ARCHIVIO ISTITUZIONALE
DELLA RICERCA

Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

Catalytic highly enantioselective transfer hydrogenation of β-trifluoromethyl nitroalkenes. An easy and general entry to optically active β-trifluoromethyl amines

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:
Emilie, M., Anna Chiara, V., Mancinelli, M., Mazzanti, A., Zani, P., Bernardi, L., et al. (2015). Catalytic highly enantioselective transfer hydrogenation of β-trifluoromethyl nitroalkenes. An easy and general entry to optically active β-trifluoromethyl amines. CHEMICAL COMMUNICATIONS, 51, 658-660 [10.1039/C4CC07801B].

Availability:
This version is available at: https://hdl.handle.net/11585/396755 since: 2022-02-25

Published:

DOI: http://doi.org/10.1039/C4CC07801B

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (https://cris.unibo.it/).
When citing, please refer to the published version.

(Article begins on next page)

11 November 2026

This is the final peer-reviewed accepted manuscript of:

Martinelli, E., et al. "Catalytic Highly Enantioselective Transfer Hydrogenation of β-Trifluoromethyl Nitroalkenes. an Easy and General Entry to Optically Active β-Trifluoromethyl Amines." *Chemical Communications*, vol. 51, no. 4, 2015, pp. 658-660.

The final published version is available online at: http://dx.doi.org/10.1039/C4CC07801B

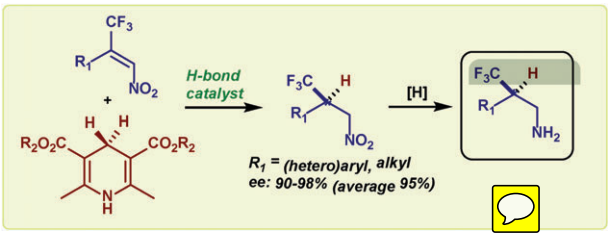
Rights / License:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (https://cris.unibo.it/)

When citing, please refer to the published version.

Chemical Communications c4cc07801b



the scheme is not clear. Please check it.

Catalytic highly enantioselective transfer hydrogenation of β-trifluoromethyl nitroalkenes. An easy and general entry to optically active β-trifluoromethyl amines

Q1 Q2

Emilie Martinelli, Anna Chiara Vicini, Michele Mancinelli, Andrea Mazzanti, Paolo Zani, Luca Bernardi* and Mariafrancesca Fochi*

An easy, general and highly enantioselective entry to optically active β-trifluoromethyl amines *via* organocatalytic transfer hydrogenation of β-trifluoromethyl nitroalkenes is presented.

Please check this proof carefully. **Our staff will not read it in detail after you have returned it.**

Translation errors between word-processor files and typesetting systems can occur so the whole proof needs to be read. Please pay particular attention to: tabulated material; equations; numerical data; figures and graphics; and references. If you have not already indicated the corresponding author(s) please mark their name(s) with an asterisk. Please e-mail a list of corrections or the PDF with electronic notes attached – do not change the text within the PDF file or send a revised manuscript. Corrections at this stage should be minor and not involve extensive changes. All corrections must be sent at the same time.

Please bear in mind that minor layout improvements, e.g. in line breaking, table widths and graphic placement, are routinely applied to the final version.

Please note that, in the typefaces we use, an italic vee looks like this: ν, and a Greek nu looks like this: ν.

We will publish articles on the web as soon as possible after receiving your corrections; **no late corrections will be made.**

Please return your **final** corrections, where possible within **48 hours** of receipt, by e-mail to: chemcomm@rsc.org

Queries for the attention of the authors

Journal: **ChemComm**

Paper: **c4cc07801b**

Title: **Catalytic highly enantioselective transfer hydrogenation of β-trifluoromethyl nitroalkenes. An easy and general entry to optically active β-trifluoromethyl amines**

Editor's queries are marked on your proof like this Q1, Q2, etc. and for your convenience line numbers are indicated like this 5, 10, 15, ...

Please ensure that all queries are answered when returning your proof corrections so that publication of your article is not delayed.

