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Introduction

Beyond *N*-heterocyclic carbene (NHC) catalysed formation of acyl anions,¹ advances in the field have revealed subsequent umpolung events that provide acyl azoliums, their enols, and enolates.² Collectively these redox isomerisation reactions have emerged as the dominant paradigm, allowing aldehyde containing substrates (**1**) to be converted to functionalised, and often enantioenriched, esters (**2**) (Fig. 1, eqn (1)).^{2–7} In contrast, to the best of our knowledge, the reverse, in which esters (**3**) undergo redox isomerisation to give aldehydes (**4**), are unknown (eqn (2)). Herein, we report an NHC catalysed redox isomerisation with ester reduction (**3** → **4**).

N-Heterocyclic carbene catalysed redox isomerisation of esters to functionalised benzaldehydes[†]

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N-Heterocyclic carbene catalysed redox isomerisation with reduction about the carbonyl has been developed in the transformation of trienyl esters to tetrasubstituted benzaldehydes. The reaction proceeds in good to excellent yield, and in cases that provide 2,2'-biaryls, enantioselectivity is observed. Mechanistic studies demonstrate the intermediacy of a cyclohexenyl β -lactone, while implicating formation of the homoenolate as turnover limiting.

Over the last 5 years, studies from our group have revealed NHC catalysed (4 + 2) annulations which define an approach to cyclohexenes orthogonal to the Diels–Alder reaction.⁸ Mechanistically, these reactions commence with a vinylogous Michael/aldol/lactonisation cascade to produce cyclohexenyl β -lactones.^{8c} These can decarboxylate,^{8b} be trapped with nucleophilic reagents^{8c} and, in some cases, be isolated.^{8a} Within this family of reactions we recently developed an enantioselective cycloisomerisation of triene **6** to cyclohexenyl β -lactone **7** (Fig. 2).^{8a} Whilst developing this transformation, a remarkable switch in reactivity was observed through subtle changes to catalyst and solvent. Specifically, this allowed the conversion of trienyl ester **6** to benzaldehyde **5** via the previously described cascade, coupled with a redox isomerisation resulting in reduction about the carbonyl group (eqn (3)). This type of redox isomerisation is rare. Chi *et al.* has reported related reactivity, although in their studies a subsequent isomerisation returned ester containing products.^{9f,i} Aside from the novelty of this redox isomerisation, discovery of this reaction adds to the limited family of known NHC-catalysed reactions with ester substrates,^{2k,8–11} while also defining a new approach to heavily substituted benzaldehyde derivatives.¹² In this edge article, we report the development, scope and mechanistic study of this reaction.

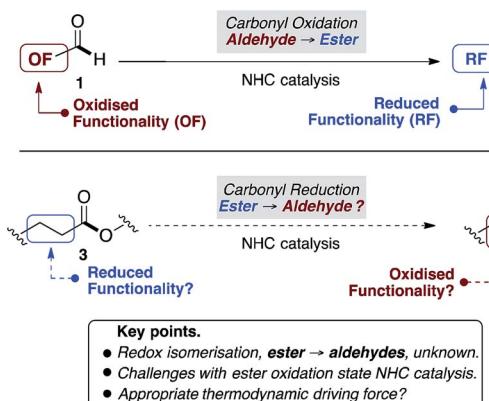


Fig. 1 Conceptual background.

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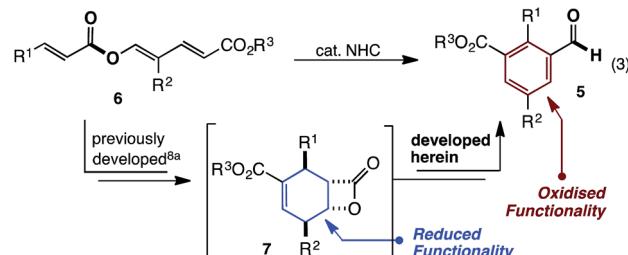


Fig. 2 Developed herein.



