Mechanistic Insight Driven Rate Enhancement of Asymmetric Copper-Catalysed 1,4-Addition of Dialkylzinc Reagents to Enones

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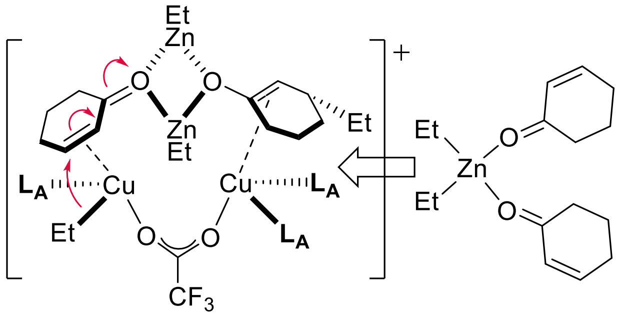
S *Supporting Information*

■ ABSTRACT

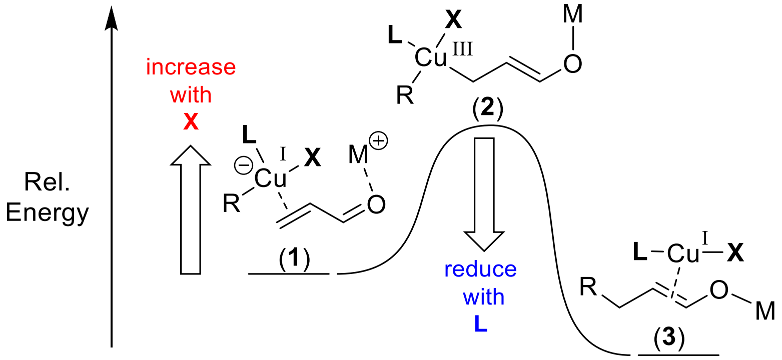


Combination of $[Cu(MeCN)_4]TFA \cdot TFAH$ (TFA = O_2CCF_3) with Feringa's phosphoramidite ligand (**L**$\mathbf{L_A}$) provides an exceptionally active (0.75 mol%) catalyst for asymmetric conjugate additions of ZnR_2 (R = Et, Me at –40 to –80 °C) to enones. Kinetic and other studies of the addition of $ZnEt_2$ to cyclohex-2-en-1-one indicate a transition state stoichiometry composition: $(ZnEt_2)_3(enone)_4Cu_2(\mathbf{L_A})_3$ that is generated by transmetalation from $Et_2Zn(enone)_2$. Catalyst genesis is significantly slower than turnover (which has limited previous attempts to attain useful kinetic data); in the initial stages varying populations of catalytically inactive, off-cycle, species are present. These issues are overcome by a double-dosing kinetic analysis protocol. A rest state of $[\mathbf{L_A}Cu(Et)(\mu\text{-}TFA)(\mu\text{-}\{(enone)(ZnEt)_2(enolate)\})Cu\mathbf{L_{A2}}]^+$ (through the equivalence of enolate = enone + $ZnEt_2$) is

supported by DFT studies (ωB97X-D/SRSC). Rate determining $ZnEt_2(enone)_2$ transmetalation drives the exceptionally high catalytic activity of this system.

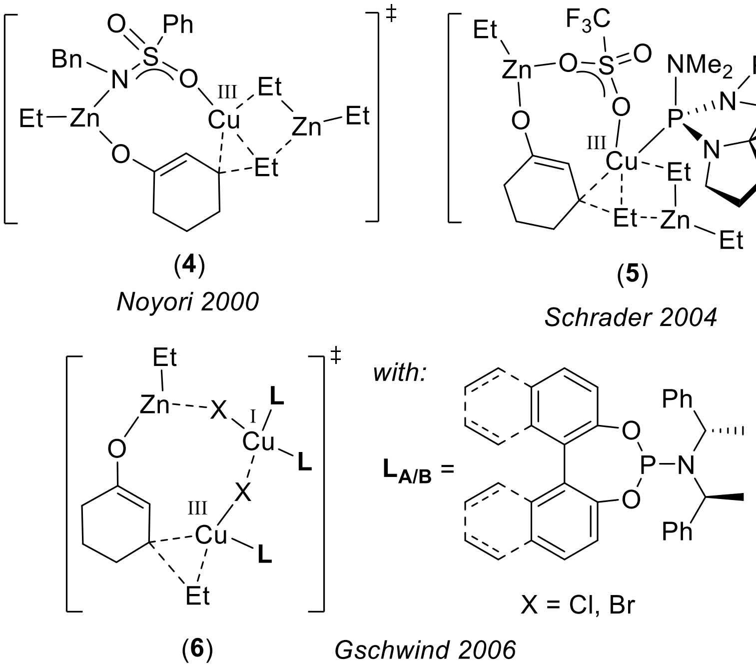
■ INTRODUCTION

The copper-catalysed 1,4-addition of organometallics to enones is typically proposed to proceed via evolution of a π-enone complex, akin to **1**, to a fleeting copper(III) intermediate (**2**) whose reductive elimination to product **3** is commonly proposed to be rate limiting (Scheme 1).[1,2] In Asymmetric Conjugate Addition (ACA)[1,2] versions of such reactions, this latter step also defines the stereochemistry in the 1,4-product. Identifying ligands (**L**) which reduce the transition state barrier to reductive elimination is a commonly understood concept in achieving fast catalysis. Phosphoamidites and carbene (NHC) ligands have proved particularly effective in this regard. However, the alternative strategy of destabilizing the ground state energy of precursor (**1**) by anionic '**X**' ligand selection is much less appreciated; despite the screening of libraries of copper salts being commonplace in ACA reaction development. Complete understanding of the intimate details of Scheme 1[2] responsible fast turnover is highly desirable, as mechanism-inspired faster catalysis would particularly benefit sluggish organozinc additions where problematic lower reactivity (e.g. $ZnMe_2$) reagents are a known problem (see Supporting Information, Table S1B, refs. S17-S95 for examples).