Query reference	Query	Remarks
Q1	For your information: You can cite this article before you receive notification of the page numbers by using the following format: (authors), Chem. Commun., (year), DOI: 10.1039/c4cc07801b.	
Q2	Please carefully check the spelling of all author names. This is important for the correct indexing and future citation of your article. No late corrections can be made.	all author names are correct
Q3	Do you wish to add an e-mail address for the corresponding author?	yes, please: luca.bernardi2@unibo.it, mariafrancesca.fochi@unibo.it
Q4	Ref. 8a–c: Please provide the name of the patentee(s).	the name of the Inventors have been added. See the note at page 3

ChemComm

COMMUNICATION

Catalytic highly enantioselective transfer hydrogenation of β-trifluoromethyl nitroalkenes. An easy and general entry to optically active β-trifluoromethyl amines†

Cite this: DOI: 10.1039/c4cc07801b

Received 2nd October 2014,
Accepted 7th November 2014

DOI: 10.1039/c4cc07801b

www.rsc.org/chemcomm

Emilie Martinelli,‡[a] Anna Chiara Vicini,‡[b] Michele Mancinelli,[b] Andrea Mazzanti,[b] Paolo Zani,[b] Luca Bernardi*[b] and Mariafrancesca Fochi*[b]

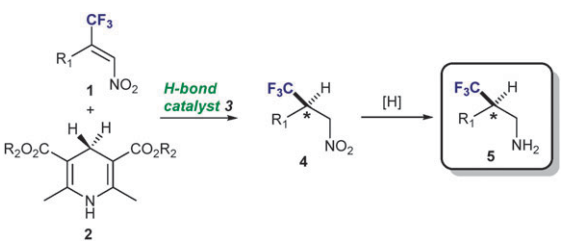
In the presence of a thiourea catalyst, β-CF_3 nitroalkenes react with Hantzsch esters in a highly enantioselective fashion, giving a broad range of β-CF_3 amine precursors with a tertiary stereocentre at the β-position. This reaction represents the first general catalytic enantioselective approach to this important class of β-CF_3 amines.

The importance of fluorine containing compounds can hardly be overestimated. The distinctive features of the fluorine atom, characterised by a very high electronegativity and oxidation potential, along with a small size, strongly affect the properties of fluorinated compounds.[1] The introduction of fluorine in a molecule is in fact one of the workhorses of agro- and medicinal chemistry.[2] Besides increased metabolic stability, fluorinated molecules often show peculiar biological profiles, due to the influence exerted by fluorine on their lipophilicity, acidity and conformations.[3] On the other hand, the unique effects offered by fluorine are also widely exploited in the realm of materials science (polymers, dyes, responsive materials, *etc.*),[4] and in the design and realisation of (organo)catalysts.[5]

In this context, the trifluoromethyl group occupies a prominent position. Accordingly, the development of synthetic methods giving access to trifluoromethylated compounds is an extremely active research area,[6] and several examples of catalytic asymmetric generation of trifluoromethylated chiral centres have been reported.[7] However, only very few entries to enantioenriched β-trifluoromethyl amines, and in particular to amines **5** bearing a tertiary stereocentre at the β-position, have been disclosed so far, despite the importance of these units in the agro- and medicinal chemistry fields.[8] The only catalytic asymmetric approaches to amines **5** are in fact represented by two enamine catalysed α-trifluoromethylations of aldehydes,[9] which followed by reductive amination give *N*-benzyl amines related to **5** with a slight loss of enantioenrichment. Given the problematic involvement of arylacetaldehydes in enamine catalysed processes, these methods do not guarantee access to β-aryl-β trifluoromethyl amines (*i.e.* R_1 = aryl in **5**).

To fill these gaps, we set out to study the H-bond driven[10] transfer hydrogenation reaction of readily available β-trifluoromethyl nitroalkenes **1**[11] with Hantzsch esters **2**[12,13] (Scheme 1). Given the ease of both the obtainment of nitroalkenes **1** from the corresponding α,α,α-trifluoromethylketones[11] and the reduction of the nitro group in the adducts **4**, we considered the overall sequence a straightforward and general approach to β-trifluoromethyl amines **5**. It must be noted that even if β-trifluoromethyl nitroalkenes **1** have already been exploited in catalytic asymmetric settings, their utilisation has been so far directed to the preparation of some specific β-trifluoromethyl amine structures (tryptamine[11a–c] and β-hydroxy[11d] derivatives) bearing α-trifluoromethyl quaternary stereocentres.

