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Efficient Synthesis of γ-Keto Sulfones by NHC-Catalyzed Intermolecular Stetter Reaction

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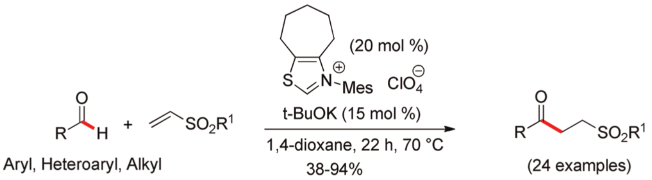
ABSTRACT



The N-heterocyclic carbene-catalyzed intermolecular Stetter reaction of aldehydes with α,β-unsaturated sulfones allows the atom-economic and selective formation of γ-keto sulfones in good yields. Key to the success of this unique transition-metal-free carbon–carbon bond-forming reaction is the right choice of the NHC precursor and base. The reaction tolerates a broad range of different aldehydes.

The Stetter reaction, the nucleophilic heterocyclic carbene (NHC)-organocatalyzed umpolung of aldehydes followed by their reaction with Michael acceptors, constitutes a highly valuable and widely used catalytic protocol for the synthesis of 1,4-bifunctional compounds such as 1,4-diketones, 4-ketonitriles, and 4-ketoesters, thus leading to an unnatural functional group distance, which is difficult to realize using traditional methods.[1,2] These reactions proceed via the formation of nucleophilic acyl anion intermediates, which can react with various activated, polarized,[3] and even electron neutral[4] C–C double bonds. Intriguingly, however, whereas the NHC-catalyzed generation of the Breslow intermediate (**A**)[5] and its subsequent interception with a variety of Michael acceptors are well documented (Scheme 1, eq 1),[3] the analogous reaction with α,β-unsaturated sulfones as electrophiles is extremely rare, presumably due to the formation of undesired side

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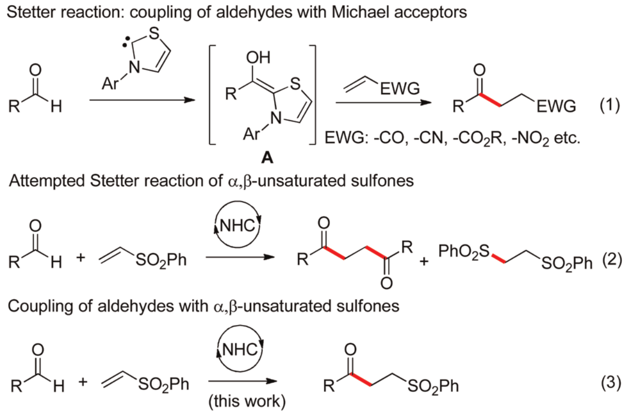
products under basic conditions. In 1978, Stetter et al. reported the first NHC-catalyzed addition of aldehydes to vinyl sulfones (eq 2).[6] Surprisingly, however, the product was not the expected γ-keto sulfone but was a 1:1 mixture of 1,4-diketone and γ-disulfone. The NHC-catalyzed umpolung addition of aldehydes to vinyl sulfones leading to the formation of γ-keto sulfones, the intermolecular hydroacyalation of α,β-unsaturated sulfones, are, to the best of our knowledge, unknown (eq 3). Herein, we report the NHC-catalyzed intermolecular Stetter reaction of α,β-unsaturated sulfones leading to the formation of γ-keto sulfones. It is important to note, however, that keto sulfones are attractive synthetic targets, since they are potent and selective 11β-hydroxysteroid dehydrogenase type I inhibitors.[7]

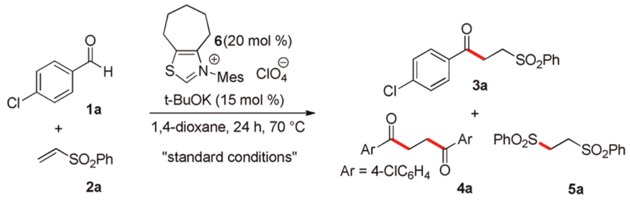
Scheme 1. NHC-Catalyzed Stetter Reaction