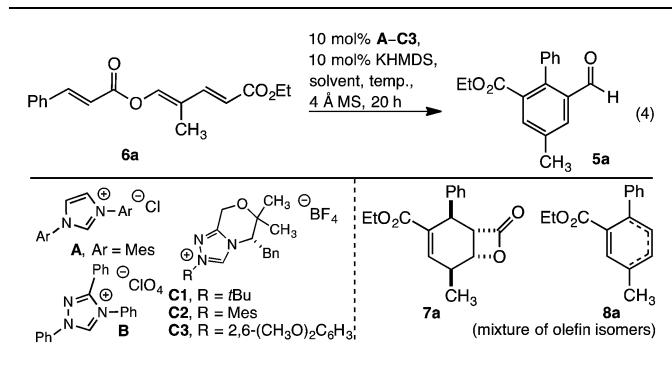
Results and discussion

Reaction development commenced with triene **6a**. Upon heating in THF, with an NHC derived from precatalyst **A**, the desired redox isomerised aldehyde **5a** formed as a minor component, along with β -lactone **7a** and cyclohexadiene **8a** (Table 1, entry 1). Formation of benzaldehyde **5a** generated water, which may protonate the NHC. To eliminate this pathway, a desiccant was introduced thereby improving the yield of **5a** to 43% (Table 1, entry 2). The reaction displayed significant sensitivity to solvent. Thus while dioxane disfavoured benzaldehyde formation (Table 1, entry 3), toluene and benzene both improved selectivity, with the latter giving **5a** in 64% isolated yield when heated at reflux (Table 1, entries 4 and 5). Unfortunately, longer reaction times favoured decarboxylation, and the yield of **5a** was not increased. To improve the outcome, and avoid decarboxylation, modification of the catalyst was examined. While Ender's TPT precatalyst **B** and *N*-*t*Bu or *N*-Mes morpholinone precatalysts **C1** or **C2** failed to improve the outcome (Table 1, entries 6–8), 2,6-dimethoxyphenyl **C3** gave aldehyde **5a** in a moderately improved yield (Table 1, entry 9).¹³ In contrast to the reaction with **A**, conducting the reaction with **C3** for an extended period improved the outcome; with aldehyde **5a** isolated in 87% yield without appreciable decarboxylation (Table 1, entry 10).

Reaction scope

The generality of the reaction was examined with the transformation of trienyl esters **6a–n** (Table 2) using precatalysts **A**

Table 1 Selected optimisations



Entry	Precat	Solvent	Temp	5a : 7a : 8a ^a	Yield ^b
1 ^c	A	THF	66	1 : 2 : 1	11%
2	A	THF	66	1 : 1 : 0	43%
3	A	Dioxane	101	1 : 17 : 0	Trace
4	A	Toluene	110	2 : 3 : 0	24%
5	A	Benzene	80	7 : 3 : 0	64%
6	B	Benzene	80	—	—
7	C1	Benzene	80	—	Trace
8	C2	Benzene	80	2 : 3 : 0	32%
9	C3	Benzene	80	11 : 2 : 0	67%
10 ^d	C3	Benzene	80	20 : 1 : 0	87%

^a Determined by ¹H-NMR analysis. ^b Isolated yield following flash column chromatography. ^c Without 4 Å MS. ^d Reaction conducted for 42 hours.

Table 2 Scope

Entry	Precat	5/6	R ¹	R ²	R ³	Yield ^a
						(%)
1a	C3	a	Ph	CH ₃	Et	87%
b	A	a	Ph	CH ₃	Et	65%
2a	C3	b	p-CH ₃ C ₆ H ₄	CH ₃	Et	91%
b	A	b	p-CH ₃ C ₆ H ₄	CH ₃	Et	65%
3a	C3	c	p-CH ₃ OC ₆ H ₄	CH ₃	Et	71%
b	A	c	p-CH ₃ OC ₆ H ₄	CH ₃	Et	51%
4a	C3	d	p-BrC ₆ H ₄	CH ₃	Et	68%
b	A	d	p-BrC ₆ H ₄	CH ₃	Et	57%
5	A	e	p-NO ₂ C ₆ H ₄	CH ₃	Et	43%
6	C3	f	2-Furyl	CH ₃	Et	56%
7	C3	g	Ph	Bn	Et	80%
8	C3	h	p-CH ₃ C ₆ H ₄	Bn	Et	85%
9	C3	i	Ph	Et	Et	52%
10	C3	j	p-CH ₃ C ₆ H ₄	Et	Et	59%
11	C3	k	Ph	iPr	Et	Trace
12	C3	l	Ph	CH ₃	CH ₃	77%
13	C3	m	p-CH ₃ C ₆ H ₄	CH ₃	CH ₃	72%
14	C3	n	p-CH ₃ C ₆ H ₄	CH ₃	iPr	81%