Scheme 1. Strategies for increasing the rate of (asymmetric) conjugate addition reactions of organometallics (RM); acrolein is shown as an exemplary enone.

We speculated that the ground state instability of unligated $Cu(O_2CCF_3)$, which has remained only scantly described since its initial discovery in 1939,[3] would lead to ligated copper catalysts showing rapid 1,4-addition of diorganozincs to enones. Further, we postulated that its putative high copper Lewis acidity and the presence of a ^{19}F NMR tag would render it more amenable to mechanistic study than traditional copper carboxylate salts. Mechanistic kinetic study of ligand promoted copper(I) catalysed ZnR_2 1,4-addition to Michael acceptors is rather limited: essentially just the seminal work of Noyori,[4] and Schrader.[5] The former concluded **4** was the transition state for copper(I) sulphonamide catalysed additions of $ZnEt_2$ to cyclohex-2-en-1-one and the latter **5** for the same transformation catalysed by $Cu(OTf)_2$ in the presence of chiral phosphoramide ligands (Scheme 2). As induction periods[4-6] and poor rate reproducibility[7] have frequently complicated kinetic studies of copper-based ACA reactions, other approaches to arriving at catalytic cycle proposals have been sought. Transition state **6** has been proposed based on NMR studies of model complexes.[8] While no kinetic data is available for **6**, combined computational and synthetic studies also indirectly support this proposal.[9]


(**4**)
Noyori 2000
(**5**)
Schrader 2004
(**6**)
Gschwind 2006

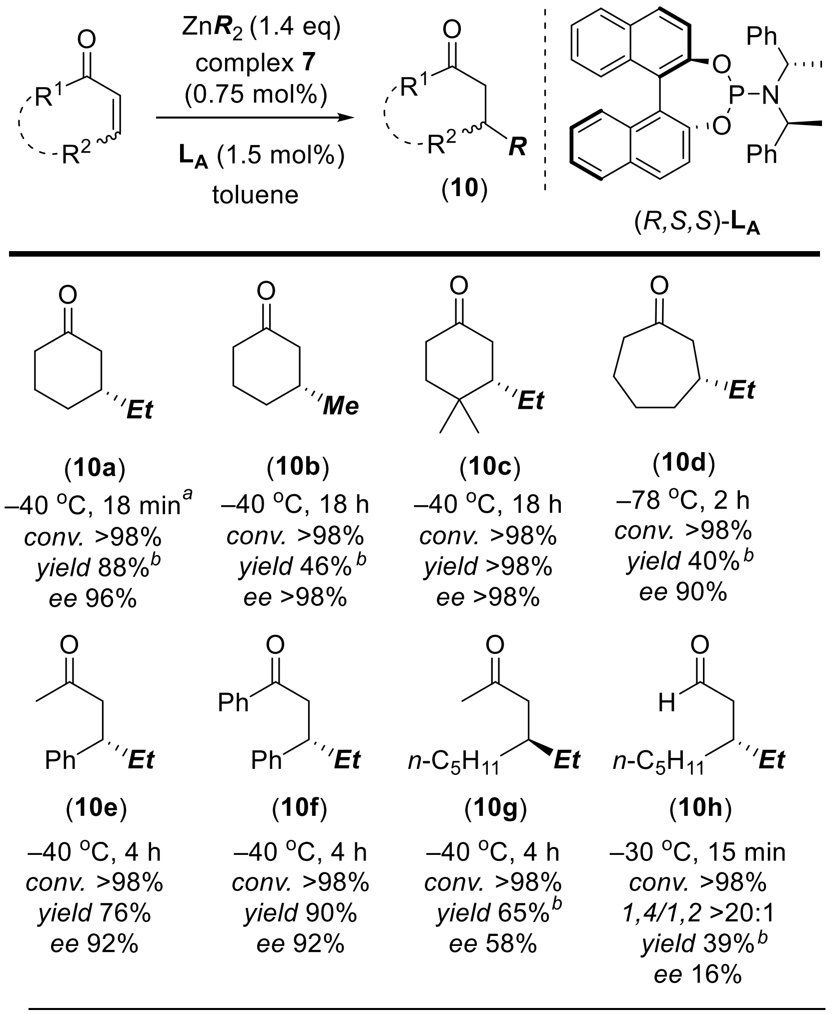
Scheme 2. Published proposals for the transition state of copper(I)-catalyzed 1,4-additions of $ZnEt_2$ to cyclohex-2-en-1-one. Ligand $\mathbf{L_A}$ contains a binaphthyl unit, $\mathbf{L_B}$ a biphenyl.

Aside from the early contributions of refs. 4, 5, and the NMR studies of ref. 8, unsupported conjecture has become the norm for mechanistic descriptions of copper-catalysed ZnR_2 additions to enones. Quantified description of the reaction behaviour would be preferable for rational ACA Cu-catalyst development, such analysis is the target of this present paper.

