ChemComm



COMMUNICATION

View Article Online



Cite this: Chem. Commun., 2022, **58**, 6886

Received 4th April 2022, Accepted 20th May 2022

DOI: 10.1039/d2cc01936a

rsc.li/chemcomm

Isothiourea-catalyzed formal enantioselective conjugate addition of benzophenone imines to β -fluorinated α , β -unsaturated esters†

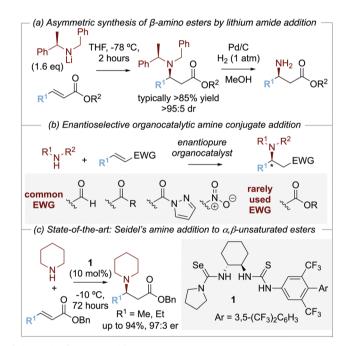
Jerson E. Lapetaje, Claire M. Young, D Chang Shu and Andrew D. Smith D*

The isothiourea-catalyzed formal enantioselective conjugate addition of 2-hydroxybenzophenone imine derivatives to α,β-unsaturated paranitrophenyl esters has been developed. Investigations of the scope and limitations of this procedure showed that \beta-electron withdrawing substituents within the $\alpha_i\beta$ -unsaturated ester component are required for good product yield, giving rise to a range of β-imino ester and amide derivatives in moderate to good isolated yields with excellent enantioselectivity (20 examples, up to 81% yield and 97:3 er).

The development of methods for the enantioselective synthesis of β-amino acid derivatives^{1a} is of widespread importance due to the prevalence of this structural motif in natural products and medicinally relevant compounds. Among the synthetic methods that have been developed for the preparation of β-amino acid derivatives, arguably the most simple and elegant involves the asymmetric conjugate addition of an ammonia equivalent to an α,β -unsaturated carbonyl motif. As an example of this approach, the conjugate addition of enantiomerically pure lithium amide derivatives to α,β-unsaturated esters has been developed and exploited extensively by Davies and coworkers. Conjugate addition of lithium N-benzyl-N-αmethylbenzylamide to an α,β -unsaturated ester gives the corresponding β-amino ester with high diastereoselectivity (>95:5 dr), with N-deprotection through hydrogenolysis giving the corresponding β-amino ester derivatives (Scheme 1a).²

Over the last two decades, several enantioselective organocatalytic approaches to amine conjugate addition have been introduced. To date, these successful approaches rely upon enals,3 enones,4 N-acyl pyrazoles,5 and nitro-olefins6 as Michael acceptors, with the use of bifunctional thiourea 4a,5b,7,8a-c,e or squaramide^{4,5c,8a,b,e} organocatalysts, or Lewis basic pyrrolidines^{3,8} commonplace. Catalytic enantioselective amine conjugate additions to α,β-unsaturated esters are rare, reflecting the recognized

EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St. Andrews KY16 9ST, UK. E-mail: ads10@st-andrews.ac.uk



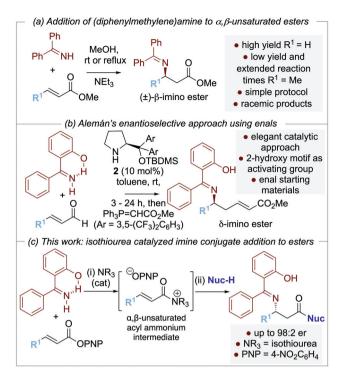
Scheme 1 Synthesis of β-amino ester derivatives.

recalcitrance of α,β-unsaturated esters as Michael acceptors (Scheme 1b). To date, the current state-of-the-art organocatalytic approach is represented by Seidel and co-workers, demonstration of the conjugate addition of cyclic secondary amines to βalkyl-α,β-unsaturated benzyl esters using a selenourea-thiourea catalyst 1 (Scheme 1c). Although limited to β-alkyl substituted Michael acceptors, this impressive methodology was applicable to a range of cyclic amines and the kinetic resolution of (\pm) -cyclic 2-arylamines.

