enantiomer of the ligand (see Figure 1). In this communication we report such a redox-reconfigurable "ambidextrous" chiral catalyst

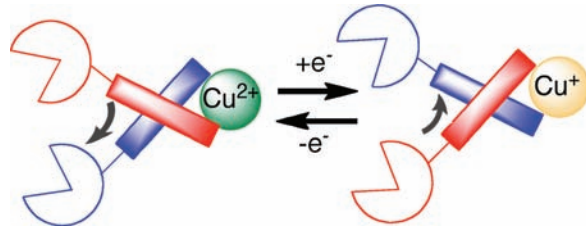

Figure 1. Schematic of redox-inversion of chiral cleft.

capable of delivering either enantiomer of a nitro Michael addition product dependent on the oxidation state of a single copper atom. For catalyst **Δ/Λ−1** (Figure 2b), urea groups were selected as reactive components due to their remarkably robust ability to behave as general acid catalysts via hydrogen bonding.[13]

The catalyst ligand was synthesized using commercially available L-methioninol in five steps with an overall 61% yield (Supporting Information). Subsequent complexation of the ligand with $Cu(ClO_4)_2$ afforded **Δ−1**, whereas **Λ−1** was isolated by complexation with $Cu(CH_3CN)_4PF_6$.

Electronic spectra of the copper complexes of **Δ/Λ−1** (Figure 2a) are qualitatively similar to those reported for a similar unsubstituted quinoline derivative of L-methioninol[14] but display additional features, most likely due to the presence of additional aromatic substituents in **Δ/Λ−1** that may absorb in the UV wavelength region of the spectra. The absorption spectrum of **Δ−1** (Cu^{2+}) shows a flattened peak suggesting transitions of similar intensity near 247 and 258 nm. The transition near 247 nm is likely due to the ^1B_b transition with transition dipole oriented in the longitudinal direction crossing both rings and giving rise to an exciton couplet in the CD spectrum with trough at 251 nm, null near 238 nm, and peak near 230 nm. The latter is likely due to a $\pi-\pi^*$ transition involving the quinoline and attached phenyl ring. A possibly related additional trough appears in the CD spectrum near 260 nm. The **Λ−1** (Cu^{+}) compound shows a broad peak near 248 nm and associated peak, null, and trough at 252, 239, and 232 nm, respectively.[15] Overall, the CD spectra give significant mirror image ECCD character for the **Δ−1** and **Λ−1** complexes, consistent with inversion of the asymmetric orientation of the chromophores.

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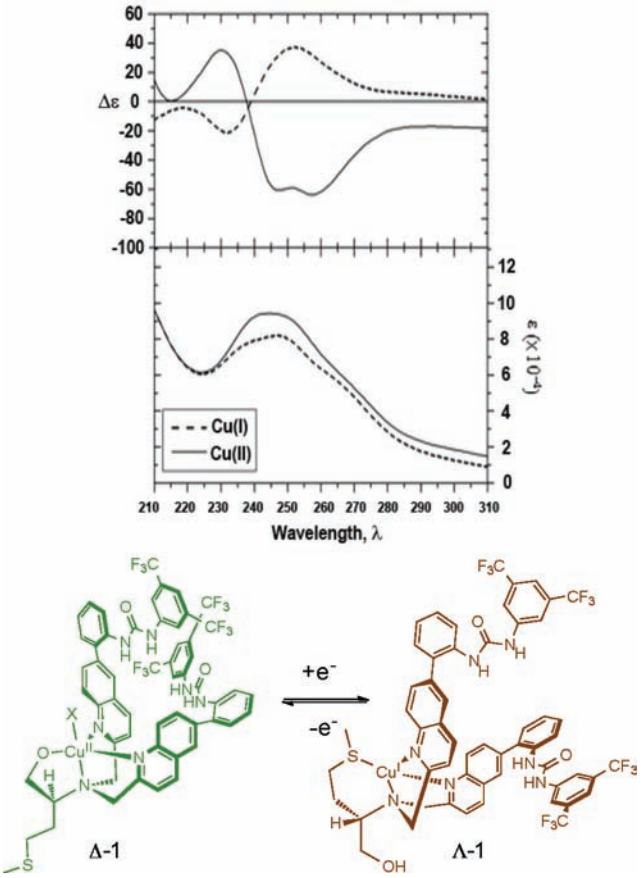
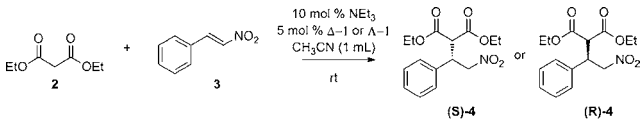


Figure 2. Redox-triggered switching between **Δ−1** and **Λ−1**. CD (L mol^{-1} cm^{-1}) and UV (L mol^{-1} cm^{-1}) of **Δ/Λ−1** (59 uM, acetonitrile).