■ RESULTS

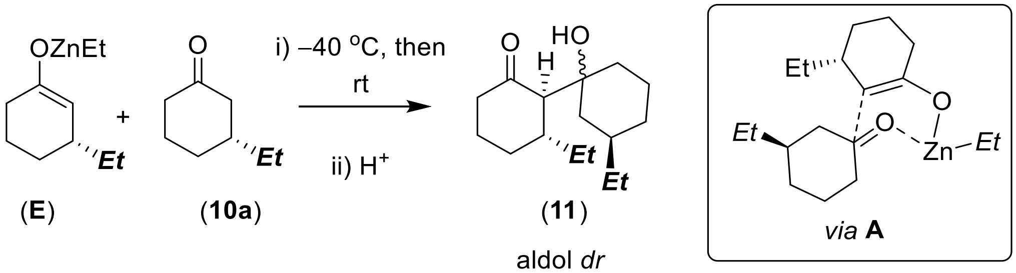
Pre-catalyst preparation While unligated Cu(O_2CCF_3) is stated to be intrinsically unstable[3] we reasoned [Cu(MeCN)$_4$]TFA (TFA = $F_3CO_2^-$) would be an equivalent catalyst precursor, but an isolable salt similar to others of this type.[10] Reaction of Cu_2O with 2.55 equivalents of trifluoroacetic acid (TFAH) in MeCN at room temperature leads to rapid formation of colourless [Cu(MeCN)$_4$]TFA·TFAH (**7**) in 74% yield. All spectroscopic and analytical data are consistent with this formulation. In solution, especially above –20 °C in the absence of added ligands, **7** decomposes over 24-36 h to $\{[Cu(MeCN)_4]_2[A]\}_\infty$ **8** where A is the chain-linked polynuclear anion $[Cu_4(TFA)_{10}]^{2-}$ detectable by X-ray crystallography (see Supporting Information, Figure S1). At room temperature, however, solutions of **7** retain their integrity for at least 60 min allowing characterisation by ^{1}H, ^{31}P (via P-ligation) and ^{19}F NMR spectroscopy and confirming (^{1}H NMR) the CF_3CO_2H (TFAH) solvation.[11] The viability of using **7** in solution as a P-ligand catalyst precursor is indicated by the observation that addition of PCy$_3$ (2 equiv.) leads to rapid formation of Cu(TFA)(PCy$_3$)$_2$ **9** which is isolated in quantitative yield. In the solid-state **7** is stable at 22 °C for at least a day. Significant decomposition of solid **7** occurs above 30 °C, even under inert atmospheres, due to MeCN lability, while at –20 °C, **7** is stable for at least one month.

Demonstrating catalytic competence As [Cu(MeCN)$_4$]TFA·TFAH (**7**) had never been used as a 1,4-catalyst precursor comparisons were made against benchmark enones using the typical phosphoramidite (*R*,*S*,*S*)-**L$_A$** (Feringa's ligand) in toluene (Scheme 3). Pleasingly, formation of a very active catalyst system for 1,4-ZnR$_2$ (R = Et, Me) addition products **10** using only 0.75 mol% **7** was observed (Scheme 3) even at rather low temperatures (–80 °C). For comparison, of the 100 published most active and selective (≥80% *ee*) literature ZnR$_2$ Cu-catalysed ACA reactions to cyclohex-2-en-1-one (**CX**) we could find, only four afford any conversion below –75 °C (Supporting Information, Table S1). For both ethyl and methyl additions to **CX** the catalyst **7**/**L$_A$** was the highest performing catalyst in terms of activity, with excellent stereoselectivity across this wide family.



Scheme 3. Benchmarking enone studies demonstrating the high activity of the (**7**)/**L**$_{\mathbf{A}}$ catalyst. [a] Full conversion is attained within 2 h at –80 °C. [b] The lower isolated yields reflect isolation issues for volatile products **10** associated with toluene solvent removal, using Et_2O results in yields in line with conversion. Quantification against internal standards indicated excellent conversion and mass balance.

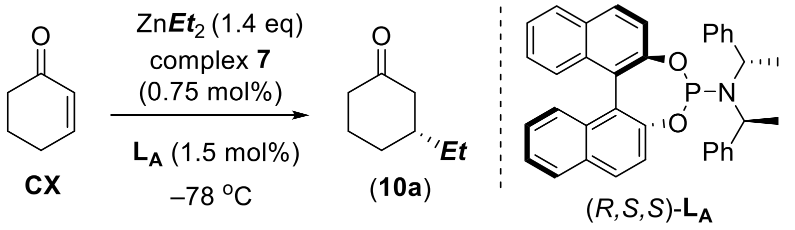
Quantified yields of **10** against internal standards were good to excellent, although volatile products caused isolation issues when using toluene, an issue that could be avoided by using Et_2O as the solvent. The reactions are extremely clean, unexpected by-product formation was noted only in HCl quenching of the kinetic enolate (**E**). Such approaches result in partial formation of the aldol product **11** (Scheme 4) resulting from direct reaction of liberated **10a** with its own partially quenched enolate. This behaviour could be confirmed by independent reaction with authentic **10a** giving moderate yields (59%) of **11**. The reaction is quite stereoselective and in accord with the expected Zimmerman-Traxler control (**A**, Scheme 4). Surprisingly, **11** has apparently not been reported before, but is likely the source of at least some of the poorer characterised 'dimer' products that have been previously noted in ACA reactions of cyclohex-2-en-1-one (**CX**).[12] By-product **11** could, however, be completely avoided by initial quenching of the reaction mixture at –40 °C with methanol, prior to HCl addition.



aldol *dr*
85:15 (>96% *ee*)

Scheme 4. Formation of byproduct **11**, apparently previously erroneously attributed to cyclohex-2-en-1-one (**CX**) 'double Michael addition' in some cases.

