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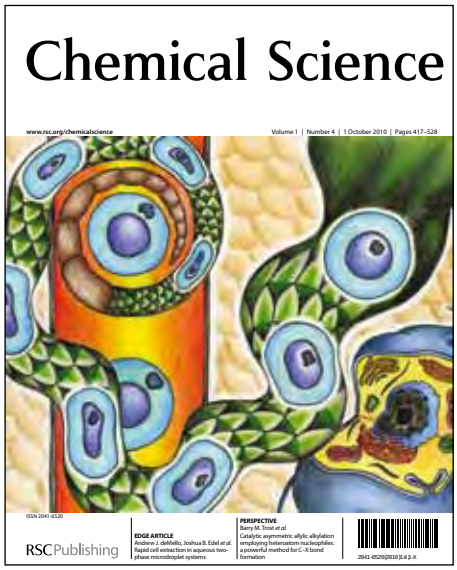

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EDGE ARTICLE

Mechanistic insights into the triazolylidene-catalysed Stetter and Benzoin Reactions: role of the *N*-aryl substituent

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The *in situ* observation, isolation and reversible formation of intermediate 3-(hydroxybenzyl)azolium salts derived from NHC addition to a range of substituted benzaldehydes is probed. Equilibrium constants for the formation of these 3-(hydroxybenzyl)azolium salts, as well as rate constants of hydrogen-deuterium exchange (k_{ex}) at C(α) of these intermediates for a range of *N*-aryl triazolinylidenes is reported. These combined studies give insight into the preference of *N*-pentafluorophenyl NHCs to participate in benzoin and Stetter reaction processes.

Introduction

N-Heterocyclic carbenes (NHCs) have been widely employed as organocatalysts,[1] with the triazolylidene molecular class showing remarkable activity in a diverse range of catalytic processes that proceed through acyl anion,[2] azolium enolate,[3] azolium homoenolate,[4] acyl azolium[5] or α,β-unsaturated acyl azolium intermediates.[6] Within the triazolylidene family, the *N*-aryl substituent plays a decisive role in determining catalytic reactivity and selectivity,[7] with 2,6-substituted *N*-aryl units showing unique reactivity profiles.[8] For example, *N*-mesityl (*N*-Mes) triazolylidenes are preferred for transformations utilising α-functionalised aldehydes,[9] while *N*-pentafluorophenyl (*N*-C_6F_5) derivatives usually exhibit increased catalytic activity in Stetter and benzoin processes.[10] Insightful studies from Bode have ascribed the *N*-Mes effect to irreversible addition of the *N*-Mes substituted NHC to the α-functionalised aldehyde, accelerating the formation of the Breslow intermediate (Figure 1).[11] To date, a mechanistic rationale for the enhanced performance of electron-deficient *N*-aryl triazolylidenes (*N*-C_6F_5 or *N*-2,4,6$Cl_3C_6H_2$) in Stetter and benzoin processes has yet to be offered.[7]

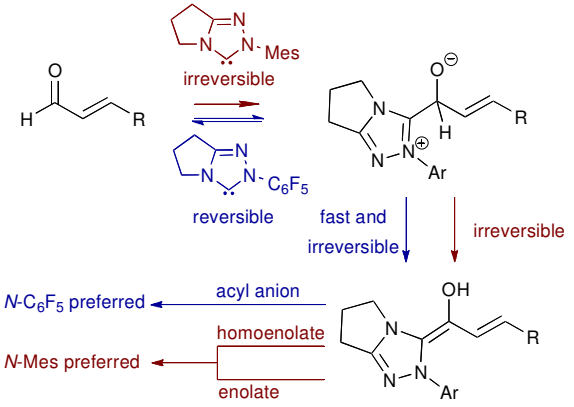
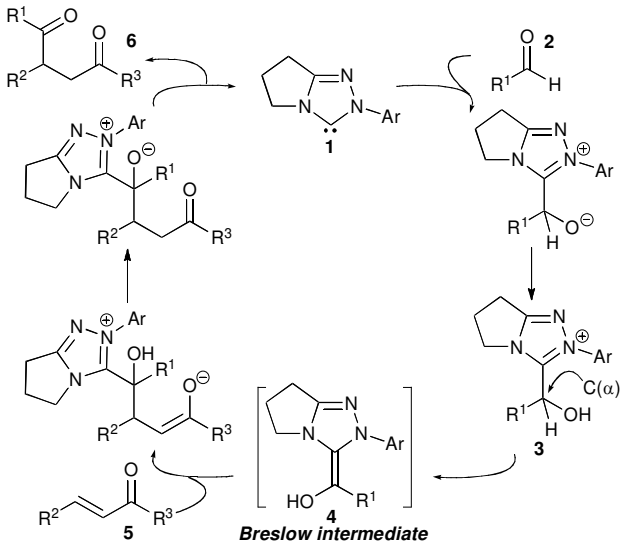


Figure 1: Bode's work: The *N*-Mes effect in NHC-mediated processes.

Central to the observed catalytic activity in the benzoin and Stetter reactions is the formation of a common enaminol or Breslow intermediate **4**. Nucleophilic addition of NHC **1** to aldehyde **2** gives tetrahedral intermediate **3**, with deprotonation at C(α) leading to **4**. Onward reaction with an electrophilic Michael acceptor **5**, followed by proton transfer and catalyst regeneration, leads to the product **6** (Scheme 1).[12] While intermediates of the imidazolinylidene[13] and thiazolinylidene[14] promoted benzoin reaction similar to **3** have been observed, only limited related studies of triazolinylidene-catalysed reactions have been made.[15] Enders and Teles have isolated the 3-(hydroxymethyl)azolium salt addition product of formaldehyde and an NHC,[16] but the concentrations of this intermediate during the reaction have not been monitored. Notably, related structural studies of intermediates in the Stetter reaction have not been established, although mechanistic studies from Rovis indicate that proton transfer from the tetrahedral intermediate **3** is a kinetically significant and irreversible step.[17]



Scheme 1: Mechanism of the Stetter reaction.