Encouraged by spectroscopic evidence indicating helical chirality inversion, the catalytic behavior of **Δ−1** was assessed. The Michael addition of diethyl malonate (**2**) to *trans*-*β*-nitrostyrene (**3**, Scheme 1) has high synthetic utility as such

Scheme 1. Asymmetric Conjugate Addition Reaction



Michael adducts[16] have previously shown to be amenable to catalysis by several thio(urea) organocatalysts.[17] We envisioned that the urea moieties of **Δ−1** and **Λ−1** should lead to nearly enantiomeric transition states allowing the user to choose between (*S*)-**4** or (*R*)-**4** simply by choosing the redox state of the copper ion.

To test the catalytic ability of **Δ−1**, a solvent screen was performed using 1 mL of solvent, 10 mol % NEt_3, and 5 mol % catalyst **Δ−1** at room temperature (Table 1). Of the solvents tested, acetonitrile provided the highest yield (55%) and ee (72%) of product (*S*)-**4** (Figure 3). Significantly, in the presence of **Δ−1** all solvents screened yielded product (*S*)-**4**. The same reaction, using 5 mol % of **Λ−1** as the catalyst, demonstrated a preference for enantiomeric product (*R*)-**4** in all of the solvents tested. Remarkably, a similar ee (70%) was obtained in acetonitrile compared to the result with **Δ−1**. Several amine bases were examined (Table 2) that gave the

Table 1. Solvent Dependence of Catalyzed Reaction[a]

	Δ−1		**Λ−1**	
solvent	% ee of (*S*)-**4**[b]	% yield of **4**[c]	% ee of (*R*)-**4**	% yield of **4**
toluene	24	55	51	33
THF	48	33	57	78
MeCN	72	55	70	40
$CHCl_3$	30	40	68	34
CH_2Cl_2	46	44	74	43
hexane	51	30	60	30

[a]All reactions were carried out using diethylmalonate **2** (0.68 mmol, 2 equiv), *β*-nitrosytrene **3** (0.34 mmol, 1 equiv), and NEt_3 (0.034 mmol, 0.1 equiv) in solvent (1 mL) with 5 mol % catalyst (**Δ−1** or **Λ−1**) at room temperature for 24 h. [b]Determined by chiral HPLC analysis. [c]Isolated yields

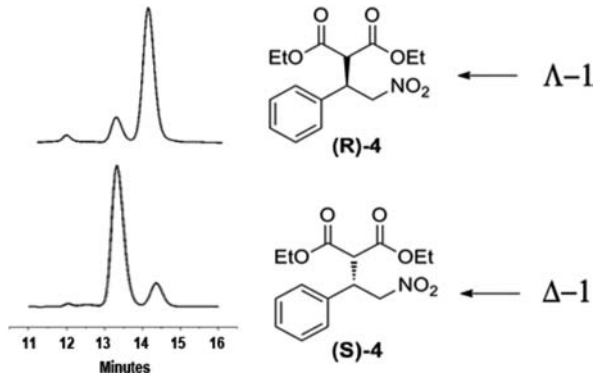


Figure 3. HPLC traces of reaction product when using both forms of the catalyst in acetonitrile.

Table 2. Base Screen for Different Complex Oxidation States[a]

	Δ−1		**Λ−1**	
base	% ee of (*S*)-**4**[b]	% yield of **4**[c]	% ee of (*R*)-**4**	% yield of **4**
NEt_3	72	55	70	40
DIPEA	70	38	56	32
DABCO	66	44	30	48
DBU	34	40	7	34
DMAP	57	21	31	32

[a]All reactions were carried out using diethylmalonate **2** (0.68 mmol, 2 equiv), *β*-nitrosytrene **3** (0.34 mmol, 1 equiv), and base (0.034 mmol, 0.1 equiv) in MeCN (1 mL) with 5 mol % catalyst (**Δ−1** or **Λ−1**) at room temperature for 24 h. [b]Determined by chiral HPLC analysis. [c]Isolated yields.

same enantiomer product, with more nucleophilic bases affording lower yields and ee. This may be due to competitive catalysis of the competing anionic polymerization of the *trans*-*β*-nitrostyrene starting material.[18]

We then set out to test the effects of catalyst loading, concentration, and temperature (Table 3). Changes in temperature and concentration appeared to have little effect on the ee and yield of the reaction. Interestingly, increasing the loading of the catalyst to 10 mol % (entry 3) caused no change in enantioselectivity. The catalyst still proved to be effective at 0.5 mol % loading (entry 5) producing (*S*)-**4** at 62% ee. The yield in this case may benefit from the lower concentration of base used. Control experiments indicate that the free ligand catalyzes the reaction (entry 8), which is consistent with electrophilic catalysis provided by the urea groups and suggests

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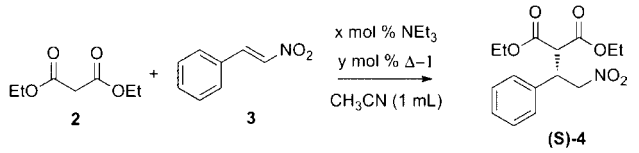
Table 3. Effects of Concentration and Loading[a]