Solvent effects and cyclohex-2-en-1-one (CX) Lewis acid binding Cyclohex-2-en-1-one (**CX**) conversion to **10a** (by low temperature MeOH quench) after 45 mins reaction at –78 °C was monitored by ^{1}H NMR spectroscopy as a function of solvent (Scheme 4). The behaviour of EtOAc and THF suggests inhibition by base binding to a Lewis acidic component of the catalyst system. However, the inhibition trend does not follow published solvent donor abilities. As $ZnEt_2$ is expected to be the most Lewis acidic component within the catalyst system its behaviour towards cyclohex-2-en-1-one (**CX**) was studied by ReactIR in toluene and Et_2O. Both these solvents afford rapid catalytic conversion, despite their very different classical donor number ratings[13] (Scheme 5).

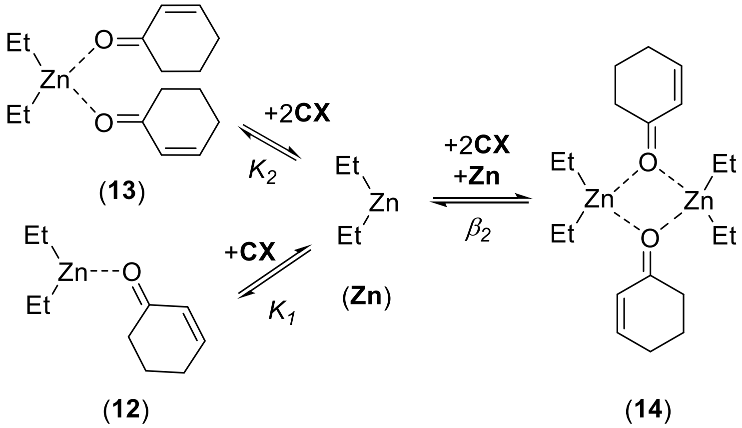


Solvent	**CX** Conv. (% at 45 mins)[a]	Donor Number[b] (kcal mol^{-1})
Et_2O	>98	19
toluene	90	0.1
CH_2Cl_2	60	1
EtOAc	40	17
THF	<5	20

Scheme 5. Relative conversion of cyclohex-2-en-1-one **CX** *vs*. reaction solvent. [a] Determined by ^{1}H NMR spectroscopy after quench with methanol; all reactions, except those in THF, proceeded to completion if left long enough. [b] Solvent binding energy to the ‘hard’ Lewis acid $SbCl_5$.[13]

In both toluene and Et_2O two carbonyl bands at ca. 1685 and 1660 cm^{-1} are seen as $ZnEt_2$ is titrated into **CX** (Supporting Information, Figure S1). The former corresponds to free **CX** and the latter to a $ZnEt_2$ bound adduct(s). Unlike our previous work with $AlEt_3$,[6] no significant color change is seen for these adducts. We compared the fit of $ZnEt_2$ (**Zn**) binding isotherms leading to mono (**12**) and di (**13**) cyclohex-2-en-1-one (**CX**) adduct formation and for the formation of dimeric (**14**) (Scheme 6). Free coordination sites were assumed to be bound by solvent (whose bulk concentration remains unchanged). For both toluene and Et_2O formation of mono adduct (**12**) is nominally the best fit, but not significantly favoured over di-coordinated (**13**). The fit to dimer (**14**) formation is poorer, but with high β_2 values. The correlation of the equilibria values of Scheme 6 (assuming that the **CX** substrate acts as a simple ketone-like donor) vs. classical solvent donor number order[13] indicates the inhibition of Scheme 5 is associated with Cu(I) Lewis acid coordination, not $ZnEt_2$ binding. The potential for **12-14** to undergo rapid exchange is supported by additional experiments in CH_2Cl_2 where a broad envelope of signals is seen in the ReactIR spectrum (Supporting Information, Figure S2). Potential rapid exchange of **12-14** means that the transmetalating species involved in reloading the Cu-catalyst cannot easily be uniquely identified or accurately quantified. For this reason we chose to monitor catalytic reactions by formation of the product enolate (**E**) (Scheme 4). Dichloromethane is the preferred ReactIR solvent for these studies as the ν(C-O) at

1145 cm^{-1} of enolate **E** is easily detected in this solvent, while overlaps with solvent vibrations are encountered in toluene and Et_2O solvents. A further advantage of CH_2Cl_2 is that the rate of the catalytic 1,4-addition is slow enough in this solvent to allow direct monitoring of the reaction mixture by both multinuclear NMR and ReactIR under identical conditions.



	Value, R^2 fit in toluene	Value,R^2 fit in Et_2O
K_1 (M^{-1})	4.5(3), 0.99	0.69(1), >0.99
K_2 (M^{-2})	11(2), 0.98	1.4(1), 0.99
β_2 (M^{-3})	~90,[a] 0.90	~50,[a] 0.94

Scheme 6. Adduct formation between cyclohex-2-en-1-one (**CX**) and $ZnEt_2$ (**Zn**). The figures in parentheses after the equilibrium values indicate the standard deviation in the last significant figure. [a] Large standard deviations occur for high values of β_2 attained by such titration methods (see Supporting Information, Figure S5 and ref. S97). However, the much poorer fit of the data to **14** indicates formation of **12-13** are very significantly more favoured.

