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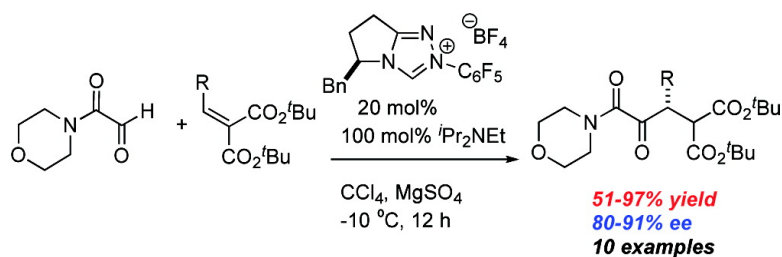
Catalytic Asymmetric Intermolecular Stetter Reaction of Glyoxamides with Alkylidenemalonates

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Catalytic Asymmetric Intermolecular Stetter Reaction of Glyoxamides with Alkylidenemalonates

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The inversion of the normal mode of reactivity (Umpolung) of aldehydes catalyzed by cyanide or heteroazolium salt derived carbenes (**2**) opens up new synthetic pathways for the construction of carbon−carbon bonds.[1] An application of this concept is the conjugate addition of acyl-anion equivalents (**3**) to electrophilic alkenes (**4**) for the formation of 1,4-dicarbonyl compounds, a transformation known as the Stetter reaction (eq 1).[2,3] Building on some key early studies of Enders,[4] we have recently reported several examples of triazolylidene carbene-catalyzed asymmetric intramolecular Stetter reactions.[5,6]

$$R^1\text{-}CHO \xrightarrow{\textbf{2}} \text{[3]} \xrightarrow{\textbf{4}} R^1\text{-}5 \quad (1)$$
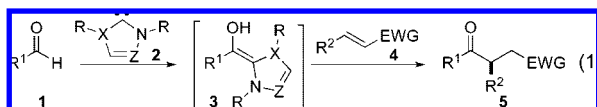
While catalysts and reaction protocols are well established for the enantioselective intramolecular version, the asymmetric *intermolecular* Stetter reaction remains a challenge. Two reports by Enders and co-workers describe intermolecular examples utilizing *n*-butanal and chalcone, albeit with low enantiomeric excess and yield.[7−9] In a related process, Johnson has published an asymmetric metallophosphite-catalyzed Stetter-like reaction of acyl silanes.[10,11]

A close examination of Stetter's pioneering work on this reaction reveals that Michael acceptors bearing β-substituents often result in diminished reactivity and are typically restricted to chalcones or other highly activated alkenes such as fumarates.[2c] Interestingly, thiazolylidene-catalyzed addition of glyoxamides to β-substituted Michael acceptors seems to be an exception to this tendency.[12] We envisioned that this combination of aldehyde with electrophilic alkene could result in an enantioselective transformation using enantioenriched *N*-heterocyclic carbenes (NHC) as catalysts. Herein, we report the application of the new triazolium salt **9** as precatalyst in the asymmetric intermolecular Stetter reaction of glyoxamides and alkylidenemalonates.

We began our study by screening different aldehyde partners. The test reaction involved exposure of glyoxamides (or glyoxylate ester) **6a−d** and Michael acceptor **7** to a catalytic amount of the phenylalanine-derived precatalyst **9** and triethylamine (Table 1). First, ethyl glyoxylate was found to be very reactive for this transformation, but the enantioselectivity is not promising with our current catalysts (entry 1). A secondary glyoxamide affords racemic product (entry 2) while a tertiary one gives a 42% ee in 24% yield (entry 3). Generally, tertiary amides derived from cyclic amines proved best, with the desired Stetter adduct **8d** isolated in a promising 50% yield and 51% ee (entry 4). Electron-deficient carbenes proved optimal for this transformation (entry 4−6). The *N*-phenyl analogue **10** is unreactive while triazolium salt precatalyst **11** leads to the desired Stetter adduct with 65% ee but only 12% isolated yield (entry 6). These results reinforce the impact of the *N*-aryl substituent on carbene activity.[13] Further optimization revealed that yields are higher in nonpolar solvents, CCl₄ being optimal, and the enantioselectivity is constant in a series of polar and nonpolar solvents, suggesting a concerted enantio-determining step.[14]

Table 1. Glyoxamide Screen
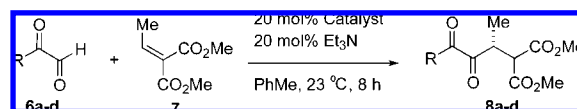
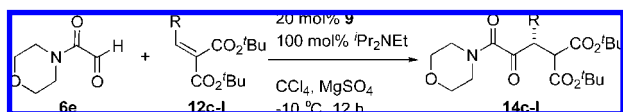| Entry	R	Catalyst	Product (**8**)	Yield (%)[a]	ee (%)[b]
1	EtO	**9**	**a**	100	23
2	BnHN	**9**	**b**	51	<5
3	Me₂N	**9**	**c**	24	42
4	(CH₂)₄N	**9**	**d**	50	51
5	(CH₂)₄N	**10**	**d**	trace	−
6	(CH₂)₄N	**11**	**d**	12	65

