Asymmetric intermolecular Stetter reactions catalyzed by a novel triazolium derived N-heterocyclic carbene†

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Received (in Cambridge, UK) 11th June 2008, Accepted 2nd July 2008
First published as an Advance Article on the web 25th July 2008
DOI: 10.1039/b809913h

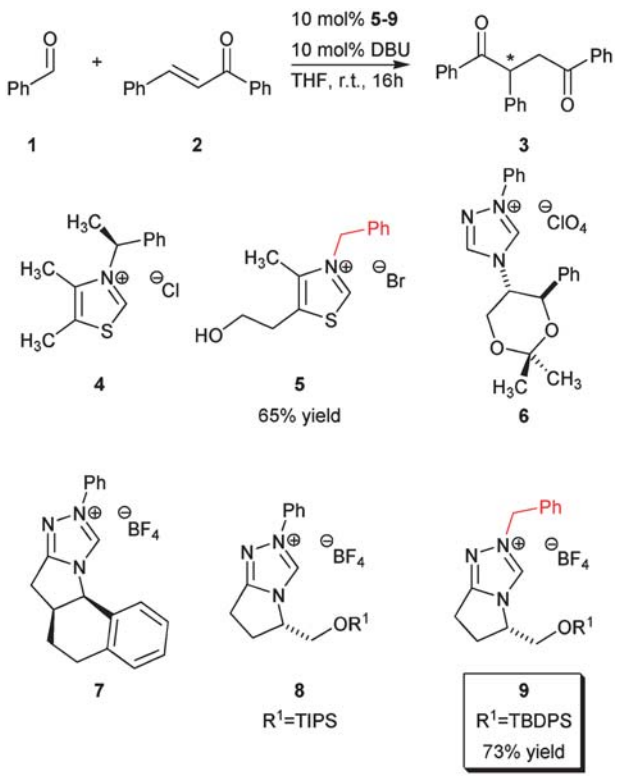
The asymmetric intermolecular Stetter reaction is catalyzed by a novel triazolium salt derived N-heterocyclic carbene leading to 1,4-diketones in moderate to excellent yields (49–98%) and moderate to good enantioselectivities (56–78% ee), which could be enhanced by one recrystallization to excellent levels (90–99% ee).

Within the rapidly expanding field of organocatalysis, N-heterocyclic carbenes (NHCs) have received considerable attention due to their capability of catalysing a broad range of synthetic transformations.[1] The intrinsic ability of NHCs to invert the classical reactivity (Umpolung) of certain functional groups is unique in organic chemistry and is used in the Stetter reaction, the catalytic nucleophilic acylation of a Michael acceptor.[2]

Since a new stereocenter is usually generated within the Stetter product, attention has been paid to the development of enantioselective versions of this reaction. The first report concerning an asymmetric *intramolecular* Stetter reaction was published by our research group[3] and later Rovis and co-workers made improvements to the method.[4] They also extended the reaction scope to products with quaternary stereocenters,[5] investigated the use of aldehydic substrates with pre-existing stereocenters[6] and developed a diastereo- and enantioselective variant involving α,β-disubstituted Michael acceptors.[7] However the asymmetric *intermolecular* Stetter reaction is much less studied. A first enantioselective version was published in 1993 by our research group.[8] The chiral thiazolium precatalyst **4** promoted the reaction of *n*-butanal with chalcone providing the corresponding 1,4-diketone in 30% yield an 40% ee. Herein, we report the application of a novel chiral triazolium salt as a carbene precatalyst in the enantioselective intermolecular Stetter reaction leading to practical enantiomeric excesses.

