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Catalytic Asymmetric Transfer Hydrogenation of α-Ketoesters with Hantzsch Esters

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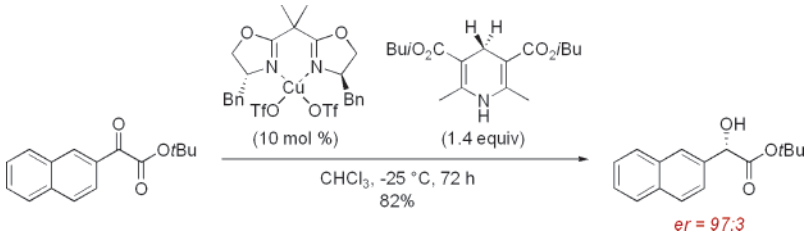
ABSTRACT



***C*$_2$-symmetric chiral copper(II)-bisoxazolines function as alcohol dehydrogenase mimics and catalyze highly enantioselective transfer hydrogenations of α-ketoesters with Hantzsch esters as a synthetic NADH analogue to give α-hydroxy esters in excellent enantioselectivities.**

The enantioselective reduction of α-ketoesters is a useful method for the preparation of optically active α-hydroxy esters, which are of considerable significance in the pharmaceutical, cosmetic, and chemical industries, e.g., as chiral building blocks.[1] Commonly used methodologies to access optically active α-hydroxy esters and their derivatives include the use of chiral boranes,[2] diastereoselective reductions involving chiral auxiliaries,[3] homogeneous asymmetric catalytic hydrogenations and hydrogen transfer reactions,[4] heterogeneous catalytic enantioselective hydrogenations such as those with Pt cinchona modifiers,[5] enzymatic or biomimetic methods,[6] and (dynamic) kinetic resolution of racemic α-hydroxy esters.[7]

Recently, we have developed catalytic enantioselective transfer hydrogenations employing readily available achiral

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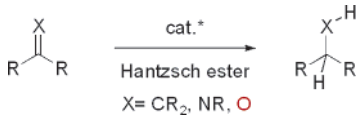
Hantzsch esters as the hydrogen source. Successfully used substrates contain either C=C or C=N bonds.[8] Here we extend these studies to the reduction of compounds with a C=O bond. We found that C_2-symmetric chiral Cu(II)-bisoxazoline complexes catalyze the enantioselective reduction of *tert*-butyl-α-ketoesters to the corresponding alcohols in high enantioselectivities (Scheme 1).

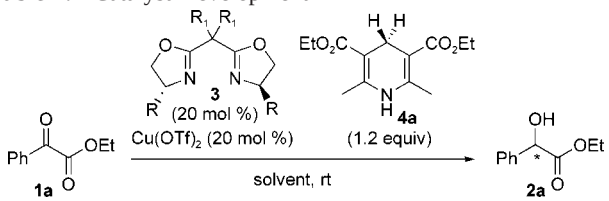
Scheme 1. Asymmetric Transfer Hydrogenation of C=C, C=N, and C=O with a Hantzsch Ester



C_2-symmetric chiral Lewis acidic Cu(II)-bisoxazoline complexes are versatile catalysts for asymmetric carbon−carbon and carbon−heteroatom bond formations such as Diels−Alder,[9] aldol,[10] cycloaddition,[11] ene,[12] Michael,[13] amination,[14] Friedel−Crafts,[15] Henry,[16] Mannich,[17] benzoylation,[18] Claisen rearrangement,[19] and allylic oxidation reactions.[20,21] These catalysts work particularly well with chelating substrates such as glyoxalates. We reasoned that Cu(II)-bisoxazoline complexes may also be suitable for the reduction of α-ketoesters if combined with the established hydride delivery potency of Hantzsch esters.[22] In this sense, such a system could be described as an alcohol dehydrogenase mimic,[23] the Cu(II)-bisoxazoline complex functioning as the zinc-metalloenzyme equivalent and the Hantzsch ester mimicking the NADH cofactor. Previously, such Lewis acid mediated reductions have been described only using a stoichiometric amount of chiral Hantzsch esters.[6e−i]