^a Isolated yield following flash column chromatography.

and **C3**. While commercially available IMes precatalyst **A** was adequate in most cases, the yield was generally enhanced using **C3**. For example, while examining the impact of electronics about the cinnamoyl portion, it was found that electron neutral, rich, or moderately poor trienes **6a–d** gave the expected aldehydes **5a–d** in 68–91% yield using **C3** (Table 2, entries 1a, 2a, 3a and 4a) and 11–26% lower yield using IMes **A** (Table 2, entries 1b, 2b, 3b and 4b). In contrast, the highly electron poor *p*-NO₂C₆H₄ triene **6e** only reacted with IMes precatalyst **A** (Table 2, entry 5). The reaction's capacity to tolerate heteroaromatic substituents was examined using furan containing triene **6f**, which in-turn provided benzaldehyde **5f** in acceptable yield (Table 2, entry 6). Next, modification of the R² substituent within the diene was investigated. A benzyl group was tolerated, with benzaldehydes **5g** and **h** prepared in 80 and 85% yield respectively (Table 2, entries 7 and 8). Similarly, ethyl benzaldehydes **5i** and **j** could be prepared, albeit in modest yields (Table 2, entries 9 and 10). The isopropyl group was not tolerated, with only traces of the expected aldehyde **5k** observed (Table 2, entry 11). Finally, the reaction was found to be insensitive to the nature of the ester, with methyl and isopropyl esters reacting smoothly to give the expected benzaldehydes **6l**, **m** and **n** in good yield (Table 2, entries 12–14).

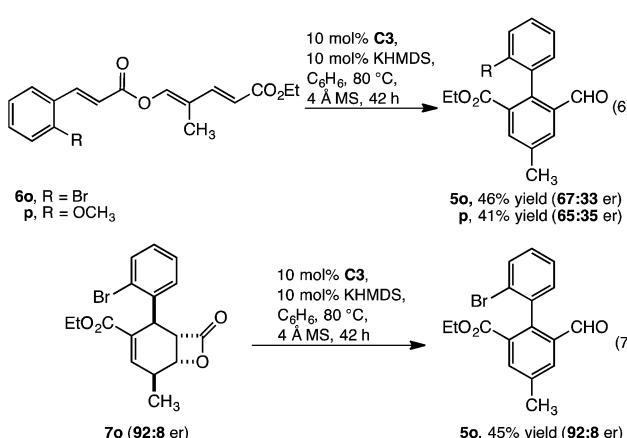
Enantioselectivity and mechanistic studies

The transformation, as catalysed by homochiral **C3**, introduces a potential approach to enantioenriched axially chiral products. This was realised, with **6o** and **p** converted to enantioenriched

