

## Copper-Catalysed Asymmetric Conjugate Addition of Organometallic Reagents to Linear Enones Using Thiourethane Ligands

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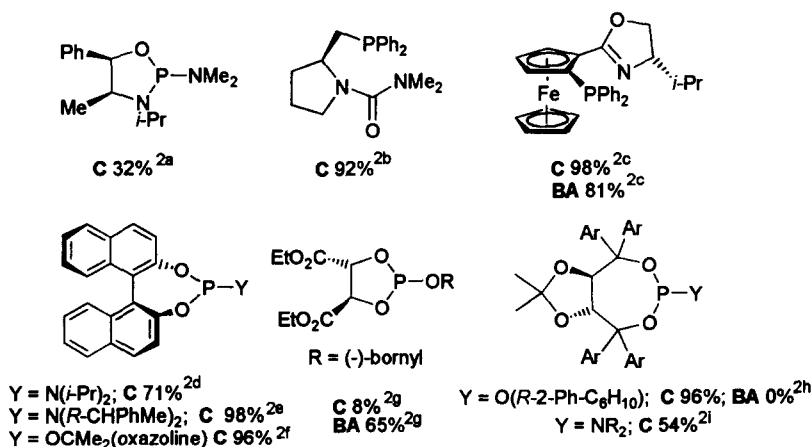
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Received 23 November 1998; accepted 21 December 1998

**Abstract:** In the presence of chiral thiourethane ligands  $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$  forms active catalysts for the conjugate addition of  $\text{MeMgBr}$ ,  $\text{ZnEt}_2$  and  $\text{AlR}_3$  ( $\text{R} = \text{Me}, \text{Et}$ ) to non-3-en-2-one, hept-3-en-2-one, and 5-methylhex-3-en-2-one. Enantioselectivities of up to 51% are realised for these difficult substrates; for cyclohex-2-enone an e.e. of 42% is attained. © 1999 Elsevier Science Ltd. All rights reserved.

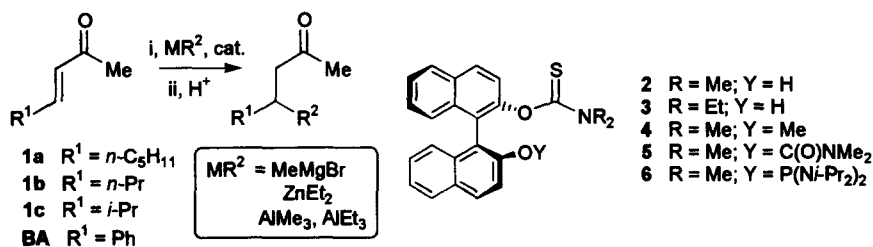
Recently, there has been considerable interest in asymmetric copper-catalysed 1,4-additions of organometallic reagents to Michael acceptors.<sup>1</sup> In the presence of phosphorus ligands derived from chiral diols, ephedrine, or oxazolines, significant levels of enantioselectivity have been realised for organometallic addition to cyclohex-2-enone (**C**) and benzylideneacetone (**BA**).<sup>2</sup> Typical ligands and their highest selectivity (% e.e.) are shown in Scheme 1. In general, the selectivities of these phosphorus systems are higher than those realised by thiolate-based catalysts<sup>3</sup> and other ligands.<sup>4</sup> However, at present no one ligand system affords a copper catalyst showing uniformly superb selectivity against a wide range of substrate variables (*e.g.* cyclic vs. acyclic enones, cyclic enones with different ring sizes, *etc.*). Such a goal may be unattainable and there is therefore a need for the development of new families of ligands and catalysts outside the scope of those reported in Scheme 1.



Scheme 1.

