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COMMUNICATION

N-Heterocyclic carbene-catalysed intermolecular Stetter reactions of acetaldehyde†

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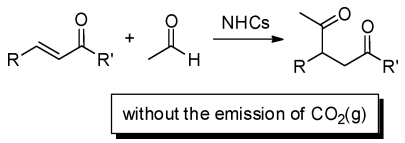
A facile method for the intermolecular Stetter reaction of various Michael acceptors with acetaldehyde as a biomimetic acylanion source was realized using *N*-heterocyclic carbene catalysis. This catalytic system has also been applied to the enantioselective Stetter reaction and resulted in moderate to good enantioselectivities for the corresponding Stetter products.

Introduction

N-Heterocyclic carbene (NHC) catalysis is a highly dynamic and rapidly growing area of asymmetric organocatalysis research.[1] The Stetter reaction is a well-defined umpolung process in which NHCs have been successfully applied to the construction of 1,4-dicarbonyl compounds and related derivatives, such as 1,4-diketones, 1,4-ketoesters, and 1,4-ketonitriles, depending on the particular Michael acceptors.[2] After the initial discovery of a chiral NHC-catalysed intramolecular asymmetric Stetter reaction by the Enders group in 1996,[3] several groups have extensively investigated the asymmetric version of the intramolecular reaction,[4] and recently, the Rovis group has reported significant improvements in enantioselectivity with triazolium salts derived from 2-aminoindanol.[4a] On the other hand, despite a steadily growing interest in the enantioselective intermolecular Stetter reaction,[5] the reaction of *trans*-chalcone derivatives with unmodified aldehydes remains challenging in terms of enantioselectivity. Until now, a single example of such a reaction has been reported with moderate to good enantioselectivities (56–78% ee),[5e] but an enzymatic Stetter reaction has recently been reported that proceeds in abysmally low yield but with high enantioselectivity.[5f]

Given the importance of acetaldehyde as a simple nucleophile in asymmetric organocatalysis,[6] we hypothesized that acetaldehyde could be used as an acylanion source in the Stetter reaction. Generally, in the enzymatic asymmetric cross-benzoin condensation reaction,[7] the acylanion equivalent is derived from pyruvate *via* decarboxylation catalysed by pyruvate decarboxylase (PDC), one of the thiamine diphosphate (ThDP)-dependent enzymes. Indeed, this concept has recently been applied to the enzymatic Stetter reaction.[5f]

In the search for a more efficient method of generating acylanion, we have found that acetaldehyde could be employed as a surrogate for the combination of pyruvate with ThDP-dependent enzymes, resulting in the substantial benefit of eliminating carbon dioxide emission in an environmentally benign process (Scheme 1).



Scheme 1 Generation of an acylanion equivalent from acetaldehyde without the emission of CO_2 (g).

Herein, we describe NHC-catalysed intermolecular nonasymmetric and asymmetric Stetter reactions of acetaldehyde with a variety of Michael acceptors. To the best of our knowledge, acetaldehyde has not previously been used as an acylanion source in this reaction.

Results and discussion

In our initial studies, we examined the reaction of *trans*-chalcone **3a** with acetaldehyde at room temperature using either thiazolium **1** or triazolium **2** precatalyst with Cs_2CO_3 (Table 1).

A quick screen of reaction parameters (*e.g.* catalyst and solvent) allowed us to determine that good conversions could be achieved in the presence of 10 mol% of thiazolium salt **1** and Cs_2CO_3 in dry THF at room temperature for 24 h (Table 1, entry 1).

Having identified appropriate conditions, the general applicability of the system was thoroughly investigated, and representative results are summarized in Table 2. The thiazolium precatalyst **1** was applicable to a broad range of electron-deficient alkenes (*e.g. trans*-chalcones **3a–g**,[8] methyl vinyl ketone **3h**, and diethyl fumarate **3i**) as Michael acceptors. In most cases, various *trans*-chalcone derivatives with either electron-withdrawing or electron-donating substituents on the aromatic ring gave the corresponding

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† Electronic supplementary information (ESI) available: Experimental procedures, characterizations for all new compounds, and chiral HPLC analysis for compound **5**. See DOI: 10.1039/c0ob01178a

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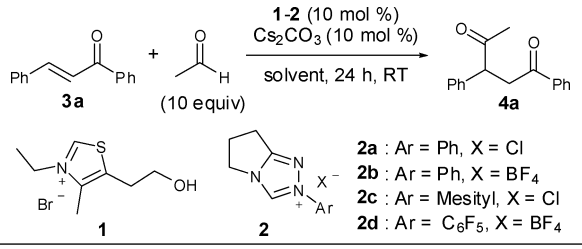
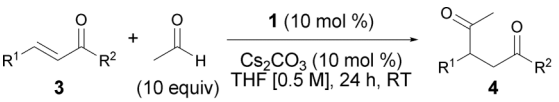
Table 1 Screening parameters for optimization of the Stetter reaction[a]



