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Enone structure as a probe to Lewis acid carbonyl binding in copper-catalysed asymmetric conjugate addition

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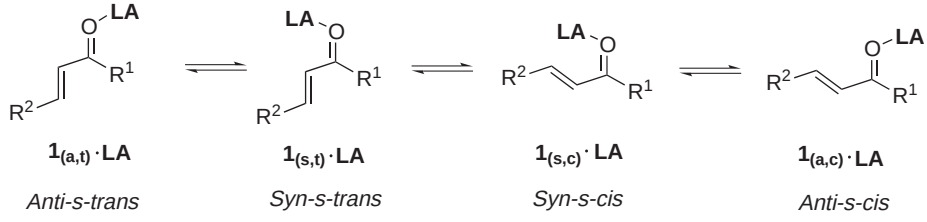
Abstract—Systematic changes in the substitution pattern of linear enones ($R^1COCH{=}CHR^2$) helps identify the reactive conformation (*s-trans* versus *s-cis*) of the enone in copper-catalysed asymmetric 1,4-$ZnEt_2$ addition. Pointers to the binding mode of the Lewis Acid (*syn* or *anti* to the 'ene' function) are also gathered. Enantioselectivities of up to 79% have been realised in these reactions.

Despite recent successes in the area of asymmetric copper-catalysed 1,4-organometallic additions to Michael acceptors[1] there is an ongoing quest for improved systems showing very high enantioselectivities. One problematic substrate class for this reaction are linear aliphatic enones **1** (Scheme 1). The high conformational mobility of these species together with the presence of only subtle substrate–catalyst steric interactions makes the design of effective enantioselective systems a real challenge.[2–4] The accepted mechanism of 1,4-cuprate addition involves activation of the enone through Lewis acid (**LA**) carbonyl binding.[5–10] All mechanistic studies we are aware of have been carried out with lithium cuprate species (**LA** = Li^+). However, the best enantioselective catalysts use Lewis acids derived from AlR_3[3,4] and ZnR_2.[1,2] The carbonyl oxygen binding of such **LA** species is highly covalent and may occur either *anti* (**a**) or *syn* (**s**) with respect to the $CH{=}CHR^2$ function (Scheme 1).[10]

As conformational exchange between the *s-trans* (**t**) and *s-cis* (**c**) forms swaps the enone face presented to the chiral catalyst the relative populations of the four species (**a**,**t**; **s**,**t**; **a**,**c**; **s**,**c**; Scheme 1) are expected to profoundly affect the derived catalyst enantioselectivity. Because of the lack of literature data we sought for a simple means to interrogate these ideas and settled on enone structure as the easiest experimental variable.[†] The catalyst system $ZnEt_2/(S_a)$-**L***/$[Cu(MeCN)_4]BF_4$ affords reasonable levels of enantioselection in additions to linear aliphatic enones and was selected for the test (Scheme 2).[3,4] A range of enones **1a**–**k** were prepared whose structures were expected to weight significantly the population of one of the four reacting species



Scheme 1. *Syn*/*anti* and *s-cis*/*s-trans* exchange in Lewis acid (**LA**) ligated linear enones.

Keywords: enones; mechanisms; thioethers; zinc and compounds.

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† Enones **1a** and **2** are commercially available. The remaining substrates were prepared by either aldol or Wittig–Horner/Wadsworth–Emmons techniques. All enones used were a single *E* isomer as determined by ^1H NMR spectrometry. All compounds gave acceptable ^1H and ^{13}C spectra together with combustion analysis or HRMS data.

