

Enantio- and Diastereoselective
Intermolecular Stetter Reaction of
Glyoxamide and Alkylidene Ketoamides

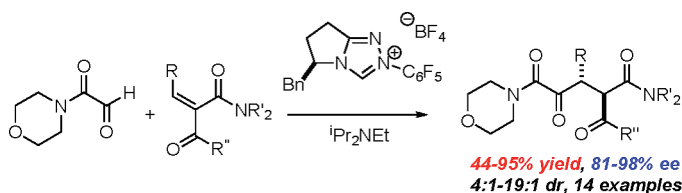
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ABSTRACT

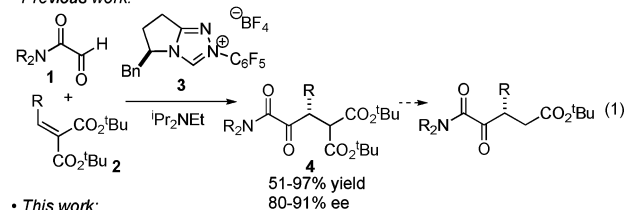


A triazolynylidene carbene catalyzed intermolecular Stetter reaction of glyoxamide and alkylidene ketoamides has been developed. 1,4-Dicarbonyl products are afforded in good to excellent yields, enantioselectivities, and diastereoselectivities. Further derivatization of the products affords useful intermediates for organic synthesis.

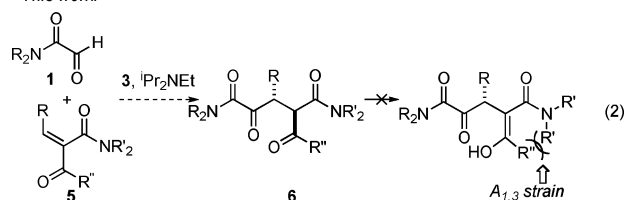
The Stetter reaction,¹ the N-heterocyclic carbene (NHC) catalyzed addition of aldehydes to Michael acceptors, is a prototypical example of the emerging class of catalyzed umpolung reactions.² Following a seminal early report by Enders and Teles,³ we⁴ and others⁵ have extensively investi-

gated the asymmetric intramolecular Stetter reaction. The asymmetric intermolecular Stetter, on the other hand, has remained a much more significant challenge.⁶ In 2008, Enders reported an asymmetric intermolecular Stetter reaction of aromatic aldehydes and chalcones proceeding in good yield and modest selectivities.⁷ Concurrently, we reported the enantioselective intermolecular Stetter reaction of glyoxamides **1** with alkylidene malonates **2** (eq 1).⁸

• Previous work:



• This work:



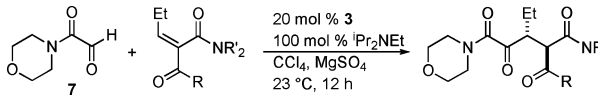
A shortcoming of the use of alkylidene malonates **2** is the need for the second ester group. We considered that the use of

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alkylidene ketoacid derivatives would provide an opportunity to incorporate synthetically useful substituents on the second carbonyl (eq 2). However, the reaction would generate mixtures of diastereomers, a situation that could be rectified through the use of alkylidene ketoamides. We have already demonstrated that the protonation event in the asymmetric Stetter is highly diastereoselective,^{4d} and it has been well-documented that tertiary β -ketoamides, bearing a stereocenter between the carbonyls, are configurationally stable due to strong $A_{1,3}$ strain in the enolate.⁹ Interestingly, catalytic asymmetric transformations that generate ketoamide stereocenters are surprisingly rare.¹⁰

A Knoevenagel reaction of various ketoamides and aldehydes generates the requisite substrates **5** as single olefin isomers.¹¹ Adducts were subjected to our previously developed reaction conditions, Table 1. At ambient

Table 1. Screen of Michael Acceptors



entry	R	R'	product	yield (%) ^a	ee (%) ^b	dr ^c
1	Me	Me	8	68	82	6:1
2		Et	9	66	77	14:1
3	Ph	Me	10	60	7	14:1
4	Et	Me	11	92	89	5:1
5 ^d		Me	11	90	92	12:1

