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Mechanistic Investigation of the Enantioselective Intramolecular Stetter Reaction: Proton Transfer Is the First Irreversible Step

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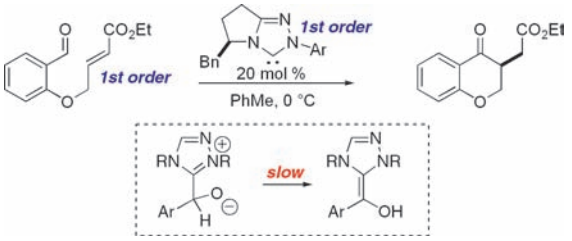
ABSTRACT



A study on the mechanism of the asymmetric intramolecular Stetter reaction is reported. This investigation includes the determination of the rate law, kinetic isotope effects, and competition experiments. The reaction was found to be first order in aldehyde and azolium catalyst or free carbene. A primary kinetic isotope effect was found for the proton of the aldehyde. Taken together with a series of competition experiments, these results suggest that proton transfer from the tetrahedral intermediate formed upon nucleophilic attack of the carbene onto the aldehyde is the first irreversible step.

The seminal example of the reversal of functional group polarity, the benzoin reaction, dates to 1832, when Wöhler and Liebig reported that cyanide catalyzes the formation of benzoin from 2 equiv of benzaldehyde.[1,2] In 1943, Ukai et al. showed that thiazolium salts catalyze the homodimerization of aldehydes in the presence of base.[3] A related *Umpolung*[4] transformation is the Stetter reaction, the conjugate addition of the aldehyde into a Michael acceptor.[5] Utilizing thiazolylidene carbenes as catalysts, Stetter demonstrated that a variety of aromatic and aliphatic aldehydes are competent nucleophilic coupling partners with a wide range of α,β-unsaturated ketones, esters, and nitriles.[6] The ability to bring two different electrophilic partners together and form a new carbon−carbon bond enhances the potential utility of this transformation.

Our group has developed chiral triazolinylidene carbenes and precursors, **1**−**3** (Figure 1), for a variety of carbene-mediated transformations.[2a,b] We have shown that the carbenes derived from **1** and **2** are capable of inducing the cyclization of aromatic and aliphatic aldehydes to α,β-unsaturated esters, ketones, thioesters, amides, aldehydes, and nitriles.[7] More recently, we have extended this reaction to preliminary reports of

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(1) Woehler, F.; Liebig, J. *Ann. Pharm.* **1903**, *3*, 249.

(2) For reviews, see: (a) Moore, J. L.; Rovis, T. *Top. Curr. Chem.* **2009**, *290*, 77. (b) Read de Alaniz, J.; Rovis, T. *Synlett* **2009**, *8*, 1189. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

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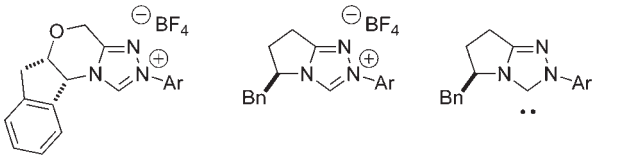

1a Ar = *p*-MeOC$_6$H$_4$ **2a** Ar = Ph **3a** Ar = Ph
1b Ar = Ph **2b** Ar = *p*-CF$_3$C$_6$H$_4$ **3b** Ar = *p*-CF$_3$C$_6$H$_4$
1c Ar = C$_6$F$_5$ **2c** Ar = C$_6$F$_5$

Figure 1. Catalysts used in the Stetter reaction.

asymmetric intermolecular reactions.[8,9] Nevertheless, limitations remain.

Mechanistic insight into organocatalytic reactions is important for the development of general transformations.[10] To the best of our knowledge a detailed study probing the mechanism of the Stetter reaction has not been reported. In the absence of such a study the working model of the Stetter reaction is based on the Breslow mechanism for the thiamin-catalyzed benzoin reaction.[11,12] The mechanism is closely related to Lapworth's mechanism for cyanide anion catalyzed benzoin reaction.[13] As with the cyanide-catalyzed benzoin reaction, the thiazolinylidene-catalyzed reaction is reversible.[14]

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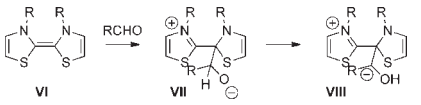
(12) Lopez-Calahorra and co-workers proposed an alternative mechanism involving thiazolium dimer **VI** with the reaction occurring through nucleophilic attack of this species on benzaldehyde to yield **VII**, followed by formation of intermediate type **VIII**, lacking stabilization of the carbanion. See, for example: Lopez-Calahorra, F.; Rubires, R. *Tetrahedron* **1995**, *51*, 9713. For a counterpoint, see: Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241.



