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Strong ligand accelerated catalysis by an Arduengo-type carbene in copper-catalysed conjugate addition

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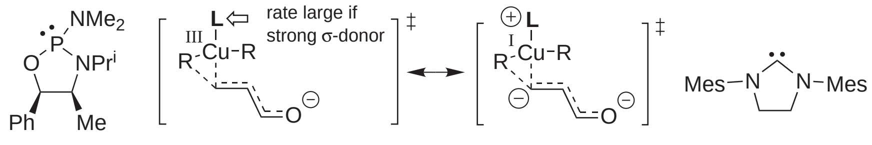
Abstract—The addition of stabilised carbene ligand:$\overline{\text{CNMesCH}_2\text{CH}_2\text{N}}\text{Mes}$ (Mes = 2,4,6-$\text{Me}_3\text{C}_6\text{H}_2$) results in a dramatic rate increase in the Cu(OTf)_2-catalysed conjugate addition of ZnEt_2 to enones (OTf = triflate anion). © 2001 Elsevier Science Ltd. All rights reserved.

The recent successes in the field of copper-catalysed additions of organozinc reagents to Michael acceptors,[1] especially enones, may be traced to the seminal discovery of Alexakis of the strong rate acceleration provided by **1** in copper-catalysed ZnEt_2 addition to cyclohexenone.[2] Current theoretical thinking suggests that the origin of the ligand accelerated catalysis (LAC[3]) shown by **1**, and related electron-rich phosphoramidite ligands, is σ-donor stabilisation of the putative copper(III) transition state.[4] One representation of this effect is shown in structures **2a**–**b** (Scheme 1). Electron density transfer between the σ-donor and the developing enolate product avoids the need to attain a high energy Cu^{3+} 3d^8 configuration at the metal centre; a similar felicitous bonding scheme to that observed in isolable $[\text{Cu(CF}_3)_4]^-$.[5] Such effects should be independent of the nature of the σ-donor. We reasoned that the stabilised carbene ligand **3**, introduced by Arduengo,[6] should provide similar strong LAC effects due to its electronic similarity to electron-rich phosphorus ligands. While a few copper(I) complexes are known[7–11] we are not aware of any copper-catalysed reactions using such ligand types.

In our studies ligand **3** was generated by deprotonation of the precursor imidazolium salt by Bu^{t}OK in THF and this solution reacted with Cu(OTf)_2 in toluene/THF to form the pre-catalyst in situ. This catalyst system (3 mol% Cu; 3.5 mol% **3**) was exposed to ZnEt_2 (1.0 M in hexane) and cyclohexenone **4a** which led to rapid formation of the conjugate addition product (after quenching with aq. HCl). The time dependence of this reaction was compared to a ligand free run under otherwise identical conditions (Fig. 1).[†] The presence of



1 **2a** **2b** **3**

Scheme 1. Ligands and mechanisms for LAC effects in conjugate addition.

Keywords: enones; carbenes and carbenoids; zinc and compounds.

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[†] Procedure for Fig. 1 conjugate additions: A stock solution of **3** was generated by addition of Bu^{t}OK (1.1 equiv., 21.6 mg, 0.193 mmol) in THF to the precursor imidazolium salt[6] (60.0 mg, 0.175 mmol) in THF. An aliquot of this solution (0.5 mL, 0.035 mmol, 3.5 mol%) was added to a suspension of Cu(OTf)_2 (11.0 mg, 0.030 mmol, 3.0 mol%) in toluene (0.5 mL) affording a 1:1 THF:toluene solution and the mixture stirred (5 min, −20°C). At −20°C ZnEt_2 (1.1 mL of 1.0 M hexane solution, 1.10 mmol) was added. Enone **4a** (97 μL, 1.00 mmol) was introduced rapidly but dropwise via a μL-syringe. The reaction mixture was stirred for the time indicated then quenched with HCl (aq.); undecane (50 μL) was added and the mixture filtered (twice) through flash silica. The chemical yield was then obtained by GC (as described before[12]) or by isolation. Control runs were made under identical conditions (including the mixed THF/toluene solvent) but in the absence of **3**.

Runs in Tables 1 and 2 were conducted in a similar manner using increased loadings of copper [derived from Cu(OTf)_2 (18.0 mg, 0.045 mmol, 4.5 mol%) and **3** (0.05 mmol, 5 mol%)]. These runs were also allowed to warm to −12°C over 30 min. The runs in Table 2 were also conducted with increased amounts of ZnEt_2 (1.5 mL of a 1.0 M hexane solution, 1.50 mmol).