Entry	Catalyst	Solvent [M]	Yield (%)[b]
1	**1**	THF [0.5 M]	99
2	**2a**	THF [0.5 M]	—
3	**2b**	THF [0.5 M]	7
4	**2c**	THF [0.5 M]	—
5	**2d**	THF [0.5 M]	40
6	**1**	$CHCl_3$ [0.5 M]	52
7	**1**	CH_2Cl_2 [0.5 M]	50
8	**1**	PhMe [0.5 M]	35
9	**1**	Et_2O [0.5 M]	97

[a] General conditions: *trans*-chalcone **3a** (0.5 mmol), acetaldehyde (5 mmol), **1–2** (10 mol%), Cs_2CO_3 (10 mol%), THF (1 mL), RT, 24 h. [b] Isolated yield.

Table 2 NHC-catalysed intermolecular Stetter reaction of acetaldehyde with a variety of Michael acceptors[a]



a. R^1 = Ph, R^2 = Ph
b. R^1 = 2-Naphthyl, R^2 = Ph
c. R^1 = 4-Br-C_6H_4, R^2 = Ph
d. R^1 = 4-Me-C_6H_4, R^2 = Ph
e. R^1 = Ph, R^2 = 4-Cl-C_6H_4
f. R^1 = Ph, R^2 = 4-CN-C_6H_4
g. R^1 = Ph, R^2 = 3-MeO-C_6H_4
h. R^1 = H, R^2 = Me
i. R^1 = C(=O)OEt, R^2 = OEt

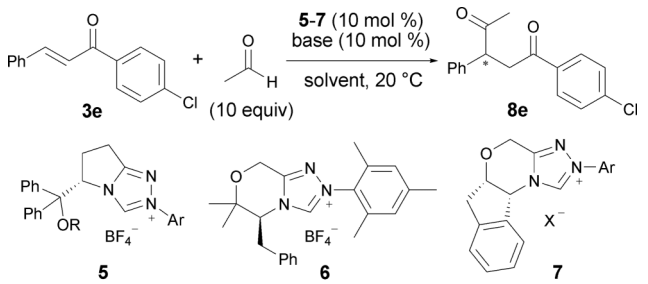
Entry	Substrate[b]	Product[c]	Yield (%)[d]
1	**3a**	**4a**	96
2	**3b**	**4b**	98
3	**3c**	**4c**	97
4	**3d**	**4d**	65
5	**3e**	**4e**	99
6	**3f**	**4f**	99
7	**3g**	**4g**	80
8	**3h**	**4h**	95
9	**3i**	**4i**	40

[a] General conditions: **3** (0.5 mmol), acetaldehyde (5 mmol), **1** (10 mol%), Cs_2CO_3 (10 mol%), THF (1 mL), RT, 24 h. [b] Substrates **3** were prepared and characterized as described in ref. 8. [c] Products **4** were obtained and characterized as described in the ESI.† [d] Isolated yield.

conjugate addition products in excellent yields (from 80% to 99%) compared to the parent system (Table 2, entries 1–3 and 5–7). An unsubstituted α,β-unsaturated ketone, methyl vinyl ketone **3h**, was also a competent coupling partner in the reaction (Table 2, entry 8). Notably, the electron-donating *para*-methyl substituted *trans*-chalcone derivative **3d** and diethyl fumarate substrate **3i** provided the target products in moderate yields (Table 2, entries 4 and 9).

After identifying an efficient and practical set of conditions for the Stetter reaction with acetaldehdye as the biomimetic acylanion source, we focused our effort on obtaining asymmetric induction in a model reaction using chiral NHC precatalysts and bases. We

Table 3 Optimization of the reaction conditions[a]



Entry	Catalyst	Base	Solvent [M]	Yield (%)[b]	ee (%)[c]
1	**5**	Cs_2CO_3	THF [0.5]	NR	—
2	**6**	Cs_2CO_3	THF [0.5]	NR	—
3	**7a**	Cs_2CO_3	THF [0.5]	80	62
4	**7b**	Cs_2CO_3	THF [0.5]	7	—
5	**7a**	DBU	THF [0.5]	76	56
6	**7a**	Cs_2CO_3	$PhCH_3$ [0.5]	45	54
7	**7a**	Cs_2CO_3	$CHCl_3$ [0.5]	44	60

[a] General conditions: **3e** (0.5 mmol), acetaldehyde (5 mmol), **5–7** (10 mol%), Cs_2CO_3 (10 mol%), THF (1 mL), 20 °C, 24 h. [b] Isolated yield. [c] The enantioselectivity was determined by HPLC analysis using a chiralcel OJ-H column with *n*-hexane–*i*PrOH (92 : 8) as eluent.

initiated these studies by combining a *p*-chloro-substituted *trans*-chalcone derivative **3e** as the model substrate with acetaldehyde in the presence of 10 mol% of NHC precatalysts **5–7** and base in THF at room temperature.

