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Enantioselective bifunctional iminophosphorane catalyzed sulfa-Michael addition of alkyl thiols to unactivated β -substituted- α,β -unsaturated esters†

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The highly enantioselective sulfa-Michael addition of alkyl thiols to unactivated β -substituted- α,β -unsaturated esters catalyzed by a bifunctional iminophosphorane (BIMP) organocatalyst is described. The low acidity of the alkyl thiol pro-nucleophiles is overcome by the high Brønsted basicity of the catalyst and the chiral scaffold/thiourea hydrogen-bond donor moiety provides the required enantiofacial discrimination in the addition step. The reaction is broad in scope with respect to the alkyl thiol and β -substituent of the α,β -unsaturated ester, affords sulfa-Michael adducts in excellent yields (up to >99%) and enantioselectivity (up to 97 : 3 er) and can operate down to 1 mol% catalyst loading.

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Unactivated β -substituted- α,β -unsaturated esters, such as methyl crotonate, methyl cinnamate and their homologues, are a class of low reactivity electrophiles that offer a wealth of untapped potential in the field of enantioselective organocatalysis.¹ To date, these esters have remained a persistent challenge as Michael acceptors in asymmetric catalysis using both metal-rich and metal-free catalyst systems, largely due to their low inherent electrophilicity² and low propensity for catalyst activation and enantioface discrimination.^{3,4} They are commercial and cheap, or are readily prepared by a variety of standard methods and are stable. In contrast to commonly used (reactive) Michael acceptors such as nitroolefins, they lie at the bottom of the Mayr electrophile reactivity (E) scale,^{5,6} and unlike enal and enone Michael acceptors they cannot be activated through iminium ion formation with chiral amine catalysts.⁷ Related literature examples employ activated carboxylic derivatives⁸ such as *N*-enoyl imides, *N*-enoyl oxazolidinones, perfluorinated alkyl esters, thioamides, *N*-enoyl pyrroles and, most recently, aryl esters.⁹ Alternatively, activating substituents at the α - or β -positions can also be used to gain reactivity and/or stereoselectivity. To illustrate the case in point, to date there has not been a single report of a highly enantioselective addition of a pro-nucleophilic reagent [a carbon-centered (C–H) or heteroatom-centered (X–H) acid] to unactivated alkyl cinnamate or crotonate esters under organocatalytic conditions.¹⁰ Effectively, these cheap chemical feedstocks are out of reach of existing chiral organocatalysts and accordingly are a very attractive ‘simple’ target class of

electrophiles for new enantioselective organocatalytic reaction development (Fig. 1).

A proven strategy to overcome low substrate electrophilicity in base-catalyzed polar addition reactions is to increase the concentration of the nucleophilic conjugate base in the pot – and therefore the rate of the nucleophilic addition reaction – by enhancing the Brønsted basicity of the catalyst relative to tertiary amine catalysts.^{11–13} To this end, we disclosed that bifunctional iminophosphorane (BIMP) catalysts, containing a novel organo-superbase were highly efficacious in the first general enantioselective organocatalytic ketimine nitro-Mannich reaction.^{12b,d} Likewise, very recently, high catalyst performance (in terms of

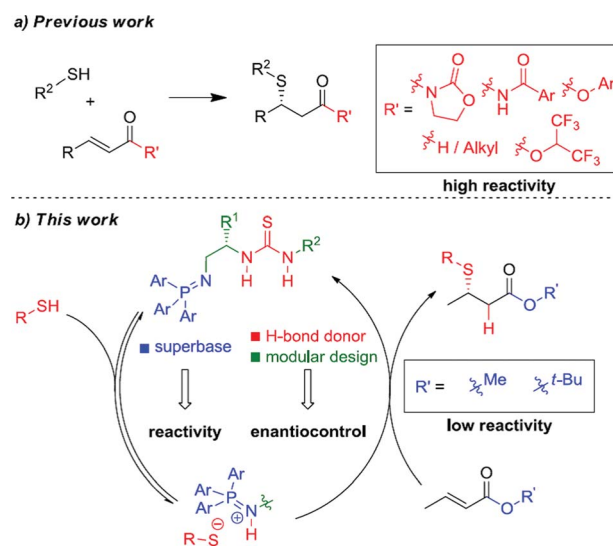


Fig. 1 Bifunctional Brønsted base/H-bond donor organocatalytic SMA to α,β -unsaturated ester derivatives.

