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Extending the Stetter Reaction with 1,6-Acceptors

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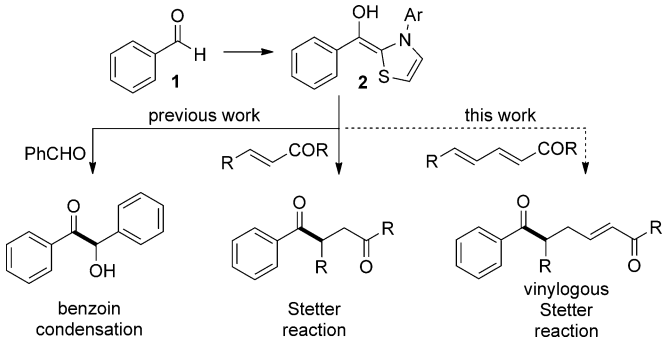
The advent of readily accessible *N*-heterocyclic carbenes (NHCs) has fuelled a reinvigoration of acyl anion chemistry. The archetypical acyl anion reaction, the benzoin condensation, was reported as early as 1824 (Scheme 1).[1] Pioneering



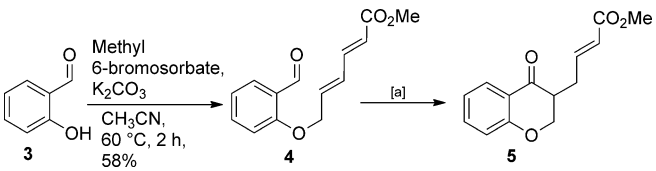
Scheme 1. The proposed vinylogous Stetter reaction.

studies by Liebig and Wöhler in 1832 and then Fischer in 1882,[2] firmly entrenched this reaction in the toolkit of synthetic chemists. Although those early examples required catalytic cyanide, Ukai discovered that this highly toxic species could be replaced with less hazardous thiazolium-derived NHCs.[3] The mechanism of the condensation, originally proposed by Lapworth[4] and later adapted by Breslow,[5] is commonly held to involve nucleophilic addition of an NHC onto benzaldehyde (**1**; Scheme 1), followed by proton transfer to give the reactive intermediate **2** in which the carbon atom of the aldehyde has undergone a formal polarity reversal (umpolung) and become nucleophilic. Treatment of **2** with a second equivalent of aldehyde yields the benzoin product. Despite recent advances including the invention of mixed cross-benzoin condensations and enantioselective variants,[6] the benzoin reaction is restricted by the relatively narrow synthetic utility of the α-hydroxyketone products.

In 1973, Stetter and Schreckenberg reported the first "vinylogous benzoin condensation" (Scheme 1).[7] That eponymous reaction involves the conjugate addition of the intermediate **2** onto an α,β-unsaturated carbonyl to give a 1,4-dicarbonyl containing product.[7a,8] In the 40 years since that seminal publication, the Stetter reaction has been significantly improved upon by the use of more reactive azolium (pre)catalysts, enabling both intra- and intermolecular variants, and the rendering of the reaction both enantio- and diastereoselective.[6b,c,9] The heightened synthetic potential of the 1,4-dicarbonyl (or equivalent) products significantly increases the value of the transformation over and above that of the parent benzoin condensation.

We reasoned that the utility of the process could be further enhanced by conducting a "vinylogous Stetter reaction". That is, effecting the inversion of conventional aldehyde reactivity using an NHC and treating the generated intermediate **2** with an α,β,γ,δ-unsaturated carbonyl compound (Scheme 1). The product of this transformation would contain a minimum of three sites for further synthetic manipulation. Investigations of 1,6-additions have undergone a recent renaissance.[10] However, given the decreased electrophilicity associated with such polyunsaturated systems and the possibility of a competing hetero-Diels–Alder process,[11] the success of the vinylogous Stetter reaction was far from certain. To favour 1,6-addition over 1,4-addition, we elected to concentrate our initial efforts on the intramolecular variant. The outcomes of those investigations are reported below.

Alkylation of salicylaldehyde (**3**) with methyl bromosorbate gave **4**, a suitable substrate to test the feasibility of the vinylogous Stetter reaction (Scheme 2). Our first task was to



Scheme 2. Synthesis of compound **4**; [a] see Table S1 in the Supporting Information.

uncover reaction conditions under which the proposed 1,6-additions would take place. To that end, the catalytic effectiveness of NHCs generated from various, representative azolium salts was examined (Figure 1). The NHC generated from the commercially available and inexpensive thiazolium salt **6** furnished the desired product **5** in low yield under a range of reaction conditions (Table 1 in the Supporting In-

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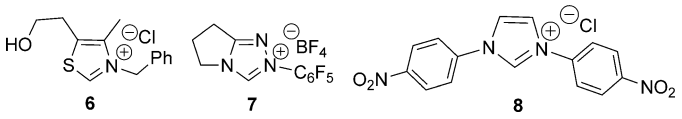