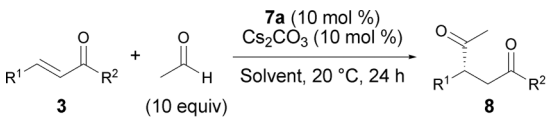
No reaction took place when NHC precatalyst **5** or **6** were employed (Table 3, entries 1–2). In contrast, the use of chiral *cis*-2-aminoindanol-derived triazolium salt **7a** bearing a *N*-pentafluorophenyl substituent on the triazole ring provided the Stetter product in 80% yield and 62% ee (Table 3, entry 3). It is notable that the achiral bicyclic triazolium salts **2** had low catalytic activity in the non-asymmetric reaction (Table 1, entries 2–5).

To optimize the enantioselectivity, we investigated the effect of subtle electronic differences on the reactivity and stability of catalyst **7**. Switching the *N*-substituents on the bicyclic triazole ring of precatalyst **7** from pentafluorophenyl to mesityl **7b**, led to a dramatic decrease in catalytic performance and enantioselectivity (Table 3, entry 4). In further experiments, other reaction parameters (*e.g.* solvent and base), influencing the reaction were investigated employing precatalyst **7a**, and the results are summarized in Table 3. Variations of the base or solvent had a negligible effect on enantioselectivity (Table 3, entries 5–7).

Representative examples of other Michael acceptors reacting with acetaldehyde catalysed by **7a** with Cs_2CO_3 in THF or chloroform at 20 °C for 24 h, are summarized in Table 4.

In most cases, the corresponding Stetter adducts were obtained in satisfactory chemical yields (up to 85%) within acceptable reaction times. The highest enantioselectivity (76%) was obtained for substrate **3b**, bearing the 2-naphthyl group (Table 4, entry 2).

Table 4 NHC-catalysed intermolecular asymmetric Stetter reaction of acetaldehyde with a variety of Michael acceptors[a]



a. R^1 = Ph, R^2 = Ph
b. R^1 = 2-Naphthyl, R^2 = Ph
e. R^1 = Ph, R^2 = 4-Cl-C_6H_4
f. R^1 = Ph, R^2 = 4-CN-C_6H_4
g. R^1 = Ph, R^2 = 3-MeO-C_6H_4

Entry	Substrate	Product	Solvent	Yield (%)[b]	ee (%)[c]
1	**3a**	**8a**[d]	THF	42	57
2	**3b**	**8b**	THF	62	76
3	**3e**	**8e**	THF	78	62
4	**3f**	**8f**	$CHCl_3$	85	60
5	**3g**	**8g**	THF	43	58

[a] General conditions: **3** (0.5 mmol), acetaldehyde (5 mmol), **7a** (10 mol%), Cs_2CO_3 (10 mol%), THF (1 mL), 20 °C, 24 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral column. [d] The absolute configurations were determined as described in ref. 5f.

Conclusions

In summary, we have developed the NHC-catalysed non-asymmetric intermolecular Stetter reaction of acetaldehyde as a complementary method to the enzymatic generation of the acylanion. These reactions were conducted with a variety of Michael acceptors in the presence of *N*-heterocyclic carbene catalysts, resulting in chemical yields above 95% in most cases. We also conducted the asymmetric intermolecular Stetter reaction of acetaldehyde with a variety of Michael acceptors in the presence of *cis*-aminoindanol-based chiral NHC catalyst **7a** to create 1,4-diketones with moderate to good enantioselectivities (up to 76% ee). Investigations to uncover a highly enantioselective variant of this reaction is currently underway.

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Notes and references

1 For general reviews on NHC catalysis, see: (*a*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (*b*) K. Zeitler, *Angew. Chem., Int. Ed.*, 2005, **44**, 7506; (*c*) J. S. Johnson, *Angew. Chem., Int. Ed.*, 2004, **43**, 1326.

2 (*a*) H. Stetter and M. Schreckenberg, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 81; (*b*) H. Stetter and H. Kuhlmann, *Org. React.*, 1991, **40**, 407; (*c*) D. Enders and T. Balensiefer, *Acc. Chem. Res.*, 2004, **37**, 534; (*d*) M. Christmann, *Angew. Chem., Int. Ed.*, 2005, **44**, 2632; (*e*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606; (*f*) T. Rovis, *Chem. Lett.*, 2008, **37**, 2.