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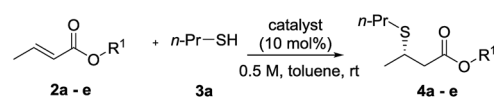
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, copies of ^1H and ^{13}C NMR spectra and HPLC and GC chromatograms. See DOI: 10.1039/c6sc02878k

reactivity and enantioselectivity) with a second generation BIMP catalyst was also witnessed in the first organocatalytic conjugate addition of alkyl thiols to unactivated α -substituted acrylate esters (such as methyl methacrylate).^{12e} In both of these transformations an organosuperbase was demonstrated to be essential for reactivity.

We speculated that the reluctance of unactivated β -substituted- α,β -unsaturated esters to undergo organocatalytic Michael addition reactions could be overcome using our BIMP catalyst family. To exemplify this we chose the sulfa-Michael addition (SMA) of alkyl thiols as this is a reaction of central importance for the asymmetric construction of chiral sulfides possessing a stereogenic centre at the β -carbon and no organocatalytic enantioselective version has previously been reported.^{14,15} We reasoned that the high Brønsted basicity of our BIMP catalysts could activate the high pK_a alkyl thiol pro-nucleophile ($pK_{a(\text{DMSO})} = 17$ for $n\text{-BuSH}$)^{16,17} and the modular design of the catalyst family, through its variable backbone scaffold, hydrogen-bond donor group and iminophosphorane superbase would expedite optimal catalyst identification. Herein, and as part of our research program towards the development of novel asymmetric reactions with challenging electrophile/pro-nucleophile combinations, we wish to report our investigations leading to the highly enantioselective SMA reaction of alkyl thiols to unactivated β -substituted- α,β -unsaturated esters.

We chose commercially available methyl crotonate (**2a**) and 1-propanethiol (**3a**) as our model system and investigated reactivity using first generation BIMP catalyst **1a** (Table 1, entry 1). In toluene, at room temperature using 10 mol% catalyst we were delighted to observe an exceptional reactivity profile; β -mercaptoester product **4a** was afforded in near quantitative yield after only 2 hours with low but significant enantiocontrol (55 : 45 er).¹⁸ With good reactivity established we next investigated the performance of a small library of second generation BIMP catalysts featuring variations around the amide-thiourea motif that we recently reported^{12e} (Table 1, entries 2–6). The modular design of our BIMP catalysts allowed rapid library

Table 1 Catalyst screening studies and reaction optimization^a



Entry	Cat.	R ¹	Product	Time (h)	Yield ^b (%)	er ^c
1	1a	Me	4a	2	94	55 : 45
2	1b	Me	4a	2	98	55 : 45
3	1c	Me	4a	2	94	52 : 48
4	1d	Me	4a	2	93	59 : 41
5	1e	Me	4a	2	>99	75 : 25
6	1f	Me	4a	2	97	62 : 38
7 ^d	1g	Me	4a	3	>99	81 : 19
8	1g	Et	4b	3	95	84 : 16
9	1g	i-Pr	4c	3	>99	85 : 15
10	1g	Bn	4d	3	>99	81 : 19
11 ^d	1g	<i>t</i> -Bu	4e	8	94	92 : 8
12 ^{d,e}	1g	<i>t</i> -Bu	4e	8	95	94 : 6
13 ^f	1g	<i>t</i> -Bu	4e	24	94	96 : 4
14 ^g	1g	<i>t</i> -Bu	4e	72	94	97 : 3

^a Reactions were carried out with 0.20 mmol of **2** and 0.60 mmol of **3a**.

^b Isolated yield. ^c Determined by HPLC analysis on a chiral stationary phase. ^d Reaction performed on 0.10 mmol scale of **2a**. ^e Reaction performed at 0 °C. ^f Reaction performed at 0 °C in Et₂O. ^g Reaction performed at –15 °C in Et₂O.

generation and our attention focussed on the amide-thiourea moiety as the H-bond donor group and the tris-(4-methoxyphenylphosphine) derived iminophosphorane as the Brønsted basic group (Fig. 2).

