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Novel unsymmetric chiral Schiff bases possessing two different donor moieties: unique tetradentate ligands from combination of salicylaldehyde and acetylacetone units

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Abstract

A new class of novel chiral Schiff base ligands has been developed using a stepwise approach. The key feature of these new ligands is that they possess two different donor units, one of them is aromatic while the other is non-aromatic.

The chiral chelating ligands that afford metal centers with a chiral environment are essential components for the development of chiral catalysts. Chiral Schiff bases have received considerable interest since they are one of the most effective classes of ligands leading to high performance chiral catalysts such as Jacobson catalyst from **1**.[1,2] Tetradentate ligands such as **1** have been widely studied because of their facile synthesis via direct condensation of one equivalent of chiral diamine and two equivalents of a salicylaldehyde derivative. Very few chiral tetradentate Schiff base ligands prepared from a chiral diamine and two different salicylaldehyde derivatives have appeared in the literature, until our recent report of tetradentate Schiff base ligands such as **2**.[3] These ligands were prepared in two steps, involving the initial preparation of a chiral half unit **4**[3] by condensation of (1*R*,2*R*)-(−)-diaminocyclohexane with salicylaldehyde (Scheme 1), followed by condensation of **4** with a salicylaldehyde derivative. In light of the reactivity of **4** towards aromatic salicylaldehyde derivatives, we decided to examine the reactivity of the free amine group in **4** with 1,3-diketones in an attempt to prepare ligands with mixed donors. We report here a unique class of new chiral tetradentate ligands **3** prepared based upon **4** and its analogue **5** with 1,3-diketones. Of particular interest is the development of synthetic methodology for the preparation of the ligands **3** from trifluoromethyl-containing 1,3-diketones.

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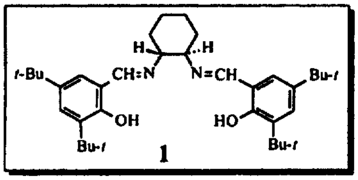

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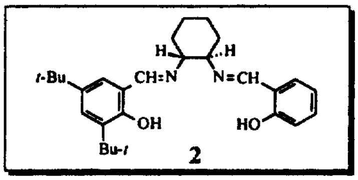

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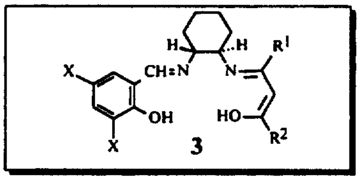

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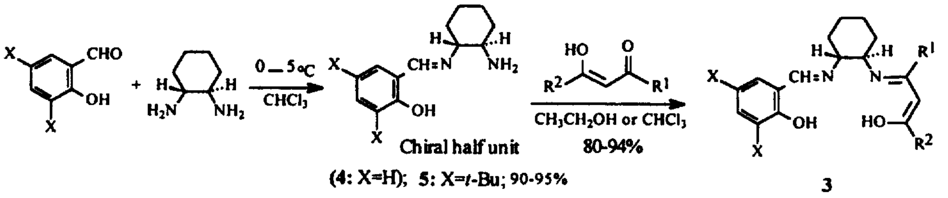
We first examined the reaction of the readily available chiral half unit **4** with 2,4-pentanedione. Thus, addition of an ethanol solution of 2,4-pentanedione to an ethanol solution of **4** at room temperature, followed by heating the mixture at 60°C for 6 hours afforded **3a** (entry 1, Table 1) in 94% isolated yield.[4] This reaction also proceeded smoothly in chloroform giving **3** in high yield (entry 2, Table 1). Based upon this initial success, we examined the reaction of **4** with 1-phenyl-1,3-butanedione, which bears two different keto-units (PhCO and CH_3CO). This reaction could give a mixture of two products. However, we found that the reaction is very chemoselective, giving only **3b** (entries 3 and 4, Table 1), which resulted from the selective condensation with the methyl ketone, and no product was obtained from the reaction with the phenyl ketone.