Preliminary studies led us to determine that $Cu(OTf)_2$, in combination with certain chiral bisoxazoline ligands and Hantzsch ester **4a**, gave appreciable reactivity and enantioselectivity in the reduction of ketone **1a** (Table 1). As revealed in Table 1, exposure of ethyl benzoylformate to commercially available Hantzsch ester **4a** in the presence of a catalytic amount of $Cu(OTf)_2$ and box ligands **3a**−**e** resulted in an inefficient (≤20%) reduction (Table 1, entries 1−5). In contrast, a dramatic increase in reaction efficiency and enantioselectivity was achieved using the [(*S*,*S*)-benzyl-box **3f**]−$Cu(OTf)_2$ complex (entry 8, 91:9 er). A survey of reaction media for this reduction revealed that $CHCl_3$

Table 1. Catalyst Development



entry	ligand	R	R_1	solvent	yield (%)[a]	er[b]
1	**3a**	^{t}Bu	H	CH_2Cl_2	<5	nd
2	**3b**	Ph	H	CH_2Cl_2	<5	nd
3	**3c**	Bn	H	CH_2Cl_2	<5	nd
4	**3d**	^{t}Bu	Me	CH_2Cl_2	<5	nd
5	**3e**	Ph	Me	CH_2Cl_2	20	91:9
6	**3f**	Bn	Me	CH_2Cl_2	80	90:10
7	**3f**	Bn	Me	THF	80	92:8
8	**3f**	Bn	Me	$CHCl_3$	90	91:9

[a] Isolated yield. [b] Determined by chiral HPLC analysis on a Chiralcel OD-H column.

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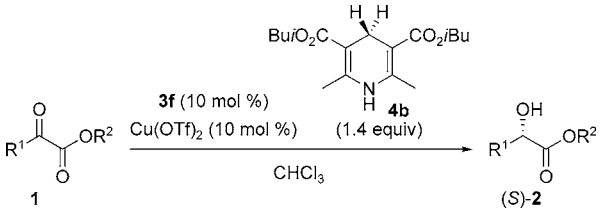
provides the highest yield and reaction rate at room temperature (Table 1, entry 8, 90% yield). The utility of various Hantzsch esters has been investigated (see Supporting Information). Diisobutyl ester **4b** showed the highest reaction rate without significantly lowering the enantioselectivity (Table 2).

Table 2. Cu(II)-bisoxazoline-Catalyzed Asymmetric Transfer Hydrogenation of α-Ketoesters[a]



entry	1/2	R_1	R_2	temp (°C)	time (h)	yield (%)[b]	er[c]
1	**b**	Ph	Me	rt	12	90	91:9
2	**c**	Ph	Bn	rt	5	90	89:11
3	**d**	Ph	^{t}Bu	rt	3	96	91:9
4	**d**	Ph	^{t}Bu	−25	48	89	96:4
5	**e**	4-NO_2-C_6H_4	^{t}Bu	−25	36	94	90:10
6	**f**	4-Cl-C_6H_4	^{t}Bu	−25	48	93	94:6
7	**g**	4-Me-C_6H_4	^{t}Bu	−25	48	80	96:4
8	**h**	4-MeO-C_6H_4	^{t}Bu	−25	72	83	97:3
9	**i**	2-naphthyl	^{t}Bu	−25	72	82	97:3
10	**j**	2-furyl	^{t}Bu	−25	72	80	97:3
11[d]	**k**	Cy	^{t}Bu	−25	72	72	90:10
12[d]	**l**	^{t}Bu	^{t}Bu	−25	72	71	92:8

[a] The reactions were run with a catalyst prepared in situ from chiral ligand **3f** and $Cu(OTf)_2$ (each 10 mol %), substrates **1** (0.5 mmol), and Hantzsch ester **4b** (1.4 equiv) in $CHCl_3$ (2.5 mL) at −25 °C under argon. [b] Yield of the isolated product. [c] Determined by chiral HPLC or GC analysis. [d] 20 mol % of the catalyst was used in this case.

