

Highly enantioselective copper(I)-phosphoramidite-catalysed additions of organoaluminium reagents to enones†

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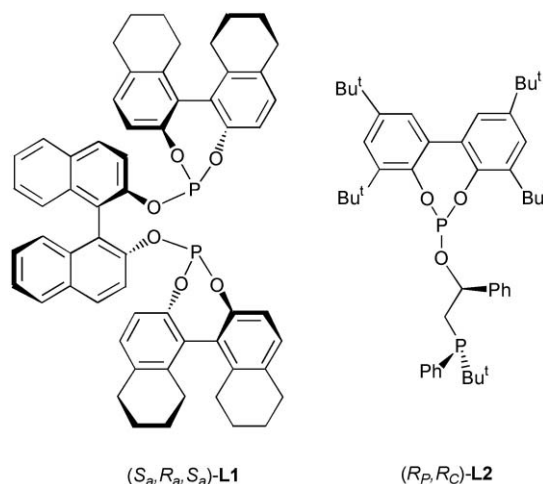
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Simple phosphoramidite ligands afford good to excellent levels of enantioselectivity in 1,4-additions of AlR_3 species to enones; sequential carboalumination–ACA cascades are possible.

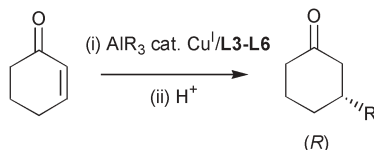
Ligand-driven catalytic asymmetric processes that attain widespread popularity typically display two features: technical simplicity and widespread (preferably commercial) availability of both enantiomers of the chiral ligand. In the last five years this position has been reached for the addition of organozinc reagents (especially ZnEt_2) to many Michael acceptors.^{1,2} In studies parallel to these we have developed an interest in the utilisation of organoaluminium reagents, especially AlR_3 ($\text{R} = \text{Me}, \text{Et}, \text{etc.}$) species, in related Asymmetric Conjugate Addition (ACA) reactions.^{3,4} As a significant range of organoaluminium reagents are either commercially available, or attained by technically simple hydro- and carboalumination reactions, they offer high potential for use in synthesis. Despite this reports in this area have been rather limited due to an apparent need for specialist ligands. Aside

from our own reports Chan attained 96% ee in the addition of AlMe_3 to 2-cyclohexenone using (S_a, R_a, S_a) -L1 (2 mol%) and $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (1 mol%); together with related additions to 2-cyclopentenone.⁵ Van Leeuwen and Claver reached 62% ee in related additions of AlEt_3 using the complex ligand (R_P, R_C) -L2.⁶



† Electronic supplementary information (ESI) available: supporting experimental data. See <http://www.rsc.org/suppdata/cc/b5/b503074a/>
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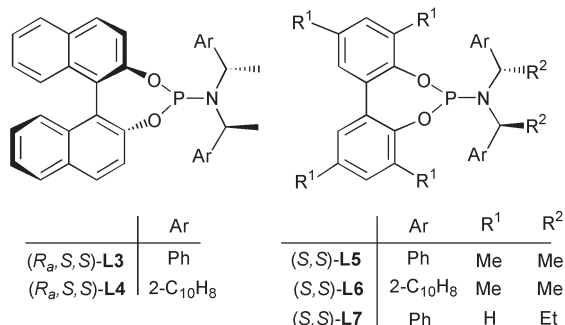
Table 1 Optimisation of AlR_3 ($\text{R} = \text{Et}, \text{Me}$) ACA to 2-cyclohexenone^a