Figure 1. Azolium salts evaluated as NHC precatalysts.

formation). The effects of altering the solvent, temperature and base were examined and convenient conditions for effecting the vinylogous Stetter reaction with a thiazolium-based NHC were identified as 30 mol% of both thiazolium salt **6** and cesium carbonate in a non-polar solvent at 70°C (conditions A). Although this combination of reagents delivered the desired product in only moderate yield, it allowed for recovery of unreacted aldehyde **4**. Employing the more nucleophilic NHC generated from the triazolium salt **7** enabled the reaction to proceed at room temperature. A similar survey of the reaction conditions revealed that suitably convenient conditions for effecting the vinylogous Stetter reaction with a triazolium-based NHC employed 10 mol% of both triazolium salt **7** and DBU in a non-polar solvent at room temperature (conditions B). As expected, the NHC generated from the imidazolium salt **8** failed to give the desired product **5**. It is pertinent to note that the hetero-Diels–Alder adduct was not observed during the course of these studies, even under those reaction conditions in which heating was applied.

Having demonstrated that the vinylogous Stetter reaction is a viable synthetic procedure, we turned our attention to ascertaining the scope of the reaction. As shown in Figure 2, the aldehyde unit was systematically varied to assess the effect of both electron-donating and electron-withdrawing groups appended to the aromatic ring. In general, electron-withdrawing substituents were well tolerated, giving the vinylogous Stetter products **9**–**11** in good yield. Electron-donating substituents can also be employed. The 3-methoxysalicylaldehyde derivatives cyclised to give **12** and **13** in yields comparable to the parent compound **5** using both thiazolium and triazolium-derived NHCs. The 4-methoxysalicylaldehyde derivative cyclised to give **14** in moderate yield under the action of thiazolium- and triazolium-derived NHCs. Even the highly electron-donating 4-diethylamino-substituted compound participated in the triazolium-catalysed vinylogous Stetter reaction to give compound **15**.

The reaction is not restricted to salicylaldehyde derivatives. As depicted in Scheme 3, other heteroatoms can be incorporated into the tether. The aniline derivative **16** cyclised under the standard thiazolium-based conditions to give the tetrahydroquinolinone **17**. Cyclisation using the corresponding triazolium-derived NHC was frustrated by the insolubility of compound **16** in toluene at room temperature. Use of the non-preferred solvent dichloromethane allowed the reaction to proceed, albeit in reduced yield. Nor is the reaction limited to the generation of 6-membered rings. The pyrrole derivative **18** cyclised smoothly to give the substituted pyrrolizinone **19** and the aliphatic aldehyde **20** cyclised to the pyrrolidinone **21** in good yield.

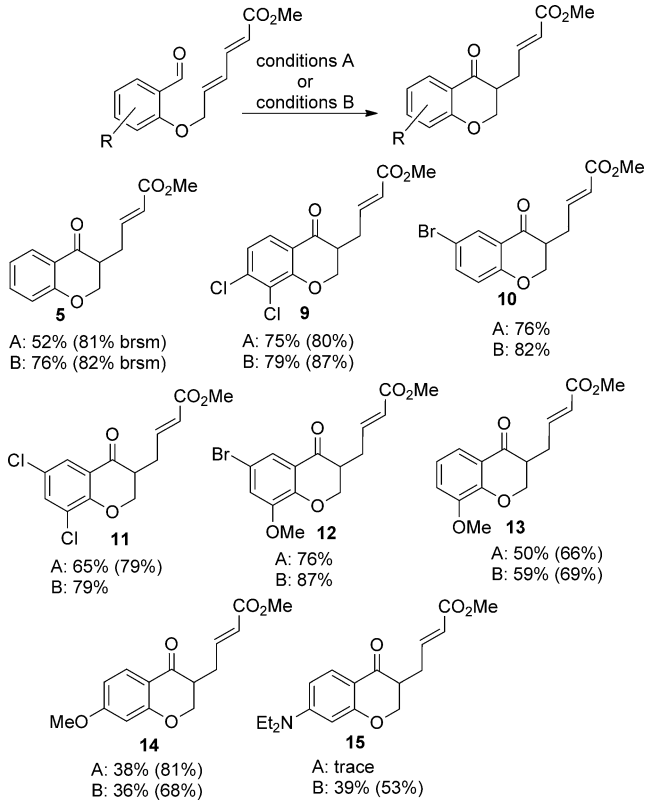
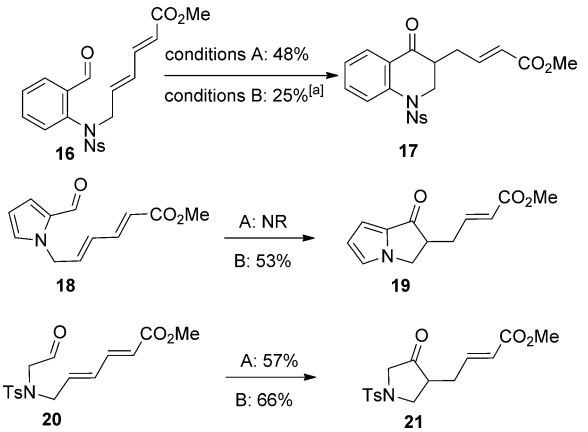