As part of our studies regarding NHC-catalysed reaction processes,[18] this manuscript describes the *in situ* observation, isolation and reversible formation of intermediate 3-(hydroxybenzyl)azolium salts derived from NHC addition to aldehydes. Equilibrium constants for the formation of these 3-(hydroxybenzyl)azolium salts, as well as rate constants of hydrogen-deuterium exchange (k_{ex}) at C(α) of these intermediates for a range of *N*-aryl triazolinylidenes is reported. These combined studies give insight into the preference of *N*-C_6F_5 NHCs to participate in benzoin and Stetter reaction processes.

In Situ NMR studies: 3-(hydroxybenzyl)azolium salt observation and equilibrium values

To demonstrate the varying catalytic activity of a series of *N*-aryl triazolylidenes, initial *in situ* ^{1}H NMR spectroscopic studies of the Stetter reaction simply monitored the rate of formation of product **15** from **7** with variation of the *N*-aryl group of the triazolium salt precatalyst (Figure 2).[19] Under catalytic conditions using NEt_3 as a base, electron-deficient *N*-aryl triazolium precatalysts give markedly superior rates of product formation (Ar = C_6F_5 > 2,4,6-$Cl_3C_6H_2$ > 4-FC_6H_4 > Ph > 4-$OMeC_6H_4$ > 2,6-$OMeC_6H_3$ > Mes).[20]

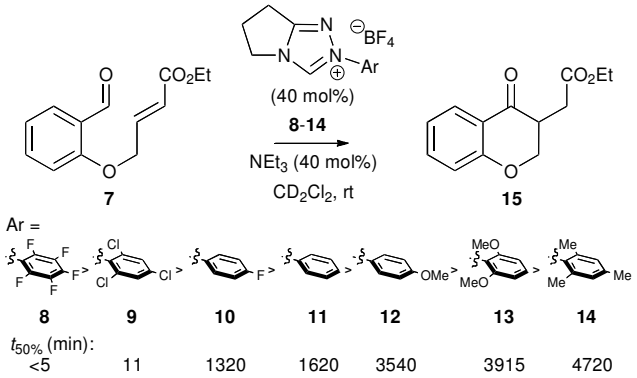


Figure 2: Time taken to reach 50% conversion ($t_{50\%}$) of **7** to **15** with variation of *N*-aryl triazolium substituent.

Further studies utilised ^{1}H NMR spectroscopic analysis to follow the course of the Stetter reaction of **7** (0.04 M) employing sub-stoichiometric quantities (0.008 M) of *N*-phenyl triazolium precatalyst **11**. Monitoring the reaction in anhydrous CD_2Cl_2 using NEt_3 (0.008 M) as the base showed the initial rapid appearance of an intermediate 3-(hydroxybenzyl)azolium salt **16**, with slower subsequent formation of product **15** over time (Figure 3).[21] Unambiguous structural determination of **16** was obtained by simply mixing equimolar quantities of triazolium precatalyst **11** with **7** and NEt_3, giving, after 10 minutes, **16** that could be isolated by silica chromatography in 48% yield (Table 1).[22] The tetrahedral C(α) geometry within **16** was confirmed by HSQC correlation, complimenting the keto tautomer of the Breslow intermediate characterised by NMR spectroscopic analysis by Berkessel and co-workers, who generated this species using a free isolated NHC in THF.[23] Although a small number of related 3-(hydroxybenzyl) thiazolium and imidazolium salts have been prepared by analogous routes,[13-14] it is notable that **16** can be isolated from synthetically relevant conditions.

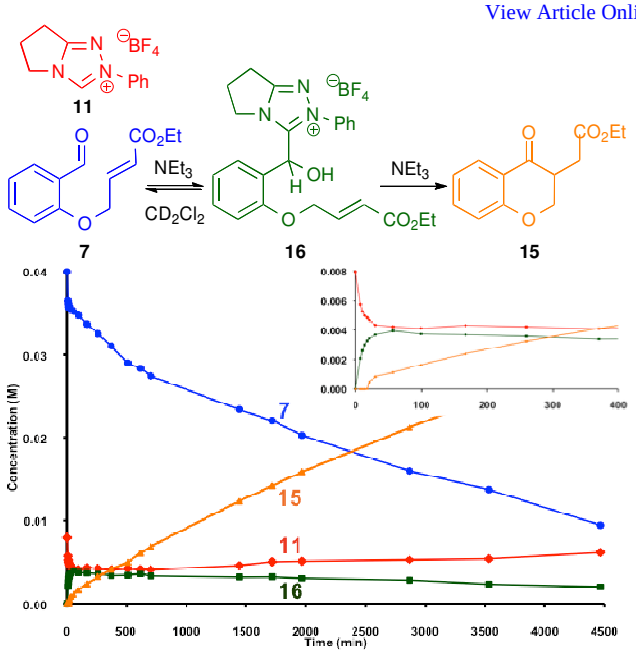
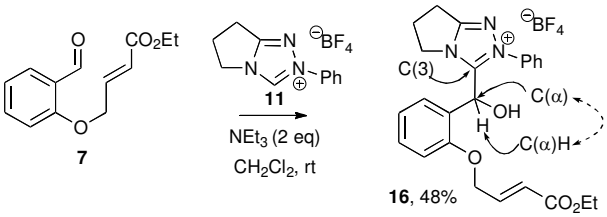


Figure 3: Reaction profile of the Stetter reaction of **7** (0.04 M), catalysed by NHC precursor **11** (0.008 M) with NEt_3 (0.008 M). Inset: expansion of initial time period (<400 min).

