


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

 Received 4th April 2022,
Accepted 20th May 2022

DOI: 10.1039/d2cc01936a

rsc.li/chemcomm

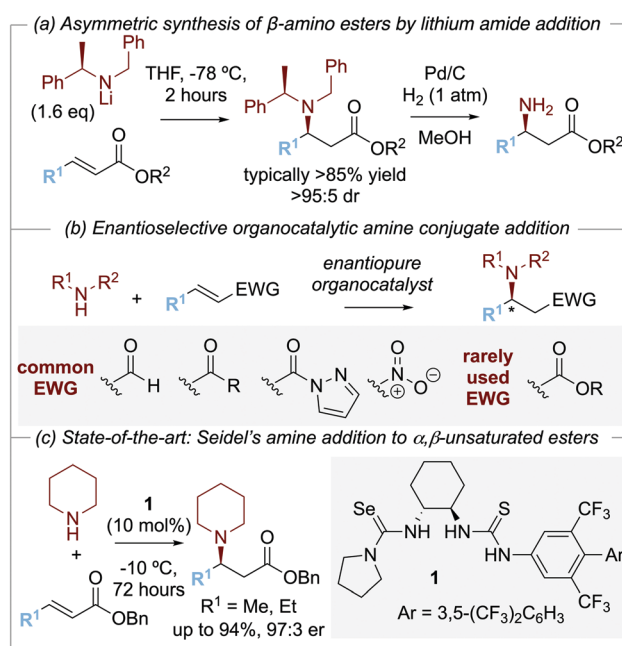
Isothiourea-catalyzed formal enantioselective conjugate addition of benzophenone imines to α,β -fluorinated α,β -unsaturated esters†

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

The isothiurea-catalyzed formal enantioselective conjugate addition of 2-hydroxybenzophenone imine derivatives to α,β -unsaturated *para*-nitrophenyl esters has been developed. Investigations of the scope and limitations of this procedure showed that β -electron withdrawing substituents within the α,β -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.¹ 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 co-workers. Conjugate addition of lithium *N*-benzyl-*N*- α -methylbenzylamide 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


 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-workers⁹ demonstration of the conjugate addition of cyclic secondary amines to β -alkyl- 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

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 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 isothiurea-catalyzed enantioselective addition of 2-hydroxybenzophenone imines to β -fluorinated α,β -unsaturated *para*-nitrophenyl 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 isothiurea 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 ^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 ₂ O	1 : 2	30	96 : 4
13 ^c	7 (20)	rt	CH ₂ Cl 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

^a 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. ^e Ar = 2,4,6-Cl₃C₆H₂. ^f Ar = C₆F₅. ^g Ar = 3,5-(CF₃)₂C₆H₃.

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 an 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



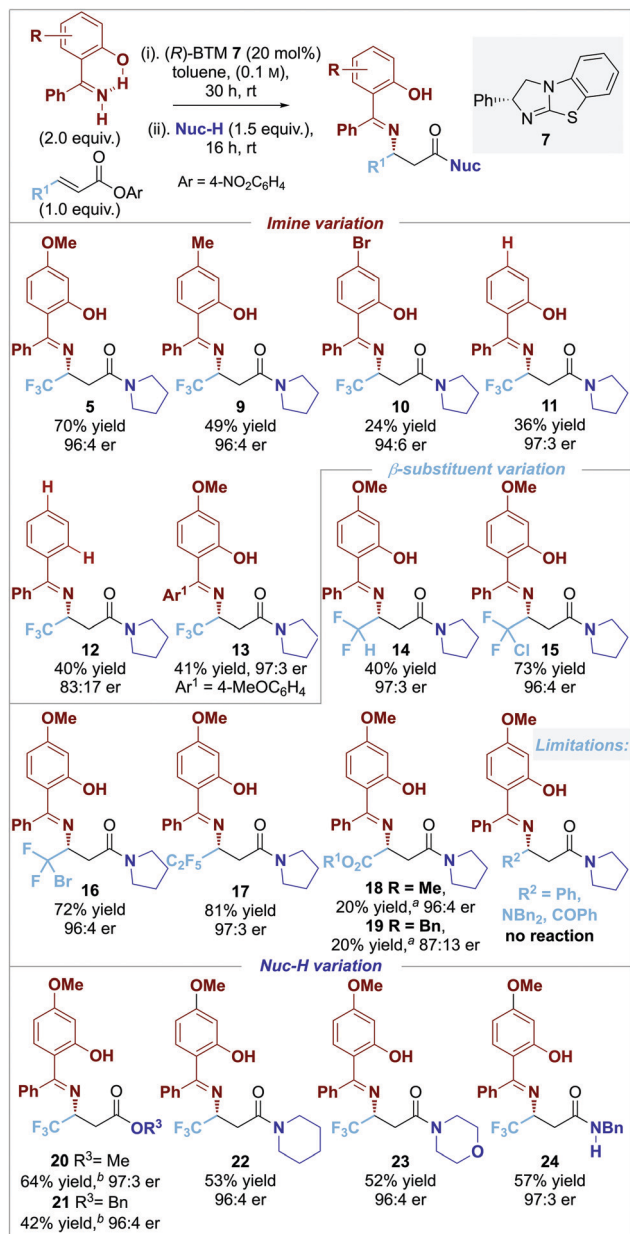
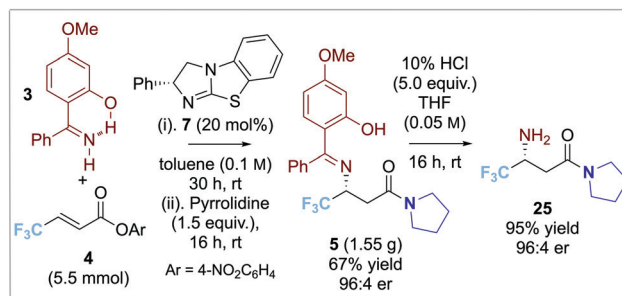