We also examined the influence of the size of the ester group of the substrate (Table 2, entries 1−3). Interestingly, we found that, compared to the methyl and benzyl ester, the *tert*-butyl ester group in the substrate significantly improved the reactivity. After further optimization, which included lowering the catalyst loading to 10 mol % and the reaction temperature to −25 °C, a number of *tert*-butyl α-ketoesters could be reduced with good to excellent results (Table 2, entries 4−12).[24] In general, if the substrates contain an R^1 = aryl residue, enantiomeric ratios exceeded 95:5. Reduced enantioselectivity was observed only with the 4-nitro-substituted substrate, possibly due to competing coordination of the nitro group to the copper catalyst. Aliphatic α-ketoesters are also suitable substrates but gave slightly lower enantioselectivities (Table 2, entries 11 and 12).

Consistent with previously suggested transition-state models,[25] the observed sense of asymmetric induction can be explained with a square planar transition state as shown in Figure 1. In this complex, two glyoxylate carbonyl oxygen

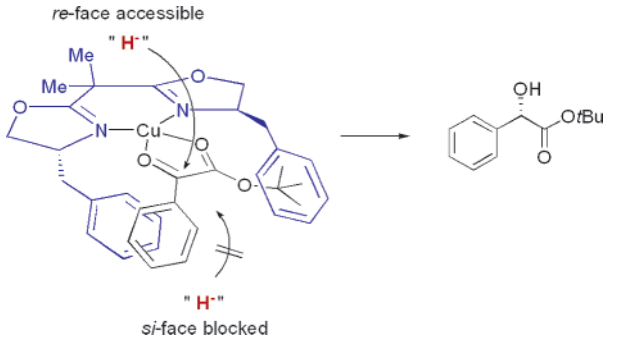


Figure 1. Proposed transition state.

atoms and the bisoxazoline ligand each chelate the Cu(II) ion. The *si*-face of the coordinated substrate is blocked by a benzyl group of the bisoxazoline ligand, leading to a preferential nucleophilic attack of hydride to its *re*-face.

In summary, we have developed a highly enantioselective reduction of α-ketoesters **1** with Hantzsch ester **4b** as a biomimetic hydrogen donor and a Cu(II)-bisoxazoline complex as the chiral catalyst. Further work on expanding the range of suitable substrates to include other carbonyl compounds such as nonactivated ketones for our asymmetric reduction is in progress.

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

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(24) General procedure for Cu(II)-bisoxazoline-catalyzed asymmetric transfer hydrogenation of α-ketoesters with Hantzsch esters: To a flame-dried Schlenk tube was added $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) and [(*S*,*S*)-benzyl-box] **3f** (18.1 mg, 0.05 mmol). The mixture was dried under a vacuum for 0.5 h, and distilled anhydrous $CHCl_3$ (2.5 mL) was added. After stirring for 1 h, *tert*-butyl benzoylformate **1d** (103.1 mg, 0.5 mmol) was added and the mixture was cooled to −25 °C. After addition of Hantzsch ester **4b** (216.6 mg, 0.7 mmol), the mixture was stirred under argon at the same temperature until disappearance of the starting material (48 h). After conclusion of the reaction, the mixture was washed using H_2O and the aqueous layer was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo to yield the crude product as an off-white solid. Purification by column chromatography (15% EtOAc/hexanes) gave the pure product as a white solid (92.2 mg, 89%), identical in all respects to previously described *tert*-butyl (*S*)-mandelate **2d**. $[\alpha]_D$ +90.7 (*c* 1.0, MeOH) [$[\alpha]_D$ +97.4 (*c* 1.0, MeOH), for >99:1 er].

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