Our approach to enantioselective amine conjugate addition focused upon the use of imines as nucleophiles. The conjugate addition of (diphenylmethylene)amine to α,β-unsaturated esters, nitriles and ketones in racemic form has been demonstrated by de Meijere et al. MeOH was optimal as a solvent and

[†] Electronic supplementary information (ESI) available. See DOI: https://doi.org/

Communication ChemComm

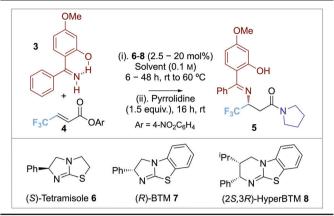


Previous imine conjugate additions and this work.

a basic additive (such as NEt₃) led to effective product formation (Scheme 2a).10 In 2018, Alemán and co-workers successfully demonstrated an enantioselective aza-Michael addition of nucleophilic imines to enals using secondary amine catalyst 2 (Scheme 2b). 11 Trapping of the resultant β-imino aldehydes with a phosphorane gave the corresponding δ -imino esters in good yield and enantioselectivity. Notably, 2-hydroxybenzophenone imines showed increased reactivity and enantioselectivity compared with the parent benzophenone imine, attributed to an increase in acidity of the imine proton caused by intramolecular hydrogen bonding. 12,13 In previous work, we and others have demonstrated a range of enantioselective Michael-addition processes of in situ generated α,β-unsaturated acyl ammonium species. 14,15 Building on these precedents, we report herein the formal isothiourea-catalyzed enantioselective addition of 2-hydroxybenzophenone imines to β -fluorinated α , β -unsaturated paranitrophenyl esters via an α,β-unsaturated acyl ammonium intermediate, giving products in up to 98:2 er (Scheme 2c).

Preliminary investigations used β -CF₃-substituted α,β unsaturated para-nitrophenyl ester 4 (1.0 equiv.) in toluene as standard. Given the moderate reactivity of α,β -unsaturated acyl ammonium ions, imine 3 (2.0 equiv.) bearing an electron donor 4-OMe-substituent was postulated to enhance nucleophilicity (Table 1). Attempted isolation of the para-nitrophenyl ester product led to low and irreproducible product yields, so addition of pyrrolidine to give the isolable amide 5 was adopted. Screening of isothiourea catalysts 6-8 (10 mol%) at 1:2 substrate ratio of ester 4: imine 3 (entries 1-3) showed that tetramisole 6 and BTM 7 gave promising product yield ($\sim 50\%$) whereas HyperBTM 8 showed poor catalytic activity (<10% yield). Excellent enantioselectivity (96:4 er) was observed using BTM 7. Altering the

Table 1 Reaction optimisation



Entry	Catalyst (mol%)	Temp. (°C)	Solvent	3:4	$Yield^a$ (%)	er ^b
1 ^c	6 (10)	rt	Toluene	1:2	50	12:88
2^c	7 (10)	rt	Toluene	1:2	54	96:4
3^c	8 (10)	rt	Toluene	1:2	< 10	68:32
4^{c}	7(10)	rt	Toluene	1:1.5	42	95:5
5^c	7 (10)	rt	Toluene	1.5:1	38	97:3
6 ^c	7 (10)	40	Toluene	1:2	52	94:6
7^c	7 (10)	60	Toluene	1:2	47	91:9
8 ^c	7 (2.5)	rt	Toluene	1:2	< 10	91:9
9^c	7 (5.0)	rt	Toluene	1:2	18	96:4
10^c	7 (20)	rt	Toluene	1:2	71 ^d	96:4
11^c	7 (20)	rt	THF	1:2	31	96:4
12^c	7 (20)	rt	Et_2O	1:2	30	96:4
13 ^c	7 (20)	rt	CH_2Cl_2	1:2	37	96:4
14^e	7 (20)	rt	Toluene	1:2	31	98:2
15^f	7 (20)	rt	Toluene	1:2	42	96:4
16 ^g	7 (20)	rt	Toluene	1:2	36	96:4

