Mechanistic studies on the asymmetric alkylation of amino ester enolates using a copper(II)salen catalyst

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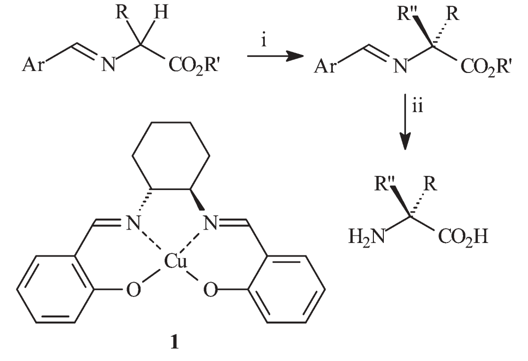
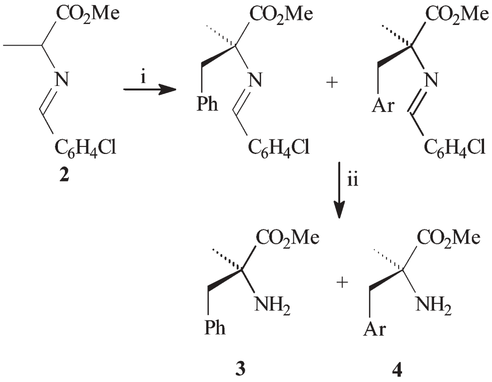
Hammett data indicate that the asymmetric alkylation of enolates catalysed by copper(II)salen complex 1, proceeds by an asynchronous S_N2 reaction and that the role of the catalyst is to enhance the nucleophilicity of the enolate.

There is currently considerable interest in the use of asymmetric phase transfer catalysis to prepare non-racemic α-amino acids or α,α-disubstituted amino acids from achiral amino-ester derived enolates.[1–4] Most work in this area has focused upon the use of quaternary ammonium salts as the phase transfer catalyst, with excellent results being obtained using cinchona alkaloid derivatives[2] and C_2-symmetric binaphthyl compounds.[3] In recent papers, we have demonstrated that copper(II)salen complex **1** will also catalyse the asymmetric alkylation of enolates of amino esters under solid–liquid phase transfer conditions as shown in Scheme 1.[5,6]

The range of alkylating agents that can be used for the chemistry shown in Scheme 1 is intriguing since benzylic, allylic and propargylic bromides all give high yields of α,α-dialkylated amino esters. In contrast, methyl iodide, ethyl iodide and ethyl triflate totally failed to react.[5] This suggested that the reaction might not be a simple S_N2 reaction between the alkylating agent and a copper-coordinated enolate since only electrophiles which could stabilise a charged transition state reacted. To investigate this aspect of the reaction, the experiment shown in Scheme 2 was designed. In this experiment, alanine derivative **2** was allowed to react with an excess of benzyl bromide and an excess of a second *meta*- or *para*-substituted benzyl bromide. Initially, the second alkylating agent was *para*-nitrobenzyl bromide. A reaction with a build-up of positive charge in the transition state (in the extreme case an S_N1 reaction) would be expected to favour the more electron-rich benzyl bromide, whilst if the reaction was a synchronous S_N2 reaction little or no reactivity difference would be expected between the two alkylating agents. In the event however, the reaction displayed an 8:1 preference for reaction with the more electron-deficient *para*-nitrobenzyl bromide, giving product **4** (Ar = 4-nitrophenyl) in preference to amino ester **3** as determined by ^{1}H NMR spectroscopy. This clearly ruled out any possibility of the transition state possessing a significant amount of positive charge, and to obtain further mechanistic information a range of other competition experiments involving benzyl bromide and another *meta*- or *para*-substituted benzyl bromide were carried out (Table 1) to construct a Hammett type plot† (Fig. 1: diamonds).[7]



Scheme 1 Reagents: (i) **1** (2 mol%), NaOH, R″Br, toluene, room temperature; (ii) H_3O^+.



Scheme 2 Reagents: (i) **1** (2 mol%), NaOH, BnBr (1.2 eq.), $ArCH_2Br$ (1.2 eq.); (ii) MeOH, AcCl.

