# Enantioselective Stetter Reactions of Enals and Modified Chalcones Catalyzed by N-Heterocyclic Carbenes**

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Organocatalytic activation of readily available substrates has led to the rapid development of many enantioselective reactions in the last decade.[1] In N-heterocyclic carbene (NHC) catalysis,[2] reactions of enals with enones or enone derivatives have been extensively investigated and are reported to undergo a diverse set of transformations based on the catalytically generated enolate and homoenolate equivalents as intermediates.[3,4] In contrast, the NHC-catalyzed enantioselective Stetter-type Michael additions[5] of enals to enones remain challenging in part due to the competing and often dominant homoenolate or enolate[3] pathways. Herein we report an enantioselective Stetter reaction of enals and modified chalcones using triazolium-based NHC catalysts [Eq. (1)]. The previously reported
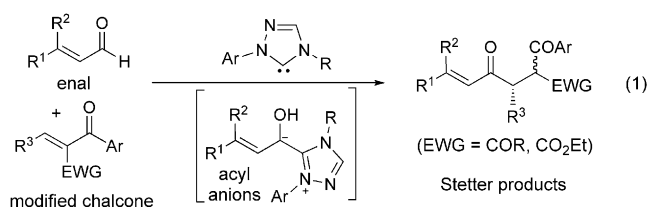
typical homoenolate and enolate pathways[3,4] were largely suppressed especially when β-alkyl enals were used as the acyl anion precursors and alkylidene diketones as the Michael acceptors. Enals having two β substituents can also behave as effective acyl anion precursors. A relevant and elegant enantioselective Stetter reaction between enals and nitroalkenes using NHC and catechol cocatalysts was reported by Rovis and co-workers recently.[6]

Our development of the Stetter reaction with enals as substrates was first initiated by an observation of a low yielding Stetter adduct as a side product during our recent study of Diels–Alder reactions of β-aryl enals with modified chalcones.[7] We next found that by using β-alkyl enals as acyl

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anion precursors, the Stetter products could be obtained in good yields. The initial studies and optimization of the reaction conditions for the enantioselective intermolecular Stetter reaction using the enal **1a** and modified chalcone **2a** as the model substrates with triazolium-based NHCs as the catalysts are summarized in Table 1. The reaction proceeded

Table 1: Stetter reaction between enal **1a** and modified chalcone **2a**: optimization of reaction conditions.[a]

Entry	NHC	Base	Solvent, T	Yield [%][b]	ee [%][c]
1	A	DBU	THF, RT	90	–
2	B	DBU	THF, RT	80	67
3	B	Et₃N	THF, RT	33[d]	91
4	B	DIPEA	THF, RT	30[d]	90
5	B	DMAP	THF, RT	40[d]	92
6	B	LHMDS	THF, RT	22	84
7[e]	B	DBU	THF, 0°C	86	90
8[e]	C	DBU	THF, 0°C	22	n.d.
9[e]	C	DBU	Toluene, 0°C	54	29
10[e]	D	DBU	THF, 0°C	16	n.d.
11[e]	E	DBU	THF, 0°C	43	60

[a] Reaction conditions: **1a** (0.45 mmol), **2a** (0.15 mmol), NHC (20 mol%), base (20 mol%), solvent (1.5 mL), 12 h. [b] Yield of isolated product based on **2a**. [c] Enantiomeric excess of **3a** determined by chiral-phase HPLC analysis; absolute configuration was determined by X-ray structure analysis of its analogue **3i** (Table 2; see the Supporting Information).[11] [d] Diels–Alder products were also formed in about a 1:1 ratio with the Stetter products. [e] Used 30 mol% NHC, 20 mol% base. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = 2,4,6-trimethylphenyl, DIPEA = N,N′-diisopropylethylamine, DMAP = 4-(dimethylamino)-pyridine, LHMDS = lithium bis(trimethylsilyl)amide, Mes = 2,4,6-trimethyl-phenyl, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene, THF = tetrahydrofuran, n.d. = not determined.