Fig. 1 0.10 mmol scale. Isolated product yield; er determined by HPLC analysis on a chiral stationary phase; [a] 40 °C for step i; [b] DMAP 20 mol% in step ii.

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 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

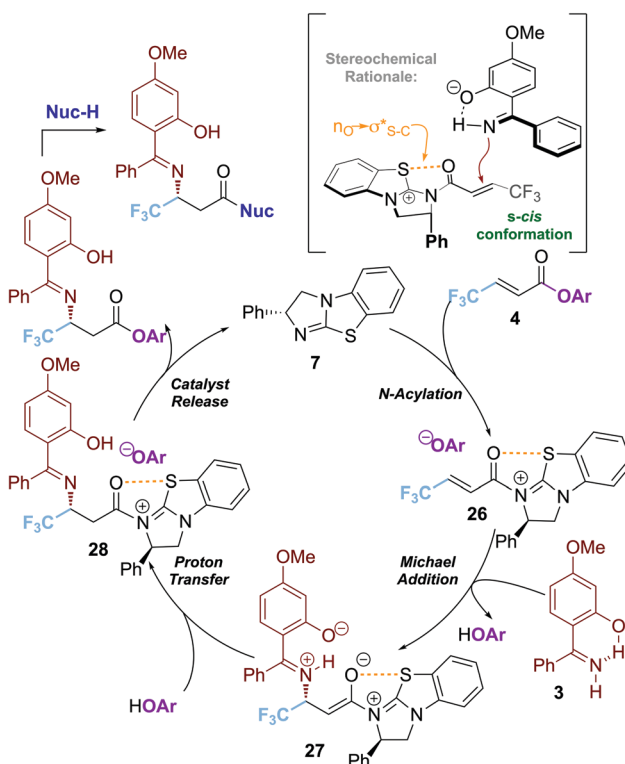


Scheme 3 Gram scale synthesis of product **5**.

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.



An intramolecular chalcogen 1,5-S··O interaction ($n_{\text{O}} \rightarrow \sigma^*_{\text{S-C}}$)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 isothiuronium **26 anti-** to the stereodirecting phenyl substituent of the isothiurea catalyst generates the ammonium enolate intermediate **27**. Proton transfer generates the β -imino acyl isothiuronium intermediate **28**, with catalyst turnover facilitated by the aryloxide counterion to form the product and release the isothiurea catalyst BTM **7**.¹⁸

In summary, enantioselective organocatalytic conjugate addition of 2-hydroxybenzophenone imines to α,β -unsaturated esters using the isothiurea 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

- For selected discussions of β -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. Poulter, *Curr. Med. Chem.*, 1998, 5, 195–204; (d) S. Kosemura, T. Ogawa and K. Totsuka, *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. Ibrahim, 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. 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.
- 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. 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. Pasupathy 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. Veticatt, 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.
- (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 β -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 isothiurea 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. 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. Cockcroft 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>.