Table 1: Preparation and isolation of 3-(hydroxybenzyl)azolium **16**.



Solvent	δ_H C(α)H[a]	δ_C C(3)[a]	δ_C C(α)[a]
CD_2Cl_2	6.30 (s)	63.2	152.2
DMSO	6.33 d, (*J* = 5.4)	63.2	152.0
CD_3OD/DCl	6.36 (s)	65.0	153.7

HSQC correlation (CD_2Cl_2) δ_H 6.30 - δ_C C(3) 63.2

The stability and reversibility of **16** was then probed using control studies that showed tetrahedral intermediate **16** is stable under either acidic or neutral conditions in CD_2Cl_2. However, treatment of **16** with NEt_3 facilitated rapid equilibration to a mixture of aldehyde **7**, precatalyst **11** and **16**, with relatively slow onwards formation of product **15** (Figure 4).[19] Performing this experiment with **16** (0.008 M) in the presence of additional aldehyde **7** (0.032 M), gave rise to a similar reaction profile to that obtained starting from **7** (0.04 M) and **11** (0.008 M). These observations indicate that **16** is a reversibly formed intermediate from the addition of NHC to the aldehyde, with slower subsequent onwards reaction, presumably through the expected Breslow intermediate, generating product **15**.[19]

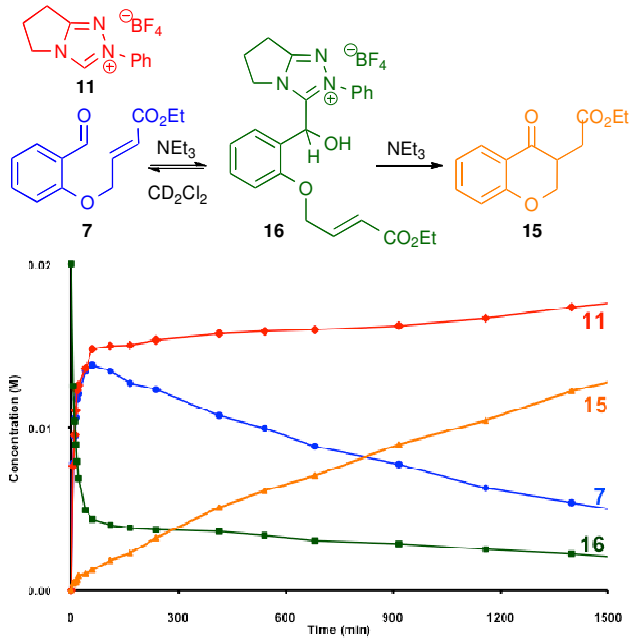


Figure 4: Reaction profile of the reaction of *N*-Ph 3-(hydroxybenzyl)azolium salt **16** (0.02 M) with NEt_3 (0.02 M).

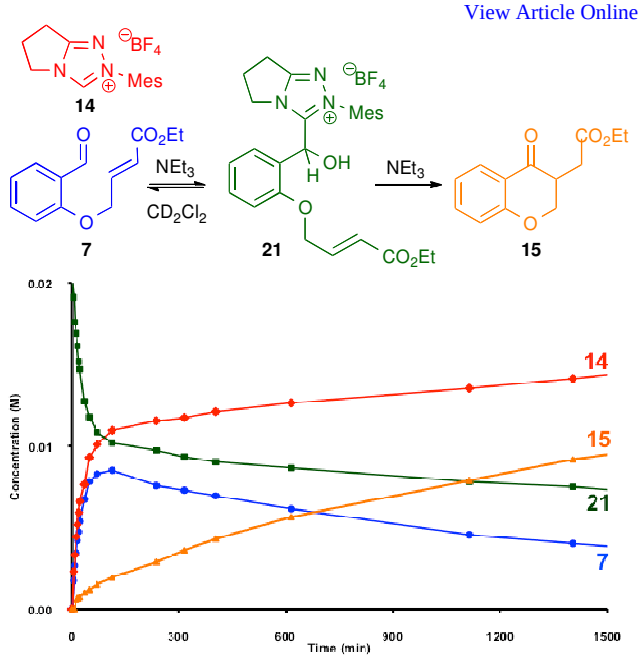
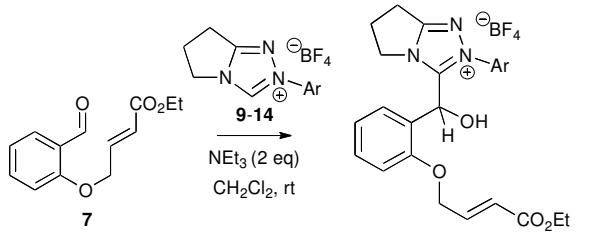


Figure 5: Reaction profile of the reaction of *N*-Mes 3-(hydroxybenzyl)azolium salt **21** (0.02 M) with NEt_3 (0.02 M).

To probe the generality of these studies, the synthesis and isolation of a range of 3-(hydroxybenzyl)azolium salts was investigated. Treatment of a series of *N*-aryl triazolium precatalysts and aldehyde **7** (1:1) with excess NEt_3 gave the corresponding 3-(hydroxybenzyl)azolium salts **17**-**21** in 16-96% yield (Table 2). Using the *N*-C_6F_5 triazolium precatalyst, the desired tetrahedral intermediate could not be isolated due to rapid conversion into product under these reaction conditions, although electron-deficient *N*-2,4,6-$Cl_3C_6H_2$ and *N*-4-FC_6H_4 analogues **17** and **18** could be isolated and characterised.

Table 2: Preparation of 3-(hydroxybenzyl)azolium salts.