Stetter reaction: coupling of aldehydes with Michael acceptors

Attempted Stetter reaction of α,β-unsaturated sulfones

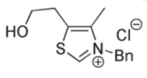
Coupling of aldehydes with α,β-unsaturated sulfones

Table 1. Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions[a]	yield of **3a** (%)[b]	yield of **4a** (%)[b]	yield of **5a** (%)[b]
1	None	56	10	<1
2	**7** instead of **6**	9	3	<1
3	**8** instead of **6**	<1	50	44
4	**9** instead of **6**	<1	23	23
5	**10** instead of **6**	<1	20	2
6	K_2CO_3 instead of t-BuOK	47	12	<1
7	Na_2CO_3 instead of t-BuOK	<1	<1	<1
8	Et_3N instead of t-BuOK	37	8	<1
9	DBU instead of t-BuOK	<1	43	30
10	THF instead of 1,4 dioxane	34	19	18
11	Toluene instead of 1,4-dioxane	48	7	7
12	Ethanol instead of 1,4-dioxane	<1	29	17
13	Reaction run at 60 °C	35	3	<1
14	(15 mol %) of **6**, (10 mol %) t-BuOK	34	8	<1
15	(1.4 equiv) of **1a**, reaction time: 22 h	80 (81)	8 (8)	<1

[a] Standard conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), NHC·HX (20 mol %), t-BuOK (15 mol %), 1,4-dioxane (1.0 mL), 70 °C and 24 h. [b] The yields were determined by ^{1}H-NMR analysis (DMSO-d_6) of crude products using CH_2Br_2 as the internal standard. Isolated yield in 1.0 mmol scale in parentheses.



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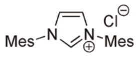

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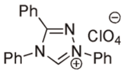

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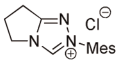

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Our present study commenced with the treatment of 4-chlorobenzaldehyde **1a** and phenyl vinyl sulfone **2a** with the thiazolium salt **6** originally developed by Glorius et al.[8] and 15 mol % of *t*-BuOK. Delightfully, a facile reaction occurred leading to the formation of the γ-ketosulfone **3a** in 56% yield (based on ^{1}H NMR spectroscopy, Table 1, entry 1). Interestingly, under this condition, the undesired side products **4a** and **5a** derived from the base-induced elimination of the sulfonyl group of **3a** was observed in low yields. We believe that the key to success might be the use of a strong base, which will be mostly protonated by the thiazolium salt **6** so that a minimum amount of free base that might induce the elimination in **3a** is present in the reaction medium.[9] Remarkably, in contrast to this NHC, other common NHCs derived from **7**−**10** are far less effective (entries 2−5). Other bases such as K_2CO_3, Na_2CO_3, Et_3N, and DBU furnished the desired product **3a** in reduced yields (entries 6−9), and solvents other than 1,4-dioxane resulted in inferior reactivity and/or selectivity (entries 10−12). The reaction is sluggish at 60 °C (entry 13), and the yield of **3a** was reduced considerably when the amount of **6** and *t*-BuOK was reduced (entry 14). Finally, increasing the amount of **1a** to 1.4 equiv and reducing the reaction time to 22 h improved the reactivity, with **3a** obtained in 81% yield (entry 15).[10] Under the optimized conditions, the symmetric 1,4-diketone **4a** was isolated in 8% yield and no disulfone **5a** was formed.

With these optimized reaction conditions in hand, we then examined the substrate scope of this unique intermolecular Stetter reaction (Scheme 2). The unsubstituted parent system worked well, and a variety of electron-donating and -withdrawing groups at the 4-position of the aromatic ring were well tolerated, leading to γ-keto