Catalysts **1b–d** possessing a thiourea constructed from two (*S*)-configured *tert*-leucine derived residues, the tris-(4-methoxyphenylphosphine)-derived iminophosphorane and a variable terminal amide group gave poor enantioselectivity in all cases (Table 1, entries 2, 3, and 4). When catalyst **1e** – the diastereomer of **1d** – was trialled however, a significant boost to the enantioselectivity was witnessed (Table 1, entry 5, 75 : 25 er).¹⁹

A comparison with an analogous catalyst possessing a phenylglycine and a *tert*-leucine residue (**1g**) resulted in a slight improvement to the enantioselectivity (Table 1, entry 7, 81 : 19 er). At this stage, the effect of varying the ester group of the crotonate on the enantioselectivity in the SMA was investigated. A range of simple, commercial or readily synthesized alkyl crotonate esters were trialled and a correlation between the size of the ester group and the enantioselectivity was observed – pleasingly *tert*-butyl crotonate (**2e**) afforded the product **4e** in 92 : 8 er albeit in a slightly increased reaction time of 8 h (Table 1, entry 11). A reoptimization of the reaction conditions to 0.5 M in Et₂O at 0 °C (Table 1, entries 12 & 13 and ESI†) resulted in a significant boost to the enantioselectivity (96 : 4 er) and cooling the reaction temperature further to –15 °C afforded β -mercaptoester **4e** in 94% yield and 97 : 3 er (Table 1, entry 14).

With optimized reaction conditions established, the scope of the transformation with respect to the thiol pro-nucleophile and the α,β -unsaturated ester was investigated (Fig. 3). Minimal variation to the enantioselectivity was observed across a good range of linear (propyl to decyl) or branched (cyclic and acyclic)

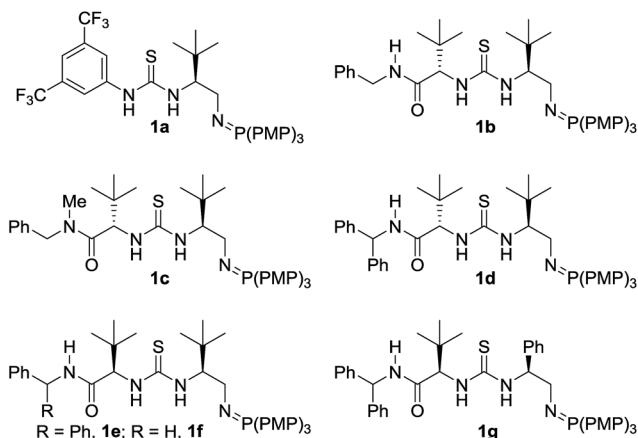
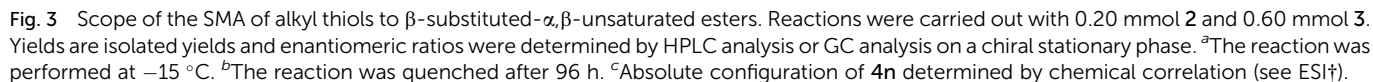
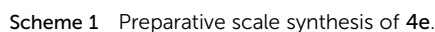


Fig. 2 Bifunctional iminophosphorane (BIMP) organocatalysts used in the optimization of the SMA reaction. PMP = *p*-methoxyphenyl.

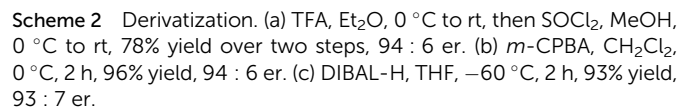




Similarly, excellent yields of the β -mercaptoesters **4o–r** were obtained from the corresponding primary alkyl β -substituted- α,β -unsaturated esters with very good levels of enantiocontrol. β -Mercaptoesters **4s** and **4t** containing a terminal *N*-Boc protected amine and TBS protected hydroxyl group respectively



To demonstrate synthetic utility of the β -mercaptoester products a selection of standard chemical transformations were carried out (Scheme 2). Thus β -mercaptoester **4e** (95 : 5 er) was transesterified to the methyl ester **4a** in a two step process;



initial acidic cleavage of the *tert*-butyl ester and subsequent methyl ester formation under acidic conditions afforded **4a** in 78% yield without compromising stereochemical integrity. Oxidation of **4e** afforded sulfone **5a** without any observable racemization in near quantitative yield. Finally, β -mercaptoester **4m** was reduced to the alcohol in excellent yield, without appreciable loss of enantiopurity.²⁰

