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

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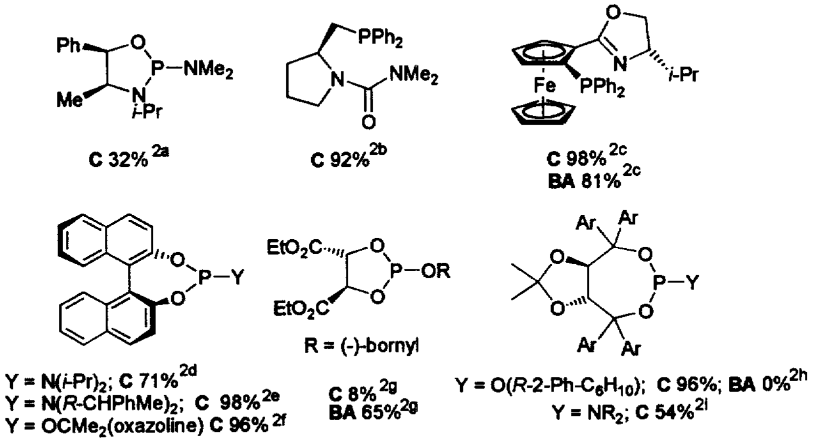
Abstract: In the presence of chiral thiourethane ligands $[Cu(MeCN)_4]BF_4$ forms active catalysts for the conjugate addition of MeMgBr, $ZnEt_2$ and AlR_3 (R = Me, Et) to non-3-en-2-one, hept-3-en-2-one, and 5-methylhex-3-en-2-one. Enantioselectivities of up to 51% are realised for these difficult substrates; for cyclohex-2-enone an e.e. of 42% is attained.

Recently, there has been considerable interest in asymmetric copper-catalysed 1,4-additions of organometallic reagents to Michael acceptors.[1] 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**).[2] 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[3] and other ligands.[4] 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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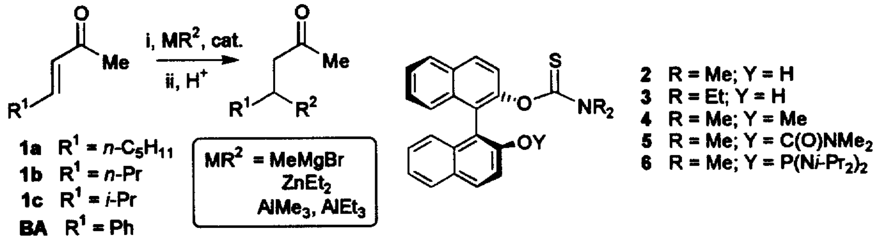
Linear enones possessing only aliphatic substituents are a demanding substrate class for asymmetric conjugate addition.[5] We are seeking new copper(I) catalysts which engender 1,4-addition with good enantioselectivity to these compounds. Routine screening for effective ligands revealed thiourethanes to be a promising new class of ligand for these challenging substrates. Addition of $AlMe_3$ to (*E*)-non-3-en-2-one **1a** (Scheme 2) was selected as an initial model using *in situ* catalysts formed from $[Cu(MeCN)_4]BF_4$ and two equivalents of ligands **2-6**[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 $AlMe_3$ (1.5 equivalents) to (*E*)-non-3-en-2-one **1a** in the presence of $[Cu(MeCN)_4]BF_4$ (10 mol%) and ligands **2-6** (20 mol%).[7]

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 ($ZnEt_2$, AlR_3) conjugate addition in the absence of copper(I). In all catalysed runs the Kubas compound,[8] $[Cu(MeCN)_4]BF_4$, proved superior to other copper salts tried [CuBr, $Cu(OTf)_2$]. Changing the catalyst stoicheiometry to 1:1 led to an inferior system (run 1), as did use of other organometallics (runs 2-4). The addition of $AlMe_3$ 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

$AlMe_3$. Reducing the length of the alkyl substituent in the enone **1a** *vs.* **1b** leads to a reduction in e.e. as does α 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 $[Cu(MeCN)_4]BF_4$ and Ligand **2**.

Run	RM	Enone	Cu/ mol%	**2**/ mol%	Temp/°C (solvent)	1,4- Yield/%	e.e. /%
1	$AlMe_3$	**1a**	10	10	-20 (THF)	62	47
2	$AlEt_3$	**1a**	10	20	-20 (THF)	40	32
3	MeMgBr	**1a**	10	20	-20 (THF)	81	0
4	$ZnEt_2$	**1a**	10	20	-20 (THF)	66	35
5	$AlMe_3$	**1a**	10	20	-20 (toluene)	79	8
6	$AlMe_3$	**1a**	10	20	-20 (Et_2O)	49	16
7	$AlMe_3$	**1a**	10	20	-20 (THF/DMI)	0	0
8	$AlMe_3$	**1a**	10	20	-20 (THF/NMP)	0	0
9	$AlMe_3$	**1a**	5	10	-20 (THF)	47	51
10	$AlMe_3$	**1a**	10	20	-40 (THF)	34	37
11	$AlMe_3$	**1a**	10	20	-50 (THF + TMSCl)	3	12
12	$AlMe_3$	**1a**	10	20	-50 (THF + $BF_3 \cdot OEt_2$)	7	4
13	$AlMe_3$	**1b**	10	20	-20 (THF)	51	46
14	$AlEt_3$	**1b**	10	20	-20 (THF)	42	26
15	$AlMe_3$	**1c**	10	20	-20 (THF)	43	43
16	$AlEt_3$	**1c**	10	20	-20 (THF)	36	10
19	$AlEt_3$	C	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.[9] 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

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7. Representative procedure: MeMgBr, ZnEt$_2$, or AlR$_3$ 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)$_4$]BF$_4$ (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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