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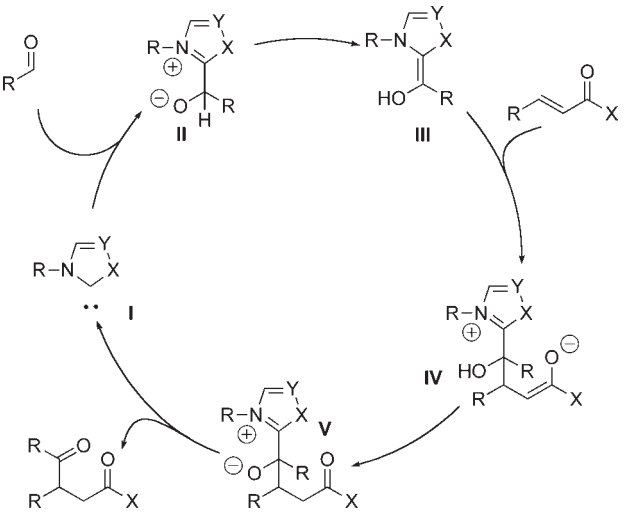
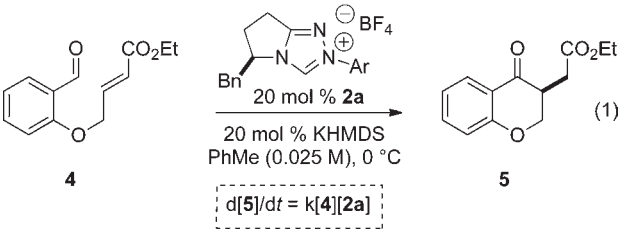
Scheme 1. Proposed General Mechanism for the Stetter Reaction



The proposed catalytic cycle is as follows: the carbene **I** (Scheme 1), formed *in situ* by base deprotonation of the corresponding azolium salt, adds to the aldehyde to form **II**. A proton transfer event generates acyl anion equivalent **III**, termed the nucleophilic alkene or Breslow intermediate. Subsequent addition into the Michael acceptor forms a new carbon−carbon bond to generate **IV**. A second proton transfer event then provides **V**. Finally, collapse of this tetrahedral intermediate **V** to form a Stetter product is accompanied by liberation of the active catalyst. As we strive to understand differences in catalysts and continue to work toward the development of the enantioselective intermolecular reactions, we believe that the results from a detailed mechanistic study may provide insight toward the rational attainment of these goals. Herein we report a series of mechanistic experiments that shed light on the nuances that govern reactivity in the intramolecular Stetter reaction.



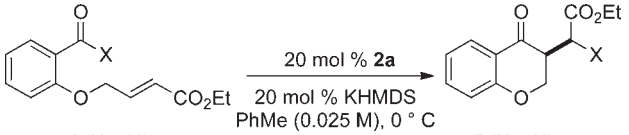
As salicylaldehyde derived aldehyde **4** is used as a benchmark to measure the efficiency and selectivity of newly developed catalysts for the Stetter reaction, it was chosen as the substrate for this study, eq 1. Under standard reaction conditions, aldehyde **4** is subjected to 20 mol % **2a** and 20 mol % KHMDS in toluene (0.025 M) at 0 °C; the observed rate of the reaction is 2.65×10^{-3} M^{-1} s^{-1}. Gas chromatography was utilized for the analysis of cyclized product **5** by using 4,4′-di-*tert*-butyl biphenyl (DBB) as an internal standard (t_R 4.8 min) and monitoring the disappearance of aldehyde **4** (t_R 2.0 min) and concurrent

appearance of keto-ester **5** (t_R 2.9 min). Standard kinetic analysis using the conversion of aldehyde **4** to keto-ester **5** exhibits a first order dependence as a function of aldehyde concentration versus time over four half-lives.[15]

The catalyst dependence was found to be first order, determined by varying the concentration of catalyst from 0.0025 to 0.0100 M. These experiments establish a second order rate law (eq 1).[16]

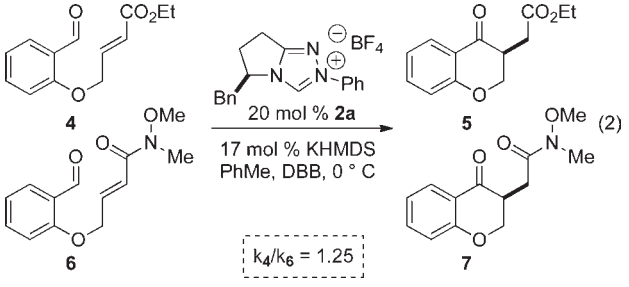
The ^{2}H kinetic isotope effect (KIE) study was conducted under standard reaction conditions with **4** and its deuterated isotopologue (ArCDO), and the k_H/k_D was found to be 2.62 (Scheme 2). These experiments suggest that proton transfer is turnover limitting.