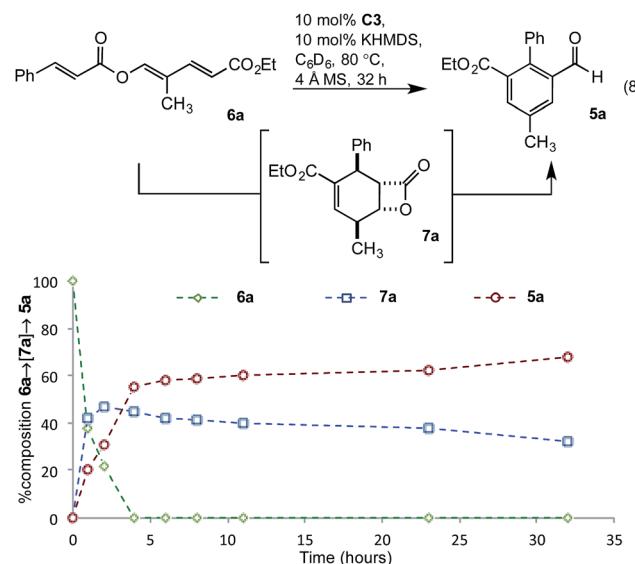
2,2' biaryls **5o** and **p** with moderate enantioselectivity and yield (eqn (6)). Although considerable effort was directed towards improving the level of enantioselectivity, this was not possible. To understand this limitation, we investigated whether the low enantioselectivity was connected to limitations in (i) point to axial chirality relay¹⁴ or (ii) establishing point chirality. Thus, when the enantioenriched β -lactone intermediate **7o** (92 : 8 er) was prepared^{8a} and subsequently converted to **5o** by catalyst **C3** complete stereoretention was observed (eqn (7)). This result indicates that the limitations are likely linked to accessing enantioenriched β -lactone intermediate **7** with catalyst **C3** (Scheme 1). Supporting this observation, when conversion of **6o** to **5o** was monitored (eqn (6)), the enantiopurity of the intermediate β -lactone **7o** was found to be low (~60 : 40 er).¹⁵ Thus, the challenge in realising this reaction as a highly enantioselective process is centred on developing a catalyst that allows both (i) a highly enantioselective β -lactone synthesis and (ii) redox isomerisation. On-going studies are focused on addressing this challenge.

To gain greater insight into the mechanism of the transformation, studies probing the intermediacy of the β -lactone and the nature of the turnover-limiting step were undertaken. Thus, conversion of triene **6a** to benzaldehyde **5a** was monitored by *in situ* ^1H -NMR spectroscopic analysis in deuterated benzene (eqn (8)). After two hours, extensive consumption of triene **6a**, along with formation of β -lactone **7a** as the major product and benzaldehyde **5a** as a minor component, was observed (Fig. 3). By the fourth hour, benzaldehyde **5a** was the major product and levels of β -lactone **7a** had decreased, consistent with the β -lactone serving as an intermediate *en route* to **5a**. In contrast to the reaction in undeuterated solvents (Tables 1 and 2), this transformation was slower and failed to progress beyond 32 hours. Thus, all subsequent kinetic investigations were terminated after 32 hours.

The impact of deuteration on reaction rate was examined with dideuterated cinnamate **6q**. Using the standard reaction conditions aldehyde **5q** was isolated in a modest 39% yield, along with 27% β -lactone **7q** (eqn (9)). The magnitude of the rate decrease implicated impedance of the redox isomerisation by a



Scheme 1

Fig. 3 Intermediacy of β -lactone **7a**.

primary kinetic isotope effect (KIE). To deconvolute these results, monodeuterated substrates **6r**, **s** and **t** were prepared. ^1H -NMR spectroscopic monitoring of the consumption of deuterio-diene **6r** and α -deutero cinnamate **6s** showed similar rates of consumption to **6a**. However, conversion of β -deutero cinnamate **6t** was significantly retarded (Fig. 4). While a full kinetic analysis is required to eliminate possible involvement of a secondary KIE, the results were consistent with turnover limiting proton transfer to form the homoenolate (*vide infra*).

From these studies, a mechanism that involves two linked catalytic cycles can be proposed. The transformation begins with fragmentation of trienyl ester **6a** to give α , β -unsaturated acyl azonium **I** and dienolate **II** (Fig. 5). These unite in a

