



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

Received 4th April 2022,  
Accepted 20th May 2022

DOI: 10.1039/d2cc01936a

rsc.li/chemcomm

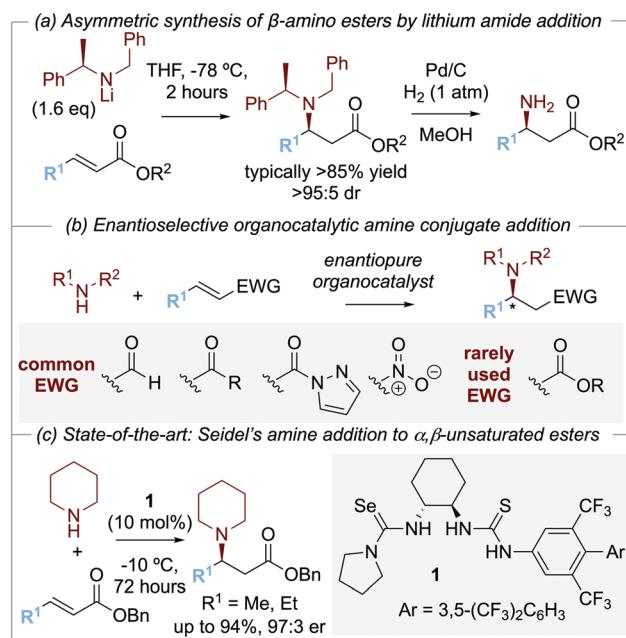
The isothiourea-catalyzed formal enantioselective conjugate addition of 2-hydroxybenzophenone imine derivatives to  $\alpha,\beta$ -unsaturated *para*-nitrophenyl esters has been developed. Investigations of the scope and limitations of this procedure showed that  $\beta$ -electron withdrawing substituents within the  $\alpha,\beta$ -unsaturated ester component are required for good product yield, giving rise to a range of  $\beta$ -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  $\beta$ -amino acid derivatives<sup>1a</sup> is of widespread importance due to the prevalence of this structural motif in natural products and medicinally relevant compounds.<sup>1</sup> Among the synthetic methods that have been developed for the preparation of  $\beta$ -amino acid derivatives, arguably the most simple and elegant involves the asymmetric conjugate addition of an ammonia equivalent to an  $\alpha,\beta$ -unsaturated carbonyl motif. As an example of this approach, the conjugate addition of enantiomerically pure lithium amide derivatives to  $\alpha,\beta$ -unsaturated esters has been developed and exploited extensively by Davies and co-workers. Conjugate addition of lithium *N*-benzyl-*N*-methylbenzylamide to an  $\alpha,\beta$ -unsaturated ester gives the corresponding  $\beta$ -amino ester with high diastereoselectivity (>95:5 dr), with *N*-deprotection through hydrogenolysis giving the corresponding  $\beta$ -amino ester derivatives (Scheme 1a).<sup>2</sup>

Over the last two decades, several enantioselective organocatalytic approaches to amine conjugate addition have been introduced. To date, these successful approaches rely upon enals,<sup>3</sup> enones,<sup>4</sup> *N*-acyl pyrazoles,<sup>5</sup> and nitro-olefins<sup>6</sup> as Michael acceptors, with the use of bifunctional thiourea<sup>4a,5b,7,8a-c,e</sup> or squaramide<sup>4,5c,8a,b,e</sup> organocatalysts, or Lewis basic pyrrolidines<sup>3,8</sup> commonplace. Catalytic enantioselective amine conjugate additions to  $\alpha,\beta$ -unsaturated esters are rare, reflecting the recognized

## Isothiourea-catalyzed formal enantioselective conjugate addition of benzophenone imines to $\beta$ -fluorinated $\alpha,\beta$ -unsaturated esters<sup>†</sup>

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



Scheme 1 Synthesis of  $\beta$ -amino ester derivatives.

