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Novel thiolated amino-alcohols as chiral ligands for copper-catalyzed asymmetric nitro-aldol reactions

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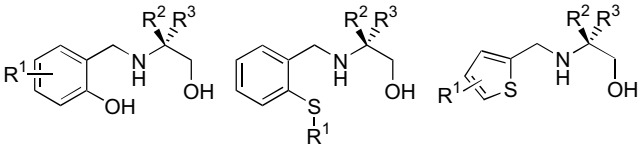
Abstract—Thiolated amino-alcohols have been synthesized and evaluated as a potential new class of chiral ligands for copper-catalyzed nitro-aldol reactions. The model nitro-aldol reaction took place smoothly at ambient temperature in the presence of catalytic amounts (5–15 mol %) of the ligands and copper(II) acetate to afford the nitro-aldol product in good to excellent yield without accompanying dehydration. Amino-alcohol ligands bearing *N*-(2-alkylthio)benzyl substituents provided only modest enantioselectivities (22–46% ee) while those carrying *N*-2-thienylmethyl substituents provided better enantioselectivities (up to 75% ee). A range of aromatic aldehydes were acceptable for the nitro-aldol reaction with nitromethane, giving moderate to good enantioselectivities (69–88% ee).

The nitro-aldol reaction is an important route for carbon–carbon bond formation. Nitro-aldol products, especially in optically active forms, are valuable intermediates for the synthesis of biologically active compounds.[1] The first catalytic asymmetric nitro-aldol reaction was reported in 1992.[2] Despite its long history, relatively few chiral ligands have been successfully employed for catalytic asymmetric nitro-aldol reactions. Binaphthols[2] or amino-alcohols[3–7] have typically been used in combination with Li-lanthanides or dialkylzinc. Only very recently have combinations of nitrogen-based ligands and transition metals emerged as catalyst systems for asymmetric nitro-aldol reactions[8–13] following pioneering work by Jorgensen[14] and Evans.[15] Chiral organocatalysts constitute another class of catalyst emerging for asymmetric nitro-aldol reactions.[16–18] Often, such catalysts are large and complex molecules containing multiple stereogenic centers and, hence, are difficult to obtain on a large scale, especially when both enantiomers are desired. Furthermore, reactions involving highly reactive lanthanoid or zinc complexes usually require low temperature and anhydrous conditions. The use of transition metal catalysts is particularly attractive since it enables the reactions to be carried out at or close to ambient temperature without the requirement for strictly anhydrous conditions.



1 **2** **3**

Recently we discovered that simple tridentate chiral amino-alcohols **1** are effective ligands for titanium-catalyzed asymmetric Strecker reactions.[19] A related asymmetric cyanosilylation of aldehydes by **1** has also been reported.[20] We considered that substitution of one or more of the hard oxygen atoms of **1** with soft donor atoms like sulfur would lead to ligands such as **2** and **3** having affinities for copper and might be better chiral ligands for copper-catalyzed asymmetric reactions.

Ligand **2** was viewed as a logical starting point for the development of thiolated amino-alcohols related to ligand **1**. Ligand **2a** ($R^1 = 4\text{-}ClC_6H_4$; $R^2 = Bn$; $R^3 = H$) was prepared from readily available starting materials

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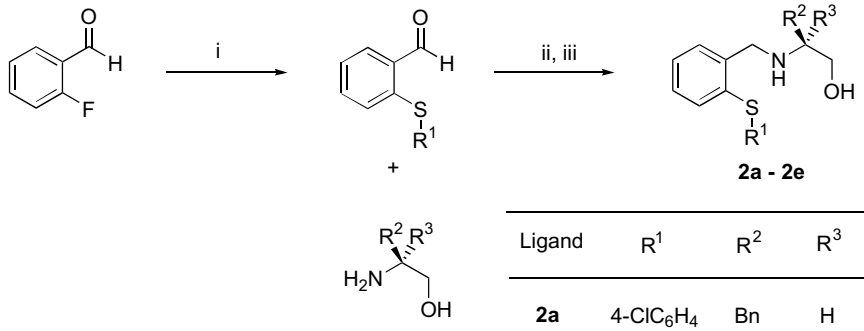
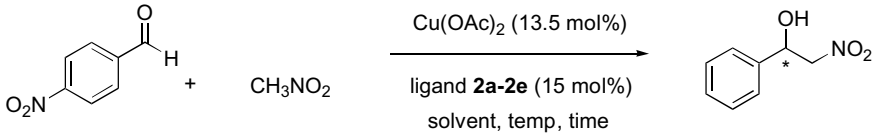


Ligand	R^1	R^2	R^3	yield(%)
2a	4-ClC_6H_4	Bn	H	85
2b	C_6H_5	H	Ph	73
2c	C_6H_5	^{t}Bu	H	80
2d	Et	H	Ph	87
2e	Me	H	Ph	83