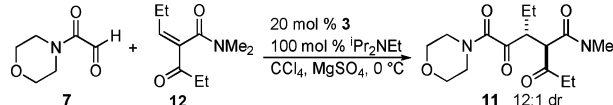
^a Reaction conducted with 1 equiv of **7** and 2 equiv of Michael acceptor at 23 °C. ^b Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. ^c Diastereomer ratio determined by ¹H NMR. ^d Reaction conducted at 0 °C.

temperature, the carbene derived from triazolium salt **3** catalyzes the reaction of glyoxamide **7** with β -keto-amide derived Michael acceptors in good to excellent yield and high diastereoselectivities. As shown in Table 1, with a dimethylamide Michael acceptor, the product **8** is isolated

in 68% yield, 82% ee, and 6:1 dr (Table 1, entry 1). When the diethylamide is employed, the product **9** is obtained in similar yield, high dr, but lower ee (Table 1, entry 2). The use of a phenylketone on the Michael acceptor results in a nearly racemic product **10** (Table 1, entry 3). With longer alkyl ketone substituents, the product **11** is formed in 92% yield, 89% ee, and 5:1 dr (Table 1, entry 4). Lastly, we found that optimal conditions involved conducting the reaction at 0 °C (Table 1, entry 5).

A primary concern at the outset of this study was the configurational stability of the newly formed stereocenters. A control experiment using 20 mol % precatalyst **3** and 1 equiv of Hünig's base was performed in carbon tetrachloride at 0 °C, shown in Table 2. It was found that the conversion

Table 2. Control Experiment To Test for Epimerization



entry	time (h)	conversion (%) ^a	ee (%) ^b
1	1	18	92
2	3	38	92
3	5	47	92
4	8	65	92
5	12	90	92

^a Reaction conducted with 1 equiv of **1** and 2 equiv of **12** at 0 °C. ^b See Table 1.

of **11** gradually increases with reaction time, with the reaction complete in 12 h. Fortunately, no epimerization was observed under these basic conditions, consistent with our hypothesis.

A series of Michael acceptors with different substitution were then synthesized and tested using the optimized reaction conditions, with the results shown in Table 3. When the alkylidene substituent is a methyl group, the product **14** is obtained in excellent yield and 89% ee, with 7:1 dr (Table 2, entry 1). Similar results are observed with other alkyl substituents (Table 2, entry 3–5). The reaction also tolerates a variety of functional groups; substrates with tethered benzyl ether, olefin, and alkyne give desired products in excellent enantioselectivities and good diastereoselectivities (Table 2, entries 7, 9, 10). Compounds with tethered halogen or protected aldehyde are also obtained in good yield and good stereoselectivities (Table 2, entry 8, 11). Substrates with different ketone R groups were also made and subjected to the optimized reaction conditions. When R is propyl, the Stetter adduct **34** is generated in 92% yield, 92% ee, and 11:1 dr (Table 2, entry 12). Finally, substrate **37** with a tethered olefin on the ketone leads to product **38** in 94% yield, 90% ee, and 9:1 dr.

In order to explain the stereochemistry of this transformation, a plausible mechanism is proposed in Scheme 1. Reaction of glyoxamide **7** with carbene derived from **3** will

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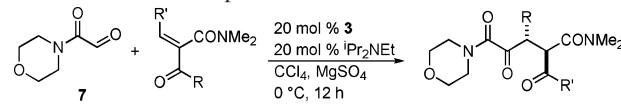
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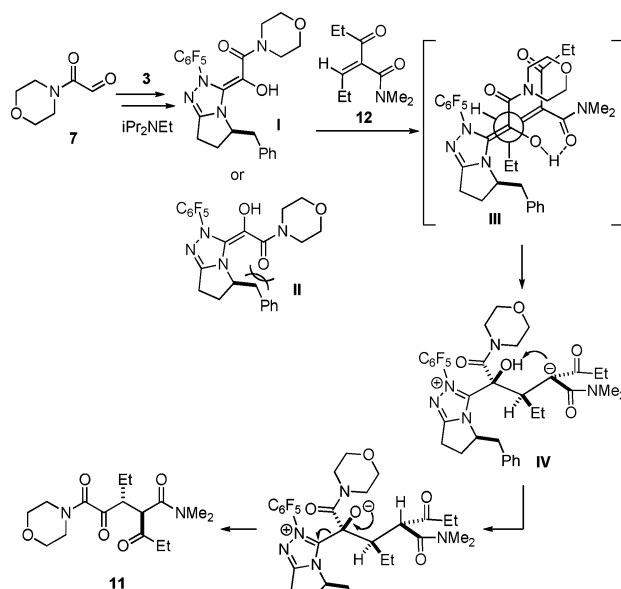
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Table 3. Substrate Scope


