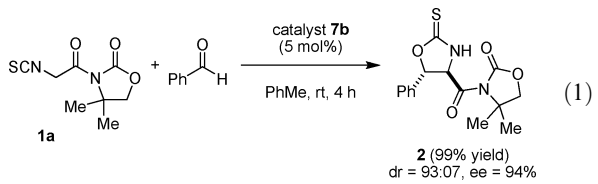
Catalytic enantioselective aldol additions of α-isothiocyanato imides to α-ketoesters†

Matthew K. Vecchione, Le Li and Daniel Seidel*

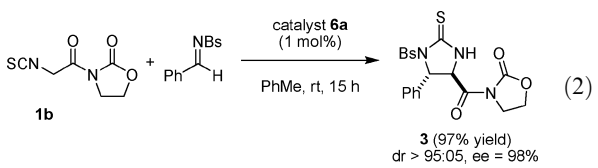
Received 24th March 2010, Accepted 27th April 2010
First published as an Advance Article on the web 19th May 2010
DOI: 10.1039/c0cc00556h

A readily available bifunctional thiourea catalyst promotes aldol additions of α-isothiocyanato imides to α-ketoesters under mild reaction conditions to form β-hydroxy-α-amino acid derivatives with high levels of enantioselectivity.

The development of methods that allow for the enantioselective construction of β-hydroxy-α-amino acid derivatives remains an important goal as these structural motifs constitute important building blocks.[1,2] In addition to chiral auxiliary based diastereoselective approaches,[3,4] a number of catalytic enantioselective methods have been reported.[5] While these methods have mostly focused on the addition of glycine equivalents to aldehydes, the corresponding reaction with ketones as electrophiles has seen much less development.[6] Here we report catalytic enantioselective additions of α-isothiocyanato imides to α-ketoesters.[7]



(1)

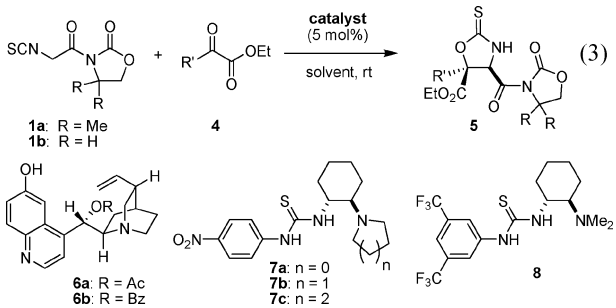


(2)

We have recently reported catalytic enantioselective aldol reactions between α-isothiocyanato imide **1a** and aldehydes (eqn (1)).[8] The bifunctional thiourea compound **7b** proved to be an excellent catalyst for this reaction, providing products **2** with high levels of stereoselectivity. In addition, we have reported Mannich additions of α-isothiocyanato imide **1b** to benzenesulfonyl imines to give rise to protected *syn*-α,β-diamino acid derivatives in good yields and stereoselectivities, using the quinidine based catalyst **6a** (eqn (2)).[9] Prior to our work with organocatalysts, Willis and coworkers have used imide **1b** in highly enantioselective magnesium catalyzed aldol and Mannich reactions.[10] Subsequently, Zhong *et al.* reported an approach to *syn*-α,β-diamino acid derivatives that is related to the process outlined in eqn (2).[11] More recently, Shibasaki *et al.* reported catalytic enantioselective additions of α-isothiocyanato esters to aryl alkyl ketones, employing chiral magnesium Schiff base catalysts.[6] Most recently, Wang and coworkers have reported catalytic enantioselective additions of α-isothiocyanato imides to α-ketoesters, using a rosin derived amine-thiourea catalyst.[7]

We initiated our studies by evaluating reactions between α-isothiocyanato imides **1**[4] and ketoesters **4** using catalysts that had previously provided aldol and Mannich products in

Table 1 Optimization of reaction parameters[a]



(3)