We started our studies by testing various typical H-bond donor catalysts (thioureas, ureas, squaramides, diols, phosphoric acids, *etc.*) in the reaction between α,α,α-trifluoroacetophenone derived nitroalkene **1a** and ethyl Hantzsch ester **2a**. Even if most catalysts were able to afford the desired adduct **4a** with good conversion (see ESI†), only the 1,2-diaminocyclohexane derived amido-thiourea **3a** gave a promising enantioselectivity in the reaction (Table 1, entry 1). Taking advantage of the modularity of the catalyst structure, variations in the two thiourea *N*-substituents were undertaken. These experiments showed that enantioselectivity is driven by the amide portion of the



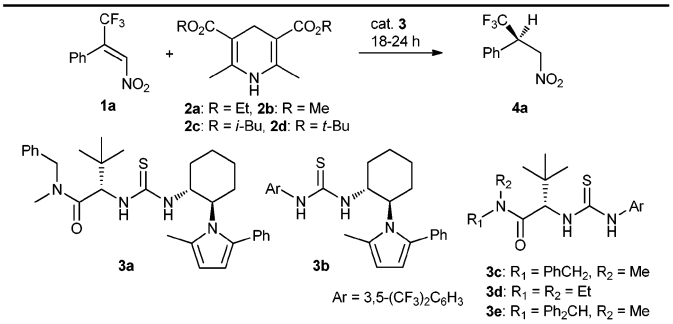
Scheme 1

[a] *Chimie ParisTech – École Nationale Supérieure de Chimie de Paris, 11, rue Pierre et Marie Curie, 75231 Paris Cedex 05, France*
[b] *Department of Industrial Chemistry "Toso Montanari", School of Science, Alma Mater Studiorum – University of Bologna, V. Risorgimento 4, 40136 Bologna, Italy*

† Electronic supplementary information (ESI) available: Further optimisation results, determination of the absolute configuration of compounds **4**, experimental details and copies of NMR spectra and HPLC traces. See DOI: 10.1039/c4cc07801b

‡ These authors contributed equally to this work.

Table 1 Selected optimisation results[a]



Entry	2	3 (mol%)	Solvent (M)	T (°C)	Conv.[b] (%)	ee[c] (%)
1	**2a**	**3a** (10)	Tol (0.125)	40	>95	48
2	**2a**	**3b** (10)	Tol (0.125)	40	85	−15
3	**2a**	**3c** (10)	Tol (0.625)	40	>95	77
4	**2b**	**3c** (10)	Tol (0.625)	40	>95	69
5	**2c**	**3c** (10)	Tol (0.625)	40	>95	70
6	**2d**	**3c** (10)	Tol (0.625)	40	>95	89
7	**2d**	**3c** (10)	CH_2Cl_2 (0.13)	40	61	66
8	**2d**	**3c** (10)	MTBE (0.13)	40	60	39
9	**2d**	**3c** (10)	THF (0.13)	40	60	4
10	**2d**	**3c** (10)	Tol (0.625)	−20	>95	94
11	**2d**	**3d** (10)	Tol (0.625)	−20	>95	77
12	**2d**	**3e** (10)	Tol (0.625)	−20	>95	92
13	**2d**	**3c** (10)	$PhCF_3$ (0.625)	−20	>95	95
14	**2d**	**3c** (5)	$PhCF_3$ (0.625)	−20	>95	92
15	***2d***	***3c (10)***	***$PhCF_3$ (0.30)***	***−20***	***>95***	***97***
16[d]	***2d***	***3c (19)***	***$PhCF_3$ (0.30)***	***−20***	***>95 (94)***	***95***

[a] Conditions: **1a** (0.05 mmol), cat. **3** (× mol%), solvent, **2** (0.06 mmol), 18–24 h. [b] Determined on the crude mixture by ^{19}F NMR analysis. [c] Determined by chiral stationary phase HPLC. [d] On a 4.0 mmol scale, isolated yield in parentheses.