Using ¹H NMR spectroscopic analysis and 1,3,5-trimethoxybenzene as internal standard. b Ratio of (R):(S) enantiomers determined by HPLC analysis on a chiral stationary phase. c Ar = 4-NO₂C₆H₄. d Isolated yield. $Ar = 2,4,6-Cl_3C_6H_2$. f $Ar = C_6F_5$. g $Ar = 3,5-(CF_3)_2C_6H_3$.

reaction stoichiometry (entries 4 and 5) led to reduced product yield. A detrimental effect on product enantioselectivity (91:9 er) was observed when the reaction temperature was increased to 40 °C or 60 °C (entries 6 and 7). Lowering the catalyst loading showed a significant decrease in product yield and enantioselectivity (entries 8 and 9), while using 20 mol% BTM 7 gave increased yield (71% yield, 96:4 er, entry 10). Screening of a alternative solvents gave high product enantioselectivity but reduced yields (entries 11-13). Further optimisation probed the effectiveness of alternative electron-deficient aryl esters. Comparison of para-nitrophenyl with 2,4,6-trichlorophenyl, pentafluorophenyl, and 3,5-bis(trifluoromethyl)phenyl esters (entries 14–16) showed that excellent enantioselectivities were observed in each case (up to 98: 2 er), with the para-nitrophenyl ester leading to the best product yield (71%).

The scope and limitations of the developed process was explored through variation of the nucleophilic imine reaction component (Fig. 1). Variation of the electronic bias of the 4-aryl substituent within the imine component showed that decreased product yield was observed upon changing from an electrondonating 4-MeO- (5, 70% yield) to 4-Me (9, 49% yield), 4-H (11, 36% yield) and electron-withdrawing 4-Br substituent (10, 24%) yield) all with >96:4 er. This is consistent with increasing ChemComm

(i). (R)-BTM 7 (20 mol%) toluene, (0.1 M), 30 h. rt Nuc-H (1.5 equiv.). (2.0 equiv.) 16 h. rt $Ar = 4-NO_2C_6H_4$ (1.0 equiv.) Imine variation 11 5 10 36% yield 70% vield 49% vield 24% vield 96:4 er 94:6 er 97:3 er -substituent variation OMe OH 12 14 15 40% yield 83:17 er 41% yield, 97:3 er 73% yield 96:4 er 40% yield $Ar^1 = 4-MeOC_6H_4$ OMe OMe Limitations Br 16 18 R = Me 17 $R^2 = Ph$ 20% yield,^a 96:4 er 72% yield 81% yield NBn₂, COPh 19 R = Bn no reaction 20% yield,^a 87:13 er Nuc-H variation

Fig. 1 $\,$ 0.10 mmol scale. Isolated product yield; er determined by HPLC analysis on a chiral stationary phase; [a] 40 °C for step i; [b] DMAP 20 mol% in step ii.

23

52% yield

22

53% yield

20 R3= Me

64% vield.b 97:3 er

21 R3= Bn

42% yield,^b 96:4 er

NRn

24

57% yield

electron density within the imine component leading to increased product yield. Interestingly, comparing the yield and er of products **11** and **12** indicates that the 2-hydroxy-substituent within the imine is essential for high product er, but does not affect product yield. The incorporation of an additional electron-donating 4-MeO substituent led to product **13** in reduced yield but maintained high product er. Variation of the β -substituent within the α,β -unsaturated ester indicated that the incorporation of polyhalogenated or ester electron-withdrawing groups was necessary for reactivity as alkyl, aryl, ketone and amide substituted acceptors gave no significant product formation. For example, the introduction of halogenated (CF₂H) and polyhalogenated

Scheme 3 Gram scale synthesis of product 5.

substituents (CF₂Cl, CF₂Br, and C₂F₅) led to products **14–17** in up to excellent yields with high enantioselectivity (40% to 81%; >96:4 er), while the incorporation of ester substituents gave **18–19** in poor 20% product yield in up to 96:4 er. Variation of the post catalysis nucleophilic component (Nuc-H) to incorporate alcohols as well as cyclic secondary and acyclic primary amines gave a range of ester and amide products **20–24** in good yield (42% to 64%) and excellent enantioselectivity (\geq 96:4 er).