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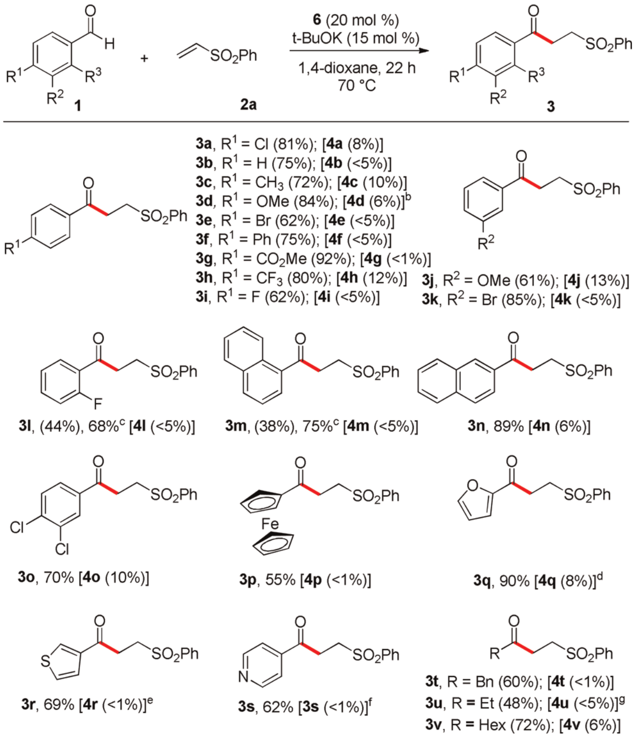
(10) For details, see the Supporting Information.

Scheme 2. NHC-Catalyzed Synthesis of γ-Ketosulfones: Variation of the Aldehyde Moiety[a]

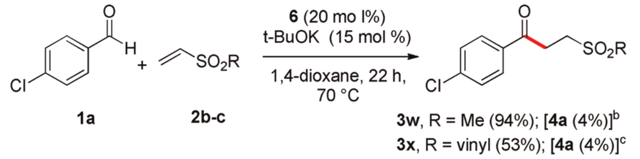


[a] General conditions: **2a** (1.0 mmol), **1** (1.4 mmol), **6** (20 mol %), *t*-BuOK (15 mol %), 1,4-dioxane (2.0 mL), 70 °C, and 22 h. Yields of isolated products are given. [b] Reaction was run for 30 h. [c] Yield based on recovered **2a**. [d] The product was inseparable from the corresponding diketone; NMR yield given. [e] Reaction was run for 18 h. [f] Reaction was run for 15 h. [g] Reaction run on 0.5 mmol scale using 5.0 equiv of *n*-propanal.

sulfones in 62–92% yield (**3a**–**i**). Moreover, 3-substituted aldehydes resulted in the smooth conversion to the product (**3j**, **3k**). Although 2-substituted benzaldehydes result in significantly lower yields in NHC-organocatalysis, 2-fluorobenzaldehyde and 1-naphthaldehyde still provided a moderate yield of the corresponding product (**3l**, **3m**). Furthermore, 2-naphthaldehyde as well as disubstituted aldehyde worked well (**3n**, **3o**). Interestingly, challenging aldehydes such as ferrocenecarboxaldehyde as well as heterocyclic aldehydes also furnished moderate to good yields of the desired products, further expanding the scope of this intermolecular Stetter reaction (**3p**–**s**).[11] Additionally, this novel hydroacylation reaction is not limited to aromatic aldehydes. Gratifyingly, aliphatic aldehydes also worked well leading to the formation of the desired products (**3t**–**v**) in moderate to good yields.

In view of these interesting results, we further investigated the scope of the reaction using various alkyl substituted α,β-unsaturated sulfones (Scheme 3). Gratifyingly, alkyl and vinyl substituents at the sulfone moiety are well tolerated leading to the formation of γ-keto sulfones **3w**–**x** in moderate to excellent yields. It is noteworthy, however, that in preliminary experiments β-substituted α,β-unsaturated sulfones failed to undergo this transformation under the optimized reaction conditions.

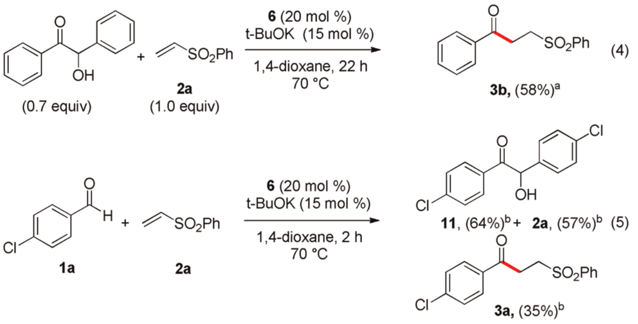
Scheme 3. NHC-Catalyzed Synthesis of γ-Ketosulfones: Variation of the Sulfone Moiety[a]



[a] The yield of the 1,4-diketone **4a** is in parentheses. [b] Reaction run using 1.4 equiv of **1a**. [c] Reaction run using 1.0 equiv of **1a**.