As can be seen from Fig. 1, in all cases electron-withdrawing substituents on the aryl ring accelerated the rate of reaction relative to benzyl bromide, though the correlation is not linear,‡ and appears to be slightly U shaped with a minimum around $\sigma = 0$ since the 4-*tert*-butyl derivative also reacted slightly faster than benzyl bromide. It was not experimentally feasible to extend the study to electrophiles with σ-values significantly less than zero as these are so reactive that they react with the sodium hydroxide under the experimental conditions. The observed trend is however similar to that previously reported for an asynchronous S_N2 reaction involving a negatively charged nucleophile, where a U-shaped curve with considerable scatter about the best fit curve was observed.[8]

Additional mechanistic evidence came from a series of experiments in which the reaction shown in Scheme 2 was repeated but with the omission of any catalyst (Fig. 1: squares). The data for the uncatalysed reaction (Table 1) show the same

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Table 1 Percentage yields for products **3** and **4** from competition experiments[a]

Ar	σ[c]	Catalysed	Yield (%)[b] **3**	Yield (%)[b] **4**	Ratio[b] **4**:**3**
4-$(NO_2)C_6H_4$	0.78	Yes	5	42	8.4:1
4-$(NO_2)C_6H_4$	0.78	No	13	47	3.7:1
4-$(SO_2Me)C_6H_4$	0.73	Yes	6	31	4.7:1
4-$(SO_2Me)C_6H_4$	0.73	No	13	31	2.3:1
3-$(NO_2)C_6H_4$	0.72	Yes	10	24	2.4:1
3-$(NO_2)C_6H_4$	0.72	No	13	30	2.3:1
4-$(CN)C_6H_4$	0.66	Yes	5	27	5.3:1
4-$(CN)C_6H_4$	0.66	No	11	27	2.4:1
4-$(CO_2Me)C_6H_4$	0.39	Yes	15	29	1.9:1
4-$(CO_2Me)C_6H_4$	0.39	No	24	29	1.2:1
4-BrC_6H_4	0.23	Yes	11	21	1.9:1
4-BrC_6H_4	0.23	No	20	24	1.2:1
4-FC_6H_4	0.06	Yes	10	22	2.3:1
4-FC_6H_4	0.06	No	16	24	1.5:1
4-(*t*-Bu)C_6H_4	−0.2	Yes	20	34	1.7:1
4-(*t*-Bu)C_6H_4	−0.2	No	32	32	1.0:1

[a] Reactions were carried out as specified in Scheme 2. [b] The percentage yields are for the unseparated products and were calculated from the total isolated mass and the ratio of **4**:**3** determined by ^{1}H NMR spectroscopy. [c] σ-Values were taken from reference 7.

trend as for the catalysed reaction, but in all cases the ratio of products **4**:**3** was lower for the uncatalysed reaction than for the catalysed reaction.

The enhanced reactivity observed for aromatic bromides bearing electron-withdrawing groups indicates that electron transfer from the enolate to the alkyl bromide is faster than the cleavage of the carbon–bromine bond, leading to a build-up of negative charge at the benzylic carbon in the transition state. The degree of electron transfer is greater in the catalysed reaction than in the uncatalysed reaction, indicating that part of the role of catalyst **1** is to enhance the nucleophilicity of the enolate formed from ester **2**. The degree of asynchronicity varies from substrate to substrate, resulting in a non-linear correlation and in the case of the 4-*tert*-butyl derivative, the cleavage of the carbon–bromine bond may be slightly faster than formation of the carbon–enolate bond. Complete transfer of an electron from the enolate to the alkyl halide would correspond to formation of a radical-anion species. The possibility of a radical mechanism was investigated by the use of alkyl halides such as cyclopropylmethyl bromide and hex-5-enyl bromide which would ring-open/ring-close under radical conditions. However, no evidence to support such a mechanism was obtained from these experiments. Furthermore, addition of TEMPO to a standard alkylation reaction (to form compound **3** from substrate **2** and benzyl bromide) resulted in no change to the yield or enantiomeric excess of the product. Thus, it appears that electron transfer from the enolate to the alkyl halide, whilst faster than the breaking of the carbon–bromine bond, is incomplete in the transition state of the reaction.