To further demonstrate the synthetic utility of this transformation, it was applied to the gram-scale synthesis of product 5 with consistent yield and enantioselectivity (67%, 96:4 er, Scheme 3). Hydrolysis gave the free β -amino amide product 26 in high yield and enantioselectivity (95%, 96:4 er). ¹⁶

A proposed mechanism of this transformation is shown in Scheme 4. Reversible acylation of the isothiourea with the α,β -unsaturated ester **1a** generates the key α,β -unsaturated acyl isothiouronium ion pair **26**.

Scheme 4 Proposed reaction mechanism.

Communication ChemComm

An intramolecular chalcogen 1,5-S···O interaction $(n_O \rightarrow \sigma^*_{S-C})^{17}$ provides a plausible stabilising effect and conformational lock. Hydrogen bonding between the 2-hydroxy-substituent and the imine N serves to conformationally restrict this functionality and facilitate deprotonation. 11-13 Subsequent conjugate addition to the s-cis conformation of the α,β-unsaturated acyl isothiouronium 26 anti- to the stereodirecting phenyl substituent of the isothiourea catalyst generates the ammonium enolate intermediate 27. Proton transfer generates the β-imino acyl isothiouronium intermediate 28, with catalyst turnover facilitated by the aryloxide counterion to form the product and release the isothiourea catalyst BTM 7.18

In summary, enantioselective organocatalytic conjugate addition of 2-hydroxybenzophenone imines to α,β-unsaturated esters using the isothiourea BTM as an organocatalyst gives enantioenriched β-imino amides in modest to good yield (20-81%) and excellent enantioselectivity (typically >95:5 er). 19

The DOST-SEI and DOST-Foreign Graduate Scholarship Program of the Philippines are thanked for a PhD scholarship (J. E. L) and the Royal Society for a Newton Fellowship (C. S.).

Conflicts of interest

There are no conflicts of interests to declare.

Notes and references

- 1 For selected discussions of β-amino acids: (a) G. Cardillo and C. Tomasini, Chem. Soc. Rev., 1996, 25, 117-128; (b) C. Shih, S. Gossett, J. M. Gruber, C. S. Grossman, S. L. Andis, R. M. Schultz, J. F. Worzalla, T. H. Corbett and J. T. Metz, Bioorg. Med. Chem. Lett., 1999, 9, 69-74; (c) W. J. Hoekstra and B. L. Poulter, Curr. Med. Chem., 1998, 5, 195-204; (d) S. Kosemura, T. Ogawa and K. Totsuka, Tetrahedron Lett., 1993, 34, 1291-1294.
- 2 (a) S. G. Davies and O. Ichihara, Tetrahedron: Asymmetry, 1991, 2, 183–186 for reviews see; (b) S. G. Davies, A. D. Smith and P. D. Price, Tetrahedron: Asymmetry, 2005, 17, 2883-2891; (c) S. G. Davies, A. M. Fletcher, P. M. Roberts and J. E. Thomson, Tetrahedron: Asymmetry, 2012, 23, 1111-1153.
- 3 Selected examples for aza-Michael additions to enals: (a) Y. K. Chen, M. Yoshida and D. W.-C. MacMillan, J. Am. Chem. Soc., 2006, 128, 9328-9329; (b) J. Vesely, I. Ibrahem, R. Rios, G.-L. Zhao, Y. Xu and A. Córdova, Tetrahedron Lett., 2007, 48, 2193-2198; (c) H. Jiang, J. B. Nielsen, M. Nielsen and K. A. Jørgensen, *Chem. – Eur. J.*, 2007, **13**, 9068–9075; (*d*) P. Dinér, M. Nielsen, M. Marigo and K. A. Jørgensen, Angew. Chem., Int. Ed., 2007, 46, 1983-1987.
- 4 Selected examples for aza-Michael additions to enones: (a) D. Pettersen, F. Piana, L. Bernardi, F. Fini, M. Fochi, V. Sgarzani and A. Ricci, Tetrahedron Lett., 2007, 48, 7805-7808; (b) X. Lu and L. Deng, Angew. Chem., Int. Ed., 2008, 120, 7824-7827; (c) S. Ma, L. Wu, M. Liu, X. Xu, Y. Huang and Y. Wang, RSC Adv., 2013, 3, 11498-11501.
- 5 Selected examples for aza-Michael additions to N-acylpyrazoles: (a) M. P. Sibi, J. J. Shay, M. Liu and C. P. Jasperse, J. Am. Chem. Soc., 1998, 120, 6615-6616; (b) L. Simón and J. M. Goodman, Org. Biomol. Chem., 2009, 7, 483-487; (c) M. Sánchez-Roselló, C. Mulet, M. Guerola, C. del Pozo and S. Fustero, Chem. - Eur. J., 2014, 20,
- 6 Selected examples for aza-Michael additions to nitroolefins: (a) L. Lykke, D. Monge, M. Nielsen and K. A. Jørgensen, Chem. - Eur.