In summary, we have developed the first organocatalytic enantioselective SMA of alkyl thiols to unactivated β -substituted- α,β -unsaturated esters. Impressive reactivity and excellent levels of enantioselectivities were achieved across a range of linear, branched, cyclic alkyl and benzylic thiols, in SMA reactions to various β -substituted- α,β -unsaturated esters using a novel bifunctional iminophosphorane catalyst. This work demonstrates that the high reactivity of the BIMP catalysts enables low reactivity electrophiles such as β -substituted- α,β -unsaturated esters to undergo highly enantioselective conjugate addition reactions for the first time and thus represents a significant advance in the field. Work to uncover further capabilities of the BIMP catalyst family is ongoing in our laboratories and the results will be disclosed in due course.

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Notes and references

- For 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*, Wiley VCH, Weinheim, 2005; (c) B. List and J. W. Yang, *Science*, 2006, **313**, 1584; (d) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638; (e) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (f) C. Palomo, M. Oiarbide and R. López, *Chem. Soc. Rev.*, 2009, **38**, 632.
- (a) S. Matsunaga, T. Kinoshita, S. Okada, S. Harada and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 7559; (b) F. López, S. R. Harutyunyan, A. Meetsma, A. J. Minnaard and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2005, **44**, 2752; (c) C. Pubill-Ulldemolins, A. Bonet, C. Bo, H. Gulyás and E. Fernández, *Chem.-Eur. J.*, 2012, **18**, 1121.
- K. Tomioka and Y. Nagaoka, *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, New York, 1999, vol. 3.
- For examples of enantioselective organocatalytic cycloaddition reactions using crotonate and cinnamate esters, see: (a) B. Mathieu, L. de Fays and L. Ghosez, *Tetrahedron Lett.*, 2000, **41**, 9561; (b) D. H. Ryu, T. W. Lee and E. J. Corey, *J. Am. Chem. Soc.*, 2002, **124**, 9992; (c) T. Gatzenmeier, M. van Gemmeren, Y. Xie, D. Höfler, M. Leutzsch and B. List, *Science*, 2016, **351**, 949.
- The electrophile-specific reactivity parameters *E* of *trans*- β -nitrostyrenes have been determined to be $-15 < E < -12$: I. Zenz and H. Mayr, *J. Org. Chem.*, 2011, **76**, 9370.
- Preliminary studies indicate the electrophile-specific reactivity parameters *E* of ethyl cinnamate and ethyl crotonate are in the range of $-25 < E < -23$: H. Mayr, personal communication.
- For a review on iminium catalysis, see: A. Erkkilä, I. Majander and P. Pihko, *Chem. Rev.*, 2007, **107**, 5416.
- For reviews on organocatalytic conjugate addition reactions, see: (a) J. L. Vicario, D. Badía, L. Carrillo and E. Reyes, *Organocatalytic Enantioselective Conjugate Addition Reactions*, Royal Society of Chemistry, Cambridge, 2010; (b) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701.
- The organocatalytic enantioselective conjugate addition of benzyl mercaptan to activated aryl crotonate esters was reported with a *N*-heterocyclic carbene catalyst: P. Yuan, S. Meng, J. Chen and Y. Huang, *Synlett*, 2016, **27**, 1068.
- To the best of our knowledge, only a single isolated example of a moderately enantioselective organocatalytic Michael addition to ethyl crotonate has been reported, see: X. Dong, X. Fang and C.-J. Wang, *Org. Lett.*, 2011, **13**, 4426.
- For reviews on Brønsted base H-bond donor bifunctional organocatalysts, see: (a) Y. Takemoto, *Org. Biomol. Chem.*, 2005, **3**, 4299; (b) S. J. Connon, *Chem. Commun.*, 2008, 2499; (c) T. Marcelli and H. Hiemstra, *Synthesis*, 2010, 1229.
- For the use of chiral organosuperbase catalysts to enhance reactivity, see: (a) J. S. Bandar and T. H. Lambert, *J. Am. Chem. Soc.*, 2012, **134**, 5552; (b) M. G. Núñez, A. J. M. Farley and D. J. Dixon, *J. Am. Chem. Soc.*, 2013, **135**, 16348; (c) T. Takeda and M. Terada, *J. Am. Chem. Soc.*, 2013, **135**, 15306; (d) A. M. Goldys, M. G. Núñez and D. J. Dixon, *Org. Lett.*, 2014, **16**, 6294; (e) A. J. M. Farley, C. Sandford and D. J. Dixon, *J. Am. Chem. Soc.*, 2015, **137**, 15992; (f) G. P. Robertson, A. J. M. Farley and D. J. Dixon, *Synlett*, 2016, **27**, 21; (g) M. A. Horwitz, B. P. Zavesky, J. Martinez-Alvarado and J. S. Johnson, *Org. Lett.*, 2016, **18**, 36.
- For the use of organosuperbases in synthesis, see: (a) T. Ishikawa, *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts*, Wiley, New York, 2009; For a review on chiral organosuperbases, see: (b) T. Ishikawa and T. Kumamoto, *Synthesis*, 2006, 737; (c) D. Leow and C.-H. Tan, *Chem.-Asian J.*, 2009, **4**, 488; (d) D. Leow and C.-H. Tan, *Synlett*, 2010, 1589; (e) T. Ishikawa, *Chem. Pharm. Bull.*, 2010, **58**, 1555; (f) X. Fu and C.-H. Tan, *Chem. Commun.*, 2011, **47**, 8210; (g) P. Selig, *Synthesis*, 2013, **45**, 703; (h) H. Krawczyk, M. Dziegielewski, D. Deredas, A. Albrecht and L. Albrecht, *Chem.-Eur. J.*, 2015, **21**, 10268. For selected examples, see: (i) E. J. Corey and M. J. Grogan, *Org. Lett.*, 1999, **1**, 157; (j) T. Ishikawa, Y. Araki, T. Kumamoto, H. Seki, K. Fukuda and T. Isobe, *Chem. Commun.*, 2001, 245; (k) B. M. Nugent, R. A. Yoder and J. N. Johnston, *J. Am. Chem. Soc.*, 2004, **126**, 3418; (l) M. Terada, H. Ube and Y. Yaguchi, *J. Am. Chem. Soc.*, 2006, **128**, 1454; (m) D. Uraguchi, S. Sakaki and T. Ooi, *J. Am. Chem. Soc.*, 2007, **129**, 12392; (n) T. A. Davis, J. C. Wilt and