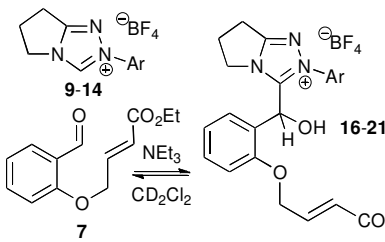


16, Ar = Ph, 48%
17, Ar = 2,4,6-$Cl_3C_6H_2$, 16%
18, Ar = 4-FC_6H_4, 54%
19, Ar = 4-$OMeC_6H_4$, 55%
20, Ar = 2,6-$OMeC_6H_3$, 96%
21, Ar = Mes, 74%

In situ reaction monitoring of the model Stetter transformation using NHC precursors **9**-**14**, as well as their 3-(hydroxybenzyl)azolium salt products **16**-**21** was next investigated. In all cases, starting from either the parent azolium salt precatalyst or 3-(hydroxybenzyl)azolium salt, formation of an equilibrium mixture of the corresponding azolium salt, aldehyde **7** and the 3-(hydroxybenzyl)azolium was observed, before relatively slow subsequent onwards reaction to give product **15** (Figure 5, representative example shown using *N*-Mes substituted 3-(hydroxybenzyl)azolium salt **21**).

From the resultant reaction profiles, values for *K* (the equilibrium constant for the formation of 3-(hydroxybenzyl)azolium salt) were calculated before significant (< 5%) product formation (Table 3).[24] These results show that reversible addition is observed in this system even with the *N*-Mes triazolylidene. Notably, significantly larger equilibrium constants are observed using NHC-precatalysts bearing 2,6-substituted *N*-aryl units (*N*-Mes, *N*-2,6-$OMeC_6H_3$ and *N*-2,4,6-$Cl_3C_6H_2$), whilst electronic variation of 4-substituent leads to minimal perturbation of *K*.[25] Despite the large equilibrium concentration of the *N*-Mes and *N*-2,6-$OMeC_6H_3$ 3-(hydroxybenzyl)azolium salts, the rates of product formation are slower than with NHC precatalysts **8**-**12**.

Table 3: Equilibrium constants of 3-(hydroxybenzyl)azolium salts.



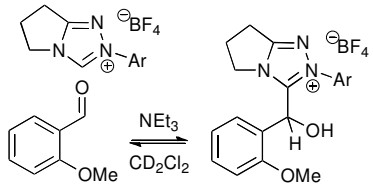
Ar	*K* (M^{-1})
2,4,6-$Cl_3C_6H_2$	336
4-FC_6H_4	28
Ph	27
4-$OMeC_6H_4$	31
2,6-$OMeC_6H_3$	1283
Mes	140

Starting concentrations: **7** 0.04 M, NHC 0.008 M, NEt_3 0.008 M.

Whilst this proved instructive, the effect of the *N*-C_6F_5 substituent upon the equilibrium values could not be evaluated within this system due to rapid onwards reactivity to product. Given the typical recalcitrance of 2-substituted benzaldehydes to participate in homo-benzoin processes,[10c, 10d] a series of model 3-(hydroxybenzyl)azolium salts **22**-**27** were prepared from 2-methoxybenzaldehyde, allowing an evaluation of their *K* values (Table 4).[26] Using precatalysts **8**, **9** and **11**-**14** a similar trend was observed, with 2,6-substituted *N*-aryl NHCs yielding significantly larger *K* values. The use of *N*-C_6F_5 precatalyst **8** also led to a high *K* value, suggesting that both steric effects from 2,6- substituents

and electron-withdrawing electronic effects within the *N*-aryl substituent lead to increased *K* values. This increase in *K* reflects the relative stabilities of the respective 3-(hydroxybenzyl)azolium salt in comparison to the starting materials. Simplistically, we assume that 2,6-*N*-aryl substitution within the NHC forces the *N*-aryl ring to adopt an essentially orthogonal orientation with respect to the triazole ring.[27] Furthermore, in all 3-(hydroxybenzyl)azolium salts the *N*-aryl group presumably adopts a non-coplanar conformation with the triazole in order to minimize 1,2-steric interactions, with orthogonality enforced with 2,6-*N*-aryl substitution. 3-(Hydroxybenzyl)azolium salt formation may then be favoured for 2,6-*N*-aryl substituted NHCs due to better accomodation of the 3-(hydroxybenzyl) substituent by the *N*-aryl unit. Furthermore, the reverse process may then deviate from expected leaving group ability, being more favourable for non-2,6-*N*-aryl substituted NHCs. Further work will generate additional mechanistic insight by quantifying the rates of the individual processes.

Table 4: Equilibrium constants of 3-(hydroxybenzyl)azolium salts.



22, Ar = C_6F_5
23, Ar = 2,4,6-$Cl_3C_6H_2$
24, Ar = Ph
25, Ar = 4-$OMeC_6H_4$
26, Ar = 2,6-$OMeC_6H_3$
27, Ar = Mes

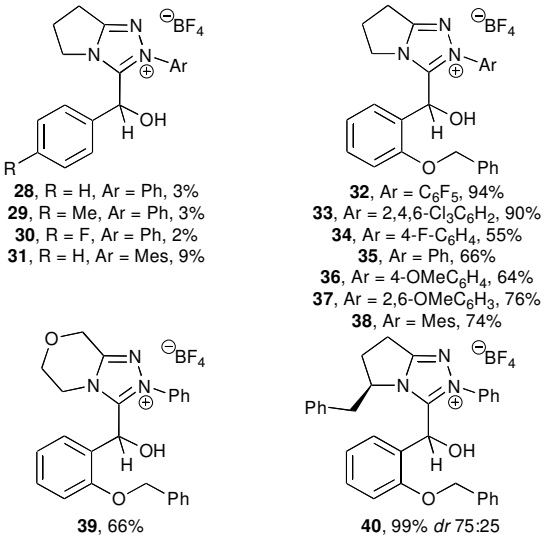
Ar	*K* (M^{-1})
C_6F_5	521
2,4,6-$Cl_3C_6H_2$	601
Ph	56
4-$OMeC_6H_4$	46
2,6-$OMeC_6H_3$	741
Mes	143

Starting concentrations: 2-methoxybenzaldehyde 0.01 M, NHC 0.002 M, NEt_3 0.002 M.