Scheme 1.

as outlined in Scheme 1. When 2-fluorobenzaldehyde reacted with 4-chlorothiophenol, the thiolated aldehyde was obtained in 61% yield. Sodium borohydride reduction of the Schiff base formed in situ between the aldehyde and L-phenylalaninol afforded the desired ligand in 85% yield. Ligands **2b–e** with different sulfur substituents (R^1) and amino-alcohol substituents (R^2, R^3) were similarly prepared from appropriate thiolated aldehydes and chiral amino-alcohols. All ligands were stable crystalline solids. When a suspension of copper(II) acetate in toluene was treated with 1 equiv of ligand **2a**, a bright blue color was observed in the toluene phase suggesting that the ligand had formed a toluene-soluble complex with copper(II) ion. We were pleased to find that this complex efficiently catalyzed the reaction between 4-nitrobenzaldehyde and nitromethane to provide the nitro-aldol product in 69% yield after 48 h. However, the enantioselectivity as determined by chiral HPLC (Chiralcel OD) was only modest (26%). Attempts to optimize the reaction parameters including varying solvent and temperature suggested that 2-propanol was the solvent of choice and a reaction temperature of 30 °C provided a balance between good reactivity and high selectivity. Under these optimal conditions, a 90% yield of the nitro-aldol product with enantioselectivity of up to 30% was obtained in the presence of 13.5 mol % of $Cu(OAc)_2$ and 15 mol % of ligand **2a**. Changing the steric nature of the sulfur substituent (R^1) resulted in no significant improvement in terms of yield and enantioselectivity (Table 1). A slightly improved enantioselectivity was observed on replacing the benzyl group in **2a** with a phenyl group in **2b**. On the other hand, substitution with the more sterically hindered ^{t}Bu group resulted in a negligible enantioselectivity. In all cases no significant amount of the 2-nitroalkene dehydration product was observed.

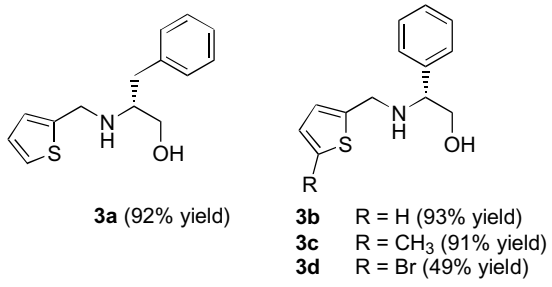
Table 1. Evaluation of amino-alcohols **2a–2e** as chiral ligands in copper-catalyzed asymmetric nitro-aldol reactions[21]



Entry	Ligand	Solvent	Time (h) (temp (°C))	% Yield	% ee[a] (abs. config.)[b]
1	**2a**	Toluene	48 (30)	69	26 (*R*)[c]
2	**2a**	CH_2Cl_2	48 (30)	76	22 (*R*)[c]
3	**2a**	^{i}PrOH	48 (30)	90	30 (*R*)[c]
4	**2b**	^{i}PrOH	48 (30)	92	35 (*S*)[c]
5	**2b**	^{i}PrOH	24 (30)	92	35 (*S*)[d]
6	**2b**	^{i}PrOH	192 (0)	89	46 (*S*)[d]
7	**2c**	^{i}PrOH	24 (30)	90	0[d]
8	**2d**	^{i}PrOH	24 (30)	88	29 (*S*)[d]
9	**2e**	^{i}PrOH	24 (30)	87	24 (*S*)[d]

[a] Determined by chiral HPLC (Chiralcel OD).
[b] Determined by comparison of optical rotation value and retention time (chiral HPLC) with literature values.
[c] 55 equiv of CH_3NO_2 was employed.
[d] 10 equiv of CH_3NO_2 was employed.

