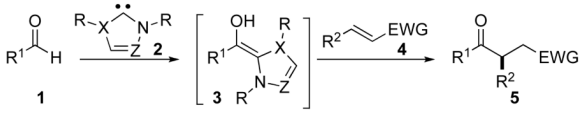
Published in final edited form as:
*J Am Chem Soc*. 2008 October 29; 130(43): 14066–14067. doi:10.1021/ja805680z.

# Catalytic Asymmetric Intermolecular Stetter Reaction of Glyoxamides with Alkylidenemalonates

**Qin Liu**, **Stéphane Perreault**, and **Tomislav Rovis**
*Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523*

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]



(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.[7,8,9] In a related process, Johnson has published an asymmetric metallophosphite-catalyzed Stetter-like reaction of acyl silanes.[10,11]

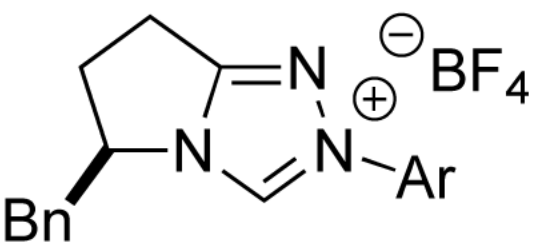
A close examination of Stetter's pioneering work on this reaction reveals that Michael acceptors bearing β-substituents often result in diminished reactivity and are typically restricted to chalcones or other highly activated alkenes such as fumarates.[2c] Interestingly, thiazolylidene-catalyzed addition 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

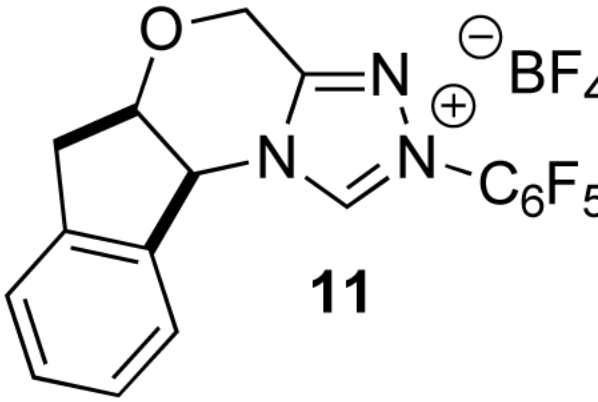
Correspondence to: Tomislav Rovis.
E-mail: rovis@lamar.colostate.edu.

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

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 non-polar solvents, $CCl_4$ being optimal, and the enantioselectivity is constant in a series of polar and non-polar solvents, suggesting a concerted enantio-determining step.[14]

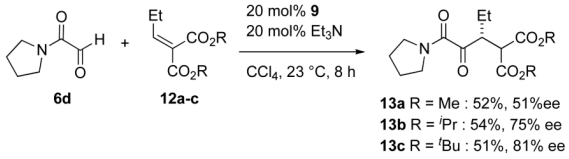



**9** (Ar = $C_6F_5$)
**10** (Ar = $C_6H_5$)

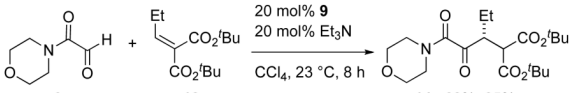



**11**

In order 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).

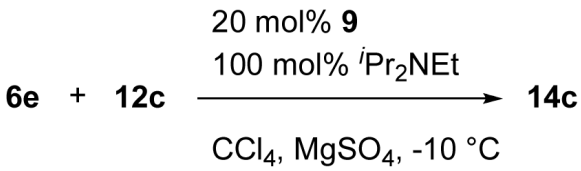



(2)




| Time (h) | Conv. (%) | ee (%) |
|---|---|---|
| 1 | 12 | 90 |
| 6 | 58 | 90 |
| 12 | 90 | 90 |
| 24 | 92 | 90 |

(3)




(4)

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 $MgSO_4$ 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. 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 **13h**, 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 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgment

We thank NIGMS (GM72586), Eli Lilly, Johnson and Johnson, and Boehringer Ingelheim for support. We thank Susie Miller, Kevin Oberg and Derek Dalton (CSU) and Joseph H. Reibenspies (Texas A&M) for crystal structures. We thank Harit Vora (CSU) for the synthesis of catalyst **9**. S.P. thanks the FQRNT for a postdoctoral fellowship. T.R. thanks the Monfort Family Foundation for a Monfort Professorship.