Figure 2. Examining the scope of the aldehyde unit in the vinylogous Stetter reaction. Conditions A: **6** (30 mol%), Cs_2CO_3 (30 mol%), toluene, 70°C; conditions B: **7** (10 mol%), DBU (10 mol%), toluene, room temperature.



Scheme 3. The vinylogous Stetter reaction of heterocyclic and aliphatic aldehydes. Conditions A: **6** (30 mol%), Cs_2CO_3 (30 mol%), toluene, 70°C; conditions B: **7** (10 mol%), DBU (10 mol%), toluene, room temperature. [a] CH_2Cl_2 as solvent; NR = no reaction.

As with the traditional Stetter reaction, a variety of α,β,γ,δ-unsaturated carbonyl units could be employed in the vinylogous Stetter reaction.[12] As detailed in Figure 3, the phenyl ketone-containing substrate cyclised in good yield under triazolium-based NHC catalysis, returning **22a** and **22b** as a 3:10 mixture favouring the non-conjugated com-

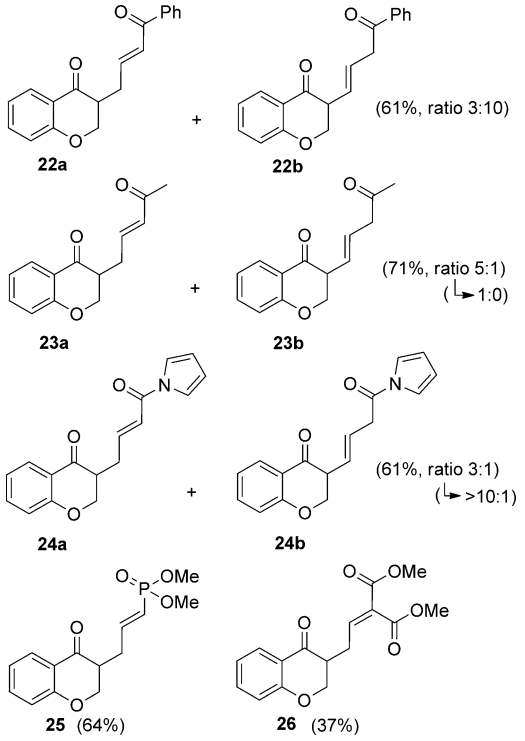
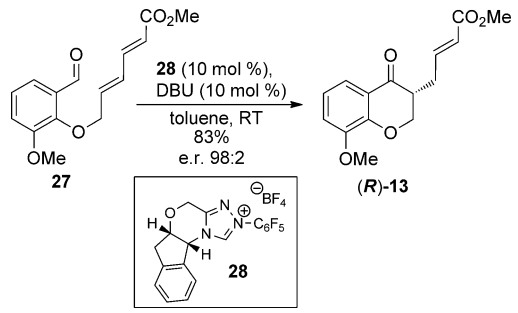


Figure 3. Examining the scope of the acceptor unit in the vinylogous Stetter reaction. Conditions B: **7** (10 mol%), DBU (10 mol%), toluene, room temperature.

pound **22b**. The analogous methyl ketones **23a** and **23b** were generated in 71% yield as a 5:1 mixture favouring the conjugated isomer. This product distribution is suggestive of a conjugate addition mechanism followed by a base-induced alkene isomerisation. Aged deuterochloroform was sufficiently acidic to effect complete isomerisation of the mixture to give solely **23a**. The heightened electrophilicity of the *N*-acylpyrrole functional group was illustrated by its ketone-like reactivity,[13] giving compound **24a** and **24b** in 61% yield as a 3:1 mixture, which could be isomerised to a >10:1 mixture by the action of catalytic PPTS in hot toluene. The phosphonate ester **25** was produced as a single isomer in 64% yield, and the malonate alkylidene substrate cyclised to **26** in modest yield (Scheme 4).



Scheme 4. The asymmetric vinylogous Stetter reaction.