- J., 2010, 16, 13330-13334; (b) S. Ma, L. Wu, M. Liu, Y. Huang and Y. Wang, Tetrahedron, 2013, 69, 2613-2618; (c) B. L. Zhao, Y. Lin, H. H. Yan and D. M. Du, Org. Biomol. Chem., 2015, 13, 11351-11361; (d) M. Moczulski, P. Drelich and L. Albrecht, Org. Biomol. Chem., 2018, 16, 376-379.
- 7 (a) Y. Sohtome, Y. Hashimoto and K. Nagasawa, Adv. Synth. Catal., 2005, 347, 1643-1648; (b) J. Wang, L. Zu, H. Li, H. Xie and W. Wang, Synthesis, 2007, 2576-2580.
- 8 Reviews on organocatalytic aza-Michael addition reactions highlighting the use of thiourea, squaramide, and Lewis base pyrrolidine catalysts: (a) D. Enders, C. Wang and J. X. Liebich, Chem. - Eur. J., 2009, 15, 11058-11076; (b) J. Wang, P. Li, P. Y. Choy, A. S. C. Chan and F. Y. Kwong, ChemCatChem, 2012, 4, 917-925; (c) C. Bhanja, S. Jena, S. Nayak and S. Mohapatra, Beilstein J. Org. Chem., 2012, 8, 1668–1694; (d) S. D. Pasuparthy and B. Maiti, *ChemistrySelect*, 2022, 7, e202104261; (e) Y. X. Song and D. M. Du, Adv. Synth. Catal., 2021, 363, 4667-4694.
- 9 Y. Lin, W. J. Hirschi, A. Kunadia, A. Paul, I. Ghiviriga, K. A. Abboud, R. W. Karugu, M. J. Vetticatt, J. S. Hirschi and D. Seidel, J. Am. Chem. Soc., 2020, 142, 5627-5635.
- 10 (a) L. Wessjohann, G. Mcgaffin and A. de Meijere, Synthesis, 1989, 359-363; (b) T. Meiresonne, S. Mangelinckx and N. De Kimpe, Org. Biomol. Chem., 2011, 9, 7085-7091.
- 11 H. Choubane, A. F. Garrido-Castro, C. Alvarado, A. Martín-Somer, A. Guerrero-Corella, M. Daaou, S. Díaz-Tendero, M. Carmen Maestro, A. Fraile and J. Alemán, Chem. Commun., 2018, 54, 3399-3402.
- 12 (a) A. Guerrero-Corella, M. A. Valle-Amores, A. Fraile and J. Alemán, Adv. Synth. Catal., 2021, 363, 3845-3851; (b) A. Guerrero-Corella, F. Esteban, M. Iniesta, A. Martín-Somer, M. Parra, S. Díaz-Tendero, A. Fraile and J. Alemán, Angew. Chem., Int. Ed., 2018, 57, 5350-5354.
- 13 For a review: A. Guerrero-Corella, A. Fraile and J. Alemán, ACS Org. Inorg. Au, 2022, DOI: 10.1021/acsorginorgau.1c00053.
- 14 (a) A. Matviitsuk, M. D. Greenhalgh, D. J.-B. Antúnez, A. M.-Z. Slawin and A. D. Smith, Angew. Chem., Int. Ed., 2017, 56, 12282-12287; (b) C. Shu, H. Liu, A. M.-Z. Slawin, C. Carpenter-Warren and A. D. Smith, Chem. Sci., 2020, 11, 241-247; (c) M. D. Greenhalgh, S. Qu, A. M.-Z. Slawin and A. D. Smith, Chem. Sci., 2018, 9, 4909-4918.