Entry	Catalyst	sm	R′	Solvent	Time/h	Yield[b] (%)	dr[c]	ee[d] (%)
1	**7b**	**1b**	Me	PhMe	1.5	85	75 : 25	75
2	**8**	**1b**	Me	PhMe	2	92	75 : 25	72
3	**6a**	**1b**	Me	PhMe	48	81	80 : 20	74
4	**6b**	**1b**	Me	PhMe	48	80	75 : 25	71
5	**7a**	**1b**	Me	PhMe	3	73	75 : 25	61
6	**7c**	**1b**	Me	PhMe	1	76	75 : 25	72
7	**7b**	**1b**	Ph	PhMe	3	85	75 : 25	86
8	**8**	**1b**	Ph	PhMe	2	98	71 : 29	74
9	**6a**	**1b**	Ph	PhMe	36	81	75 : 25	72
10	**7b**	**1a**	Ph	PhMe	2	93	80 : 20	90
11	**7b**	**1a**	Me	PhMe	4	99	83 : 17	79
12	**7b**	**1b**	Ph	Ether	8	50	67 : 33	60
13	**7b**	**1b**	Ph	Xylenes	5	60	67 : 33	69
14	**7b**	**1b**	Ph	$CHCl_3$	12	70	67 : 33	74
15	**7b**	**1b**	Ph	CH_2Cl_2	12	70	67 : 33	84
16	**7b**	**1b**	Ph	THF	7	95	67 : 33	77
17	**7b**	**1b**	Ph	CPME	4	93	67 : 33	83
18	**7b**	**1b**	Me	MTBE	1.5	99	75 : 25	74
19	**7b**	**1a**	Me	MTBE	4.5	95	88 : 12	70
20	**7b**	**1b**	Ph	MTBE	3	99	71 : 29	92
21	**7b**	**1a**	Ph	MTBE	3	93	80 : 20	95
22[e]	**7b**	**1a**	Ph	MTBE	9	71	83 : 17	90
23[f]	**7b**	**1a**	Ph	MTBE	9	71	83 : 17	81

[a] Reactions were performed at rt on a 0.17 mmol scale in solvent (0.15 M) using 1.1 equiv. of ketoester. Reactions were run to full conversion as judged by TLC analysis. The ee's were determined by HPLC analysis. [b] Combined yield of both diastereomers. [c] Determined by ^{1}H-NMR. [d] ee of major diastereomer shown. [e] Run at 0.1 M concentration. [f] Run at 0.25 M concentration. CPME = cyclopentyl methyl ether; MTBE = methyl *tert*-butyl ether.

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, 610 Taylor Road, Piscataway, New Jersey 08854, USA. E-mail: seidel@rutchem.rutgers.edu

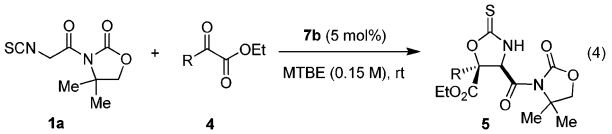
† Electronic supplementary information (ESI) available: Experimental details and characterization data for all new compounds. See DOI: 10.1039/c0cc00556h

good yields and stereoselectivities (eqn (3)).[12–14] The results of this investigation are summarized in Table 1. Different catalysts readily promoted reactions between imides **1** and ketoesters (ethyl pyruvate or ethyl 2-oxo-2-phenylacetate) in toluene at room temperature. The more sterically encumbered imide **1a** gave rise to the formation of products with higher levels of diastereo- and enantioselectivity. Amine-thiourea **7b** was identified as the most efficient and selective catalyst. An evaluation of different solvents revealed methyl *tert*-butyl ether (MTBE) to be superior to toluene with regard to overall efficiency. The best result for the reaction of imide **1a** and ethyl 2-oxo-2-phenylacetate was obtained in MTBE at 0.15 M concentration, using 5 mol% of catalyst **7b** (Table 1, entry 21). In this instance, the reaction went to completion within 3 hours and product **5a** was obtained in 93% yield (dr = 80 : 20; 95% ee, major diastereomer). Reactions conducted at lower (entry 22) or higher concentration (entry 23) gave rise to poorer results.[15]

With the optimized reaction conditions in hand, a series of different α-ketoesters was evaluated (Table 2). Electron rich and electron poor aromatic substituents with different substitution patterns provided products in generally good yields and with high enantioselectivities and moderate diastereoselectivities (entries 1–13). Heteroaromatic α-ketoesters were also viable substrates (entry 14). While Wang and coworkers achieved excellent selectivities at low catalyst loadings,[7] our best catalyst (**7b**) is more readily available and requires fewer steps for its preparation.