Formation of the active catalyst The 1,4-addition of $ZnEt_2$ (**Zn**) to cyclohex-2-en-1-one (**CX**) under **7**/$\mathbf{L_A}$ catalysis leads to **10a** (after quench) with a time (and run) independent *ee* of 96% over the ca. 700 sec needed to attain complete conversion at –40 °C. This implies a single selective copper catalyst (transition state) delivers the enolate product (*R*)-**E**. However, replicate ReactIR studies of such *first dose* addition of mixtures of **Zn** and **CX** show very poor run-to-run reproducibility with $k_1 = 4.3 \times 10^{-3}$ s^{-1} to 8.6×10^{-3} s^{-1} varying in a stochastic manner (Figure S7, Supporting Information) implying the presence of competing catalytic and non-catalytic species. Similar rate variation observations are present in the supporting data of Pfretzschner.[7] Suspecting a slow varying induction period, lasting most of the initial reaction, was the cause of the poor reproducibility in these first run dose reactions we used multiple dosing experiments to probe for this possibility (Figure 1). Addition of *second* doses, and then *third* doses of $ZnEt_2$ (**Zn**) and cyclohex-2-en-1-one (**CX**) after completion of the initial *first dose* reactions confirms the (concentration corrected) first order rate constants of the latter two additional dose reactions *are* identical and reproducible when allowing for the dilution of the reaction (Figure 1) and are independent of the enolate concentration. These observations indicate that a variable composition of copper(I) species is present during the initial dose reactions but only one of these species (**Cu**) is catalytically competent for the transformation of **CX** into 96% *ee* enolate (**E**).

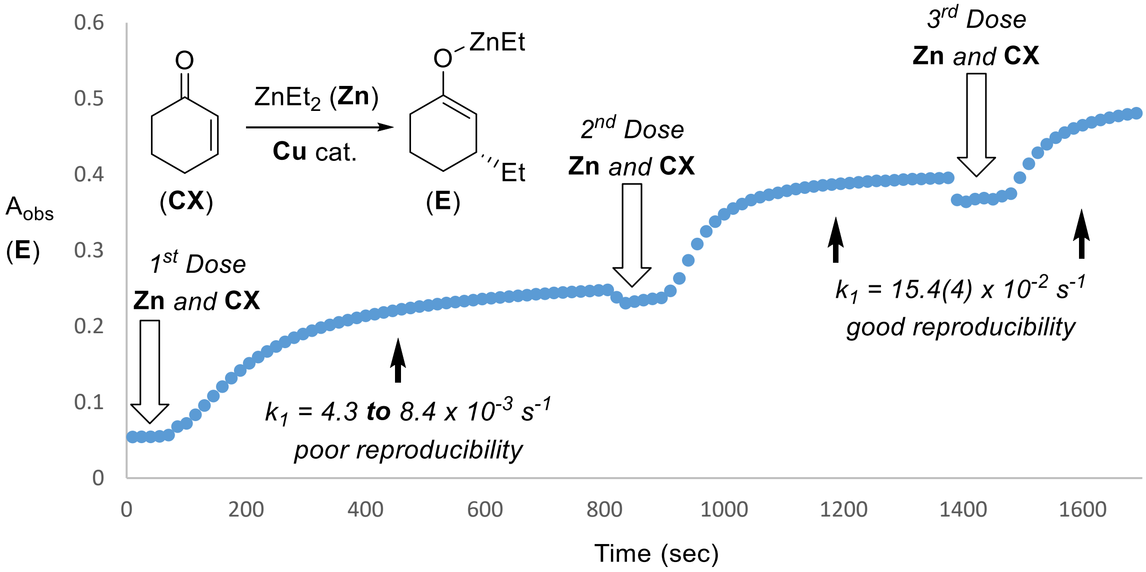
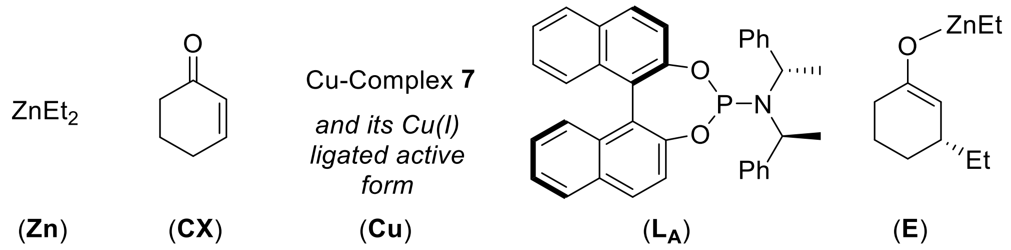


Figure 1. ReactIR observation of the **7/L$_A$** catalysed formation of enolate (**E**) via its 1145 cm^{-1} band in a multiple dosing experiment. As each reaction completes fresh $ZnEt_2$ (**Zn**) and cyclohex-2-en-1-one (**CX**) is added and catalysis restarts. First dose experiments show poor reproducibility (see Figure S7, Supporting Information), but the 2nd and 3rd dose derived first order rate constants show good reproducibility when allowing for the dilution occurring in the reaction from dose 2 to 3.