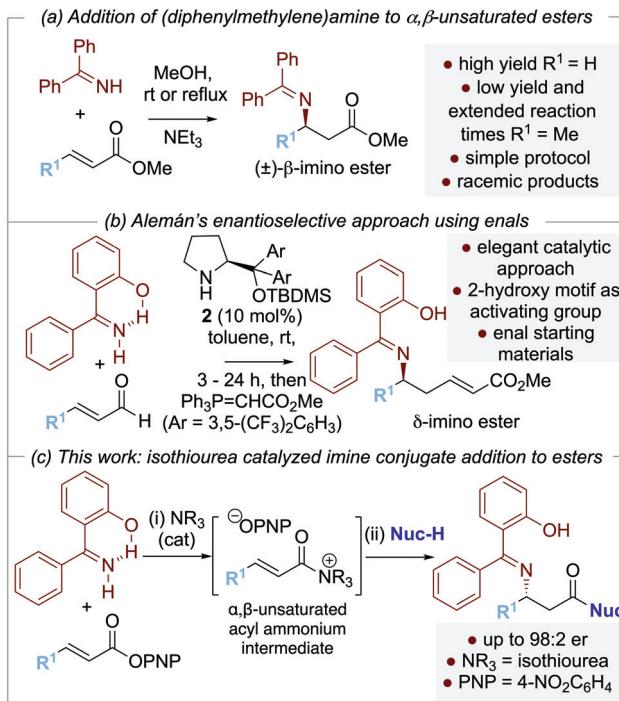
recalcitrance of  $\alpha,\beta$ -unsaturated esters as Michael acceptors (Scheme 1b). To date, the current state-of-the-art organocatalytic approach is represented by Seidel and co-workers<sup>9</sup> demonstration of the conjugate addition of cyclic secondary amines to  $\beta$ -alkyl- $\alpha,\beta$ -unsaturated benzyl esters using a selenourea-thiourea catalyst 1 (Scheme 1c). Although limited to  $\beta$ -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  $\alpha,\beta$ -unsaturated esters, nitriles and ketones in racemic form has been demonstrated by de Meijere *et al.* MeOH was optimal as a solvent and

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

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d2cc01936a>



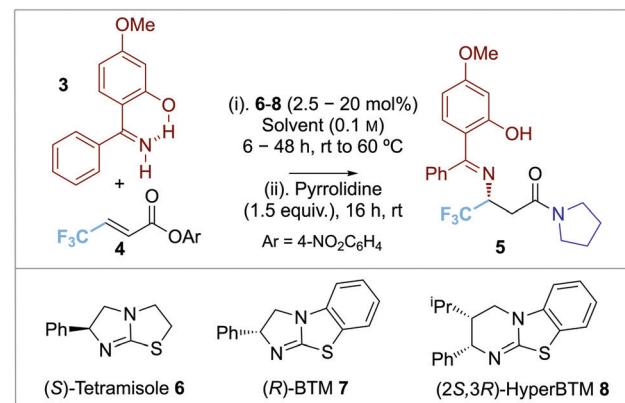


Scheme 2 Previous imine conjugate additions and this work.

a basic additive (such as  $\text{NEt}_3$ ) led to effective product formation (Scheme 2a).<sup>10</sup> 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).<sup>11</sup> Trapping of the resultant  $\beta$ -imino aldehydes with a phosphorane gave the corresponding  $\delta$ -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.<sup>12,13</sup> In previous work, we and others have demonstrated a range of enantioselective Michael-addition processes of *in situ* generated  $\alpha,\beta$ -unsaturated acyl ammonium species.<sup>14,15</sup> Building on these precedents, we report herein the formal isothiourea-catalyzed enantioselective addition of 2-hydroxybenzophenone imines to  $\beta$ -fluorinated  $\alpha,\beta$ -unsaturated *para*-nitrophenyl esters *via* an  $\alpha,\beta$ -unsaturated acyl ammonium intermediate, giving products in up to 98:2 er (Scheme 2c).

Preliminary investigations used  $\beta$ -CF<sub>3</sub>-substituted  $\alpha,\beta$ -unsaturated *para*-nitrophenyl ester 4 (1.0 equiv.) in toluene as standard. Given the moderate reactivity of  $\alpha,\beta$ -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 (~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 <sup>a</sup> (%)	er <sup>b</sup>
1 <sup>c</sup>	6 (10)	rt	Toluene	1:2	50	12:88
2 <sup>c</sup>	7 (10)	rt	Toluene	1:2	54	96:4
3 <sup>c</sup>	8 (10)	rt	Toluene	1:2	<10	68:32
4 <sup>c</sup>	7 (10)	rt	Toluene	1:1.5	42	95:5
5 <sup>c</sup>	7 (10)	rt	Toluene	1.5:1	38	97:3
6 <sup>c</sup>	7 (10)	40	Toluene	1:2	52	94:6
7 <sup>c</sup>	7 (10)	60	Toluene	1:2	47	91:9
8 <sup>c</sup>	7 (2.5)	rt	Toluene	1:2	<10	91:9
9 <sup>c</sup>	7 (5.0)	rt	Toluene	1:2	18	96:4
10 <sup>c</sup>	7 (20)	rt	Toluene	1:2	71 <sup>d</sup>	96:4
11 <sup>c</sup>	7 (20)	rt	THF	1:2	31	96:4
12 <sup>c</sup>	7 (20)	rt	Et <sub>2</sub> O	1:2	30	96:4
13 <sup>c</sup>	7 (20)	rt	CH <sub>2</sub> Cl <sub>2</sub>	1:2	37	96:4
14 <sup>e</sup>	7 (20)	rt	Toluene	1:2	31	98:2
15 <sup>f</sup>	7 (20)	rt	Toluene	1:2	42	96:4
16 <sup>g</sup>	7 (20)	rt	Toluene	1:2	36	96:4