Run	Solvent	Cu-source (mol%)	L (mol%)	Conv. / %	Yield / %	Ee / % (Config.)
AlEt_3						
1	CH_2Cl_2	$[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (1)	L3 (4)	> 98	47	76 (R)
2	Et_2O	$[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (1)	L3 (4)	40	22	45 (R)
3	Bu^tOMe	$\text{Cu}(\text{TC})$ (1)	L3 (4)	> 98	77	90 (R)
4	Et_2O	$\text{Cu}(\text{TC})$ (1)	L3 (4)	> 98	80	90 (R)
5	Et_2O^b	$\text{Cu}(\text{TC})$ (2)	L3 (4)	> 98	54	86 (R)
6	Et_2O^b	$\text{Cu}(\text{TC})$ (2)	L5 (4)	> 98	40	89 (R)
7	THF^b	$\text{Cu}(\text{TC})$ (2)	L3 (4)	> 98	28	89 (R)
8	Toluene	$\text{Cu}(\text{TC})$ (1)	L3 (4)	> 98	< 20	88 (R)
9	MeCN	$\text{Cu}(\text{TC})$ (1)	L3 (4)	20	< 5	< 5
AlMe_3						
10	Et_2O	$\text{Cu}(\text{OTf})_2$ (2)	L3 (4)	> 98	30	95 (R)
11	Et_2O	$\text{Cu}(\text{TC})$ (2)	L5 (4)	> 98	85	92 (R)
12	Et_2O	$\text{Cu}(\text{OTf})_2$ (2)	L4 (4)	> 98	77	95 (R)
13	Et_2O	$\text{Cu}(\text{TC})$ (2)	L6 (4)	> 98	64	97 (R)

^a Addition of 1.4 equiv. of AlR_3 (2 M hexane or heptane solution) to 2-cyclohexenone and Cu-salt/L at -30°C followed by 20 min reaction at this temperature. Yield by GC against internal standard, ee by chiral GC. ^b Standard conditions followed by 16 h at -30°C .

We wondered if optimal conditions could be identified whereby the simplest of monodentate phosphoramidite ligands⁷ could afford very highly enantioselective reactions across a range of cyclic and acyclic enones under easily utilised reaction conditions. This hypothesis could be confirmed by simple trial of AlR_3 ($\text{R} = \text{Et}, \text{Me}$) additions to 2-cyclohexenone (Table 1†) using the readily commercially available Feringa ligand (R_a,S,S)-**L3** and ligands **L4–L7** (all attainable in a single step from commercial materials).⁸



This initial screening revealed that reactions in diethyl ether using the versatile $\text{Cu}(\text{TC})$ source⁹ were extremely fast, completing in 20 min at $-30\text{ }^\circ\text{C}$. Use of alternative copper(I) pre-catalysts, such as $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$,¹⁰ was not effective (Runs 1–2) but in some cases $\text{Cu}(\text{OTf})_2$ was the preferred copper source (Runs 10, 12). Solvents less or more polar than Et_2O or Bu^tOME were also not effective (Runs 7–9). In cases where the yields were appreciably lower than the conversion (*e.g.* Run 10) the mass balance was accounted for by undesired trapping of the aluminium enolate on to additional unreacted 2-cyclohexenone. In Et_2O , running the reaction overnight also led to reduction in the yields and enantioselectivities realised (Runs 5–6). Subsequent adverse kinetic resolution in by-product forming reactions of the initial chiral enolate may be the explanation for this. Good stereoselectivities (82% ee) were also attained using our recently introduced air-stable equivalent of trimethylaluminium DABAL-Me₃ $[(\text{Me}_3\text{Al})_2\text{-}(\text{DABCO})]^{11}$ with ligand **L5**, but here also enolate trapping by-product formation limited the yield of 1,4-addition product (27%). As the test ACA- AlR_3 reaction conditions had proved completely robust against changes in the reaction protocols (*e.g.* different sources of AlR_3 reagents, quality of Et_2O , different batches of $\text{Cu}(\text{TC})$, presence of traces of oxygen and water) we looked to extend the range of substrates. Ligand **L3** was chosen due to its ready commercial availability in both enantiomeric forms.