- J. N. Johnston, *J. Am. Chem. Soc.*, 2010, **132**, 2880; (o) Y. Sohtome, B. Shin, N. Horitsugi, R. Takagi, K. Noguchi and K. Nagasawa, *Angew. Chem., Int. Ed.*, 2010, **49**, 7299; (p) T. A. Davis and J. N. Johnston, *Chem. Sci.*, 2011, **2**, 1076; (q) D. Uraguchi, K. Yoshioka, Y. Ueki and T. Ooi, *J. Am. Chem. Soc.*, 2012, **134**, 19370; (r) M. T. Corbett, D. Uraguchi, T. Ooi and J. S. Johnson, *Angew. Chem., Int. Ed.*, 2012, **51**, 4685; (s) T. Misaki, N. Jin, K. Kawano and T. Sugimura, *Chem. Lett.*, 2012, **41**, 1675; (t) T. E. Shubina, M. Freund, S. Schenker, T. Clark and S. B. Tsogoeva, *Beilstein J. Org. Chem.*, 2012, **8**, 1485; (u) J. S. Bandar and T. H. Lambert, *J. Am. Chem. Soc.*, 2013, **135**, 11799; (v) J. S. Bandar, A. Barthelme, A. Y. Mazori and T. H. Lambert, *Chem. Sci.*, 2015, **6**, 1537; (w) D. Uraguchi, K. Yamada and T. Ooi, *Angew. Chem., Int. Ed.*, 2015, **54**, 9954; (x) M. Işik, M. Y. Unver and C. Tanyeli, *J. Org. Chem.*, 2015, **80**, 828; (y) X. Gao, J. Han and L. Wang, *Org. Lett.*, 2015, **17**, 4596; (z) J. Chen, S. Meng, L. Wang, H. Tang and Y. Huang, *Chem. Sci.*, 2015, **6**, 4184.
- 14 For a review on asymmetric sulfa-Michael additions, see: (a) D. Enders, K. Lüttgen and A. A. Narine, *Synthesis*, 2007, 959. For selected examples using metals, see: (b) K. Nishimura, M. Ono, Y. Nagaoka and K. J. Tomioka, *J. Am. Chem. Soc.*, 1997, **119**, 12974; (c) S. Kanemasa, Y. Oderaotoshi and E. Wada, *J. Am. Chem. Soc.*, 1999, **121**, 8675; (d) K. Nishimura, M. Ono, Y. Nagaoka and K. Tomioka, *Angew. Chem., Int. Ed.*, 2001, **40**, 440; (e) Y. Hui, J. Jiang, W. Wang, W. Chen, Y. Cai, L. Lin, X. Liu and X. Feng, *Angew. Chem., Int. Ed.*, 2010, **49**, 4290; (f) S. Bonollo, D. Lanari, F. Pizzo and L. Vaccaro, *Org. Lett.*, 2011, **13**, 2150; (g) T. Kitanosono, M. Sakai, M. Ueno and S. Kobayashi, *Org. Biomol. Chem.*, 2012, **10**, 7134; (h) T. Ogawa, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2012, **51**, 8551.