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Linear enones possessing only aliphatic substituents are a demanding substrate class for asymmetric conjugate addition.<sup>5</sup> We are seeking new copper(I) catalysts which engender 1,4-addition with good enantioselectivity to these compounds. Routine screening for effective ligands revealed thiourethanes to be a promising new class of ligand for these challenging substrates. Addition of AlMe<sub>3</sub> to (*E*)-non-3-en-2-one **1a** (Scheme 2) was selected as an initial model using *in situ* catalysts formed from [Cu(MeCN)<sub>4</sub>]BF<sub>4</sub> and two equivalents of ligands **2-6** (Table 1). In general, straw-coloured homogeneous catalysts were obtained but in some cases black precipitates formed. Ligands containing free hydroxyl functions led to moderately selective systems (runs 1-2), whereas ligands with either weakly co-ordinating to strongly co-ordinating neutral donors led to much less effective catalysts (runs 3-5). In no case was 1,2-addition observed.



Scheme 2.

**Table 1.** Addition of AlMe<sub>3</sub> (1.5 equivalents) to (*E*)-non-3-en-2-one **1a** in the presence of [Cu(MeCN)<sub>4</sub>]BF<sub>4</sub> (10 mol%) and ligands **2-6** (20 mol%).<sup>7</sup>

Run	Ligand	Conversion/%	1,4-Yield/%	e.e./%
1	2	96	80	50
2	3	93	75	40
3	4	69	31	12
4	5	46	23	15
5	6	90	63	8

Several other sets of conditions were applied to ligand **2** (Table 2) to study the affect of the reaction conditions on the enantioselectivity. Control reactions indicated some (MeMgBr) or no (ZnEt<sub>2</sub>, AlR<sub>3</sub>) conjugate addition in the absence of copper(I). In all catalysed runs the Kubas compound,<sup>8</sup> [Cu(MeCN)<sub>4</sub>]BF<sub>4</sub>, proved superior to other copper salts tried [CuBr, Cu(OTf)<sub>2</sub>]. Changing the catalyst stoichiometry to 1:1 led to an inferior system (run 1), as did use of other organometallics (runs 2-4). The addition of AlMe<sub>3</sub> proceeded with lower selectivity in solvents of both lower and higher polarity (runs 5-8). Lowering the catalyst loading reduced the chemical yield but the enantioselectivity was not affected (run 9). The present catalytic system could not be used at room temperature due to decomposition; at temperatures below -20 °C the catalyst performance was also poor (run 10). Attempts to improve the catalyst activity by addition of Lewis acid promoters at -50°C strongly suppressed the reaction (runs 11-12). The optimal system was finally applied to other enone substrates (runs 13-20). In general the highest enantioselectivities were realised for the addition of

AlMe<sub>3</sub>. Reducing the length of the alkyl substituent in the enone **1a** vs. **1b** leads to a reduction in e.e. as does  $\alpha$ -branching in the substrate **1c** (runs 13-16). The present system is not suitable for cyclic enones (run 19) due to deficiencies in chemical yield and mass balance.

**Table 2.** Addition of Organometallics to Various Enones Using [Cu(MeCN)<sub>4</sub>]BF<sub>4</sub> and Ligand 2.

Run	RM	Enone	Cu/ mol%	2/ mol%	Temp/°C (solvent)	1,4- Yield/%	e.e. /%
1	AlMe <sub>3</sub>	<b>1a</b>	10	10	-20 (THF)	62	47
2	AlEt <sub>3</sub>	<b>1a</b>	10	20	-20 (THF)	40	32
3	MeMgBr	<b>1a</b>	10	20	-20 (THF)	81	0
4	ZnEt <sub>2</sub>	<b>1a</b>	10	20	-20 (THF)	66	35
5	AlMe <sub>3</sub>	<b>1a</b>	10	20	-20 (toluene)	79	8
6	AlMe <sub>3</sub>	<b>1a</b>	10	20	-20 (Et <sub>2</sub> O)	49	16
7	AlMe <sub>3</sub>	<b>1a</b>	10	20	-20 (THF/DMI)	0	0
8	AlMe <sub>3</sub>	<b>1a</b>	10	20	-20 (THF/NMP)	0	0
9	AlMe <sub>3</sub>	<b>1a</b>	5	10	-20 (THF)	47	51
10	AlMe <sub>3</sub>	<b>1a</b>	10	20	-40 (THF)	34	37
11	AlMe <sub>3</sub>	<b>1a</b>	10	20	-50 (THF + TMSCl)	3	12
12	AlMe <sub>3</sub>	<b>1a</b>	10	20	-50 (THF + BF <sub>3</sub> ·OEt <sub>2</sub> )	7	4
13	AlMe <sub>3</sub>	<b>1b</b>	10	20	-20 (THF)	51	46
14	AlEt <sub>3</sub>	<b>1b</b>	10	20	-20 (THF)	42	26
15	AlMe <sub>3</sub>	<b>1c</b>	10	20	-20 (THF)	43	43
16	AlEt <sub>3</sub>	<b>1c</b>	10	20	-20 (THF)	36	10
19	AlEt <sub>3</sub>	<b>C</b>	10	20	-20 (THF)	26	42

