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## Examination of Bidentate Thiol Derivatives as Ligands in the Ni-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Enones

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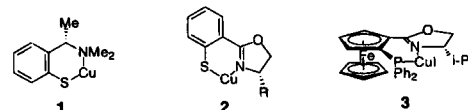
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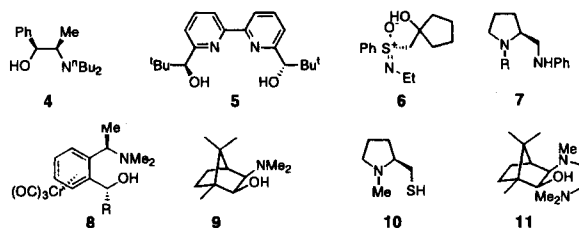
Among many highly successful asymmetric transformations, conjugate addition of alkyl group to enone lags far behind in terms of efficiency. Organocopper reagents which are the most useful reagents for racemic task have not been highly successful. Thus, development of chiral methodology which provide high levels of asymmetric induction would be especially a valuable addition. Over the last 25 years since the first attempt in 1972 by Kretschmer<sup>1</sup> to effect asymmetric conjugate addition of magnesium dialkylcuprates ( $R_2CuMgX$ ) in the presence of (-)-sparteine with optical yield of 3-6%, many approaches have been investigated to solve the problem of asymmetric conjugate addition of organocopper reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>2,3</sup> Despite of the increasingly important role of copper-mediated conjugate addition to  $\alpha,\beta$ -enones in organic synthesis, the rather slow improvement of this methodology is associated with the fact that the mechanistic details are unclear. Furthermore, many aspects of cuprate chemistry were unknown or poorly defined such as the effect of solvent and various salts on cuprate structure and reactivity.

In this regard, notable examples are some: van Koten *et al.*<sup>3</sup> described the catalytic conjugate addition using a chiral arenthiolatocopper(I) complex **1** (MeMgI, 4-phenyl-3-buten-2-one,  $\leq 57\%$  ee). Recently, is reported copper (I) thiolate complex **2** by Pfaltz (Grignard reagents, cyclopentenone (16-37% ee), cyclohexenone (60-72% ee), cycloheptenone (83-87% ee)) as enantioselective catalysts.<sup>3c</sup> And after our experiments were finished,<sup>4</sup> phosphine oxazoline complex **3**

was reported by Sammakia (n-BuMgCl, cyclopentenone (65% ee), cyclohexenone (83% ee), cycloheptenone (92% ee) and 4-phenyl-3-buten-2-one (81% ee)).<sup>3o</sup> Even though these reactions were successful with high level of enantioselectivity, except for some cases, it was not catalytic variants but stoichiometric amount of ligand was used.



One the other hand, Ni-catalyzed asymmetric 1,4-addition reactions are also known even though the mechanism for the reaction is even more elusive than the Cu-catalyzed reactions mentioned above. Following the leads by Luche,<sup>5</sup> who found that Ni(II) salts facilitate the conjugate addition of dialkylzinc to enones, and by Soai who reported that enantioselective Ni(II)-catalyzed conjugate addition of dialkylzinc reagents to prochiral enones and in the presence of



**Table 1.** Nickel(II)-catalyzed Enantioselective Conjugate Addition of Diethylzinc to *trans*-Chalcone

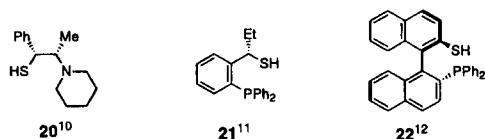
Entry	Ligand	NiX <sub>2</sub>	Solvent	Ni(mol %)	Ni:L*	Yield (%)	ee (%)
1	<b>20</b>	Ni(acac) <sub>2</sub>	CH <sub>3</sub> CN	2.5	1:2	77	62 <sup>a</sup>
2	<b>20</b>	NiCl <sub>2</sub>	CH <sub>3</sub> CN	1.5	1:20	50	74 <sup>a</sup>
3	<b>20</b>	Ni(acac) <sub>2</sub>	Toluene	2.5	1:2	53	20 <sup>a</sup>
4	<b>21</b>	Ni(acac) <sub>2</sub>	CH <sub>3</sub> CN	3.3	1:4	34	27 <sup>b</sup>
5	<b>21</b>	Ni(acac) <sub>2</sub>	Toluene	2.5	1:4	52	22 <sup>b</sup>
6	<b>22</b>	Ni(acac) <sub>2</sub>	Toluene	2.5	1:4	NR	