Scheme 2. Kinetic Isotope Effect Studies



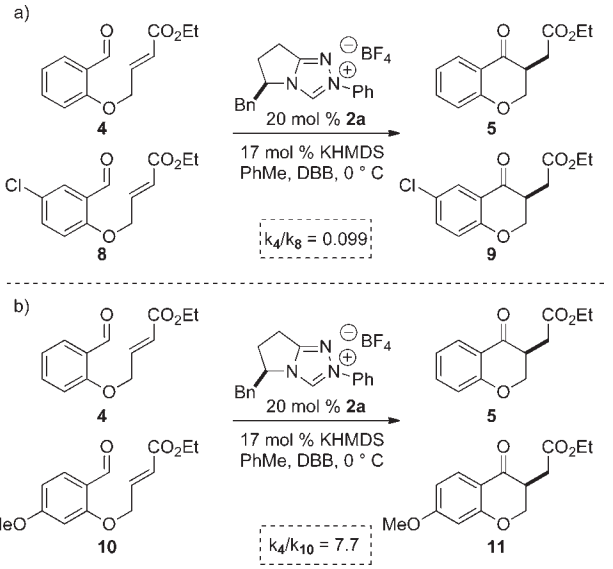
entry	X	k_{obs}(x10^{-3})	entry	X	k_{obs}(x10^{-3})
1	H	2.43	5	H	3.10
2	H	2.47	6	D	0.98
3	H	2.59	7	D	1.00
4	H	2.64	8	D	1.05

In order to shed further light onto the mechanism, we conducted a series of competition experiments. We reasoned that the sterics and electronics of the Michael acceptor should have a profound role on the reaction if the first irreversible step is the second proton transfer event (**IV** to **V**) but a negligible role if it is the first (**II** to **III**, Scheme 1). Equimolar amounts of aldehydes **4** and **6** were subjected to the reaction in the presence of an internal standard (DBB), and the reaction was monitored by GC. We found that the two substrates are consumed at nearly the same rate (k_{rel} = 1.25, k_4/k_6, eq 2). This result suggests that the initial proton transfer is the first irreversible step.



We further conducted a series of competition experiments to investigate the role of aldehyde electronics on the reaction. A more electron-deficient aldehyde is consumed ~10.1 times faster than the parent substrate **4** (Scheme 3a). Conversely, the more electron-rich substrate **10** proved more sluggish than **4** providing a k_4/k_{10} of ~7.7.

Scheme 3. Aldehyde Competition Experiments



The above observations are all consistent with the initial proton transfer (**II** to **III**, Scheme 1) being the first irreversible step.[17] The more electron-deficient substrate **8** bears a methine of increased acidity relative to the parent substrate. Similarly, substrate **10** bearing the electron-releasing *para*-methoxy group thus has a less acidic methine in its corresponding intermediate **II**, leading to a slower reaction.

What remains is to determine the mechanism of the proton transfer. A direct 1,2-proton shift is symmetry forbidden and unlikely to occur.[18] In a DFT study of a model Stetter reaction mechanism, Yates has suggested that the proton transfer event must proceed intermolecularly, most likely via a second zwitterionic intermediate (similar to **II**, Scheme 1).[19] However, if this were the mechanism for the proton transfer in our reaction, kinetics should be second order in catalyst and substrate. We have further found that the reaction involving the free carbene

(15) See Supporting Information for the details of the kinetic experiments and the corresponding graphs.

(16) The same kinetic analysis was conducted on catalyst **3a** showing little difference in the corresponding catalytic cycle.

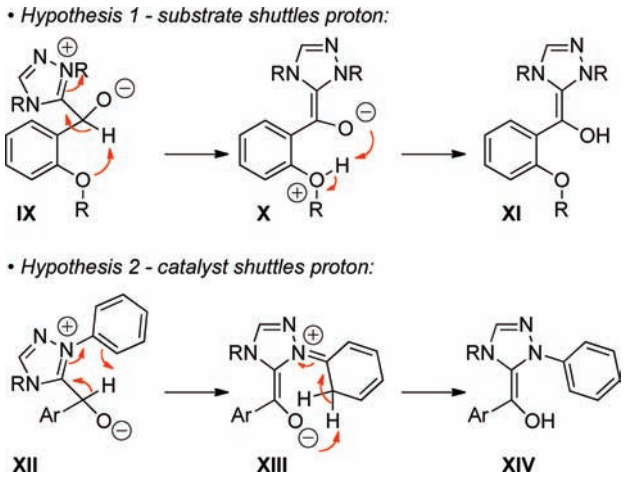
(17) This is consistent with Berkessel's observation that the catalyst resting state in the triazolylidene-catalyzed benzoin in THF is a dioxolane resulting from the tetrahedral alkoxy intermediate analogous to **II** adding another molecule of aldehyde in a reversible process. Thus, if proton transfer to generate **III** is slow, the alkoxide would prefer adding to an aldehyde to avoid the charge on oxygen in the absence of solvation. See: Berkessel, A.; Elfert, S.; Etzenbach-Effers, K.; Teles, J. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 7120.