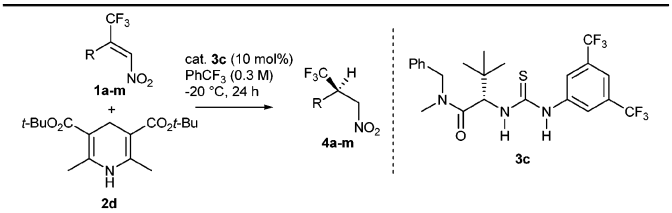
catalyst, as catalyst **3b** afforded the product with lower conversion and very poor and opposite selectivity (entry 2). In contrast, the 1,2-diaminocyclohexane moiety is not a necessary requisite, the simpler amido-thiourea catalyst **3c**[14] giving results even better than **3a** (entry 3 *vs.* 1). Whereas the utility of a 1,2-cyclohexanediamine derived catalyst such as **3a** could have been anticipated from some of the previously reported asymmetric reactions of nitroalkenes with Hantzsch esters,[12a,b] the superior efficiency of the simpler structure **3c** was an unexpected yet very pleasing result. With this catalyst, the methyl, iso-butyl and *tert*-butyl Hantzsch esters **2a–d** were tested (entries 4–6). The *tert*-butyl derivative **2d** clearly outperformed the other dihydropyridines **2a–c**.[15] Then, a short solvent screening confirmed toluene as the most suitable solvent (entries 6–9), wherein a satisfactory 94% ee value was achieved by cooling the reaction mixture to −20 °C (entry 10). At this temperature, catalysts **3d** and **3e**, closely related to **3c** but varying in the amide *N*-substituents, were applied to the reaction. The *N*,*N*-diethyl derivative **3d** performed rather poorly, while the *N*-methyl-*N*-benzhydryl amide **3e** did not give any substantial improvement compared to **3c** (entries 10–12). It was instead discovered at this point that α,α,α-trifluorotoluene as solvent provided slightly better results than toluene, when catalyst **3c** was employed (entry 13 *vs.* 10), even if a lower catalyst loading gave a small decrease in the enantioselectivity of the product **4a** (entry 14). Moving back to 10 mol% loading, slightly better results were obtained by lowering the reaction concentration (entry 15).

These conditions, applicable also on a preparative scale (4 mmol, Table 1, entry 16) although with a small erosion in the enantioselectivity, were taken as optimal to study the scope of the reaction (Table 2). Besides the phenyl derivative **1a**, the reactions with different substrates **1b–h** bearing aromatic rings substituted at different positions with either electron releasing or electron withdrawing groups afforded a series of β-aryl-β-trifluoro amine precursors **4b–h** with excellent results (>70% yield and >93% ee, entries 1–10). A 2-naphthyl substituent and two heteroaromatic substituents in substrates **1i–k** were also well tolerated by the catalytic system, the corresponding adducts **4i–k** being produced with very good yields and enantioselectivities (93–97% ee, entries 11–14). It was also very pleasing to observe that the reaction could be applied successfully to substrates **1l** and **1m** bearing aliphatic chains, which furnished the expected adducts **4l** and **4m** with very good results (entries 15–17). To demonstrate the superiority of α,α,α-trifluorotoluene as reaction medium with respect to toluene, we have performed a few reactions using toluene as the solvent (Table 2, entries 7, 9, 12 and 16): in all the examined cases the results in terms of enantioselectivity were slightly lower.

The absolute configuration of the products **4** was determined on compound **4g** by comparing its VCD and ECD spectra with the computed ones,[16] and by chemical correlation on **4l** (for details, see ESI†).

Reduction of the nitro group in adducts **4a,g,i** proved to be straightforward as expected, furnishing the corresponding amines **5** in good yields, conveniently purified as *N*-tosyl derivatives **6** (Scheme 2). Two different conditions[17] could be successfully applied in the reduction of the nitro group of

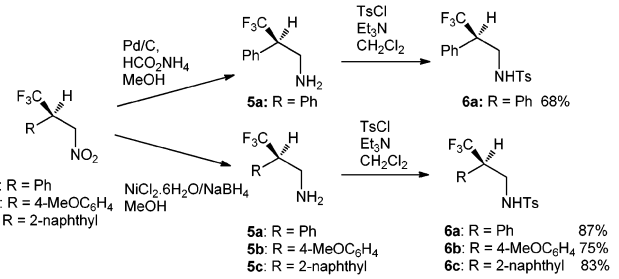
Table 2 Scope of the reaction[a]