Rates constants of exchange (k_{ex}) for 3-(hydroxybenzyl)- or 3-(methoxybenzyl)azolium salts

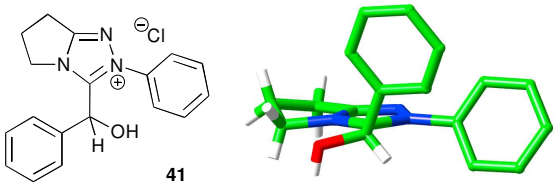
Given the proposed kinetic relevance of the deprotonation step to generate the Breslow intermediate in the Stetter reaction,[17, 28] the relative rate constants of deuterium exchange (k_{ex}, s^{-1}) at the C(α)-H position were investigated by ^{1}H NMR spectroscopy using either KOD solutions or triethylamine buffers in D_2O/CD_3OD. For Stetter derived 3-(hydroxybenzyl)azolium salts **16**-**21**, C(α)H exchange could only be monitored alongside competitive dissociation to aldehyde and NHC,[29] while attempted *O*-methylation of **16** led to extensive decomposition. To circumvent these issues a series of alternative model 3-(hydroxybenzyl)azolium salts was prepared by triazolinylidene addition to benzaldehyde and a number of substituted benzaldehyde derivatives (Table 5). Only low isolated product yields of 3-(hydroxybenzyl)azolium products were obtained for triazolinylidene addition to either benzaldehyde or 4-substituted benzaldehydes (<10%), with products **28**-**31** isolated by preparative LC. Despite these poor yields, crystallisation from DCl/D_2O allowed unambiguous structure determination of chloride salt **41** by X-ray crystal structure analysis (Figure 6).[30] NHC addition to 2-(benzyloxy)benzaldehyde gave higher isolated yields and showed increased stability to chromatographic purification, furnishing reasonable to excellent isolated yields (up to 94%) of aldehyde-NHC addition products **32**-**38**. This synthetic route was extended to morpholine-containing NHC precursors, giving **39**, while a chiral NHC precursor gave **40** as a 75:25 mixture of diastereoisomers in an excellent 99% yield.[31] 3-(Hydroxybenzyl)azolium salts **28**, **32**, **33**, **35**, **37**, **38** and **40** were subsequently *O*-methylated[32] to facilitate an evaluation of their rates of deuterium exchange.

Table 5: Synthesis of 3-(hydroxybenzyl)azolium salts.



28, R = H, Ar = Ph, 3%
29, R = Me, Ar = Ph, 3%
30, R = F, Ar = Ph, 2%
31, R = H, Ar = Mes, 9%
32, Ar = C_6F_5, 94%
33, Ar = 2,4,6-$Cl_3C_6H_2$, 90%
34, Ar = 4-F-C_6H_4, 55%
35, Ar = Ph, 66%
36, Ar = 4-$OMeC_6H_4$, 64%
37, Ar = 2,6-$OMeC_6H_3$, 76%
38, Ar = Mes, 74%
39, 66%
40, 99% *dr* 75:25

Experimental conditions: NHC precursor (1 equiv), aldehyde (1 equiv), NEt_3 (2 equiv), CH_2Cl_2, rt, 5 min - 1 h.



41

Figure 6. Representation of the X-ray crystal structure of 3-(hydroxybenzyl)azolium chloride **41** (chloride counterion and water of crystallisation not shown for simplicity).

Deuterium exchange studies were carried out upon **36** and **38** and 3-(methoxybenzyl)azolium salts **42**-**48**. In all cases deuteroxide catalysed exchange of C(α)-H for deuterium could be monitored without any detritic side reactions (Figure 7).[33] The fastest exchange was observed with electron-deficient *N*-aryl triazolium derivatives (Ar = C_6F_5 > 2,4,6-$Cl_3C_6H_2$ > Ph > 4-$OMeC_6H_4$ > Mes > 2,6-$OMeC_6H_3$, Table 6).[34] For **48**, the rate constant of exchange for both diastereoisomers could be evaluated, with the minor diastereoisomer exhibiting an enhanced k_{ex} value.[35] Within this system, the rate of exchange with variation of *N*-aryl substitution generally parallels the rate of observed product formation in the Stetter transformation.[36] This presumably reflects the increased acidity of C(α)-H of the intermediate 3-(hydroxybenzyl)azolium species with increasing electron-withdrawing *N*-aryl substituents, and is consistent with rate determining deprotonation of this species, as postulated by Rovis.[17]