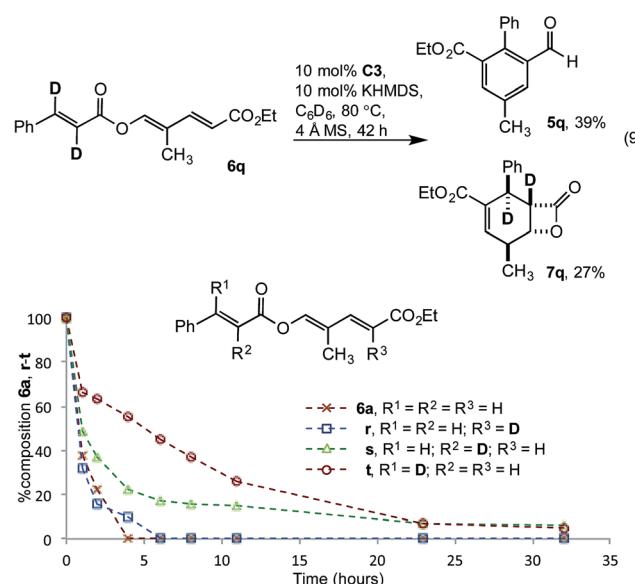


Fig. 4 Impact of substrate deuteration.



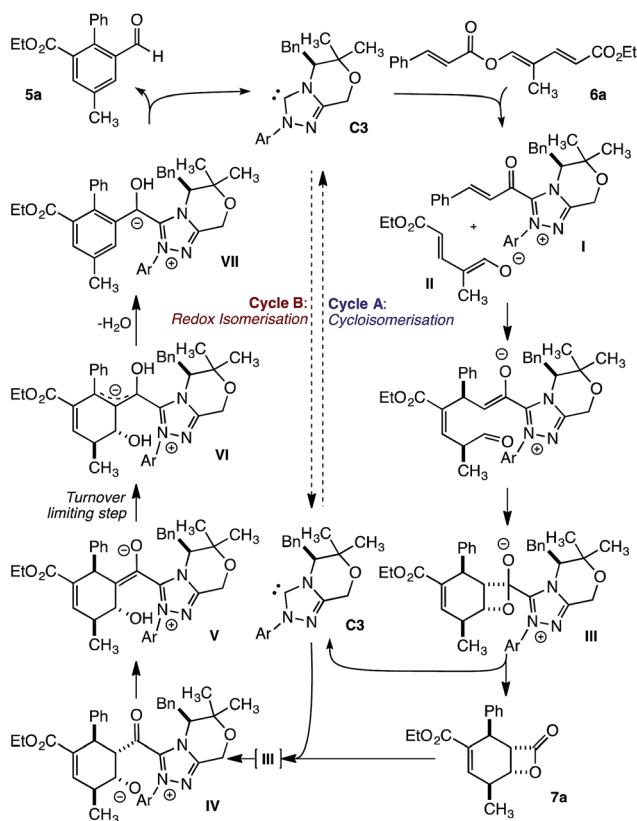


Fig. 5 Potential reaction mechanism.

vinylogous Michael addition, followed by a pseudoconcerted (2 + 2) cycloaddition^{8c} to provide β -lactone hemiacetal **III**. Loss of the catalyst provides β -lactone **7a** to complete cycle A. This pathway is dominant early in the transformation. As β -lactone **7a** accumulates, and triene **6a** is consumed, addition of the NHC to **7a** regenerates **III** *en route* to acyl azonium **IV**. Subsequent proton transfer provides acyl azonium enolate **V** and ultimately homoenolate **VI**, in the turnover limiting event, by a β -deprotonation first described by Chi.^{9f,i} Finally, elimination of water gives aromatic intermediate **VII**, while proton transfer and loss of the NHC liberates benzaldehyde **5a** and regenerates the NHC.

Conclusions

The capacity of NHCs to access acyl anions *en route* to acyl azonium intermediates has been pivotal to modern studies in NHC organocatalysis. Herein, we describe a reaction that occurs in the opposite direction. Key to achieving this has been the observation that β -lactones can undergo fragmentation rather than decarboxylation, and the use of aromatisation as a driving force to allow unusual reaction pathways. These discoveries demonstrate proof of concept for redox isomerisation with carbonyl reduction, while providing a novel synthesis of benzaldehydes **5**. Presumably, other substrates bearing internally oxidisable functionality or the use of chemoselective reducing agents,¹⁶ should enable related transformations characterised

by redox isomerisation with reduction at the carbonyl. Many questions remain with this reaction. Particularly intriguing is the reaction's remarkable sensitivity to solvent polarity and catalyst nucleophilicity and the surprising absence of benzoin condensation pathways. On-going mechanistic studies are focused on these questions.

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