As is customary, for all examples reported in Table 2, the yields and stereoselectivities correspond to all of the obtained product (solution and solid phase combined). Gratifyingly, in some instances, product precipitation offers the opportunity to directly obtain highly diastereomerically and enantiomerically

Table 2 Scope of the reaction[a]



Entry	R	Product	Time/h	Yield[b] (%)	dr[c]	ee (%)
1	Ph	**5a**	3	93	80 : 20	95
2	4-OMe–C_6H_4	**5b**	12	80	70 : 30	94
3	4-Me–C_6H_4	**5c**	7	79	75 : 25	92
4	4-Br–C_6H_4	**5d**	2	95	83 : 17	97
5	4-Cl–C_6H_4	**5e**	2.5	99	83 : 17	98
6	4-CF_3–C_6H_4	**5f**	12	95	85 : 15	97
7	4-*t*-Bu–C_6H_4	**5g**	7	90	80 : 20	96
8	3-OMe–C_6H_4	**5h**	48	82	70 : 30	96
9	3,4-Cl_2–C_6H_3	**5i**	1.5	99	83 : 17	98
10	3,5-F_2–C_6H_3	**5j**	2	96	80 : 20	97
11	2,4-Cl_2–C_6H_3	**5k**	8	86	80 : 20	93
12	2-Naphthyl	**5l**	5	93	80 : 20	97
13	2-Cl–C_6H_4	**5m**	8	70	75 : 25	87
14	2-Thienyl	**5n**	5	95	75 : 25	92
15[d]	Me	**5o**	4	99	83 : 17	79

[a] Reactions were run at rt on a 0.5 mmol scale using 1.1 equiv. of the ketoester. The ee's were determined by HPLC analysis. [b] Combined yield of both diastereomers. [c] Determined by ^{1}H-NMR. [d] Reaction was performed in PhMe.

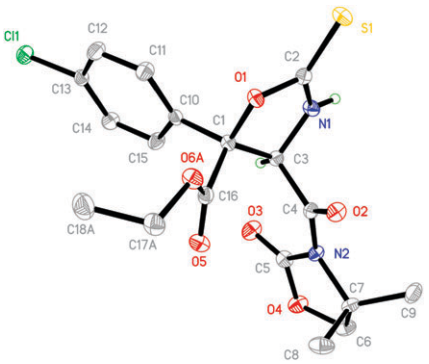


Fig. 1 ORTEP view (50% probability thermal ellipsoids) of the molecular structure of **5e**. Most hydrogen atoms have been omitted for clarity.

enriched products by simple filtration. For instance, when a reaction leading to product **5e** was worked up by filtration, followed by washing with a small amount of MTBE, this product was obtained in 66% yield as diastereomerically and enantiomerically pure material (within the limits of HPLC detection).

The absolute configuration of product **5e** was established by X-ray crystallography (Fig. 1).‡ The observed sense of induction is the same as previously established in the corresponding reactions of **1a** with aldehydes to give products such as **2**, also catalyzed by **7b**. The absolute configuration for all other products was assigned by analogy.

In summary, we have introduced a mild and facile method for catalytic enantioselective aldol additions of α-isothiocyanato imides to α-ketoesters using a readily available bifunctional thiourea catalyst that operates under mild reaction conditions.

Financial support from Rutgers, The State University of New Jersey, is gratefully acknowledged. We thank Dr Tom Emge for crystallographic analysis.

Notes and references

‡ The compound **5e** ($C_{18}H_{19}ClN_2O_6S$) crystallizes in the monoclinic space group $P2_1$ with a = 10.4991(4) Å, b = 8.7802(3) Å, c = 10.6271(4) Å, α = 90°, β = 95.8890(10)°, γ = 90°, V = 974.48(6) Å^3, Z = 2, d(calcd) = 1.455 g cm^{-3} and μ(MoKα) = 0.341 mm^{-1}. A Bruker Smart APEX CCD diffractometer with graphite monochromatized MoKα radiation (λ = 0.71073 Å) was used to collect 12 736 reflections (6370 unique) in the range $1.93 < \theta < 31.53°$ at 100(2) K giving final residual values of R_f = 0.0323 (all data) and R_f = 0.0311 ([$I > 2\sigma$ (I)]).