The reaction could also be effected in an enantioselective manner (Scheme 4). For instance, treatment of the relatively electron-rich compound **27** with Rovis's triazolium salt **28**[14] under our convenient conditions, gave (***R***)-**13** in 83% yield with a 98:2 enantiomeric ratio.[15] Altering the electron density on the aromatic ring had little impact on efficacy, with (***R***)-**5** and (***R***)-**10** being produced with similar levels of enantiocontrol (Figure 4). Although they could not be resolved by enantioselective HPLC, pyrrolidinones (***S***)-**21** and (***R***)-**21** were produced in comparable yields by the action of **28** and ***ent*-28**.

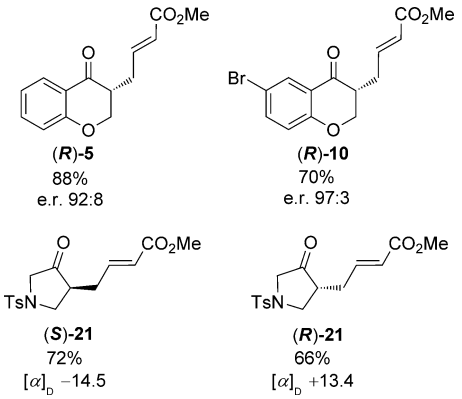
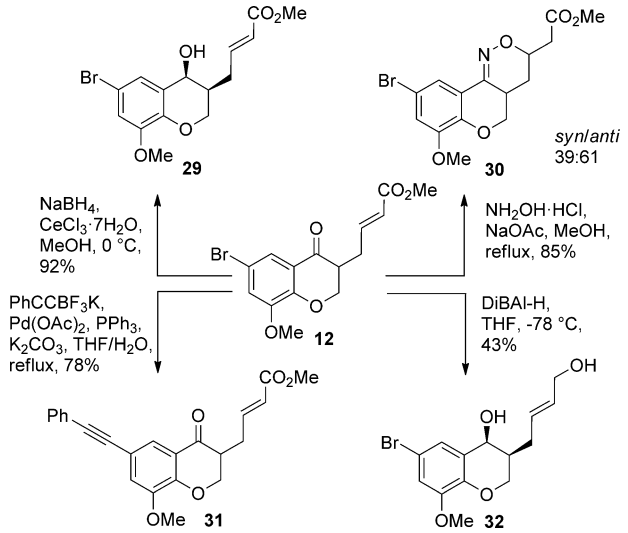


Figure 4. Examples of the asymmetric vinylogous Stetter reaction.

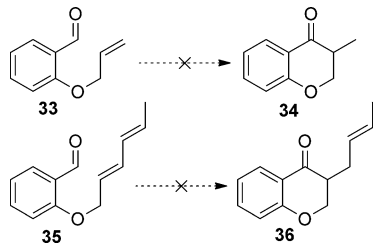
To highlight the enhanced synthetic potential of the vinylogous Stetter reaction, compound **12**, which was synthesised using this new protocol, was subjected to a number of chemoselective transformations (Scheme 5). The ketone unit of **12** underwent Luche reduction to give the *syn*-configured alcohol **29**. Oxime formation and intramolecular conjugate addition gave the oxazine-containing tricycle **30**. The aryl bromide participated in a palladium-catalysed cross-coupling re-



Scheme 5. Selected transformations of vinylogous Stetter products.

action to give **31**, and treatment of **12** with diisobutylaluminium hydride produced the *syn*-configured enediol **32**.

Finally, we have undertaken some preliminary studies towards elucidating the mechanism of the vinylogous Stetter reaction. The product distributions depicted in Figure 3 are consistent with the commonly invoked conjugate addition mechanism, but Glorius has recently reported an NHC-catalysed intramolecular hydroacylation reaction of unactivated alkenes that likely proceeds through a cycloaddition mechanism.[6b,16] To examine whether the vinylogous Stetter reaction proceeded through a similar mechanism, we subjected compounds **33** and **35** to the standard reaction conditions. Neither compound underwent cyclisation (Scheme 6).



Scheme 6. Hydroacylation studies. Conditions A: **6** (30 mol%), Cs_2CO_3 (30 mol%), toluene, 70°C; **7** (10 mol%), DBU (10 mol%), toluene, room temperature.

In summary, we report the intramolecular vinylogous Stetter reaction as a new addition to the toolkit of NHC-catalysed transformations. The reaction can be carried out with both thiazolium- and triazolium-derived catalysts. It proceeds with aromatic aldehydes and aliphatic aldehydes to give 5- and 6-membered rings. Substrates containing various heteroatom tethers participate in the reaction, and an asymmetric vinylogous Stetter reaction has been demonstrated. The products of this new transformation possess multiple sites for chemoselective functionalisation, including (but not limited to) ketones, esters and alkenes. The application of the vinylogous Stetter reaction in natural product total synthesis is underway in our laboratory.

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Keywords: *N*-heterocyclic carbenes · nitrogen heterocycles · organocatalysis · oxygen heterocycles · synthetic methods

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