We started our investigation by screening different chiral triazolium based precatalysts **6–8**, previously developed in our group (Scheme 1). As the test reaction, benzaldehyde (**1**) and chalcone (**2**) were exposed to catalytic quantities of triazolium salt **6** and DBU. Interestingly, no reaction was observed even though this precatalyst was effective in the intramolecular Stetter reaction.[3] Next, triazolium salts **7** and **8**, initially developed for the asymmetric intramolecular benzoin condensation,[9] were tested but failed to catalyze this transformation. We thus turned our attention to the preparation of a new carbene catalyst. Thiazolium salt **5** is one of the most commonly used precatalysts for the intermolecular Stetter reaction. A striking difference is that **5** contains an *N*-benzyl substituent, whereas the triazolium salts **6–8** bear *N*-phenyl substituents. Therefore, we synthesized precatalyst **9** with an *N*-benzyl group.[10] To our delight, compound **9** readily promoted this transformation and the Stetter product **3** was formed in good yield (73%). This indicated that the *N*-substituent has a dramatic impact on the activity of triazolium-based catalysts in the intermolecular Stetter reaction.

Although the precatalyst **9** was active, it gave low levels of asymmetric induction (20% ee). In order to improve the enantioselectivity the reaction parameters were varied (Scheme 2). Bases such as Et_3N, *i*-Pr_2NEt, KO*t*-Bu and KHMDS resulted in no reaction or only trace amounts of the Stetter product (Table 1, entries 2–5). Gratifyingly, when K_2CO_3 was used as the base, precatalyst **9** afforded the Stetter product in good yield



Scheme 1 Precatalysts tested in the intermolecular Stetter reaction.

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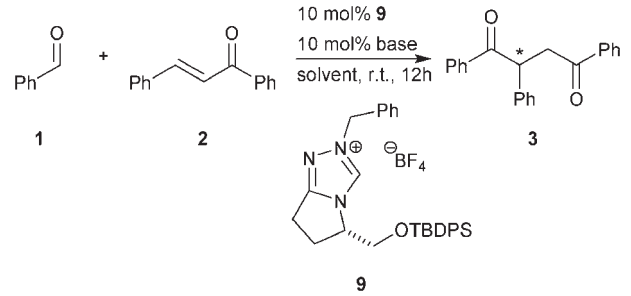
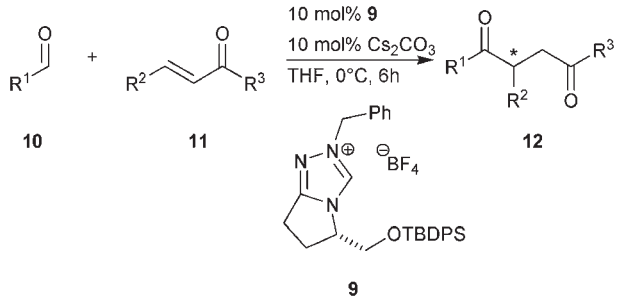
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b809913h



Scheme 2 Optimization studies for the intermolecular Stetter reaction.



Scheme 3 Enantioselective intermolecular Stetter reactions under optimized conditions.

and improved enantioselectivity (73% yield, 51% ee, entry 6). Further studies on the role of the solvent revealed that THF was the most suitable (entries 6–12). Next, the alkali-cation of the carbonate base was varied. While Li_2CO_3 resulted in no reaction, Cs_2CO_3 led to an increased enantioselectivity with no change in yield (72% yield, 62% ee, entry 14). Lowering the reaction temperature to 0 °C allowed a further enhancement in enantioselectivity at the cost of yield (65% yield, 66% ee, entry 15) and at −20 °C only benzoin condensation was observed.

Under the optimized conditions, a variety of aromatic aldehydes and substituted Michael acceptors were examined in the intermolecular asymmetric Stetter reaction (Scheme 3, Table 2). In general, acylation of α,β-unsaturated ketones **11** occurred smoothly affording the corresponding 1,4-diketones **12** in moderate yields and good enantioselectivities. Electron-rich aldehydes gave better asymmetric inductions than electron-deficient aldehydes and the highly reactive heteroaromatic aldehyde 2-furfural reacted almost quantitatively and with moderate enantioselectivity. Most importantly, the enantiomeric excesses of several products could be increased to excellent levels (90–99% ee) after a single recrystallization.