<sup>a</sup> Using <sup>1</sup>H NMR spectroscopic analysis and 1,3,5-trimethoxybenzene as internal standard. <sup>b</sup> Ratio of (R):(S) enantiomers determined by HPLC analysis on a chiral stationary phase. <sup>c</sup> Ar = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>. <sup>d</sup> Isolated yield. <sup>e</sup> Ar = 2,4,6-Cl<sub>3</sub>C<sub>6</sub>H<sub>2</sub>. <sup>f</sup> Ar = C<sub>6</sub>F<sub>5</sub>. <sup>g</sup> Ar = 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>.

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 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 electron-donating 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



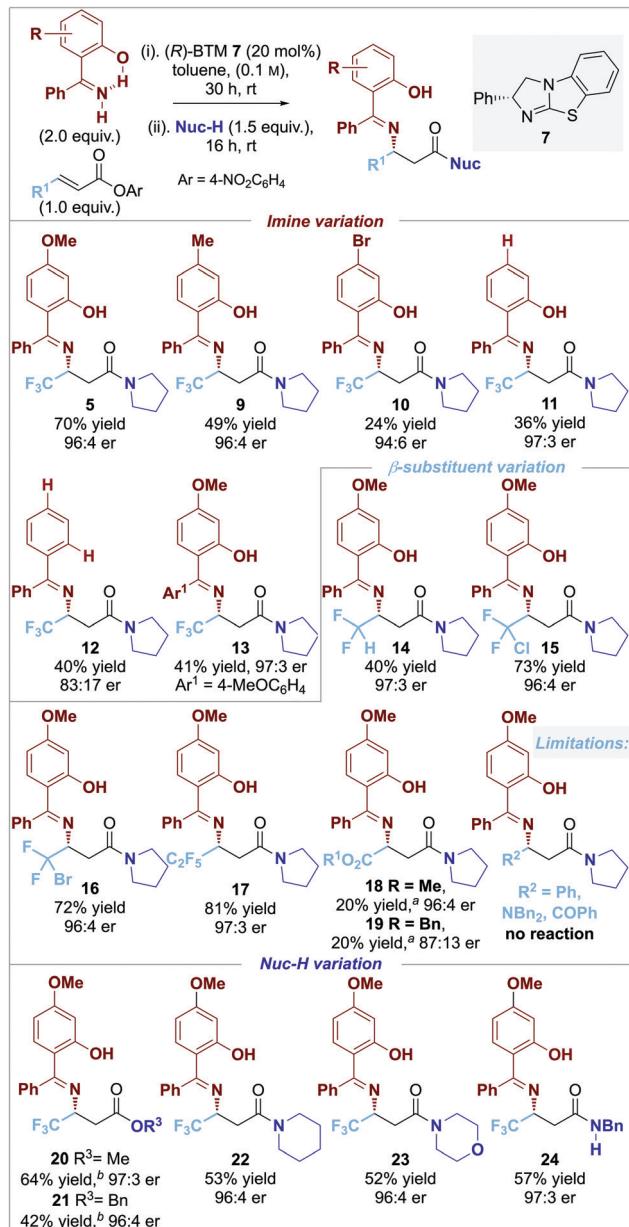
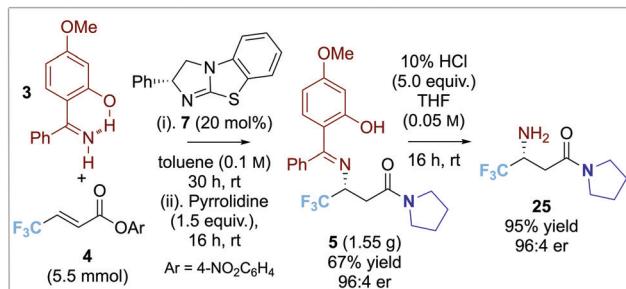


Fig. 1 0.10 mmol scale. Isolated product yield; er determined by HPLC analysis on a chiral stationary phase; [a] 40 °C for step i; [b] DMAP 20 mol% in step ii.