Scheme 1. For preparation of the chiral half unit **5** and Schiff base ligands **3**

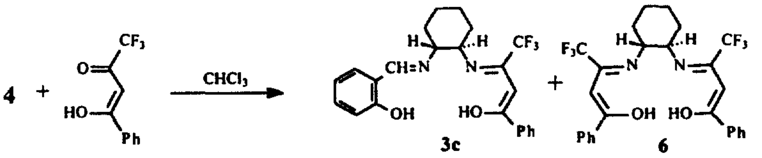
The chemoselectivity observed with 1-phenyl-1,3-butanedione is consistent with the known higher reactivity of an acetyl group relative to a benzoyl group. The 1,3-diketones used in reactions are not in pure diketone form, but in dynamic equilibrium of the diketone and ketone enol. As a matter of fact, the majority of 1,3-diketones is in ketone/enol form, for instance, 85–87% of 2,4-pentanedione is the enol form[5] while $PhCOCH_2COCH_3$ is 90.2–90.7%[6] in the enol form in chloroform. Benzoyl in the latter may actually exist in a stable enol form since the adjacent phenyl stabilizes the conjugation.

We have observed similar chemoselectivity in the reaction of 4,4,4-trifluoro-1-phenyl-1,3-butanedione with **4** in ethanol, which led to **3c** in 82% yield (entry 5, Table 1). In addition, this reaction also gave the symmetric Schiff base **6** in low yield as a byproduct (Scheme 2), indicating that a partial cleavage of the

Table 1
Summary of reactions of the chiral half units with 1,3-diketones

Entry	3	X	R^1	R^2	Reaction time (h)	Temp (°C)	Solvent	Yield (%) of 3	Others
1	**3a**	H	Me	Me	5	60	EtOH	94	
2	**3a**	H	Me	Me	5	60	$CHCl_3$	91	
3	**3b**	H	Me	Ph	5	60	EtOH	89	
4	**3b**	H	Me	Ph	5	60	$CHCl_3$	99	
5	**3c**	H	CF_3	Ph	10	40	EtOH	82	**6** (8 %)
6	**3c**	H	CF_3	Ph	10	40	$CHCl_3$	80	**6** (13 %)
7	**3d**	*t*-Bu	Me	Me	5	60	$CHCl_3$	91	
8	**3e**	*t*-Bu	Me	Ph	5	60	EtOH	88	
9	**3f**	*t*-Bu	CF_3	Ph	10	40	$CHCl_3$	87	**6** (<1%)

half unit had taken place. A similar result was obtained when ethanol was replaced with chloroform as the solvent (entry 6, Table 1). It appears that the unusual reactivity leading to the formation of **6** is unique to trifluoromethyl-containing 1,3-diketones since we have not observed occurrence of the cleavage with purely hydrocarbon 1,3-diketones, as shown in entries 1–4 (also *vide infra*). This is supported by the reaction of **4** with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione, which led to a considerable cleavage of the half unit, with none of the desirable mixed ligand isolated.



Scheme 2. For reaction of the chiral half unit with a typical fluoro-containing 1,3-diketone

With these significant results, we sought to prepare the chiral half unit **5** to extend the scope of the reaction since it has two bulky groups that could provide a steric fence. Treatment of one equivalent of 3,5-di-*t*-butylsalicylaldehyde with (*R,R*)-1,2-diaminocyclohexane gave the half unit **5** in 90–95% yield (Scheme 1).[7] When **5** was treated with 2,4-pentanedione or 1-phenyl-1,3-butanedione in a manner similar to that described for **4**, ligands **3d** and **3e** (entries 7–8, Table 1) were obtained in 91% and 88% yields, respectively. Reaction of **5** with 4,4,4-trifluoro-1-phenyl-1,3-butanedione gave **3f** in 87% yield (entry 9, Table 1) with the formation of only a trace of Schiff base **6**. Reaction of **5** with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione, in a manner similar to that described above, failed to produce any desirable Schiff base, leading only to the recovery of the original 3,5-di-*t*-butylsalicylaldehyde formed by the hydrolysis of **5**.