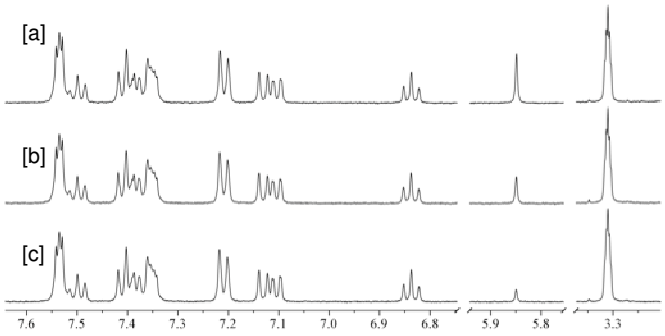
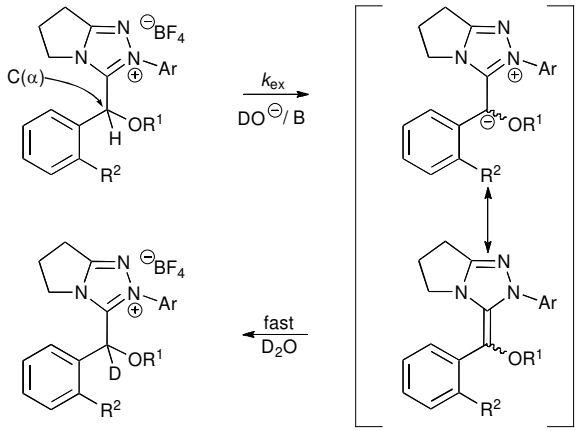


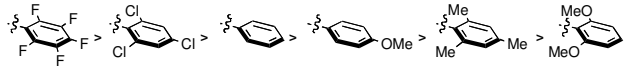
Figure 7. Deuterium exchange of C(α)H (5.85 ppm) relative to CD_3OD (3.31 ppm) of **44** (5 mM) in NEt_3 buffer in 6.5:1 D_2O:CD_3OD at p*D* 10.9 and 25 °C [a] T = 9 min. [b] T = 109 min. [c] T = 252 min.

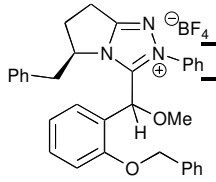
Table 6: Relative acidities of 3-(hydroxybenzyl)azolium salts.



	Ar	R^1	R^2	p*D*	k_{ex} (s^{-1})
36	4-OMeC_6H_4	D	OBn	11.9	6.02×10^{-5}
38	Mes	D	OBn	11.9	5.11×10^{-5}
42	C_6F_5	Me	OBn	10.9	2.03×10^{-3}
43	2,4,6-$Cl_3C_6H_2$	Me	OBn	10.9	7.30×10^{-4}
44	Ph	Me	OBn	10.9	9.60×10^{-5}
45	2,6-OMeC_6H_3	Me	OBn	10.9	2.32×10^{-6}
46	Mes	Me	OBn	10.9	2.61×10^{-5}
47	Ph	Me	H	10.9	3.06×10^{-4}

k_{ex}: Ar =





	p*D*	k_{ex} (s^{-1}) major	k_{ex} (s^{-1}) minor
48	10.9	1.36×10^{-4}	1.94×10^{-4}

Although the formation of the Breslow intermediate is implied by these NMR hydrogen-deuterium exchange studies, direct observation was not possible due to its transient nature in the protic solvent conditions. The direct isolation of Breslow intermediates such as **4** is a widely recognised challenge, although Jordan and co-workers have characterised an *O*-protected thiazolinylidene-derived enamine using NMR spectroscopy[37] and Goldup has reported the observation of an *O*-benzylated intermediate in an imidazolinium-mediated transesterification.[38] Most recently, Rovis and co-workers have described the isolation of nitrogen analogues of the Breslow intermediate using 2,6-substituted NHC precursors.[39] Mayr has similarly reported the isolation and reactivity of a range of *O*-methylated Breslow intermediates,[40] whilst Berkessel has reported the isolation of Breslow intermediates derived from free imidazolinium NHCs and benzaldehydes.[41] Despite not being able to observe species such as **4** in these studies, treatment of *O*-methylated derivative **47** with a 10-fold excess of potassium dimsyl in DMSO allowed the acquisition of a UV-Vis spectrum of the enamine with a characteristic λ_{max} at 380 nm and an extinction coefficient (ε) of 7846 $M^{-1}cm^{-1}$, which is consistent with the more extended conjugated system present in **49** relative to the precursor (Figure 8).[42] Under these conditions, this absorbance decayed to zero over ~20 mins, presumably due to reprotonation of **49** by adventitious water. Under analogous conditions, *O*-methylated derivative **44** exhibited a λ_{max} at 395 nm and an extinction coefficient of 5423 $M^{-1}cm^{-1}$.

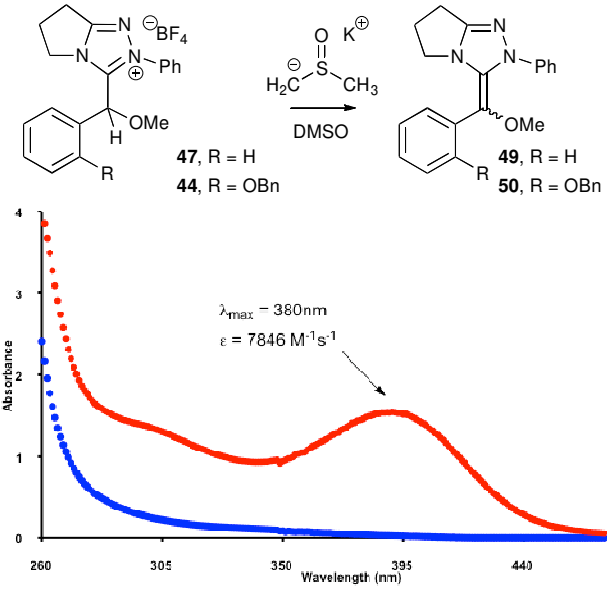


Figure 8. UV-Vis spectra of a 0.2 mM solution of 3-(methoxybenzyl)azolium salt **47** (blue) and **49** (red).