## References


(1). (a) Seebach D. Angew. Chem. Int. Ed. Engl 1979;18:239–258. (b) Johnson JS. Angew. Chem. Int. Ed. Engl 2004;43:1326–1328. [PubMed: 15368399]

(2). (a) Stetter H, Schrecke M. Angew. Chem. Int. Ed. Engl 1973;12:81. (b) Stetter H. Angew. Chem. Int. Ed. Engl 1976;15:639–647. (c) Stetter H, Kuhlmann H. Org. React 1991;40:407–496.

(3). (a) Christmann M. Angew. Chem. Int. Ed 2005;44:2632–2634. (b) Enders D, Niemeier O, Henseler A. Chem. Rev 2007;107:5606–5655. [PubMed: 17956132]

(4). Enders D, Breuer K, Runsink J, Teles JH. Helv. Chim. Acta 1996;79:1899–1902.

(5). (a)Kerr MS, Read de Alaniz J, Rovis T. J. Am. Chem. Soc 2002;124:10298–10299.10299 [PubMed: 12197730]. (b)Kerr MS, Rovis T. J. Am. Chem. Soc 2004;126:8876–8877.8877 [PubMed: 15264801]. (c)Read de Alaniz J, Rovis T. J. Am. Chem. Soc 2005;127:6284–6289.6289 [PubMed: 15853335]. (d)Liu Q, Rovis T. J. Am. Chem. Soc 2006;128:2552–2553.2553 [PubMed: 16492036]. (e)Moore JL, Kerr MS, Rovis T. Tetrahedron 2006;62:11477–11482.11482. (f)Liu Q, Rovis T. Org. Proc. Res. Dev 2007;11:598–604.604. (g)Orellana A, Rovis T. Chem. Comm 2008:730–732.732 [PubMed: 18478705]. (h)Read de Alaniz J, Kerr MS, Moore JL, Rovis T. J. Org. Chem 2008;73:2033–2040.2040 [PubMed: 18302407]. For the syntheses of the triazolium salts, see: (i) Kerr MS, Read de Alaniz J, Rovis T. J. Org. Chem 2005;70:5725–5728.5728 [PubMed: 15989360].

(6). For other contributions, see: (a)Pesch J, Harms K, Bach T. Eur. J. Org. Chem 2004:2025–2035.2035. (b)Mennen SM, Blank JT, Tran-Dube MB, Imbriglio JE, Miller SJ. Chem. Commun 2005:195–197.197. (c)Matsumoto Y, Tomioka K. Tetrahedron Lett 2006;47:5843–5846.5846

(7). Enders, D.; Breuer, K. Comp. Asym. Cat. Springer; Berlin: 1999. p. 1093-1104. (b) Enders D, Balensiefer T. Acc. Chem. Res 2004;37:534–541. [PubMed: 15311952]

(8). Scheidt has reported the asymmetric conjugate addition of a stoichiometrically generated acyl anion equivalent to nitrocyclohexene mediated by a thiourea; see: Mattson AE, Zuhl AM, Reynolds TE, Scheidt KA. J. Am. Chem. Soc 2006;128:4932–4933.4933 [PubMed: 16608309]

(9). While this manuscript was in review, an asymmetric intermolecular Stetter involving chalcones appeared: Enders D, Han J, Henseler A. Chem. Commun 2008:3989–3991.3991.

(10). Nahm MR, Potnick JR, White PS, Johnson JS. J. Am. Chem. Soc 2006;128:2751–2756. [PubMed: 16492064]

(11). For addition of acyl-silanes to chalcones generating racemic product, see: Mattson AE, Bharadwaj AR, Scheidt KA. J. Am. Chem. Soc 2004;126:2314–2315.2315 [PubMed: 14982429].

(12). Stetter H, Skobel H. Chem. Ber 1987;120:643–645.

(13). Rovis T. Chem. Lett 2008;37:2–7.