efficiently with the achiral triazolium **A** as the pre-catalyst and DBU as the base in THF to give Stetter product **3a** in 90% yield upon isolation (Table 1, entry 1). The use of the chiral pre-catalyst **B** resulted in an 80% yield with an encouraging 67% *ee* (Table 1, entry 2). Additional optimization to improve the reaction enantioselectivity by using different bases (Table 1, entries 3–6) led to improved *ee* val-

ues, but with significantly reduced reaction yields. We then realized that the relatively low enantioselectivity obtained with the catalyst **B** was primarily caused by base-mediated racemization of the Stetter product **3a**. Thus by using a slight excess of **B** (30 mol%, relative to 20 mol% DBU) and decreasing the reaction temperature to 0°C, the Stetter product was obtained in 90% *ee* with 86% yield (Table 1, entry 7). Attempts to use using the pre-catalysts **C–E** under a range of reaction conditions (Table 1, entries 8–11) did not lead to improvements in reaction yields or enantioselectivities. It is interesting to note that the choice of the NHC catalyst is important to achieve the Stetter reactions. In our previous work, by using the imidazolium-based bulky IMes catalyst the reactions with the same sets of substrates proceeded through an enal enolate pathway to give Diels–Alder products.[7]

Next we used **B** with DBU as the base in THF at 0°C (Table 1, entry 7) to investigate the scope of the Stetter reaction. We first studied the reaction using a series of β-alkyl enal substrates and alkylidene diketones (Table 2). In all cases

Table 2: Scope of the Stetter reaction using β-alkyl enals.[a]

Entry	R^1	R^2, R^3	3	Yield [%][b]	ee [%][c]
1	Me	Ph, Ph	**3a**	90	94
2	Et	Ph, Ph	**3b**	86	90
3	*n*Pr	Ph, Ph	**3c**	77	88
4	*n*-C$_5$H$_{11}$	Ph, Ph	**3d**	81	91
5	*n*-C$_7$H$_{15}$	Ph, Ph	**3e**	84	91
6	Me-CH=CH	Ph, Ph	**3f**	85	95
7	Et	3-OMeC$_6$H$_4$, Ph	**3g**[d]	68	91
8	Me	4-*i*PrC$_6$H$_4$, Ph	**3h**[d]	51	90
9	Me	4-BrC$_6$H$_4$, Ph	**3i**	80	92
10	Me	4-FC$_6$H$_4$, Ph	**3j**	71	92
11	Me	Ph, 4-BrC$_6$H$_4$	**3k**	89	85
12	Et	3-OMeC$_6$H$_4$, 4-BrC$_6$H$_4$	**3l**	86	93
13	Me	Ph, 4-ClC$_6$H$_4$	**3m**	64	94
14	Me	Ph, 4-FC$_6$H$_4$	**3n**	74	92

[a] Reaction conditions: **1** (0.45 mmol), **2** (0.15 mmol), THF (1.5 mL). [b] Yield of isolated product. [c] Enantiomeric excess of **3**, determined by chiral-phase HPLC analysis; the absolute configuration was determined by X-ray structure analysis of product **3i**. [d] Catechol (100 mol%) was used as an additive.

the reactions proceeded smoothly to afford the Stetter products with good enantioselectivities and yields. The Michael acceptor **2** having aryl groups (R^2 and R^3) with different electronic properties was investigated (Table 2, entries 7–14). Electron-donating groups on the phenyl rings generally gave products with slightly decreased yields (Table 2, entries 7 and 8); in these cases the addition of a catechol additive[8] improved the yields without affecting enantioselectivities. In all the examples studied in Table 2, the reactions exclusively proceeded to give the Stetter products without observable formation of the typical products arising from either the enolate or homoenolate pathways.

We next examined enals with β-aryl substituents. With the β-aryl enals, the enolate pathway (giving Diels–Alder products)[7] dominated and was difficult to suppress using the reaction conditions employed in Table 2 with **B** as the pre-catalyst. The use of the less bulky NHC catalyst **C** did lead to the Stetter adduct as the sole product, but with low yields and poor enantioselectivities under various reaction conditions (see the Supporting Information). We then went back to catalyst **B** and extensively optimized the reaction conditions. Although the enolate pathway[7] was still hard to eliminate after much effort, the Stetter product could be obtained with up to 49% yield and good enantioselectivities by using toluene as the solvent at 0°C (Table 3). The difference in reactivity induced by the β substituents on the enals may result from the relatively electron-rich and electron-poor properties of the alkyl and aryl groups, respectively.

Table 3: Scope of the Stetter reaction with β-aryl enals.[a]

Entry	Ar	R^2, R^3	5	Yield [%][b]	ee [%][c]
1	Ph	3-OMeC$_6$H$_4$, Ph	**5a**	40	85
2	4-BrC$_6$H$_4$	Ph, Ph	**5b**	33	82
3	2-naphthyl	Ph, 4-FC$_6$H$_4$	**5c**	39	88
4	4-OMeC$_6$H$_4$	Ph, Ph	**5d**	47	87
5	2-OMeC$_6$H$_4$	Ph, 4-BrC$_6$H$_4$	**5e**	49	92

[a] Reaction conditions: **4** (0.45 mmol), **2** (0.15 mmol), toluene (1.5 mL), 0°C. Diels–Alder products were also formed in 20-40% yields. [b] Yield of isolated product. [c] Enantiomeric excess of **5** determined by chiral-phase HPLC analysis.