The absolute configuration of the 1,4-diketone **12a** was determined to be (*R*) by comparison of its optical rotation.[11] This stereochemical outcome can be explained by the following transition state models (Fig. 1).

Table 2 Substrate scope for the intermolecular Stetter reaction

12	R^1	R^2	R^3	Yield (%)[a]	Ee (%)[b,c]
12a	Ph	Ph	Ph	65 (40)	66 (>99)
12b	4-MeC_6H_4	Ph	Ph	43 (31)	78 (>99)
12c	3-MeC_6H_4	Ph	Ph	50 (32)	70 (98)
12d	4-ClC_6H_4	Ph	Ph	55	67[d]
12e	4-BrC_6H_4	Ph	Ph	68	56[d]
12f	2-Naphthyl	Ph	Ph	65 (41)	70 (90)
12g	2-Furyl	Ph	Ph	98	56[e]
12h	Ph	4-MePh	Ph	55	64[d]
12i	Ph	4-ClPh	Ph	57 (21)	56 (94)

[a] Value in brackets is the yield after recrystallization. [b] The enantiomeric excess was determined by HPLC with a chiral stationary phase (Daicel Chiralpak AD). [c] Value in brackets is the ee after recrystallization. [d] The products were obtained as thick oil. [e] Attempt to recrystallize was unsuccessful.

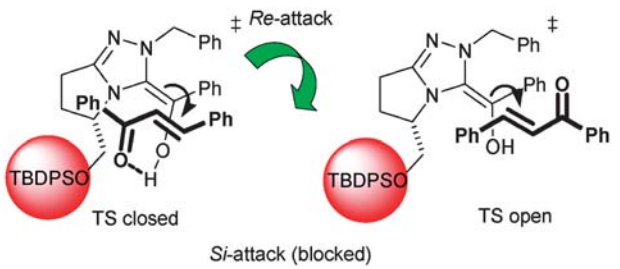


Fig. 1 Proposed transition states.

Table 1 Conditions for the optimization studies

Entry	Base	Solvent	Yield (%)	Ee (%)[a]
1	DBU	THF	73	20
2	Et_3N	THF	0	—
3	*i*-Pr_2NEt	THF	0	—
4	KHMDS	THF	0	—
5	KO*t*-Bu	THF	Traces	ND
6	K_2CO_3	THF	73	51
7	K_2CO_3	Et_2O	39	15
8	K_2CO_3	DCM	42	0
9	K_2CO_3	DMF	55	52
10	K_2CO_3	DMSO	50	33
11	K_2CO_3	MeOH	60	9
12	K_2CO_3	$PhCH_3$	67	31
13	Li_2CO_3	THF	0	—
14	Cs_2CO_3	THF	72	62
15[b]	Cs_2CO_3	THF	65	66

[a] The enantiomeric excess was determined by HPLC with a chiral stationary phase (Daicel Chiralpak AD). [b] Reaction was performed at 0 °C for 6 h.