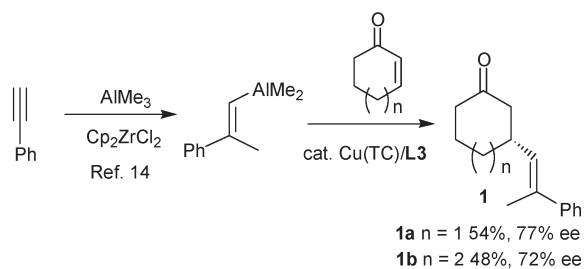
Against a range of aliphatic enones the simple $\text{Cu}(\text{TC})/\mathbf{L3}$ system gave synthetically useful enantioselectivities and chemical yields (Table 2†), although longer reaction times than with 2-cyclohexenone were necessary in all cases. The only exception was the addition of AlMe_3 to linear aliphatic enones which could only be realised in 70–72% ee with simple **L3** (Runs 7–9). However, α branching in such substrates increased the selectivity to $> 20 : 1$ (Runs 10–11). Again all the reactions proved tolerant to any organoaluminium sources used and to variations in technique of multiple researchers in two different sites.

One final attraction of organoaluminium reagents is the ease with which novel reagents can be attained by hydro- and carboalumination reactions.¹³ Carboalumination of phenylacetylene, under modified Negishi conditions¹⁴ (using 0.2 to 1.0 equiv. of Cp_2ZrCl_2) in dichloromethane led to an $> 85\%$ yield of

Table 2 ACA Reactions of AlR_3 reagents ($\text{R} = \text{Me}, \text{Et}$) to various enones catalysed by $\text{Cu}(\text{TC})/\mathbf{L3}^a$

Run	Starting material	Time/h	Yield/%	Ee/% (Config.)
AlEt₃				
1		2	87	89 (<i>R</i>)
2		16	80	90 (<i>R</i>)^b
3		16	90 ^c	86(<i>R</i>) ^c
4		3	88	84 (<i>R</i>)
5		3	85	98 (<i>R</i>)
6		8	88	> 98 (<i>S</i>)^d
AlMe₃				
7		4	55	72 (<i>R</i>)
8		2	65	70 (<i>R</i>)
9		4	60	70 (<i>R</i>)
10		2	88	96 (<i>R</i>)
11		3	89	96 (<i>R</i>)
12		3	84	92 (<i>R</i>)

^a Addition of 1.4 equiv. of AlR_3 (2 M hexane or heptane solution) to enone and $\text{Cu}(\text{TC})$ (1 mol%) (*R_a*,*S,S*)-**L3** (4 mol%) at $-30\text{ }^\circ\text{C}$ followed by 20 min reaction at this temperature. Yields by isolation, ee by chiral GC unless noted otherwise. ^b Using 2 mol% $\text{Cu}(\text{TC})$ lowering this to 1 mol% led to 82% ee. ^c Using $\text{Cu}(\text{TC})$ (2 mol% and (*R,R*)-**L7** (4 mol%); yield by GC. ^d Ee value determined by ¹³C NMR spectroscopy on (*R,R*)- $\text{PhCH}(\text{NH}_2)\text{CH}(\text{NH}_2)\text{Ph}$ derived aminal (see ref. 12); change of stereo-descriptor caused only by CIP priority rules.



Scheme 1 Enantioselective addition of *in situ* formed vinylalanes.

vinylalane after 32 h in our hands. § Removal of the CH_2Cl_2 solvent and direct addition of Et_2O to the orange residue, followed by $\text{Cu}(\text{TC})$ and $(R_c, S, S)\text{-L3}$ at -30°C , led to a useful sequential reaction on addition of 2-cyclohexenone or 2-cycloheptenone fashioning **1a–b** (Scheme 1). In both cases the (+) stereoisomer is isolated which is assigned to the same facial selectivity as the other additions herein. Remarkably, the presence of the Cp_2ZrCl_2 is largely tolerated in the subsequent asymmetric conjugate addition chemistry. To the best of our knowledge only racemic additions of such vinylalanes to enones have been reported before.¹⁵ Attempts to further increase the utility of these cascade reactions through trapping of the kinetically formed aluminium enolates are being actively pursued in our laboratories.

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Notes and references

‡ For details of the catalytic conditions and spectral and chiral chromatographic data on the products see the electronic supplementary information.

§ Carboalumination reactions are usually performed in the presence of excess AlMe_3 . To minimise competitive methylation in the subsequent ACA reaction 2 equivalents AlMe_3 were used necessitating a slightly longer reaction time (see supplementary data for experimental details).

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