Thioketone donors, and related compounds, have been rarely used as ligands in catalysis. Chiral thioureas have proved valuable additives in ruthenium-catalysed transfer hydrogenation.<sup>9</sup> However, we are not aware of any asymmetric catalytic processes using chiral thiourethanes and clearly other work is required to delineate the scope and utility of this interesting new ligand class.

#### Acknowledgements

We thank EPSRC for the award of a project studentship to SMWB (GR/K52263) and to Zeneca (Huddersfield Works) for CASE support. SW is grateful the EU for support through the COST-D2 programme and to Prof. W. A. König (Universität Hamburg) for help with the chiral assay.

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  - The only >90% e.e. catalytic conjugate additions of this substrate class are rhodium-catalysed, see: Sakai, M; Miyaura, N. *J. Am. Chem. Soc.* **1998**, 120, 5579-5580. Enantioselective addition of alkyl groups is problematic and has not been described before
  - Ligands **2** and **4-5** are literature compounds a) Azad, S. A.; Bennett, S. M. W.; Brown, S. M.; Green, J.; Sinn, E.; Topping, C. M.; Woodward, S. *J. Chem. Soc., Perkin Trans 1* **1997**, 687-694. b) Fabbri, D.; Pulacchini; Gladiali, S. *Synlett* **1996**, 1054-1056. Compounds **3** and **6** were prepared by alkylation of BINOL and **2** with Et<sub>2</sub>NC(S)Cl and ClP(Ni-Pr)<sub>2</sub> respectively. For **3**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub> 0.47 (t, 3 H, J = 7.3, Me), 1.06 (t, 3 H, J = 7.1, Me), 2.87 (dq, 1 H, J = 14.1, 7.3, CH<sub>2</sub>Me), 3.18 (dq, 1 H, J = 14.1, 7.1, CH<sub>2</sub>Me), 3.63 (m, 2 H, CH<sub>2</sub>Me), 5.93 (s, 1 H, OH), 7.08-8.07 (Ar); ν(C=S, KBr) 1213s cm<sup>-1</sup>; for **6** <sup>31</sup>P NMR (161.7 MHz, CDCl<sub>3</sub>) δ<sub>P</sub> 113.4. Correct combustion analysis or HRMS in both cases.
  - Representative procedure: MeMgBr, ZnEt<sub>2</sub>, or AlR<sub>3</sub> solution (0.05 mmol; 1 equiv. per OH) was added to a chilled THF solution (1 mL, -20 °C) containing ligand **2** (37.3 mg, 0.10 mmol) and [Cu(MeCN)<sub>4</sub>]BF<sub>4</sub> (15.7 mg, 0.05 mmol) and the mixture stirred (1 min, -20°C). Then at the desired temperature (-20°C) the organometallic (0.5 mL of 1.5 M solution, 0.75 mmol) and enone (0.5 mL of 1.0 M solution, 0.50 mmol) were introduced sequentially in a dropwise manner over 20 min. The reaction mixture was stirred for a further 20 min then quenched with HCl(aq.) and filtered (twice) through flash silica. Pentadecane (50 μL) was added and the chemical yield/e.e. obtained by GC using an *oktakis*-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin column.
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