Further insightful experiments shed light on the mechanism of this unique transformation (Scheme 4). In the context of the widely accepted mechanistic proposal for the benzoin and Stetter reaction,[12] benzoin was subjected to the optimized reaction conditions. This reaction returned the desired γ-keto sulfone **3b** in 58% yield (eq 4). Additionally, upon quenching the reaction under optimized conditions after 2 h, the 4-chlorobenzoin **11** was observed as the major product in 64% yield along with the desired product in 35% yield (eq 5). These observations indicate the reversibility of the formation of benzoin as well as the Breslow intermediate under the present reaction conditions.

Scheme 4. Studies on the General Reaction Pathway



[a] Isolated yield. [b] Determined by ^{1}H NMR analysis (DMSO-d_6) of crude products using CH_2Br_2 as the internal standard.

The mechanistic rationale for this intermolecular Stetter reaction may be advanced as follows (Scheme 5).[13] The reaction is initiated by the addition of NHC to aldehyde generating the terahedral intermediate, which undergoes proton transfer to form the nucleophilic Breslow intermediate (**A**). This acyl anion equivalent can attack the vinyl

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(11) With pyridine 4-carboxaldehyde, 5% of the disulfone **5a** was also isolated.

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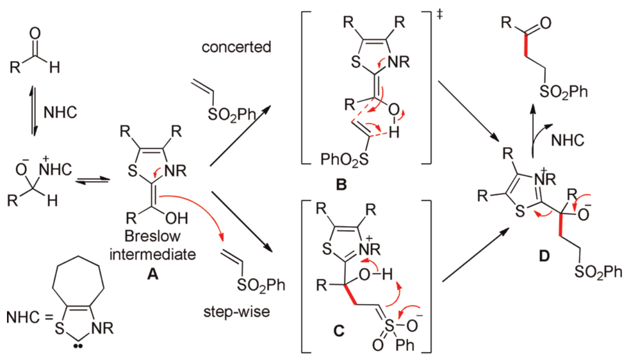
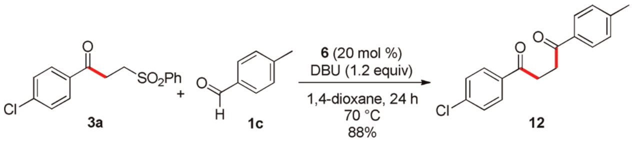
sulfone **2** in a concerted fashion[2d,4,14,15] via the five-membered transition state **B** to furnish the alkoxide intermediate **D**. Alternatively, a stepwise pathway involving the formation of the intermediate **C** can also be invoked. Elimination of NHC from **D** completes the catalytic cycle furnishing the γ-keto sulfones.

Scheme 5. Proposed Mechanistic Pathways



The synthetic utility of the γ-keto sulfones has been demonstrated by the efficient NHC-catalyzed synthesis of 2,3-unsubstituted unsymmetrical 1,4-diketones.[16] Thus treatment of **3a** with *p*-tolualdehyde **1c** in the presence of 20 mol % **6** under basic conditions afforded the 1,4-diketone **12** in 88% yield. The reaction proceeds via the DBU induced elimination of the sulfonyl group from **3a** generating the enone intermediate, which undergoes an intermolecular Stetter reaction with **1c** leading to the formation of **12** (Scheme 6). It should be noted that the unsymmetrical 1,4-diketone **12** can easily be converted into 2,5-disubstituted pyrroles and furans using the Paal–Knorr cyclization reaction.[17]

Scheme 6. NHC-Catalyzed Synthesis of Unsymmetrical 1,4-Diketones



In conclusion, we have uncovered a transition-metal-free NHC-organocatalyzed intermolecular Stetter reaction of aldehydes with α,β-unsaturated sulfones leading to the efficient formation of γ-keto sulfones in good yields. The product formation took place in spite of various selectivity issues under basic conditions. Further studies on expanding the scope of the reaction and exploring the synthetic utility of α,β-unsaturated sulfones in challenging organocatalytic reactions are ongoing in our laboratory.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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