1 For reviews, see: (*a*) K. C. Nicolaou, C. N. C. Boddy, S. Bräse and N. Winssinger, *Angew. Chem., Int. Ed.*, 1999, **38**, 2096; (*b*) C. Najera and J. M. Sansano, *Chem. Rev.*, 2007, **107**, 4584.

2 For examples of natural products containing this subunit, see: (*a*) K. Isono, K. Asahi and S. Suzuki, *J. Am. Chem. Soc.*, 1969, **91**, 7490; (*b*) C. M. Harris, H. Kopecka and T. M. Harris, *J. Am. Chem. Soc.*, 1983, **105**, 6915; (*c*) I. Uchida, N. Shigematsu, M. Ezaki, M. Hashimoto, H. Aoki and H. Imanaka, *J. Antibiot.*, 1985, **38**, 1462; (*d*) Y. Koiso, M. Natori, S. Iwasaki, S. Sato, R. Sonoda, Y. Fujita, H. Yaegashi and Z. Sato, *Tetrahedron Lett.*, 1992, **33**, 4157; (*e*) G. J. Sharman, D. H. Williams, D. F. Ewing and C. Ratledge, *Biochem. J.*, 1995, **305**, 187; (*f*) M. K. Renner, Y.-C. Shen, X.-C. Cheng, P. R. Jensen, W. Frankmoelle, C. A. Kauffman, W. Fenical, E. Lobkovsky and J. Clardy, *J. Am. Chem. Soc.*, 1999, **121**, 11273.

3 For examples of diastereoselective approaches, see: (*a*) M. A. Lago, J. Samanen and J. D. Elliott, *J. Org. Chem.*,

1992, **57**, 3493; (*b*) D. L. Boger, S. L. Colletti, T. Honda and R. F. Menezes, *J. Am. Chem. Soc.*, 1994, **116**, 5607; (*c*) D. L. Boger, M. A. Patane and J. Zhou, *J. Am. Chem. Soc.*, 1994, **116**, 8544; (*d*) C. A. Hutton, *Org. Lett.*, 1999, **1**, 295; (*e*) B. Herbert, I. H. Kim and K. L. Kirk, *J. Org. Chem.*, 2001, **66**, 4892; (*f*) S. Caddick, N. J. Parr and M. C. Pritchard, *Tetrahedron*, 2001, **57**, 6615; (*g*) J. B. MacMillan and T. F. Molinski, *Org. Lett.*, 2002, **4**, 1883; (*h*) H. Sugiyama, T. Shioiri and F. Yokokawa, *Tetrahedron Lett.*, 2002, **43**, 3489; (*i*) D. Crich and A. Banerjee, *J. Org. Chem.*, 2006, **71**, 7106; (*j*) J. Patel, G. Clavé, P.-Y. Renard and X. Franck, *Angew. Chem., Int. Ed.*, 2008, **47**, 4224; (*k*) Q. Li, S.-B. Yang, Z. Zhang, L. Li and P.-F. Xu, *J. Org. Chem.*, 2009, **74**, 1627.

4 For the use of chiral versions of **1** in aldol reactions, see: (*a*) D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, 1986, **108**, 6757; (*b*) D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, 1987, **109**, 7151.

5 For examples of enantioselective approaches, see: (*a*) Y. Ito, M. Sawamura and T. Hayashi, *J. Am. Chem. Soc.*, 1986, **108**, 6405; (*b*) S. Kobayashi, H. Ishitani and M. Ueno, *J. Am. Chem. Soc.*, 1998, **120**, 431; (*c*) M. Horikawa, J. Busch-Peterson and E. J. Corey, *Tetrahedron Lett.*, 1999, **40**, 3843; (*d*) H. Suga, K. Ikai and T. Ibata, *J. Org. Chem.*, 1999, **64**, 7040; (*e*) D. A. Evans, J. M. Janey, N. Magomedov and J. S. Tedrow, *Angew. Chem., Int. Ed.*, 2001, **40**, 1884; (*f*) C. Loncaric and W. L. Wulff, *Org. Lett.*, 2001, **3**, 3675; (*g*) H. Kim and K. L. Kirk, *Tetrahedron Lett.*, 2001, **42**, 8401; (*h*) T. Ooi, M. Taniguchi, M. Kameda and K. Maruoka, *Angew. Chem., Int. Ed.*, 2002, **41**, 4542; (*i*) L. Dong and M. J. Miller, *J. Org. Chem.*, 2002, **67**, 4759; (*j*) N. Yoshikawa and M. Shibasaki, *Tetrahedron*, 2002, **58**, 8289; (*k*) K. Makino, T. Goto, Y. Hiroki and Y. Hamada, *Angew. Chem., Int. Ed.*, 2004, **43**, 882; (*l*) J. Kobayashi, M. Nakamura, Y. Mori, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 9192; (*m*) T. Ooi, M. Kameda, M. Taniguchi and K. Maruoka, *J. Am. Chem. Soc.*, 2004, **126**, 9685; (*n*) M.-X. Xue, C. Guo and L.-Z. Gong, *Synlett*, 2009, 2191.