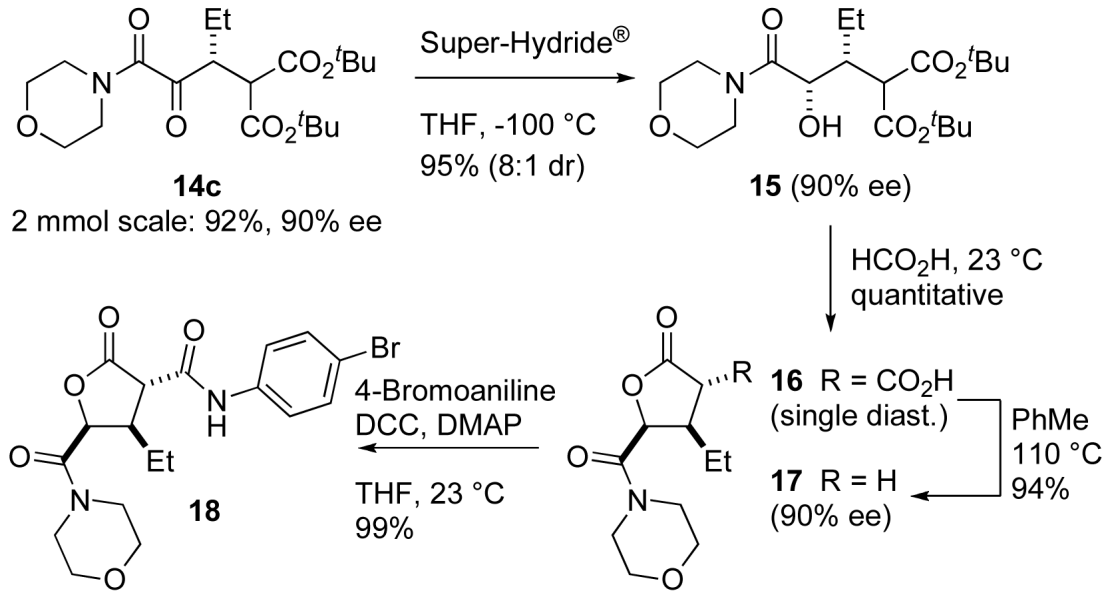
(14). See supporting information

(15). Similar products have been assembled using other strategies; (a)Uyeda C, Jacobsen EN. J. Am. Chem. Soc 2008;130:9228–9229.9229 [PubMed: 18576616]. (b)Enders D, Bonten MH, Raabe G. Angew. Chem. Int. Edit 2007;46:2314–2316.2316. (c)Enders D, Bonten MH, Raabe G. Synlett 2007:885–888.888.

(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

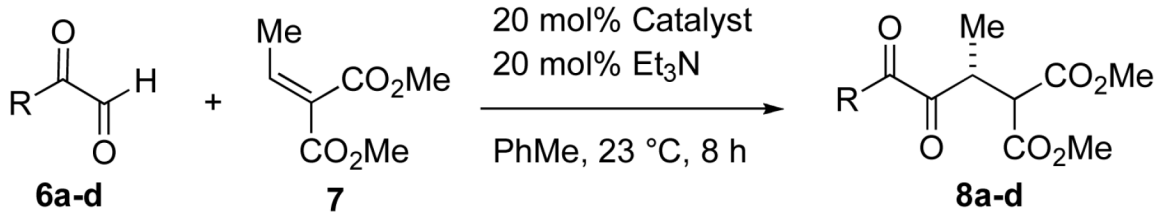
(18). Absolute configuration and relative stereochemistry were assigned by X-ray structure analysis of **16** and **18**. The opposite diastereomer of **15** is formed in $Et_2O$ at -78 °C (3:1 dr)




**Scheme 1.**
α-Ketoamide Functionalization

**Table 1**

Glyoxamide Screen



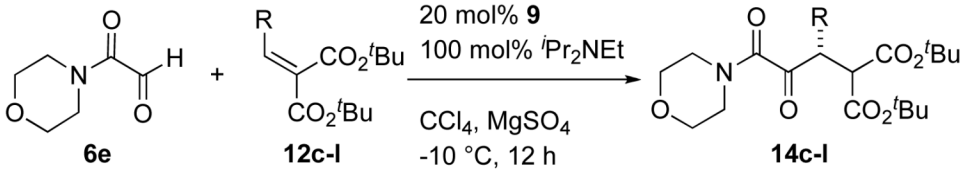

| Entry | R | Catalyst | Product (8) | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | EtO | **9** | **a** | 100 | 23 |
| 2 | BnHN | **9** | **b** | 51 | <5 |
| 3 | $Me_2N$ | **9** | **c** | 24 | 42 |
| 4 | $(CH_2)_4N$ | **9** | **d** | 50 | 51 |
| 5 | $(CH_2)_4N$ | **10** | **d** | trace | - |
| 6 | $(CH_2)_4N$ | **11** | **d** | 12 | 65 |

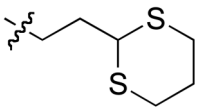
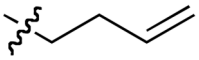
[a] All reactions conducted with 1 eq. of 6 and 2 eq. of 7 at ambient temperature.

[b] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase.

**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 | $CH_2CH_2Ph$ | **g** | 81 | 88 |
| 6[d] | $^{i}Bu$ | **h** | 51 | 91 |
| 7 | $CH_2CH_2OBn$ | **i** | 91 | 80 |
| 8 | $CH_2CH_2CH_2CI$ | **j** | 84 | 81 |
| 9 |  | **k** | 88 | 84 |
| 10 |  | **l** | 97 | 89 |

[a] All reactions conducted using 0.16 mmol 6e with 2 eq. of 12.

[b] See footnote, Table 1.

[c] Reaction time: 3 h.

[d] Reaction time: 28 h.