Hydroxybenzylazolium salts as precatalysts

Consistent with these mechanistic studies, the validity of 3-(hydroxybenzyl)azolium salts **18** and **32** as precatalysts for the Stetter reaction was investigated (Figure 9). As expected, treatment of **7** with **18** or **32** (20 mol%) and NEt_3 (20 mol%) in CH_2Cl_2 at rt gave **15** in excellent isolated yield, with the rate of product formation using the electron deficient *N*-C_6F_5 salt **30** significantly faster than the *N*-4-FC_6H_4 salt **18**. Notably, no homo- or crossed-benzoin products were observed in the reaction employing either **18** or **32** as precatalyst.

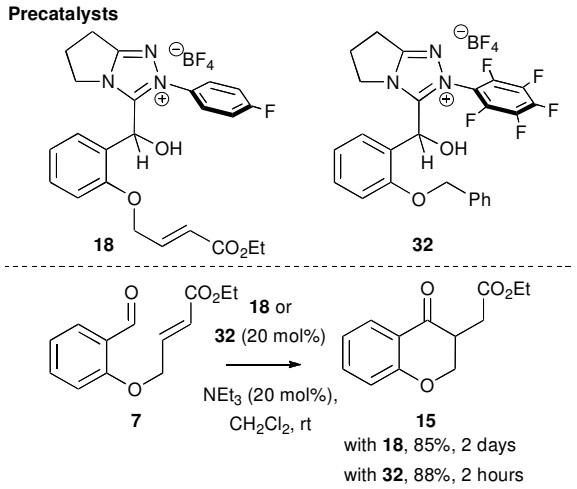


Figure 9. Use of 3-(hydroxybenzyl)azolium salts as precatalysts in the Stetter reaction.

Similarly, the use of **32** as a precatalyst for the benzoin reaction was probed through performing a crossover reaction with benzaldehyde (Figure 10). Treatment of **32** (20 mol%) with benzaldehyde and NEt_3 (20 mol%) gave preferentially the homo-benzoin product **52**, along with only 6% of the crossed benzoin product **53**. The small yield of the observed crossed product is consistent with current literature, due to the poor reactivity of the 2-substituted aldehyde as an electrophilic component in benzoin type processes. [43]

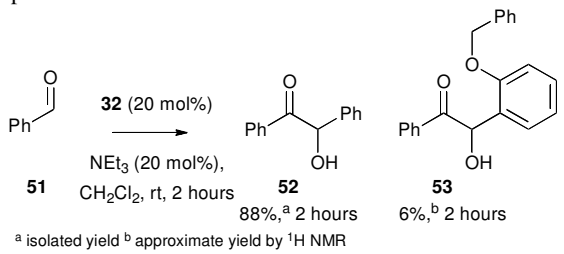


Figure 10. Use of 3-(hydroxybenzyl)azolium salt **32** as precatalyst in the benzoin condensation.

Conclusions

In conclusion, the isolation and *in situ* spectroscopic observation of aldehyde-NHC addition product intermediates of the Stetter and benzoin reactions is reported. Reaction profiles indicate these intermediates are reversibly formed (irrespective of the *N*-aryl substitution pattern), followed by relatively slow onwards reaction to yield Stetter product. Estimated *K* values suggest that the equilibrium constant is affected by both electronic and steric effects of the *N*-aryl unit, with 2,6- and electron-withdrawing *N*-aryl substitution resulting in significantly larger *K* values. By contrast, electronic variation of the 4-substituent leads to minimal pertubation of *K*. The relative acidities (k_{ex}) at C(α) of 3-(methoxybenzyl)azolium salts provided insight into the effect of catalyst architecture on the key Breslow intermediate-forming step. Despite *N*-2,6-$OMeC_6H_3$ and *N*-Mes NHC precursors **13** and **14** exhibiting enhanced *K* values (285- and 5-fold vs *N*-Ph congenor **11** respectively in the Stetter reaction), slow and presumably rate determining deprotonation[17] (as indicated by k_{ex}) inhibits their use as precatalysts in the Stetter reaction. In contrast *N*-C_6F_5 and *N*-2,4,6-$Cl_3C_6H_2$ substituted NHCs benefit from both high *K* values and rapid k_{ex} values (21- and 8- fold respectively vs *N*-Ph), rationalising why 2,6-electron withdrawing *N*-substituents are preferred in benzoin and Stetter type processes.[44] Further work from our laboratories towards developing a full kinetic understanding of these and other NHC-catalysed reaction processes are underway.

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Notes and references

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† Electronic Supplementary Information (ESI) available: all spectroscopic data and procedures for novel compounds. For ESI see DOI: 10.1039/b000000x/