				Δ−1	
entry	*x*	*y*	conc Δ−1 (mM)	% ee[b]	% yield of (*S*)-4[c]
1	10	5	17	72	55 (75)[f]
2	10	5	34	70	50
3	10	10	34	72	39
4[d]	10	5	34	74	52
5	2	0.5	1.7	62	67
6	10	0	n/a	<1	18
7	0	5	17	n/a	<1
8[e]	10	5	17	20	44

[a]All reactions were carried out using diethylmalonate **2** (0.68 mmol, 2 equiv) and *β*-nitrosytrene **3** (0.34 mmol, 1 equiv) in MeCN (1 mL) with catalyst (**Δ−1** or **Λ−1**) at room temperature for 24 h unless otherwise noted. [b]Determined by chiral HPLC analysis. [c]Isolated yield. [d]Reaction at 0 °C. [e]Reaction carried out with free ligand. [f]NMR yield.

that the copper is not involved directly in catalysis. Enantioselectivity is poor, however, in the absence of scaffolding provided by the copper ions.

As reducing agents such as ascorbate are capable of reconfiguring similar Cu^{2+} complexes,[15] we sought to determine whether the **Δ−1** complex could be reduced in situ to the **Λ−1** form and used to catalyze the same reaction. This was accomplished by stirring a mixture of ascorbate, NEt_3, and **Δ−1** and isolating the resulting **Λ−1** complex after an hour by precipitation. Nearly the same results (43% yield (***R*****)-4**, 71% ee) were obtained when performing the conjugate addition (Scheme 1) with the in situ reduced complex. It is of interest that Et_3N significantly solubilizes the Cu^{2+} complex in the solvents tested.

The exact mechanism of catalysis in the reaction is not known. The urea groups are capable of binding both the diethyl malonate (**2**) and *trans*-*β*-nitrostyrene (**3**) reactants.[20] Whether one or both urea groups play a role in the transition state is not yet clear. Molecular models (Figure 4) suggest that the urea moieties in **Δ−1** and **Λ−1** form pseudo-enantiomeric clefts, but the available space may not accommodate simultaneous hydrogen bonding of both reagents. The ligand alone in the absence of copper ion is far more flexible than the complex and likely positions the urea groups further away from one another, yet the yield of the reaction is similar to that using the complex (Table 3, entry 8). Monitoring the reaction by ^1H NMR revealed the half-life of the reaction catalyzed by free ligand to be half that of the **Δ−1** complex. This may suggest that both urea groups do not act in concert in the transition state. Further mechanistic studies are underway.

In summary, we have developed a new asymmetric urea catalyst that is capable of helical chirality inversion. ECCD techniques were used to establish that switching event was dependent on the oxidation state of a coordinated copper atom. The enantioselectivity of the asymmetric conjugate addition of diethyl malonate to *trans*-*β*-nitrostyrene was found to depend on the helicity of the catalyst. The reconfiguration allows the user to select either product enantiomer without a requirement to produce both enantiomers of the catalyst. This could be beneficial by obviating the requirement for a parallel synthesis of the opposite enantiomer, offering economic or environmental benefit depending on scale, and especially if one enantiomer is derived from an unnatural chiral source. The ambidextrous nature of the catalyst is persistent, using several different solvents and bases. Either complex is available by simply mixing ligand with the appropriate metal salt, or the **Δ−1** complex can be reduced chemically to the less air stable **Λ−1** complex and used to catalyze the conjugate addition reaction. The potential for dynamic control of enantioselectivity offers intriguing possibilities for future applications.

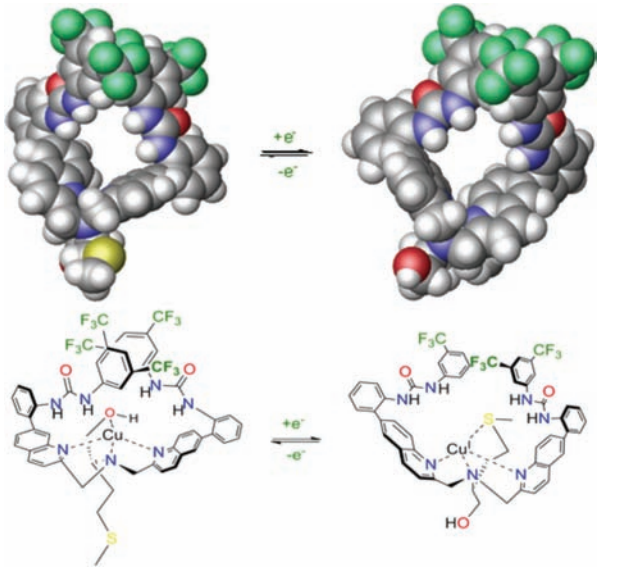


Figure 4. Space filling model of **Δ−1** (left) and **Λ−1** (right) derived by modifying X-ray coordinates of related structures.[19]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic procedures and characterization data. 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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