Multinuclear NMR studies, under identical conditions to the *first dose* addition of Figure 1, support these ideas. Mixtures of (*R*,*S*,*S*)-**L$_A$** and **7** (2:1) show broad envelope signals at δ_P ~123.9 and δ_F ~ –75.8 indicative of rapid ligand exchange at –40 °C.[14] The line broadening of the associated ^{1}H NMR methyl signals of **L$_A$** at that temperature is ~5 Hz (an exchange rate of around 16 s^{-1} can be calculated from this via standard approaches.[5] Thus, **L$_A$** exchange is >10^3 faster than the catalytic conversion of **CX** to **E**). Using standard Eyring analysis[5] this corresponds to an energy barrier for **L$_A$** exchange of 12.3 kcal mol^{-1}, similar to the value of 11.1 kcal mol^{-1} that Pfretzschner measured for a related phosphoramidite ligand.[5] After the addition of excess $ZnEt_2$ (**Zn**, 165 equiv. wrt **7** present; identical concentrations to the synthetic and kinetic studies) at –40 °C a mixture of species is formed (Figure S6) whose major components, by ^{31}P NMR are: δ_P 123.0, 123.8 and 124.8. These shifts are at similar values to those of the species: (**L$_B$**)$_2$Cu(μ-Et)(μ-I)CuEt (121.5 ppm), **L$_B$**CuEt (124.0 ppm), [**L$_B$**Cu($ZnEt_2$)]I (126.0 ppm) and (**L$_B$**)$_2$Cu(μ-Et)(μ-I)ZnEt (126.1 ppm) at –103 °C in CD_2Cl_2 at a ratio of 46:28:19:7 characterised by von Rekowski via exquisite 2D NMR techniques.[8d] However, in our case, once cyclohex-2-en-1-one (**CX**, 130 equiv. wrt initial **7**; identical concentrations to the synthetic and kinetic studies) is added to this mixture the separate ^{31}P NMR signals collapse into a broad baseline signal by the end of the 10 mins needed for complete conversion of **CX** to the enolate product (**E**). This collapse of ^{31}P NMR signal intensity is *not* due to catalyst deactivation. The NMR experiment is under identical conditions of Figure 1 where the rates in doses 2 and 3 (allowing for the dilution caused by adding additional **Zn** and **CX**) remain constant, inconsistent with any catalyst deactivation. The ^{31}P NMR behaviour is, however, consistent with *initial* formation of off-cycle copper species, related to those of von Rekowski[8d] that evolve during conversion of cyclohex-2-en-1-one (**CX**) into the true catalyst (**Cu**). The slow emergence of a final, rapidly equilibrating, catalyst is supported by the ^{19}F NMR spectra of the initial reaction mixture (Figure S6). Immediately after $ZnEt_2$ (**Zn**) addition two new major sharp signals appear at δ_F –75.7 and –76.0. The former is at a chemical shift with experimental error for independently prepared uncoordinated trifluoroacetate δ_F –75.6, the latter that for CF_3CO_2H (δ_F –76.1).[14] These signals convert to a new species at δ_F –75.8. Upon addition of cyclohex-2-en-1-one (**CX**) catalysis ensues and the ^{19}F NMR signals collapse to a broad envelope at –75.6 ppm accounting for the vast majority of the signal. Such behaviour is expected for a trifluoroacetate anion undergoing rapid exchange into a slowly formed final catalyst (**Cu**).

Reaction Component Orders for the 7/$\mathbf{L_A}$/$\mathbf{ZnEt_2}$/Cyclohex-2-en-1-one System Double dosing approaches (see Figure S8) allowed reproducible (rate ±2-4%) behaviour for the true catalyst **Cu** (derived from **7**/$\mathbf{L_A}$). Preliminary studies revealed that although the **Cu**-catalysed conversion of $ZnEt_2$/cyclohex-2-en-1-one into enolate **E** strictly follows first order kinetics (R^2 0.99 to 0.999+ for all runs)[15] non-unitary reaction orders result. Additionally, the preliminary studies showed that at [$\mathbf{L_A}$]/[**Cu**] ratios below 0.8 and above 2.1 reaction homogeneity and strong reaction inhibition respectively prevent the attainment of accurate kinetic data. The air sensitivity of the system makes determination of the order in $ZnEt_2$ (**Zn**) particularly challenging. Within these limitations we set out to estimate the reaction rate order dependence for all the components in the equation: rate $\propto$ $[\mathbf{Zn}]^{a}[\mathbf{CX}]^{b}[\mathbf{Cu}]^{c}[\mathbf{L_A}]^{d}$ for the ligand accelerated process catalysed by **7**/$\mathbf{L_A}$ by studying the dependence of the observed rate k_1 (Table 1). By targeting $[\mathbf{Cu}]_0 = 1.7\pm0.1$ mM $[\mathbf{L_A}]_0 = 3.4\pm0.4$ mM and $[\mathbf{CX}]_0 = 220\pm27$ mM we could estimate the order in $ZnEt_2$ (**Zn**) to be $[\mathbf{Zn}]^{0.217(30)}$ for [**Zn**] 76-347 mM ($R^2 = 0.94$, Figure S9). By maintaining $[\mathbf{Cu}]_0 = 1.7\pm0.06$ mM $[\mathbf{L_A}]_0 = 3.6\pm0.04$ mM and $[\mathbf{Zn}]_0 = 285\pm9$ mM the order in cyclohex-2-en-1-one (**CX**) is determined to be $[\mathbf{CX}]^{0.272(20)}$ for [**CX**] 72-275 mM ($R^2 = 0.99$, Figure S9). At $[\mathbf{Zn}]_0 = 277\pm5$ mM and $[\mathbf{CX}]_0 = 235\pm2$ mM and at fixed $\mathbf{L_A}$:**Cu** = 2.00±0.08 the order in the copper is determined as $[\mathbf{Cu}]^{0.123(4)}$ for [**Cu**] 0.87-3.61 mM ($R^2 = 0.999$, Figure S9). For $[\mathbf{Zn}]_0 = 287\pm8$ mM, $[\mathbf{CX}]_0 = 231\pm5$ mM and with $[\mathbf{Cu}]_0 = 1.75\pm0.08$ mM the ligand acceleration order is $[\mathbf{L_A}]^{0.175(20)}$ for [$\mathbf{L_A}$] 1.59-3.37 mM ($R^2 = 0.99$, Figure S9). Thus, the full rate law is of the form rate $\propto$ $[\mathbf{Zn}]^{0.217(30)}[\mathbf{CX}]^{0.272(20)}[\mathbf{Cu}]^{0.123(4)}[\mathbf{L_A}]^{0.175(20)}$. Duplicated/reanalysed data are in accord with these values and error bars. Strong ligand inhibition of the catalytic reaction, when [$\mathbf{L_A}$]/[**Cu**] ≥2, limited the range of ligand concentrations that could be employed but using the data of Table 1 a deaccelerating order of $[\mathbf{L_A}]^{-0.25}$ could be estimated for this process.