- 15 For a review on organocatalytic asymmetric SMA reactions, see: (a) P. Chauhan, S. Mahajan and D. Enders, *Chem. Rev.*, 2014, **114**, 8807. For selected examples, see: (b) H. Hiemstra and H. Wynberg, *J. Am. Chem. Soc.*, 1981, **103**, 417; (c) A. Kumar, R. V. Salunkhe, R. A. Rane and S. Y. Dike, *J. Chem. Soc., Chem. Commun.*, 1991, 485; (d) P. McDaid, Y. Chen and L. Deng, *Angew. Chem., Int. Ed.*, 2002, **41**, 338; (e) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding and Y. Wu, *Synlett*, 2005, 603; (f) D. Leow, L. Shishi, S. K. Chittimalla, X. Fu and C.-H. Tan, *Angew. Chem., Int. Ed.*, 2008, **47**, 5641; (g) Y. Liu, B. Sun, B. Wang, M. Wakem and L. Deng, *J. Am. Chem. Soc.*, 2009, **131**, 418; (h) K. L. Kimmel, M. T. Robak and J. A. Ellman, *J. Am. Chem. Soc.*, 2009, **131**, 8754; (i) N. K. Rana, S. Selvakumar and V. K. Singh, *J. Org. Chem.*, 2010, **75**, 2089; (j) L. Dai, S.-X. Wang and F.-E. Chen, *Adv. Synth. Catal.*, 2010, **352**, 2137; (k) N. K. Rana and V. K. Singh, *Org. Lett.*, 2011, **13**, 6520; (l) L. Dai, H. Yang and F. Chen, *Eur. J. Org. Chem.*, 2011, 5071; (m) C. Palacio and S. Connon, *Chem. Commun.*, 2012, **48**, 2849; (n) D. Uraguchi, N. Kinoshita, D. Nakashima and T. Ooi, *Chem. Sci.*, 2012, **3**, 3161; (o) L. Dai, H. Yang, J. Niu and F. Chen, *Synlett*, 2012, 314; (p) A. C. Breman, J. M. M. Smits, R. de Gelder, J. H. van Maarseveen, S. Ingemann and H. Hiemstra, *Synlett*, 2012, **23**, 2195; (q) X. Fang, J. Li and C.-J. Wang, *Org. Lett.*, 2013, **15**, 3448; (r) R. A. Unhale, N. K. Rana and V. K. Singh, *Tetrahedron Lett.*, 2013, **54**, 1911; (s) R. Wang, J. Liu and J. Xu, *Adv. Synth. Catal.*, 2014, **357**, 159; (t) J. P. Phelan, E. J. Patel and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2014, **53**, 11329; (u) N. K. Fu, L. Zhang, S. Z. Luo and J. P. Cheng, *Org. Lett.*, 2014, **16**, 4626.
- 16 F. G. Bordwell and D. L. Hughes, *J. Org. Chem.*, 1982, **47**, 3224.
- 17 For comparison, the pK_a of thiophenol in DMSO is 10.3. See ref. 16.
- 18 Bifunctional cinchonine derived bifunctional thiourea catalysts [890044-38-9] were found to be impotent in this transformation. After 7 days under analogous conditions no addition product **4a** was observed by 1H NMR analysis of the crude reaction mixture.
- 19 The reaction with PhSH, **2a** and catalyst **1e** proceeded with 93% yield and 66 : 34 er.
- 20 The PMB thiol can be readily cleaved to afford the free mercaptan, see for example ref. 15g.