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21. Reactions were typically followed up to 80% conversion to product **15**. See SI for full reaction profiles.
22. One referee correctly questioned wether **16** (or any other hydroxybenzyazolium salt in this manuscript) was actually the tetrafluoroborate salt as represented, or the corresponding ylide / alkoxide and Et_3NH^+. While we are unable to distinguish these possibilities in situ, the product **16** isolated after chromatographic purification contained ^{19}F NMR resonances at δ_F-153.4 and δ_F-153.5, consistent with it containing a tetrafluoroborate counterion. Similar ^{19}F NMR data was obtained for **18** and **22** and so for simplicity we represent all compounds as the tetrafluoroborate counterion.
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25. Glorius postulated that ortho-substituted *N*-aryl substituents would destabilise the initial tetrahedral adduct formed between an NHC and an aromatic aldehyde due to steric effects (See M. Schedler, R. Frohlich, C. G. Daniliuc and F. Glorius, *Eur. J. Org. Chem*., 2012, 4164-4171; N. E. Wurtz, C.G. Daniliuc and F. Glorius, *Chem. Eur. J*., 2012 doi 10.1002//chem.201202432). Whilst we believe the enhanced formation of 3-(hydroxybenzyl) azolium salt observed in the case of the *N*-2,6-disubstituted triazolium catalysts results from a more favourable orientation of the *N*-aryl ring (due to the presence of two ortho-substituents), more bulky ortho-substituents do not appear to show this effect. Analogous studies of the benzoin condensation using *N*-Mes and *N*-(2,6-diisopropylphenyl) imidazolium catalysts resulted in the appearance of hydroxybenzyl adduct only in the case of the mesityl catalyst, whilst no reaction was observed using the more sterically hindered 2,6-diisopropylphenyl catalyst (See SI for full details).
26. *K* values were determined as previously described, see SI for full details. During the course of the experiment, none of the crossed benzoin product was observed, presumably due to the poor reactivity of 2-substituted benzaldehydes in the benzoin reaction, consistent with literature studies (see L. Baragwanath, C. A. Rose, K. Zeitler and S. J. Connon, *J. Org. Chem., 2009*, **74**, 9214-9217; S. E. O'Toole and S. J. Connon, *Org. Biomol. Chem*., 2009, **7**, 3584-3593).
27. Computational and X-ray crystallographic evidence from Mayr indicates that the *N*-Mes substituent prefers to adopt an almost perpendicular conformation in a range of imidazolium and triazolium carbenes (B. Maji, M. Breugst and H. Mayr, *Angew. Chem. Int. Ed*., 2011, **50**, 6915-6919). Additionally, a study by Cavallo of NHC ligands concluded that the orientation of the *N*-aryl substituent was determined from the balance between the conjugation energy gained from co-planar geometry and the steric repulsion, with *N*-Ph substituents co-planar, whilst *N*-Mes are almost perpendicular to the heterocycle plane (F. Ragone, A. Poater and L. Cavallo, *J. Am. Chem. Soc*., 2010, **132**, 4249-4258.).

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29. However, the half-life for deuterium incorporation at C(α)H could be estimated, with fastest exchange observed with electron-withdrawing *N*-aryl units (Ar = 4-FC_6H_4 > Ph > 4-$OMeC_6H_4$ > Mes). See SI for further details.
30. **41** and the dichloride salts of **29** and **30** (**54** and **55** respectively) were characterised by single-crystal X-ray diffraction of their D_2O monosolvates which are mutually isotypic (isomorphus). Crystallographic data is available free of charge from the Cambridge Crystallographic Data Centre, www.ccdc.ac.uk/data-request/cif, as CCDC-895406 (**41**), 895407 (**54**) and 895408 (**55**).
31. Treatment of the isolated major diastereoisomer to the reaction conditions led to a 75:25 mix of diastereoisomers, suggesting the obtained *dr* is a result of a thermodynamic equilibrium.
32. 3-(Methoxybenzyl)azolium salts **42**-**48** were synthesised from methylation of **28**, **32**, **33**, **35**, **37**, **38** and **40** using diazomethane or TMS-diazomethane. See SI for further details. For these compounds, exchange could be monitored without dissociation or decomposition.
33. Experiments were carried out at a substrate concentration of 5 mM at 25 °C and *I*=1 (KCl) in 6.5:1 D_2O/CD_3OD. Exchange was monitored for two half lives and a semi-logarithmic plot of the fraction of unexchanged substrate (*f*s) against time gave k_{ex}, the pseudo-first order rate of exchange at that p*D*. In the case of **36** and **38**, measurements at other p*D* values were not possible due to competing dissociation to aldehyde and NHC at lower p*D* values and ring opening at higher p*D* values. See SI for full details.
34. It is assumed that deprotonation by deuteroxide is significantly faster than deuteration of the Breslow intermediate in all cases so that k_{ex} reflects the rate constant for formation of the solvent equilibrated enaminol/enamine. Using stopped flow spectrophotometry Jordan has measured rate constants for the reprotonation of *O*-methylated thiazolylidene-derived enamine derivatives in the range of 300-540 s^{-1} (G. L. Barletta, Y. Zou, W. P. Huskey and F. Jordan, *J. Am. Chem. Soc*., 1997, **119**, 2356-2362), which are 10^7-fold higher than corresponding rate constants for formation of the intermediate at p*H* 10.5 (~p*D* 10.9).
35. Upon completion of the deuterium exchange experiment of **48** the C(α)-deuterated **48** formed exhibited a decreased *dr*, suggesting enamine deuteration is not completely stereoselective.
36. The only exception to this is the 2,6-$OMeC_6H_3$ substituted analogue **45**, which exhibits a lower k_{ex} value than **46**, despite displaying a faster rate of product formation in the Stetter reaction. We presume that the greatly enhanced *K* value (Table 3) compensates for the slower rate of deprotonation, giving a faster overall rate of reaction. Jordan has reported a second order rate constant, k_{HO} = 0.019 $M^{-1}s^{-1}$ for hydroxide ion deprotonation of the 2-(methoxyphenylmethyl)-3,4-dimethylthiazolium salt to the corresponding enamine using stopped-flow spectrophotometry (G. L. Barletta, Y. Zou, W. P. Huskey and F. Jordan, *J. Am. Chem. Soc*., 1997, **119**, 2356-2362). Using this value, we can calculate a first order rate constant for deprotonation by hydroxide at p*H* 10.5 (~p*D* 10.9) of 8 x 10^{-6} s^{-1}, which is 3-250-fold smaller than any of the k_{ex} values in Table 6 at an equivalent p*D*.
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44. We are grateful to a referee who pointed out that the electronic determinant of reaction rate in the intramolecular Stetter transformation (superior rates with electon-deficient N-aryl triazolium precatalysts) is in contrast to many other classes of NHC-catalysed reactions. For example, typical reactions that proceed via azolium enolates appear to be dominated by steric constraints. For a computional study see: S. E. Allen, J. Mahatthananchai, J. W. Bode and M. C. Kozlowski, *J. Am. Chem. Soc*., 2012, **134**, 12098-12103.