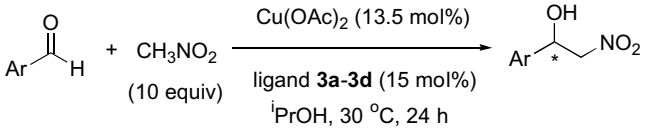
A considerable improvement was achieved when copper complexes of thiophene-substituted amino-alcohols **3a** and **3b** were used as catalysts. The ligands were prepared in 92% and 93% yield, respectively, by $NaBH_4$ reduction of the imine formed in situ from thiophen-2-carbaldehyde and the appropriate amino-alcohols as described for **2a**–**2e** (Scheme 2). Under the same screening conditions, ligand **3a** provided the nitro-aldol product in 87% yield and 53% ee (Table 2, entry 1). By changing the substituent R^3 from benzyl in **3a** to the more bulky phenyl group in **3b**, 97% yield and 75% ee of the nitro-aldol product was obtained (entry 2). A comprehensive optimization of the reaction condition (solvent, temperature, metal, and source of copper) was performed again on ligand **3b**, but this only confirmed the conditions previously used as optimal. The 5-methyl- and 5-bromo-substituted thiophene ligands **3c** and **3d** were also prepared and evaluated, but no improvement in enantioselectivity was observed (entries 3–4). To further demonstrate the generality of ligand **3b** in catalyzing nitro-aldol reactions, a few other aldehydes were employed as substrates (entries 5–10). It was found that aromatic aldehydes carrying both electron-withdrawing and electron-donating substituents were acceptable substrates. In most cases the products were obtained in good yields and enantioselectivities ranging from 69% to 88% as determined by chiral HPLC. Importantly, good enantioselectivities and reaction rates were still achieved when the amounts of ligand **3b** and $Cu(OAc)_2$ were reduced to 10 and 5 mol % (entries 11 and 12).



Scheme 2.

Only a few thiophene-based ligands have previously been employed in nitro-aldol reactions[22,23] or other asymmetric reactions.[24,25] The unsubstituted D-phenylglycinol provided only a low yield and an essentially racemic product (3% ee) when employed as ligand for the nitro-aldol reaction of 4-nitrobenzaldehyde and nitromethane. The copper complex of the non-thiolated ligand **1a** (R^1, $R^3 = H$; $R^2 = Bn$) also catalyzed the reaction enantioselectively, although to a rather poor extent (25% ee). In addition, the sense of asymmetric induction was opposite to that provided by the thiolated ligand possessing the same absolute configuration. Copper(II) acetate is a poor catalyst for this reaction in the absence of a ligand.[26] This finding suggested that the thiophene and thiobenzyl substituents must play an active role in both accelerating and governing the stereochemical outcome of the nitro-aldol reaction. The marked difference in enantioselectivity provided by 2-alkylthiobenzyl ligands **2** and 2-thienylmethyl ligands **3** is not yet fully understood. Unlike thiols and thioethers, thiophene has been described as a weakly coordinating ligand hence the Cu–S bond lengths in Cu-thioether and Cu-thiophene complexes can be quite different.[27] The detailed understanding of the nature of the copper species that catalyzes the reaction will be the subject of our next investigation.

Table 2. Evaluation of amino-alcohols **3a**–**d** as chiral ligands in copper-catalyzed asymmetric nitro-aldol reaction[21]



Entry	Ligand	Ar	% Yield	% ee[a] (abs. config.)[b]
1	**3a**	4-$O_2NC_6H_4$	87	53 (*S*)
2	**3b**	4-$O_2NC_6H_4$	97	75 (*S*)
3	**3c**	4-$O_2NC_6H_4$	92	63 (*S*)
4	**3d**	4-$O_2NC_6H_4$	97	66 (*S*)
5	**3b**	C_6H_5	77[c]	69 (*S*)
6	**3b**	4-$F_3CC_6H_4$	93	78 (*S*)
7	**3b**	2-$MeOC_6H_4$	85[c]	75 (*S*)
8	**3b**	2-$O_2NC_6H_4$	98	85 (*S*)
9	**3b**	2-$F_3CC_6H_4$	91	88 (*S*)
10	**3b**	2-FC_6H_4	92	83 (*S*)
11	**3b**[d]	4-$O_2NC_6H_4$	94	70 (*S*)
12	**3b**[e]	4-$O_2NC_6H_4$	96	69 (*S*)

[a] Determined by chiral HPLC (ChiralCel OD or ChiralCel OJ-H).
[b] Determined by comparison of optical rotation value and retention time (chiral HPLC) with literature values for Ar = 4-$O_2NC_6H_4$ and 2-$O_2NC_6H_4$.[15] Absolute configurations of other compounds were proposed by analogy.
[c] Reaction time was 48 h.
[d] 10 mol % ligand and 10 mol % $Cu(OAc)_2$.
[e] 5 mol % ligand and 5 mol % $Cu(OAc)_2$.

In conclusion, we have developed a series of chiral thiolated amino-alcohols as a potential new class of ligands for copper-catalyzed nitro-aldol reactions. The chiral amino-alcohols carrying *N*-2-thienylmethyl substituent provided much better enantioselectivities compared to those with *N*-(2-alkylthio)benzyl substituent for the nitro-aldol reaction between 4-nitrobenzaldehyde and nitromethane. A range of aromatic aldehydes were acceptable substrates giving moderate to good enantioselectivities (up to 88% ee).

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Supplementary data

General experimental protocols for the syntheses, spectroscopic, and analytical data of compounds **2a**–**e** and **3a**–**d** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.072.

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