Table 1. Summary of the ReactIR investigations carried out in this study.



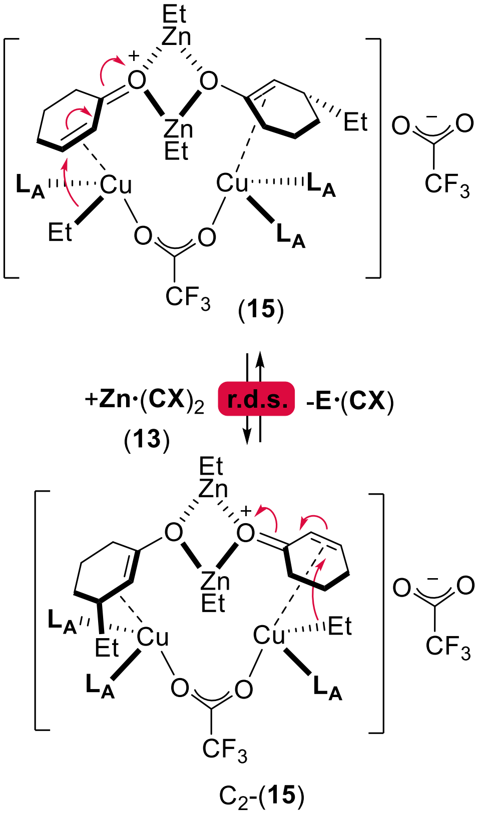
Run	[**Zn**]$_0$ (mM)	[**CX**]$_0$ (mM)	[**Cu**]$_0$ (mM)	[**L$_A$**]$_0$ (mM)	[**L$_A$**]/[**Cu**]	$k_1 \times 10^3$ (s^{-1})[a]
1	276	275	1.70	3.62	2.13	13.9(3)
2	295	72.3	1.76	3.57	2.03	9.5(1)
3	203	246	1.84	3.81	2.08	12.7(3)
4	286	233	1.75	3.65	2.08	12.9(3)
5	76.2	190	1.56	3.02	1.94	10.9(4)
6	347	221	1.70	3.44	2.03	15.4(3)
7	282	233	0.87	1.81	2.08	13.8(3)
8	278	235	3.61	7.13	1.98	17.5(1)
9	272	236	2.70	5.30	1.96	17.0(1)
10	280	235	1.86	2.40	1.28	14.3(5)
11	296	233	1.78	1.59	0.89	12.0(4)

[a] For formation of enolate **E**, a k_1 value of 13.9(3) equates to 0.00139(3) s^{-1}. All rate constants refer to catalytic conversion of second doses of $ZnEt_2$ (**Zn**) and cyclohex-2-en-1-one (**CX**) in CH_2Cl_2 at –40 °C.

■ DISCUSSION

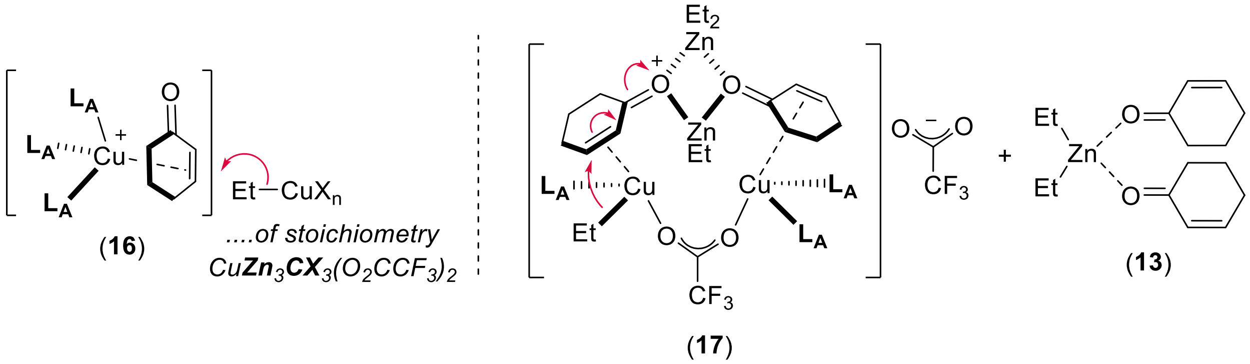
A viable mechanistic model for the **7**/**L$_A$** catalysed transformation of $ZnEt_2$ (**Zn**) and cyclohex-2-en-1-one (**CX**) into its enolate product (**E**) has to explicitly account for: (i) the non-unitary orders of the reagent dependencies and (ii) the poor '1st dose' rate reproducibility, but consistent high enantioselectivity, observed (Figure 1). The former dictates that equilibria[15] are closely tied to the rate-determining step that generates 96% *ee* **E**. The latter requires either very slow catalyst genesis or that the reaction generates a promoter, that is not initially present in the mixture, that facilitates formation of the active catalyst '**Cu**' while unpromoted copper species remain as off-cycle spectators (with k_1 ~ 0 s^{-1}). We have previously shown in related aluminum chemistry that the enolate product **E** can play such an acceleration role.[6]