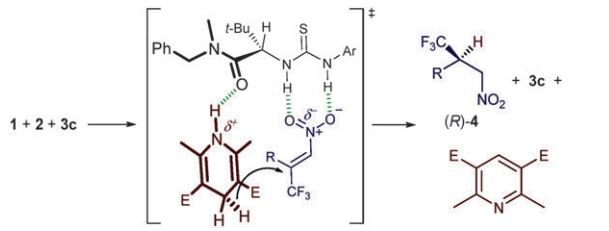
Entry	1	R	Solvent	4	Yield[b] (%)	ee[c] (%)
1	**1a**	C_6H_5	$PhCF_3$	**4a**	70	97
2	**1b**	4-MeC_6H_4	$PhCF_3$	**4b**	80	94
3	**1c**	3-MeC_6H_4	$PhCF_3$	**4c**	80	97
4	**1d**	2-MeC_6H_4	$PhCF_3$	**4d**	75[d]	96
5	**1e**	4-FC_6H_4	$PhCF_3$	**4e**	77	93
6	**1f**	4-BrC_6H_4	$PhCF_3$	**4f**	80	96
7	**1f**	4-BrC_6H_4	Tol	**4f**	86	95
8	**1g**	4-$MeOC_6H_4$	$PhCF_3$	**4g**	70	98
9	**1g**	4-$MeOC_6H_4$	Tol	**4g**	65	94
10	**1h**	4-$CF_3C_6H_4$	$PhCF_3$	**4h**	85	94
11	**1i**	2-Naphthyl	$PhCF_3$	**4i**	82	97
12	**1i**	2-Naphthyl	Tol	**4i**	88	95
13	**1j**	3-Thienyl	$PhCF_3$	**4j**	83	95
14	**1k**	3-(*N*-Tosyl)indolyl	$PhCF_3$	**4k**	78	93
15	**1l**	$PhCH_2$	$PhCF_3$	**4l**	79	90
16	**1l**	$PhCH_2$	Tol	**4l**	77	85
17	**1m**	$CH_3(CH_2)_8$	$PhCF_3$	**4m**	79	91

[a] Conditions: **1** (0.10 mmol), cat. **3c** (0.010 mmol, 10 mol%), **2d** (0.12 mmol), $PhCF_3$ (0.30 M), −20 °C, 24 h. [b] Pure product **4**, isolated by chromatography on silica gel. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed at 0 °C.

This journal is © The Royal Society of Chemistry 2014



Scheme 2



Scheme 3

adduct **4a**, as both the $NiCl_2/NaBH_4$ and the Pd/C–HCO_2NH_4 protocols gave the amine **5a** in good yields.

Building upon the previously determined conformations and mode of action of amido-thiourea catalysts related to **3c**,[14a] it is possible to propose a tentative reaction model, involving the double coordination and resulting stabilisation of a dipolar transition state of the reaction leading to the (*R*)-adducts **4** (Scheme 3). In this speculative model, the thiourea moiety binds and stabilises the negative charge at the nitro group, whereas the amide oxygen coordinates the Hantzsch ester at its NH proton, positively charged during the hydride-transfer step. An irreversible proton transfer then leads to the reaction products ((*R*)-**4** and the pyridine derivative), with concomitant release of the catalyst. Regardless of the structural accuracy of this model, it might serve to visualise that stereoselectivity in this and related reactions of nitroalkenes with Hantzsch esters **2**[12] is not due to steric clashes between the catalyst and substrates, but mainly due to a good geometrical fit between the functionalities of the catalyst and a transition state leading to (*R*)-products, which are electrostatically complementary. Therefore, such a model in which the catalyst interacts simply with the nitro and the NH functionalities explains both the tolerance of the reactions to substrates featuring different steric properties (aromatic and aliphatic substrates) and the observation previously reported that the major enantiomer obtained in these transfer hydrogenation reactions depends on nitroalkene geometry[12b] and not on the steric hindrance displayed by the substituents at the prochiral centre (*i.e.* (*E*)-nitroalkenes give (*R*)-products and (*Z*)-nitroalkenes (*S*)-products).

In conclusion, we have developed a catalytic asymmetric approach to β-trifluoromethyl amines **5** featuring unprecedented directness and generality, by demonstrating that a simple thiourea catalyst can promote the reaction between β-trifluoromethyl nitroalkenes **1** and Hantzsch ester **2** in a highly enantioselective fashion.

We acknowledge financial support from the University of Bologna (RFO program).