entry	R	R'	substrate	product	yield (%) ^a	ee (%) ^b	dr ^c
1	Et	Me	13	14	95	89	7:1
2		Et	12	11	90	92	12:1
3		Pr	15	16	81	90	6:1
4		Bu	17	18	71	92	12:1
5 ^d		ⁱ Bu	19	20	44	87	11:1
6		CH ₂ CH ₂ Ph	21	22	65	83	19:1
7		CH ₂ CH ₂ OBn	23	24	87	98	11:1
8		CH ₂ CH ₂ CH ₂ Cl	25	26	83	81	10:1
9			27	28	83	90	14:1
10			29	30	78	92	4:1
11			31	32	77	86	9:1
12	Pr	Et	33	34	92	92	11:1
13			35	36	64	94	5:1
14		Et	37	38	94	90	9:1

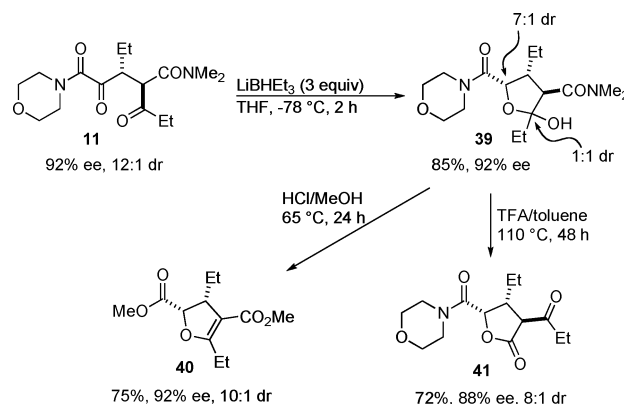
^a All reactions conducted with 1 equiv of **7** and 2 equiv of Michael acceptor at 0 °C. ^b See Table 1. ^c See Table 1. ^d Reaction time = 20 h.

Scheme 1

generate a nucleophilic olefin intermediate, which may be one of two different isomers (**I** or **II**). Conjugate addition of the favored intermediate **I**¹² to **12** would transiently generate stabilized carbanion **IV**, which may not even be a local

minimum on the energy surface should the conjugate addition/protonation event be concerted.¹³ The Michael acceptor **12** will approach **I** from the bottom face to avoid interaction with the benzyl group in the catalyst, as shown in **III**. The H-bond between the enol and the amide could also play a directing role. An intramolecular proton transfer^{4d} will lead to the desired product **11**.¹⁴

The obtained 1,4-dicarbonyl compounds could be further functionalized to useful building blocks for synthesis (Scheme 2). Reduction of **11** with Super Hydride at −78 °C affords

Scheme 2

hemiacetal **39** in 72% yield as a 1:1 mixture of diastereomers at the acetal carbon. Treatment of **39** with dry HCl in methanol at 65 °C gives tetra-substituted dihydrofuran **40**, which is a versatile intermediate¹⁵ and also is a common substructure found in many natural products.¹⁶ During this transformation, no epimerization is observed. When **39** is treated with TFA in toluene at 110 °C for 48 h, chemoselective cleavage of the dimethylamide occurs to provide lactone **41**¹⁷ with three contiguous stereocenters in 72% yield.

In conclusion, a highly enantio- and diastereoselective intermolecular Stetter reaction was developed. Catalyzed by

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(14) The absolute configuration was confirmed by single crystal XRD of **22**; see Supporting Information.

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chiral triazolinylidene carbenes at 0 °C, reactions of glyoxamide and β -keto-amide derived Michael acceptors afford 1,4-dicarbonyl compounds in good to excellent yields, enantioselectivities, and diastereoselectivities. A stereochem-

ical model is proposed to account for the absolute and relative stereochemistry. The obtained product was further functionalized to useful building blocks for organic synthesis.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds, NOE of **12**, and X-ray structures of **11** and **22**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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