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  $\beta$ -substituent within the  $\alpha,\beta$ -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 ( $\text{CF}_2\text{H}$ ) and polyhalogenated

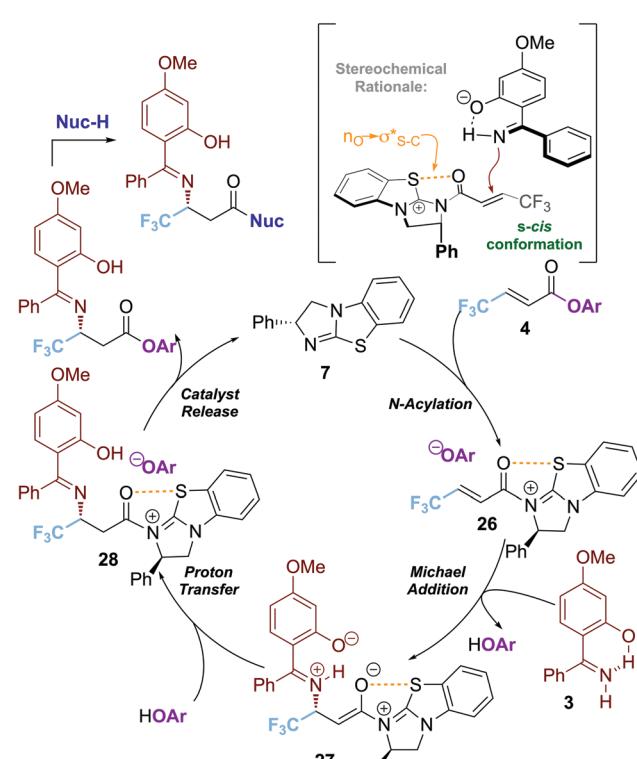


Scheme 3 Gram scale synthesis of product 5.

substituents ( $\text{CF}_2\text{Cl}$ ,  $\text{CF}_2\text{Br}$ , and  $\text{C}_2\text{F}_5$ ) 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  $\beta$ -amino amide product **26** in high yield and enantioselectivity (95%, 96:4 er).<sup>16</sup>

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



Scheme 4 Proposed reaction mechanism.

An intramolecular chalcogen 1,5-S···O interaction ( $\text{n}_\text{O} \rightarrow \sigma^*_{\text{S-C}}$ )<sup>17</sup> 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.<sup>11–13</sup> Subsequent conjugate addition to the *s-cis* conformation of the  $\alpha,\beta$ -unsaturated acyl isothiouronium **26** *anti*- to the stereodirecting phenyl substituent of the isothiourea catalyst generates the ammonium enolate intermediate **27**. Proton transfer generates the  $\beta$ -imino acyl isothiouronium intermediate **28**, with catalyst turnover facilitated by the aryloxide counterion to form the product and release the isothiourea catalyst BTM **7**.<sup>18</sup>

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

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

- For selected discussions of  $\beta$ -amino acids: (a) G. Cardillo and C. Tomasini, *Chem. Soc. Rev.*, 1996, **25**, 117–128; (b) C. Shih, L. 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. Poultier, *Curr. Med. Chem.*, 1998, **5**, 195–204; (d) S. Kosemura, T. Ogawa and K. Totzuka, *Tetrahedron Lett.*, 1993, **34**, 1291–1294.
- (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.
- 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.
- Selected examples for aza-Michael additions to enones: (a) D. Petersen, 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.
- 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**, 15697–15701.
- 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.
- (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.
- 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. Lieblich, *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.
- 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.
- (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.
- 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.
- (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.
- For a review: A. Guerrero-Corella, A. Fraile and J. Alemán, *ACS Org. Inorg. Au*, 2022, DOI: [10.1021/acsorginorgau.1c00053](https://doi.org/10.1021/acsorginorgau.1c00053).
- (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.
- For a review see: J. Bitai, M. Westwood and A. D. Smith, *Org. Biomol. Chem.*, 2021, **19**, 2366–2384.
- The absolute configuration was confirmed by hydrolysis of **25** to obtain the free  $\beta$ -amino acid (exp:  $[\alpha]_{\text{D}}^{20} = +17.9$ ; lit:  $[\alpha]_{\text{D}}^{20} = +24.4$ ): 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.
- 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 A. D. Smith, *Angew. Chem., Int. Ed.*, 2018, **57**, 3200–3206; (f) C. M. Young, A. Elmí, D. J. Pascoe, R. K. Morris, C. McLaughlin, A. M. Woods, A. B. Frost, A. de la Houlière, 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**, 3705–3710 In 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.
- For 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.
- Research data supporting publication can be accessed at <https://doi.org/10.17630/fb29b2d4-41d4-4143-a19b-5f59cb71447a>.