These results explain why only alkylating agents (benzylic, allylic or propargylic halides) which are reactive under S_N2 conditions and can stabilise a charged transition state are substrates for the asymmetric alkylation reaction. They also indicate that complex **1**

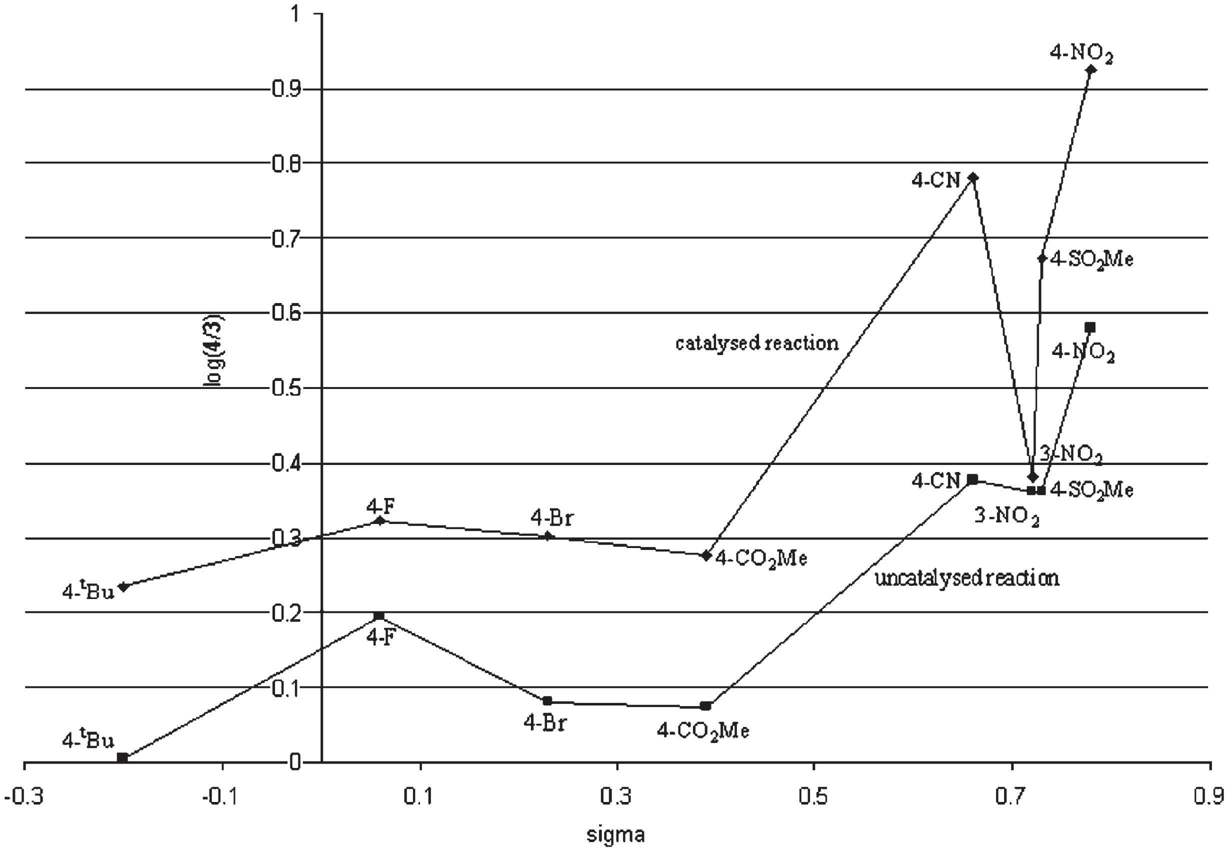

Fig. 1 Hammett plot for the catalysed (diamonds) and uncatalysed (square) reactions.

catalyses the reaction by enhancing the reactivity of the enolate derived from ester **2**.

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Notes and references

† A true Hammett plot would show the relative rates of reaction rather than the relative yields. However, the measurement of rates of reaction for these heterogeneous reactions was not feasible. As Table 1 shows, none of the reactions has given a total yield higher than 64% under the conditions used for the competition experiments. Since a total of 2.4 equivalents of alkylating agent was used in the reactions, the ratio of isolated yields should approximate to the ratio of reaction rates.

‡ Hammett type plots using σ^- or σ^+ were also not linear.

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