<sup>a</sup>(*S*)-configuration as a major enantiomer. <sup>b</sup>(*R*)-configuration as a major enantiomer.

chiral β-amino alcohol **4**,<sup>6</sup> several additional bidentate ligands, and even tri- and tetradentate ligands, have been reported.<sup>7</sup>

Herein, are reported our exploratory and preliminary results on application of chiral ligands in enantioselective conjugate addition to enone not only in catalytic but also in stoichiometric reactions. As a start, various multidentate ligands were examined in Cu(I)-catalyzed conjugate addition of PhMgCl to enones, especially *trans*-chalcone, a standard substrate in this transformation.<sup>6,7</sup> But best enantioselectivity obtained was 15%. The same reaction even with stoichiometric ligand for Cu gave less than 42% ee of the product.<sup>8</sup>

Since copper(I) has special affinity toward mercaptide and special interesting properties and the amino thiol **20** has been shown to be one of the best ligands for enantioselective addition of alkylzinc reagents to aldehydes,<sup>9,10</sup> several sulfur-containing compounds were examined such



as amino thiol **20**, and thiol phosphines **21** and **22**.

In spite of much efforts, no discernible enantioselectivity in Cu(I)-catalyzed conjugate addition of Grignard reagents and other organometallic compounds was obtained with these ligands. However, a nickel complex derived from Ni(acac)<sub>2</sub> and the amino thiol **20** catalyzed the conjugate addition of diethylzinc to *trans*-chalcone in useful asymmetric level. The ee of the product was 62%, which was determined by HPLC using chiral column (Daicel Chiralcel OD). Changing the solvent from acetonitrile to toluene lowered the enantiomeric excess of the product to 20%. In the case of thiol phosphine **21**, the reaction did not proceed to completion, and the ee yield was lowered to 22 and 27% (entry 4, 5).

In conclusion, nickel catalyzed enantioselective conjugate addition of diethylzinc to enone in the presence of amino thio ligands was known that the ee of the product was strongly dependent on the ligand concentration and nickel-to-ligand ratio. These reactions have not been studied sufficiently and many things should be investigated about enantioselective conjugate addition of diethylzinc using amino thiol **20**.

Even though this study was confined to the use of diethylzinc only, it certainly opens up the possibility of utilization

of other commercially unavailable dialkylzinc reagents, which can be prepared from alkyllithium, Grignard reagents or alkyl iodides.<sup>13</sup>

## Experimental Section

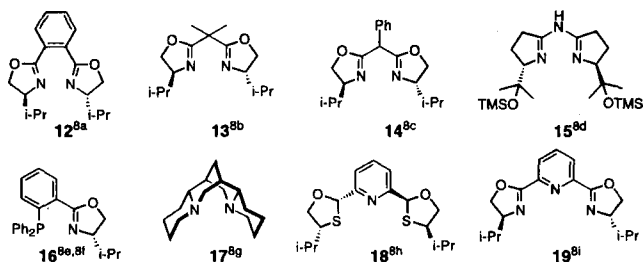
**Enantioselective Ni(II) Catalyzed Conjugate Addition.** In a round-bottomed flask Ni(II) salt (1.5-2.5 mol%) and chiral ligand (5-30 mol%) in dry acetonitrile or toluene was heated to reflux for 1 h under nitrogen. The mixture was cooled to room temperature and a solution of *trans*-chalcone (1 equiv.) in acetonitrile or toluene was added. The mixture was cooled to -30 °C and diethylzinc (2 equiv.) was added dropwise. After completion of reaction, the reaction was quenched with 1 N HCl. The mixture was extracted with methylene chloride. The combined extracts were dried over sodium sulfate. After evaporation of solvent, the residue was chromatographed to give the conjugate addition product. Chiral HPLC condition: Chiralcel OD; eluent 0.3% IPA/*n*-Hexane; flow rate (mL/min) 0.5; retention time (min) 22.5 (*S*), 25.9 (*R*).

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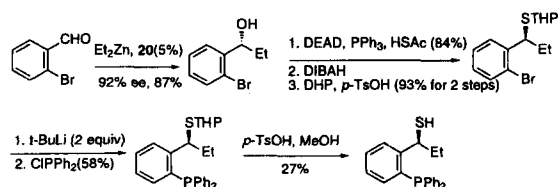
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