Notes and references

1 D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308.
2 (*a*) P. Jeschke, *ChemBioChem*, 2004, **5**, 570; (*b*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881.
3 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320.
4 P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley, Weinheim, 2004, ch. 4, pp. 203–277.
5 (*a*) L. E. Zimmer, C. Sparr and R. Gilmour, *Angew. Chem., Int. Ed.*, 2011, **50**, 11860; (*b*) K. M. Lippert, K. Hof, D. Gerbig, D. Ley, H. Hausmann, S. Guenther and P. R. Schreiner, *Eur. J. Org. Chem.*, 2012, 5919, and references therein.
6 (*a*) T. Furuya, A. S. Kamler and T. Ritter, *Nature*, 2011, **473**, 470; (*b*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (*c*) J.-A. Ma and D. Cahard, *J. Fluorine Chem.*, 2007, **128**, 975.
7 Selected reviews: (*a*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (*b*) N. Shibata, S. Mizuta and H. Kawai, *Tetrahedron: Asymmetry*, 2008, **19**, 2633; (*c*) J. Nie, H.-C. Guo, D. Cahard and J.-A. Ma, *Chem. Rev.*, 2011, **111**, 455.
8 β-Trifluoromethyl amines **5** are often subunits of more complex structures used in biological studies. See for examples: (*a*) PCT WO 106462, 2003; (*b*) PCT WO 076412, 2004; (*c*) PCT WO 126283, 2013; (*d*) N. Meurice, L. Wang, C. A. Lipinski, Z. Yang, C. Hulme and J. C. Loftus, *J. Med. Chem.*, 2010, **53**, 669.
9 (*a*) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875; (*b*) A. A. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 4986; catalytic asymmetric synthesis of CF_3-aziridines: (*c*) Z. Chai, J.-P. Bouillon and D. Cahard, *Chem. Commun.*, 2012, **48**, 9471.
10 Selected reviews: (*a*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; (*b*) Z. Zhang and P. R. Schreiner, *Chem. Soc. Rev.*, 2009, **38**, 1187; (*c*) R. R. Knowles and E. N. Jacobsen, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 20678.
11 (*a*) J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han and Y.-X. Jia, *J. Am. Chem. Soc.*, 2013, **135**, 2983; (*b*) H. Wu, R.-R. Liu and Y.-X. Jia, *Synlett*, 2014, 457; (*c*) C.-H. Ma, T.-R. Kang, L. He and Q.-Z. Liu, *Eur. J. Org. Chem.*, 2014, 3981; (*d*) F.-L. Liu, J.-R. Chen, B. Feng, X.-Q. Hu, L.-H. Ye, L.-Q. Lu and W.-J. Xiao, *Org. Biomol. Chem.*, 2014, **12**, 1057.
12 Catalytic asymmetric transfer hydrogenation of nitroalkenes with Hantzsch esters: (*a*) N. J. A. Martin, L. Ozores and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 8976; (*b*) N. J. A. Martin, X. Cheng and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 13862; (*c*) J. F. Schneider, M. B. Lauber, V. Muhr, D. Kratzer and J. Paradies, *Org. Biomol. Chem.*, 2011, **9**, 4323; (*d*) J. C. Anderson and P. J. Koovits, *Chem. Sci.*, 2013, **4**, 2897; (*e*) J. F. Schneider, F. C. Falk, R. Fröhlich and J. Paradies, *Eur. J. Org. Chem.*, 2010, 2265; (*f*) L.-A. Chen, W. Xu, B. Huang, J. Ma, L. Wang, J. Xi, K. Harms, L. Gong and E. Meggers, *J. Am. Chem. Soc.*, 2013, **135**, 10598; non enantioselective reaction: (*g*) Z. Zhang and P. R. Schreiner, *Synthesis*, 2007, 2559.
13 Selected reviews on organocatalytic transfer hydrogenation reactions with Hantzsch esters: (*a*) M. Rueping, J. Dufour and F. R. Schoepke, *Green Chem.*, 2011, **13**, 1084; (*b*) S. G. Ouellet, A. M. Walij and D. W. C. MacMillan, *Acc. Chem. Res.*, 2007, **40**, 1327; (*c*) C. Zheng and S.-L. You, *Chem. Soc. Rev.*, 2012, **41**, 2498; (*d*) L. Bernardi, M. Fochi, M. Comes Franchini and A. Ricci, *Org. Biomol. Chem.*, 2012, **10**, 2911.
14 (*a*) S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2009, **131**, 15358; (*b*) S. J. Zuend, M. P. Coughlin, M. P. Lalonde and E. N. Jacobsen, *Nature*, 2009, **461**, 968.
15 For a tentative rationalisation of the superior behaviour of *tert*-butyl Hantzsch ester **2d** in organocatalytic asymmetric reactions, see ref. 13*b*. It must also be noted that *tert*-butyl ester **2d** features improved solubility in apolar solvents, compared to **2a–c**.
16 A. Mazzanti and D. Casarini, *Wiley Interdiscip. Rev.: Comput. Mol. Sci.*, 2012, **2**, 613.
17 G. W. Kabalka and R. S. Varma, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon, Oxford, 1991, ch. 2.1, vol. 8, pp. 363–379.