The observed rate law $[\mathbf{Zn}]^{0.217}[\mathbf{CX}]^{0.272}[\mathbf{Cu}]^{0.123}[\mathbf{L_A}]^{0.175}$ provides an estimated stoichiometric ratio of $\mathbf{Zn}_{3.5}\mathbf{CX}_{4.4}\,\mathbf{Cu}_{2.0}\,\mathbf{L_A}_{2.9}$ (coefficients ±0.3) for events closely related to the transition state. One model consistent with this result is shown in Scheme 7. Catalysis proceeds by exchange between two C_2 related species **15** (Scheme 7). The rate determining step is asymmetric 1,4-addition driven by transmetalation with $Et_2Zn(\mathbf{CX})_2$ (**13**). Species **15** has stoichiometry $\mathbf{Cu}_2\mathbf{L_A}_3\mathbf{Zn}_2\mathbf{CX}_2$ (through **E** ≡ **CX** + **Zn**), which in combination with $\mathbf{Zn(CX)}_2$ (**13**), provides the observed $\mathbf{Zn}_3\mathbf{CX}_4\mathbf{Cu}_2\mathbf{L_A}_3$, transition state stoichiometry for rate determining transmetalation (see Supporting Information, Scheme S8).



Scheme 7. Proposal for catalytic turnover in **7**/$\mathbf{L_A}$ catalysed addition of $ZnEt_2$ (**Zn**) to cyclohex-2-en-1-one (**CX**).

Proposed **15** is consistent with: (i) the overall first order, but partial order in [**Cu**] behaviour, (ii) the need for enolate (**E**) to be present for maximal reproducible reaction rates, (iii) the optimal 2:3 Cu:$\mathbf{L_A}$ ratio detected in previous NMR studies of related model systems,[8] and (iv) the observation that initial mixtures of off-cycle copper-complexes[8d] converge to an equilibrating highly active single catalyst. We propose the cationic nature of (**15**) is critical to engendering the extremely rapid catalytic conjugate addition and transmetalation that are required for such rapid catalyst turnover with ZnR_2 reagents (see Table S1). Due to extensive exchange it is not possible to explicitly identify the **E**·**CX** by-product of catalytic turnover (Figure S8). However, there is strong indirect evidence that **Zn**(**CX**)$_2$ (**13**) is vital in the transmetalation. Attempted use of well characterised Et_3Al(**CX**)[6] as a terminal ethyl source in the **7**/$\mathbf{L_A}$ catalytic system leads to only background reactions at low rate strongly implying that **13** is vital for the transmetalation. Blockage of the copper(I) Lewis acid centres in (**15**) leads to complete deactivation. Either ligand $\mathbf{L_A}$ itself [forming ($\mathbf{L_A}$)$_2$CuX, X = Et, O_2CCF_3, enolate type species] (see Supporting Information, Section 7) or strongly coordinating solvents can fulfil this role. Alternative models to Scheme 7 were considered. The possibility that catalysis proceeds via a [($\mathbf{L_A}$)$_3$Cu(**CX**)]$^+$ (**16**) cation that is attacked by an unligated complex cuprate (Scheme 8) is attractive as a related phosphoamidite specie L_3CuI was identified in the seminal work of Feringa.[16]



Scheme 8. Alternative, but (computationally) disfavoured transition state compositions in accord with the derived rate law.

While calculated cation **16** (ωB97X-D/SRSC, see Figures S12 and S13) does predict that the correct *Si* enantioface of the cyclohex-2-en-1-one (**CX**) is preferentially bound, which would provide (*R*)-**E** [and ultimately (*R*)-**10a**] on attack by an external Cu-Et nucleophile, inspection of the calculated structure indicates that it is excessively cluttered and such nucleophilic attack would be extremely hindered. A transition state resulting from transmetalation of **17** (Scheme 8) with $ZnEt_2$(**CX**)$_2$ (**13**) would also be in agreement with the observed rate law, and this could not be explicitly discounted on kinetic data alone. However, on the basis of DFT modelling **15** is the preferred structure, as structure **17** (and species derived from it) are computationally very poorly behaved.

■ CONCLUSIONS

Study of the highly active ACA catalyst derived from $[Cu(MeCN)_4]$TFA·TFAH (**7**)/(*R*,*S*,*S*)-**L_A** reveals why extraction of mechanistic information from Cu(I)-catalysed reactions of enones with diorganozinc species has previously proved highly challenging.[5,7] Genesis of the active catalyst is slow compared to catalyst turnover and the fraction of active catalyst present early in the reaction is variable. This has not been appreciated before. Double dosing kinetic experiments point to a transition state of composition $(ZnR_2)_3(enone)_4Cu_2L_3$ associated with a first order transformation strongly coupled to faster exchange processes. Once simple picture consistent with this picture is a rate determining transmetalation that also triggers the ACA reaction (Scheme 7). While the real system undoubtedly has other competing processes, this appears to be the major catalytic manifold. Such a picture is also broadly consistent with the Cu_2L_3 model proposed by Gschwind[8] but some modification is required to her original proposal (see **6** within Scheme 2). Specifically, expulsion of one of the μ-X (X = O_2CCF_3) units in **6** and the coordination of additional equivalents of $ZnEt_2(enone)_2$ are required to fit the experimental data in our own particular case. It is likely that the cationic nature of **15** accounts for the higher catalytic activity that is seen in ACA systems attained from copper(I) precursors with weakly cuprophilic basic anions (pKaH ≤ 1) in general, and in the case of **7** specifically.

■ EXPERIMENTAL

Full experimental details of all compounds and kinetic procedures used are detailed in the Supporting Information.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: to be provided by the Editorial Office.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

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