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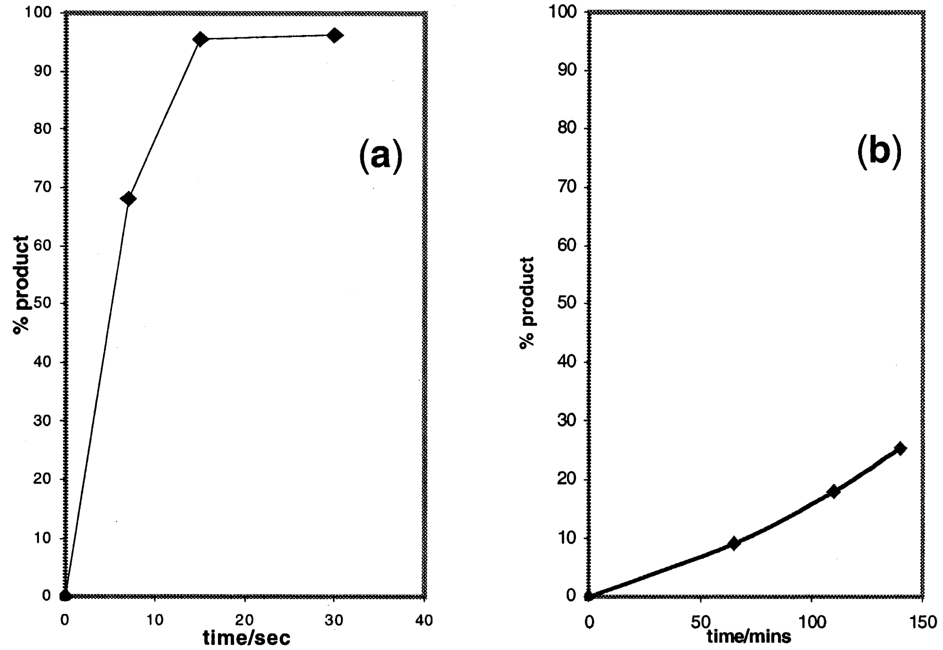
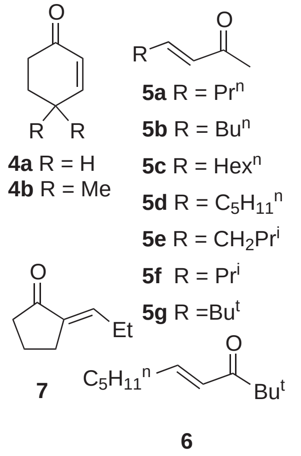


Fig. 1. Reaction of **4a** with $ZnEt_2$ in the presence (**a**) and absence (**b**) of **3**.



Scheme 2. Enones used in this study.

a strong LAC effect was clear but the background reaction, in the absence of **3**, was appreciable at long reaction times. To investigate the substrate dependence of the LAC effect addition to a series of enones (Scheme 2) were carried out in the absence and presence of **3** under identical conditions (short reaction time, increased copper loading and limited $ZnEt_2$) (Table 1).

While it was clear ligand **3** did engender a large LAC effect the substrate conversion was not complete, therefore, the reaction conditions were optimised by increasing the amount of $ZnEt_2$ used. Under these conditions a number of enones reacted satisfactorily within 30 min (Table 2).

Clearly ligand **3** is an effective additive in copper-catalysed conjugate addition. However, the present system is rather sensitive to steric requirements of the Michael acceptor. Enones **4b** and **5f** gave inferior yields versus analogous **4a** and **5a**–**d**. Somewhat more encumbered substrates (enones **5g** and **6**) did not react at all. Additionally, the exocyclic enone **7** did not participate in the reaction. In conclusion, the presence of a strong LAC effect for ligand **3** has been detected. This forms the basis of our present investigations in seeking ligands displaying higher activity and the possibility of asymmetric catalysis.

Table 1. LAC studies on 1,4-addition of $ZnEt_2$ to various enones[a]

Enone	Cu/mol% (conc./mM)	**3**/mol% (conc./mM)	Conv. (%)[b]	Yield (%)[b]
4a	4.5 (0.045)	5.0 (0.050)	83	82
4a	4.5 (0.045)	–	43	14
5b	4.5 (0.045)	5.0 (0.050)	84	62
5b	4.5 (0.045)	–	2	2
5d	4.5 (0.045)	5.0 (0.050)	84	46
5d	4.5 (0.045)	–	35	2

[a] Carried out in THF/toluene (1:1, 1.0 mL) at −20°C and allowed to warm to −12°C over 30 min.

[b] Determined by GC (versus internal standards).

Table 2. 1,4-Addition of $ZnEt_2$ to various enones under optimised conditions[a]

Enone	Cu/mol% (conc./mM)	**3**/mol% (conc./mM)	Conv. (%)[a]	Yield (%)[b]
4a	4.5 (0.045)	5.0 (0.050)	100	100
5a	4.5 (0.045)	5.0 (0.050)	100	(65)
5b	4.5 (0.045)	5.0 (0.050)	100	85
5c	4.5 (0.045)	5.0 (0.050)	100	(90)
5d	4.5 (0.045)	5.0 (0.050)	100	63
5e	4.5 (0.045)	5.0 (0.050)	100	48
5f	4.5 (0.045)	5.0 (0.050)	37	3
4b	4.5 (0.045)	5.0 (0.050)	73	(60)

[a] Carried out in THF/toluene (1:1, 1.0 mL) at −20°C and allowed to warm to −12°C over 30 min.

[b] Determined by GC (versus internal standards) or NMR and isolation (isolated yields in parentheses).

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