[a] All reactions conducted with 1 equiv of **6** and 2 equiv of **7** at ambient temperature. [b] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.
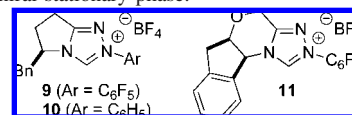
To improve the enantioselectivity, sterically different alkylidenemalonates (**12a−c**) were prepared and reacted with the pyrrolidine-derived glyoxamide **6d** (eq 2). A change from dimethylmalonate **12a** to di-*tert*-butylmalonate **12c** gives rise to an enantiomeric excess increase of 30% without loss of reactivity. A second screen of glyoxamides using alkylidenemalonate **12c** revealed that the morpholine-derived substrate **6e** is the best partner for this reaction (eq 3).
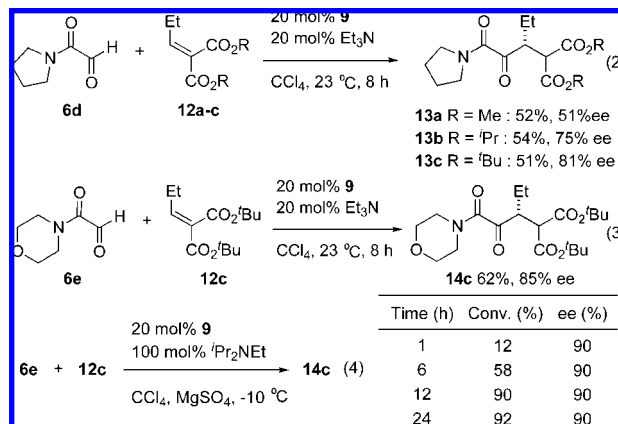
During the course of our investigation, it was found that using an equivalent of base leads to increased yield, presumably by affording more triazolylidene carbene catalyst at equilibrium. Catalyst activity was also prolonged by adding MgSO₄ to scavenge residual water. We also noticed that the previous conditions using triethylamine at room temperature result in some epimerization of the α-ketoamide products.

Table 2. Scope of the Intermolecular Stetter Reaction of Glyoxamide **6e**

Entry	R	Product (**14**)	Yield (%)[a]	ee (%)[b]
1	Et	**c**	84	90
2[c]	Me	**d**	68	87
3	Pr	**e**	83	90
4	Bu	**f**	70	90
5	CH₂CH₂Ph	**g**	81	88
6[d]	[i]Bu	**h**	51	91
7	CH₂CH₂OBn	**i**	91	80
8	CH₂CH₂CH₂Cl	**j**	84	81
9		**k**	88	84
10		**l**	97	89

[a] All reactions conducted using 0.16 mmol **6e** with 2 equiv of **12**. [b] See footnote, Table 1. [c] Reaction time: 3 h. [d] Reaction time: 28 h.

Fortunately, decreasing the temperature to −10 °C and employing a bulkier base such as Hünig's base considerably reduced the erosion of this sensitive stereocenter[15] (eq 4).[16]

A series of Michael acceptors with different alkyl groups at the β-position was synthesized and subjected to the optimized reaction conditions (Table 2). By lowering the temperature and using 100 mol% Hünig's base, Stetter adduct **14c** has been isolated in 84% yield and 90% ee (entry 1). Longer alkyl chains offer nearly the same results (entry 3−5). However, a methyl substituent is more vulnerable to epimerization (entry 2). In fact, a 12 h reaction time led to product **14d** in 97% yield with 81% ee. Stopping the reaction after 3 h resulted in 68% yield and 87% ee. Substrate **12h**, containing a bulkier *iso*-butyl side-chain, requires a longer reaction time (28 h) without any loss of enantioselectivity (entry 6).[17] The reaction is also tolerant of a wide range of functional groups, such as benzyl ether, alkyl chloride, thioacetal, and alkene (entries 7−10).

A 2 mmol scale experiment allowed us to isolate pure Stetter adduct **14c** in 92% yield and 90% ee along with a 100% recovery of excess **12c** (Scheme 1). The α-ketoamide product can be further functionalized to afford different useful intermediates. Chemo- and diastereoselective reduction of the ketone affords the secondary alcohol **15** in 8:1 dr, favoring the syn diastereomer.[18] Concomitant deprotection of the esters and lactonization can be accomplished in neat formic acid leading to **16**. Finally, thermal decarboxylation was performed to provide

Scheme 1. α-Ketoamide Functionalization
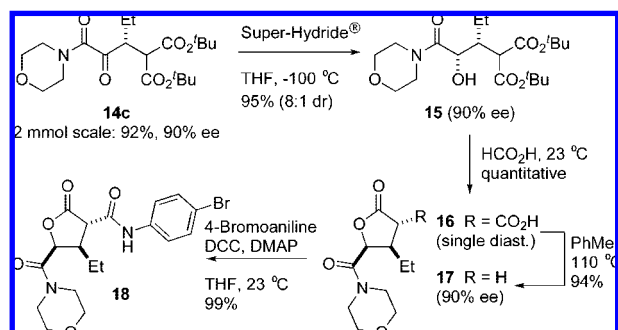
disubstituted lactone **17**. Importantly, this sequence of events leads to no epimerization, affording the final material in 90% ee.

In conclusion, we have developed an enantioselective intermolecular Stetter reaction involving glyoxamides. A variety of β-substituted alkylidenemalonates undergo this reaction in good yield with high asymmetric induction in the presence of a phenylalanine-derived carbene catalyst. Studies aimed at improving the efficiency of the catalyst and enlarging the reaction scope to different types of aldehydes and Michael acceptors are currently underway.

Supporting Information Available: Experimental procedures, characterization, ¹H/¹³C NMR spectra; CIF file for **16** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Glyoxamide is consumed in <5 min to form benzoin adduct prior to the appearance of any Stetter product, also noted by Enders (see ref 9).
(17) A Michael acceptor with an *iso*-propyl β-substituent was subjected to the same reaction conditions at 23 °C but did not afford any Stetter adduct.
(18) Absolute configuration and relative stereochemistry were assigned by X-ray structure analysis of **16** and **18**. The opposite diastereomer of **15** is formed in Et₂O at −78 °C (3:1 dr).

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