(18) A 1,2-proton shift is a symmetry forbidden transformation (Kemp, D. S. *J. Org. Chem.* **1971**, *36*, 202 and references therein) but has been calculated to have an ~29 kcal/mol barrier (thiazolylidine) and ~51 kcal/mol barrier (cyanide) in the formation of the acyl anion equivalent from formaldehyde. See:Goldfuss, B.; Schumacher, M. *J. Mol. Model.* **2006**, *12*, 591.

(19) Hawkes, K. J.; Yates, B. F. *Eur. J. Org. Chem.* **2008**, 5563.

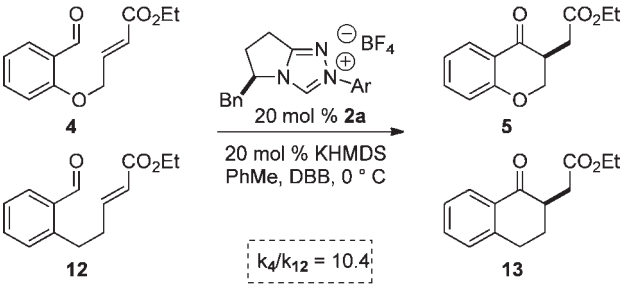
3a is similar in all respects to the **2a**/KHMDS system suggesting HMDS and KBF_4 play no role in the reaction.[20]

Scheme 4. Probing the Mechanism of the 1,2-Proton Shift



The most likely scenario that remains is that there is an agent of proton transfer within the molecule, on either the catalyst or the substrate. We envisioned two scenarios, one involving the ethereal oxygen linking the aldehyde and Michael acceptor and the second involving the aryl ring on the azolium precatalyst (Scheme 4). As a test of the latter hypothesis, we note that subjection of deuteroaldehyde **4-D** to a *N*-phenyl triazolium precatalyst under typical reaction conditions results in no observed deuteration in the catalyst architecture. A kinetic isotope effect should result in some deuteration of the ortho position on the catalyst aryl ring (compare **XIII** in Scheme 4, H vs D). The potential role of substrate in accelerating the proton transfer event was also evaluated. One can imagine that the proximity of the ether linker leads to deprotonation of the methine and generation of the derived oxonium (**X** in Scheme 4). This intermediate is presumably very short-lived, undergoing abstraction by the alkoxide generating **XI**, analogous to the nucleophilic alkene **III** in Scheme 1. As a test of this hypothesis, we conducted a competition experiment between ether-linked aldehyde **4** and substrate **12** bearing a methylene linker. Experiments shown in Scheme 3 suggest that the more electrophilic substrate **12** (bearing the more acidic methine; contrast **4** and **10**, Scheme 3b) should be consumed faster if the oxygen linker has no role in the mechanism. We found that the oxygen-linked substrate **4** is consumed in high preference over the methylene-linked substrate **12** implicating the oxygen in the proton transfer event.[21]

Scheme 5. Competition Experiment



In summary, we have provided convincing evidence that proton transfer is the first irreversible step in the triazolinylidine carbene-catalyzed asymmetric intramolecular Stetter reaction. This finding will have an impact on the design of future catalysts for the Stetter reaction. Furthermore, given the importance of generating the enolamine or nucleophilic alkene in other NHC-catalyzed reactions of aldehydes, this mechanistic nuance should also have a bearing on those areas.

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Supporting Information Available. Experimental procedures, kinetic and competition experiment data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) The protocol for generating the free carbene **3a** involves removal of volatiles including HMDS. Added HMDS did not appreciably affect the rate of the reaction. Separation of the insoluble KBF_4 shows no appreciable differences in reactivity. Furthermore, in situ ^{19}F NMR of the reaction medium shows no fluorine signals suggesting KBF_4 is completely insoluble under these conditions.

(21) That substrate **12** still undergoes reaction means that there must be another mechanism available for proton transfer, presumably either via Hypothesis II above or involving another molecule of catalyst or intermediate, as argued by Yates (see ref 19).