3 D. Enders, K. Breuer, J. Runsink and J. H. Teles, *Helv. Chim. Acta*, 1996, **79**, 1899.

4 (*a*) M. S. Kerr, J. Read de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 10298; (*b*) M. S. Kerr and T. Rovis, *Synlett*, 2003, 1934; (*c*) M. S. Kerr and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 8876; (*d*) J. Read de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2005, **127**, 6284; (*e*) M. S. Kerr, J. Read de Alaniz and T. Rovis, *J. Org. Chem.*, 2005, **70**, 5725; (*f*) N. T. Reynolds and T. Rovis, *Tetrahedron*, 2005, **61**, 6368; (*g*) J. L. Moore, M. S. Kerr and T. Rovis, *Tetrahedron*, 2006, **62**, 11477; (*h*) Q. Liu and T. Rovis, *J. Am. Chem. Soc.*, 2006, **128**, 2552; (*i*) Q. Liu and T. Rovis, *Org. Process Res. Dev.*, 2007, **11**, 598; (*j*) J. Read de Alaniz, M. S. Kerr, J. L. Moore and T. Rovis, *J. Org. Chem.*, 2008, **73**, 2033; (*k*) A. Orellana and T. Rovis, *Chem. Commun.*, 2008, 730; (*l*) J. Pesch, K. Harms and T. Bach, *Eur. J. Org. Chem.*, 2004, 2025; (*m*) S. M. Mennen, J. T. Blank, M. B. Tran-Dubé, J. E. Imbriglio and S. J. Miller, *Chem. Commun.*, 2005, 195; (*n*) Y. Matsumoto and K. Tomioka, *Tetrahedron Lett.*, 2006, **47**, 5843.

5 (*a*) Q. Liu, S. Perreault and T. Rovis, *J. Am. Chem. Soc.*, 2008, **130**, 14066; (*b*) D. Enders and J. Han, *Synthesis*, 2008, 3864; (*c*) D. A. DiRocco, K. M. Oberg, D. M. Dalton and T. Rovis, *J. Am. Chem. Soc.*, 2009, **131**, 10872; (*d*) Q. Liu and T. Rovis, *Org. Lett.*, 2009, **11**, 2856; (*e*) D. Enders, J. Han and A. Henseler, *Chem. Commun.*, 2008, 3989; (*f*) C. Dresen, M. Richter, M. Pohl, S. Lüdeke and M. Müller, *Angew. Chem., Int. Ed.*, 2010, **49**, 6600.

6 (*a*) J. W. Yang, C. Chandler, M. Stadler, D. Kampen and B. List, *Nature*, 2008, **452**, 453; (*b*) Y. Hayashi, T. Itoh, S. Aratake and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 2082; (*c*) P. García-García, A. Ladépêche, R. Halder and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 4719; (*d*) Y. Hayashi, T. Itoh, M. Ohkubo and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 4722; (*e*) Y. Hayashi, T. Okano, T. Itoh, T. Urushima, H. Ishikawa and T. Uchimaru, *Angew. Chem., Int. Ed.*, 2008, **47**, 9053; (*f*) Y. Hayashi, S. Samanta, T. Itoh and H. Ishikawa, *Org. Lett.*, 2008, **10**, 5581; (*g*) T. Kano, Y. Yamaguchi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2009, **48**, 1838; (*h*) M. Y. Jin, S. M. Kim, H. Han, D. H. Ryu and J. W. Yang, *Org. Lett.*, 2011, **13**, DOI: 10.1021/ol102937w.

7 A. Cosp, C. Dresen, M. Pohl, L. Walter, C. Röhr and M. Müller, *Adv. Synth. Catal.*, 2008, **350**, 759.

8 (*a*) *General procedure for the synthesis of trans-chalcone derivatives **3b**, **3c**, **3d**, **3e**, **3f**, **3g***, see: T. Narender and K. T. Papi Reddy, *Tetrahedron Lett.*, 2007, **48**, 3177; (*b*) *trans*-Chalcone derivatives were characterized by ^{1}H NMR and ^{13}C NMR spectra, and we are found to match previously reported data: **3b**,[8c] **3c**,[8d] **3d**,[8e] **3e**,[8f] **3f**, [8g]**3g**,[8f] see: (*c*) B. C. Ranu and R. Jana, *J. Org. Chem.*, 2005, **70**, 8621; (*d*) M.-L. Yao, M. S. Reddy, L. Yong, I. Walfish, D. W. Blevins and G. W. Kabalka, *Org. Lett.*, 2010, **12**, 700; (*e*) W.-B. Yi and C. Cai, *J. Fluorine Chem.*, 2009, **130**, 484; (*f*) T. Ishikawa, T. Mizuta, K. Hagiwara, T. Ailawa, T. Kudo and S. Saito, *J. Org. Chem.*, 2003, **68**, 3702; (*g*) B. Xin, Y. Zhang and K. Cheng, *Synthesis*, 2007, 1970.