- 15 For a review see: J. Bitai, M. Westwood and A. D. Smith, Org. Biomol. Chem., 2021, 19, 2366-2384.
- 16 The absolute configuration was confirmed by hydrolysis of 25 to obtain the free β -amino acid (exp: $\lceil \alpha \rceil 20D = +17.9$; lit: $\lceil \alpha \rceil 20D = +24.4$): N. Shibata, T. Nishimine, N. Shibata, E. Tokunaga, K. Kawada, T. Kagawa, J. L. Aceña, A. E. Sorochinsky and V. A. Soloshonok, Org. Biomol. Chem., 2014, 12, 1454-1462.
- 17 S. O interactions in isothiourea catalysis: (a) V. B. Birman, X. Li and Z. Han, Org. Lett., 2007, **9**, 37–40; (b) P. Liu, X. Yang, V. B. Birman and K. N. Houk, Org. Lett., 2012, **14**, 3288–3291; (c) M. E. Abbasov, B. M. Hudson, D. J. Tantillo and D. Romo, J. Am. Chem. Soc., 2014, 136, 4492-4495; (d) E. R.-T. Robinson, D. M. Walden, C. Fallan, M. D. Greenhalgh, P. H.-Y. Cheong and A. D. Smith, Chem. Sci., 2016, 7, 6919-6927; (e) M. D. Greenhalgh, S. M. Smith, D. M. Walden, J. E. Taylor, Z. Brice, E. R.-T. Robinson, C. Fallan, D. B. Cordes, A. M.-Z. Slawin, H. C. Richardson, M. A. Grove, P. H.-Y. Cheong and D. Smith, Angew. Chem., Int. Ed., 2018, 57, 3200-3206; (f) C. M. Young, A. Elmi, D. J. Pascoe, R. K. Morris, C. McLaughlin, A. M. Woods, A. B. Frost, A. de la Houpliere, K. B. Ling, T. K. Smith, A. M.-Z. Slawin, P. H. Willoughby, S. L. Cockroft and A. D. Smith, *Angew. Chem., Int. Ed.*, 2020, **59**, 3705–3710In medicinal chemistry: (g) B. R. Beno, K.-S. Yeung, M. D. Bartberger, L. D. Pennington and N. A. Meanwell, J. Med. Chem., 2015, 58, 4383-4438.
- discussion on aryloxide facilitated catalyst turnover: (a) A. Matviitsuk, M. D. Greenhalgh, D. J.-B. Antúnez, A. M.-Z. Slawin and A. D. Smith, Angew. Chem., Int. Ed., 2017, 56, 12282-12287; (b) W. C. Hartley, T. J.-C. O'Riordan and A. D. Smith, Synthesis, 2017, 49, 3303-3310; (c) T. H. West, D. S.-B. Daniels, A. M.-Z. Slawin and A. D. Smith, J. Am. Chem. Soc., 2014, 136, 4476-4479.
- 19 Research data supporting publication can be accessed at https:// doi.org/10.17630/fb29b2d4-41d4-4143-a19b-5f59cb71447a.