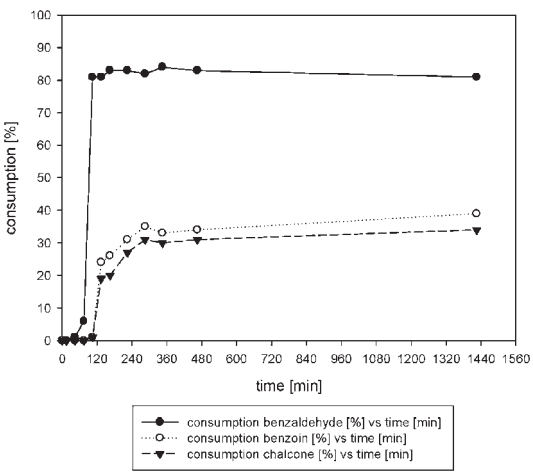
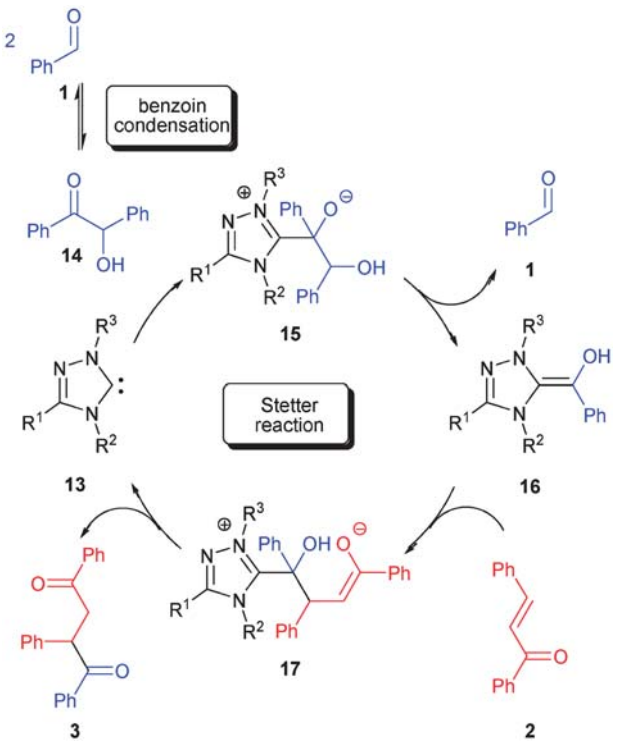


Fig. 2 Reaction control *via* gas chromatography.



Scheme 4 Catalytic cycle for the formation of the Stetter product.

Assuming that the silyl branch of the catalyst blocks the *Si*-face of the Breslow intermediate, the 1,4-addition would occur at its less hindered *Re*-face. The chalcone then reacts from its *Si*-face to give the observed (*R*)-configured Stetter product.

Under the Stetter reaction conditions used here, self-condensation of the aldehyde component always took place. To investigate the role of this competing pathway, the reaction course was monitored by gas chromatography (Fig. 2).‡ Interestingly, in the early stage of the reaction when no chalcone had been consumed, significant conversion (>80%) of benzaldehyde had already occurred to form its benzoin product. As the reaction progressed, the disappearance of the benzoin product strongly correlated with the consumption of chalcone. Based on these observations, we propose that the Stetter product forms as a result of two coupled catalytic reactions (Scheme 4). Initially, a rapid carbene-catalyzed benzoin condensation occurs prior to Stetter product formation.[12] Next, the desired 1,4-diketone is formed in a subsequent catalytic cycle initiated by the nucleophilic attack of catalyst **13** at the carbonyl function of benzoin product **14**. Elimination of benzaldehyde (**1**) from the 1,2-adduct **15** results in the formation of the Breslow intermediate **16**, which in turn attacks chalcone (**2**) leading to the tetrahedral intermediate **17**. Intramolecular proton transfer and elimination of the 1,4-diketone **3** returns the catalyst. This mechanistic proposal is in agreement with the literature. Stetter and Kuhlmann described the carbene-catalyzed benzoin condensation as highly reversible[2] and a recent study by You and co-workers revealed that, in fact, benzoin can serve as a masked benzaldehyde equivalent in a carbene-catalysed cross-coupling of aldehydes with unactivated imines.[13]

In summary a new chiral triazolium based carbene precatalyst was synthesized and successfully employed in the asymmetric *intermolecular* Stetter reaction. The resulting 1,4-diketones were obtained in moderate to excellent yields and good enantioselectivities. For several Stetter products the enantiomeric excess could be enhanced by a single recrystallization up to 99% ee. Examination of the reaction course revealed new mechanistic insights about the formation of the Stetter product.

Notes and references

‡ In addition the reaction course was monitored by HPLC removing aliquots from the reaction mixture, revealing that insignificant racemization of the Stetter product **3** was taking place (10% over 24 h).

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