6 T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 17082.

7 During the preparation of this manuscript, an approach related to ours was reported by Wang and coworkers: X. Jiang, G. Zhang, D. Fu, Y. Cao, F. Shen and R. Wang, *Org. Lett.*, 2010, **12**, 1544.

8 L. Li, E. G. Klauber and D. Seidel, *J. Am. Chem. Soc.*, 2008, **130**, 12248.

9 L. Li, M. Ganesh and D. Seidel, *J. Am. Chem. Soc.*, 2009, **131**, 11648.

10 (*a*) M. C. Willis, G. A. Cutting, V. J.-D. Piccio, M. J. Durbin and M. P. John, *Angew. Chem., Int. Ed.*, 2005, **44**, 1543; (*b*) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Köhn and M. C. Willis, *J. Am. Chem. Soc.*, 2007, **129**, 10632.

11 Z. Shi, P. Yu, P. J. Chua and G. Zhong, *Adv. Synth. Catal.*, 2009, **351**, 2797.

12 For selected general reviews on organocatalysis, see: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*b*) A. Berkessel and H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, 2005; (*c*) M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug Discovery Today*, 2007, **12**, 8; (*d*) P. I. Dalko, *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wiley-VCH, Weinheim, 2007; (*e*) B. List (guest editor), *Chem. Rev.*, 2007, **107**(12, 5413–5883 (special issue for organocatalysis); (*f*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638; (*g*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304; (*h*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178.

13 For selected reviews on thiourea catalysis, see: (*a*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289; (*b*) Y. Takemoto, *Org. Biomol. Chem.*, 2005, **3**, 4299; (*c*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; (*d*) S. J. Connon, *Chem.–Eur. J.*, 2006, **12**, 5418; (*e*) T. Marcelli, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem., Int. Ed.*, 2006, **45**, 7496; (*f*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (*g*) X. Yu and W. Wang, *Chem.–Asian J.*, 2008, **3**, 516; (*h*) C. Palomo, M. Oiarbide and R. López, *Chem. Soc. Rev.*, 2009, **38**, 632; (*i*) Z. Zhang and P. R. Schreiner, *Chem. Soc. Rev.*, 2009, **38**, 1187.

14 For selected examples involving catalysts relevant to this study, see: (*a*) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672; (*b*) H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906; (*c*) D. E. Fuerst and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2005, **127**, 8964; (*d*) F. Wu, R. Hong, J. Khan, X. Liu and L. Deng, *Angew. Chem., Int. Ed.*, 2006, **45**, 4301; (*e*) Y. Wang, X. Liu and L. Deng, *J. Am. Chem. Soc.*, 2006, **128**, 3928; (*f*) B. Wang, F. Wu, Y. Wang, X. Liu and L. Deng, *J. Am. Chem. Soc.*, 2007, **129**, 768; (*g*) M. Bandini, R. Sinisi and A. Umani-Ronchi, *Chem. Commun.*, 2008, 4360; (*h*) C. Guo, M.-X. Xue, M.-K. Zhu and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2008, **47**, 3414; (*i*) T. Bui, S. Syed and C. F. Barbas III, *J. Am. Chem. Soc.*, 2009, **131**, 8758; (*j*) Y. Zhu, J. P. Malerich and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2010, **49**, 153.

15 The use of methyl or *tert*-butyl α-ketoesters gave rise to inferior results.