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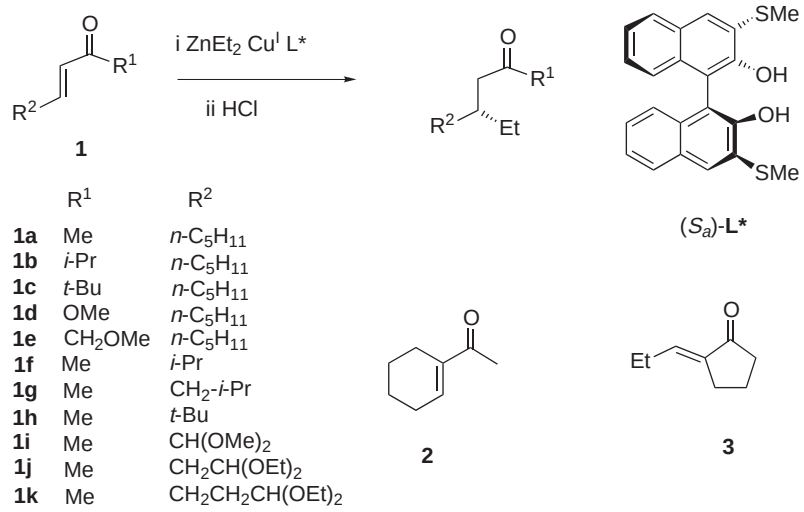


	R^1	R^2
1a	Me	*n*-C_5H_{11}
1b	*i*-Pr	*n*-C_5H_{11}
1c	*t*-Bu	*n*-C_5H_{11}
1d	OMe	*n*-C_5H_{11}
1e	CH_2OMe	*n*-C_5H_{11}
1f	Me	*i*-Pr
1g	Me	CH_2-*i*-Pr
1h	Me	*t*-Bu
1i	Me	$CH(OMe)_2$
1j	Me	$CH_2CH(OEt)_2$
1k	Me	$CH_2CH_2CH(OEt)_2$

Scheme 2. The enones and catalyst system used in this study.

(Scheme 1). These enones were subjected to catalytic asymmetric conjugate addition under identical conditions (Table 1).‡

In comparison with *trans*-3-nonen-2-one **1a**, steric hindrance in enones **1b**–**c** is expected to substantially favour *syn* over *anti* **LA** coordination. The catalytic reactions of these enones are first hindered (**1b**) then stopped (**1c**). Acrylates of type **1d** are also ineffective being both electronically deactivated and hindered at the *anti* binding site (the ester presents a (*Z*)-$C_{carbonyl}$–OMe configuration).[10] These results indicate an *anti* configuration for **LA** binding in the active catalyst. To attempt to enforce *anti* coordination **1e** was prepared. A high chemical yield was realised but the e.e. suffers suggesting that although placed *anti* to the 'ene' function the zinc Lewis acid is not easily able to accept an additional donor without significant distortion of the catalyst geometry. Enones **1f**–**h** were designed to probe *s-cis* versus *s-trans* substrate configurations. Assuming that the *s-cis* conformation places the enone in closer proximity to the Lewis acid–cuprate catalyst, very large R^2 substituents are expected to depopulate conformations $\mathbf{1}_{(s,c)}$ and to a lesser extent $\mathbf{1}_{(a,c)}$ ($\mathbf{1}_{(s,t)}$ is also slightly affected). While the transition state can clearly accommodate some steric bulk in R^2 the results for **1h** are consistent with an *s-cis* conformation in the 'loaded' catalyst state (as proposed originally by Feringa for chalcone substrates in phosphoramidite-promoted reactions).[1] These results suggested that substrates **2** and **3** should be, respectively, poor and good substrates for the reaction, as proved the case. Finally the acetals **1i**–**k** were prepared to test for the possibility of two-point substrate binding by catalysts derived from **L***. (As two Ar–OH groups are present in **L*** the possibility of a EtZn-*O*-BINAP-*O*-ZnEt catalyst structure exists.) The poor enantioselectivity realised by enone **1i** indicates that binding to the acetal oxygen appears viable, but that the higher homologues are too far away from the catalyst to suffer this detrimental effect.