It is clear that reactions of **4** and **5** with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione can not lead to any desirable ligands **3g** and **3h** under the conditions described above (entries 1 and 3, Table 2). Various experiments have been designed to pursue these requisite ligands (Table 2). A successful approach has to be beyond consideration of solvent conditions because anhydrous systems do not prevent such hydrolysis of **4** and **5**. Although the exact mechanism has yet to be determined, we hypothesize that the hydrolytic process would be depressed if an excess of 1,1,1,5,5,5-hexafluoro-2,4-pentanedione present in the reaction would be minimized or eliminated since it would be the potential source to drive the hydrolytic process. Indeed, we found that slow addition of 1,1,1,5,5,5-hexafluoro-2,4-pentanedione into **5** led to the formation of ligand **3h**.[8] This approach was found to be even more effective at lower temperature (0°C), with the compound **3h** obtained in 83% yield (entry 4, Table 2). We also found that the use of molecular sieves can effectively promote the formation of Schiff base. The use of molecular sieves increased the yield of **3h** to 90% (entry 5, Table 2). When molecular sieves were applied to the reaction of **4** with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione, the ligand **3g** was attained in 92% yield (entry 2, Table 2). In addition to molecular sieves, other dehydrating reagents such as anhydrous potassium carbonate were also found to be effective (entry 6, Table 2).

This new class of chiral Schiff base ligands can be conveniently converted to metal complexes. We have successfully prepared the Cu(II), Ni(II), and Mn(III) complexes by reaction of these ligands with related metal salts. The investigation of their asymmetric catalytic properties is currently underway.

In conclusion, we have developed a stepwise synthetic protocol for the preparation of a new class of chiral tetradentate Schiff base ligands which contain mixed donors. Special achievement in effective control of hydrolysis has been made in the preparation of the ligands from trifluoromethyl-containing 1,3-diketones. In addition to potential significance in asymmetric catalysts, these ligands will also provide new sources of complexes for modulation of DNA binding/cleaving properties.[9]

Table 2
Reactions of the chiral half units with 1,1,1,5,5,5-hexafluoro-2,4-pentanedione

Entry	3	X	R^1	R^2	Conditions[a]	Reaction time (h)	Temp (°C)	Solvent	Yield (%)of **3**
1	**3g**	H	CF_3	CF_3	normal rate	10	0	$CHCl_3$	0
2	**3g**	H	CF_3	CF_3	slow rate & 4Å m.s.	20	20	$CHCl_3$	92
3	**3h**	*t*-Bu	CF_3	CF_3	normal rate	10	20	$CHCl_3$	0
4	**3h**	*t*-Bu	CF_3	CF_3	slow rate	5	0	$CHCl_3$	83
5	**3h**	*t*-Bu	CF_3	CF_3	slow rate & 4Å m.s.	10	20	$CHCl_3$	90
6	**3h**	*t*-Bu	CF_3	CF_3	slow rate & K_2CO_3	5	20	$CHCl_3$	90

Acknowledgements

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4. A typical procedure for **3a**: To an ethanol solution (20 mL) of the chiral half unit (1.1 mmol) was added dropwise[8] 2,4-pentanedione (1.1 mmol) in 10 mL of ethanol at ambient temperature. The mixture was gradually heated to 60°C and then this temperature was maintained for 5 hours. The solvent was removed under vacuum to give a yellow oil, which was redissolved in hot hexane. Upon cooling at −20°C, **3a** was collected with a pipette as a yellow oil and dried under vacuum, yield 0.31 g, 95%. Anal. for $C_{18}H_{24}N_2O_2$: C: 72.04, H: 7.81. Calcd C: 72.00, H: 8.00.
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7. The chiral half unit **5**: 3,5-di-*t*-butylsalicylaldehyde (6.38 mmol) in chloroform (50 mL) was added dropwise over 5 hours to a vigorously stirred solution of (1*R*,2*R*)-(−)-diaminocyclohexane (6.38 mmol) in chloroform (150 mL) containing 4 Å molecular sieves at 0°C to give a yellow solid, yield 1.94 g, 93%. For the detailed work-up, see Ref. 3.
8. Normal rate: addition completed within 5–10 minutes; slow rate: addition completed over 1 hour. All the reactions for trifluoromethyl-containing 1,3-diketones are run in anhydrous solvents.
9. For recent leading references for interaction of Schiff base complexes with DNA: Gravert, D. L.; Griffin, J. H. *Inorg. Chem.* **1996**, *35*, 4837.