The tolerance of β,β-disubstituted enals in the Stetter reaction was also tested. Previously under NHC catalysis these types of enals were mainly used in self-redox reactions.[9] We reasoned that the additional β substituent (especially an alkyl group) might enhance the electron density of the resulting enal acyl anions and thus make these enals behave more effectively in the Stetter reaction than the corresponding monosubstituted β-aryl enals. We first tested the reaction between the β,β-disubstituted enal **6a** and modified enone **2a** by using the reaction conditions employed in Table 3. To our delight, the Stetter product **7a** was obtained in 89% yield with an acceptable enantioselectivity (Table 4, entry 1). The substrate scope was then briefly examined (Table 4). An enal having an electron-donating group on the phenyl ring showed high reactivity and afforded products with excellent yields, albeit with slightly decreased enantioselectivities (Table 4, entries 3 and 4). The diaryl-substituted enal reacted as well, but the yield was low even after attempted optimization which included the use of catechol additives (Table 4, entry 5). Good yield was achieved when the dialkyl-substituted enal was used, but with decreased enantioselectivity (Table 4, entry 6). The enone substrates having electron-withdrawing groups such as COMe or CO$_2$Et were not effective when using simple enals, but proved to be reactive

Table 4: Scope of the Stetter reaction with β,β-disubstituted enals.[a]

Entry	R¹, R²	R³, R⁴, R⁵	7	Yield [%][b]	ee [%][c]
1	Ph, Me	Ph, Ph, Ph	7a	89	83
2	Ph, Me	Ph, 4-BrC₆H₄, 4-BrC₆H₄	7b	90	88
3	4-OMeC₆H₄, Me	4-BrC₆H₄, Ph, Ph	7c	93	70
4	4-OMeC₆H₄, Me	4-iPrC₆H₄, Ph, Ph	7d	91	74
5	4-MeC₆H₄, 4-MeC₆H₄	3-OMeC₆H₄, Ph, Ph	7e	33	65
6	PhCH₂CH₂, Me	Ph, Ph, Ph	7f	81	42
7	Ph, Me	Ph, Me, Ph	7g	70	87 / 94[d]
8	Ph, Me	Ph, OEt, Ph	7h	65	97[e]
9	Ph, Me	Ph(CH₂)₂, Ph, Ph	7i	35	56

[a] Reaction conditions: **6** (0.45 mmol), **2** (0.15 mmol), toluene (1.5 mL). [b] Yield of isolated product. [c] Enantiomeric excess of **7** determined by chiral-phase HPLC analysis. [d] The ee values of both diastereomers; 1.3:1 d.r. [e] The ee value of the major diastereomer; 2.8:1 d.r.

with β,β-disubstituted enals (Table 4, entries 7 and 8).[10] Finally, an alkylidene diketone with an alkyl group (R³) also afforded the corresponding Stetter product, albeit with low yield and moderate enantioselectivity (Table 4, entry 9).

Notably, simple chalcones that were previously demonstrated to be good electrophiles for reacting with enal-derived enolate and homoenolate intermediates,[3] failed to undergo the Stetter reaction with enals in our studies. We also noticed that the use of simple aryl and alkyl aldehydes (e.g. benzaldehyde and 3-phenylpropanal, respectively) as potential acyl anion precursors did not lead to an observable Stetter reaction with these modified chalcones (e.g. **2a**) under our reaction conditions. Given the same set of substrates, the choice of the NHC catalyst (e.g. imidazolium-based IMes and the triazolium-based NHCs) can affect the reaction pathway.[7] These results indicated that the stereoelectronic properties of the enal-derived Breslow intermediates and the unique reactivity of modified chalcones were crucial for the enantioselective Stetter reaction to occur.

In summary, we have disclosed the enantioselective Stetter reaction between enals and modified chalcones. The reactions are believed to proceed through a Michael-type addition of NHC-bound enal acyl anions to the modified chalcones. Through an alteration of the reaction partners (the electrophiles) and the proper choice of the NHC catalyst, selective capturing of the enal acyl anion intermediates was realized. Additional mechanistic studies for a specific understanding of the origins of the experimental observations with respects to both substrate and catalyst effects are in progress.

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[11] CCDC 839736 (**3i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.