In conclusion it appears that simple, but logical, variation of enone substitution patterns is an effective way of probing the identity of unknown catalyst transition states in this reaction. The data obtained here strongly

Table 1. Asymmetric conjugate addition of $ZnEt_2$ catalysed by $[Cu(MeCN)_4]BF_4$ (10 mol%) and (S_a)-**L*** (20 mol%) in THF at −20°C

Enone	R^1	R^2	C.y./%[a]	E.e./%[b]
1a	Me	*n*-C_5H_{11}	85	72 (+)
1b	*i*-Pr	*n*-C_5H_{11}	61	39 (+)
1c	*t*-Bu	*n*-C_5H_{11}	0	–
1d	OMe	*n*-C_5H_{11}	0	–
1e	CH_2OMe	*n*-C_5H_{11}	65	24 (−)
1f	Me	*i*-Pr	59	77 (+)
1g	Me	CH_2-*i*-Pr	43	79 (+)
1h	Me	*t*-Bu	0	–
1l	Me	$CH(OMe)_2$	52	18 (+)[c]
1j	Me	$CH_2CH(OEt)_2$	58	70 (+)[c]
1k	Me	$CH_2CH_2CH(OEt)_2$	65	69 (+)[c]
2	–	–	0	–
3	–	–	54	–[d]

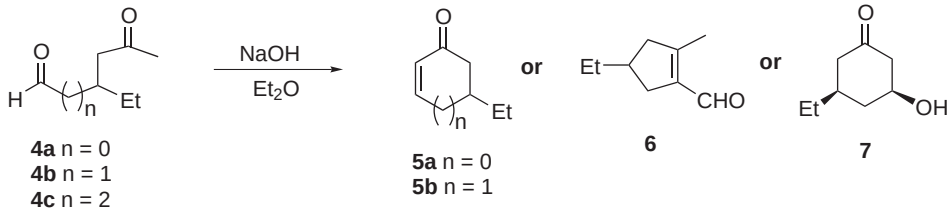
[a] Determined by GC (calibrated versus an undecane internal standard) or isolated; in all cases except **1f**–**g** the conversion was >90% (for **1f**–**g** the conversions were 61 and 44%).

[b] Determined by GC.

[c] Determined on derived aldehyde.

[d] 1:1 Mixture of stereoisomers at C(2) due to unselective protonation; no chiral centre formed from 1,4-addition.

‡ Representative procedure for the asymmetric conjugate additions: $ZnEt_2$ (0.2 mmol; 1 equiv. per OH) was added to a chilled THF solution (1 mL, −20°C) containing ligand (S_a)-**L*** (37.9 mg, 0.10 mmol) and $[Cu(MeCN)_4]BF_4$ (15.7 mg, 0.05 mmol) and the mixture stirred (1 min, −20°C). At −20°C $ZnEt_2$ (0.75 mL of 1.0 M solution, 0.75 mmol) and enone (0.5 mL of 1.0 M solution, 0.50 mmol) were introduced via syringe pump over 20 min. The reaction mixture was stirred for another 20 min then quenched with HCl (aq.) and undecane (50 μL) added. The organic layer was filtered (twice) through flash silica and the chemical yield/e.e. obtained by GC using *oktakis*-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin[11] for all the conjugate addition products except those derived from **1e** and **1g** [these split on *oktakis*-(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin[12]].



Scheme 3. Base-promoted cyclisations.

suggest that linear enones bind this particular catalyst in an *anti-s-cis* arrangement prior to 1,4-delivery of the ethyl nucleophile. Finally, we note that the product aldehydes derived from **1i**–**h** are useful precursors in simple base-promoted cyclisations (Scheme 3).[§] In all cases the thermodynamic product is favoured, e.g. **6** is formed from **4c** instead of the expected 7-ring product. By running the reaction of at 0°C some aldol product **7** may be isolated as a single *syn* diastereomer from **4b**; but the majority of the species readily looses water fashioning **5b**.

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[§] Diethyl ether solutions of **4** (2.0 mL of a 0.08 M solution, 0.16 mmol) were stirred with NaOH (2.0 mL of 1% w/w aq. solution) at ambient temperature. Normal extractive workup followed by flash chromatography afforded **5**–**6** in (80–87% yield). Reaction of **4b** at 0°C afforded **7** together with **5b**.