Advanced Synthesis & Catalysis

DOI: 10.1002/adsc.201600061

Organocatalytic Enantioselective Transfer Hydrogenation of β-Amino Nitroolefins

Antonino Ferraro,[a] Luca Bernardi,[a] and Mariafrancesca Fochi[a,*]

[a] Department of Industrial Chemistry "Toso Montanari", University of Bologna, V. Risorgimento 4, 40136 Bologna, Italy
E-mail: mariafrancesca.fochi@unibo.it

Received: January 15, 2016; Revised: February 12, 2016; Published online: April 19, 2016

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600061.

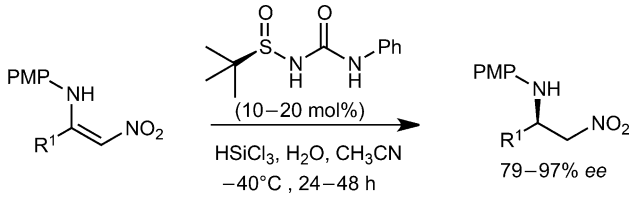
Abstract: The asymmetric organocatalytic transfer hydrogenation of β-acylamino and β-*tert*-butyloxycarbonylamino nitroolefins has been successfully realised in excellent enantioselectivities and yields (up to >99% *ee*, 97% yield) with a simple thiourea catalyst and a Hantzsch ester as hydrogen source, giving a direct access to enantiomerically pure β-amino nitroalkanes.

Keywords: alkenes; asymmetric synthesis; hydrogen bonds; organocatalysis; reduction

Enantiomerically pure β-amino nitroalkanes are versatile intermediates in organic synthesis, owing to their easy conversion into a variety of useful compounds[1] such as α-amino acids,[2] 1,2-diamines,[3] monoamines,[4] α-amino carbonyls and to various moieties present in biologically active molecules[5] and pharmaceuticals such as clopidogrel,[6] oseltamivir,[7] and asimadoline.[8]

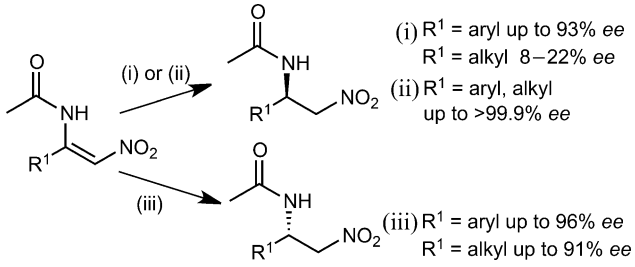
Traditionally, the preparation of chiral β-amino nitroalkanes mainly counts on asymmetric aza-Henry (nitro-Mannich) reactions,[9] in which chiral metal complexes and organocatalysts were utilised to afford moderate to high enantio-/diastereoselectivities. Suitable alternative approaches are represented by the asymmetric aza-Michael addition of amines to nitroalkenes,[10] and by the addition of aldehydes to β-amino nitroalkenes proceeding *via* enamine catalysis.[11]

The asymmetric catalytic reduction of β-amino nitroolefins constitutes a complementary straightforward pathway to form chiral β-amino nitroalkanes, owing to the easy availability of starting materials. In this context, in 2012 the asymmetric hydrosilylation of β-*p*-methoxyphenylamino nitroolefins using 10 to 20 mol% of a simple *N*-sulfinylurea as a bifunctional catalyst was reported (Scheme 1).[12] β-Amino nitroalkanes with good to high enantioselectivities (79–97% *ee*) were obtained.



Scheme 1. Asymmetric hydrosilylation of β-*p*-methoxyphenylamino nitroolefins

More recently, enantioselective metal-catalysed asymmetric hydrogenations[13] of β-acylamino nitroolefins have been developed. In 2013, Wang and Zhang used a Rh-Tangphos complex achieving high enantioselectivities for β-aryl β-amino nitroalkenes (up to 93% *ee*) but rather poor enantioselectivities for alkyl substrates (only 8–22% *ee*) [Scheme 2, (i)].[14] Afterward, a highly efficient enantioselective hydrogenation of β-acylamino nitroolefins has been successfully accomplished employing an Ir-spiroPhos complex and 20 atm H_2 as reported by Hou[15] [Scheme 2, (ii)] and by a rhodium/bifunctional bisphosphine-thiourea li-



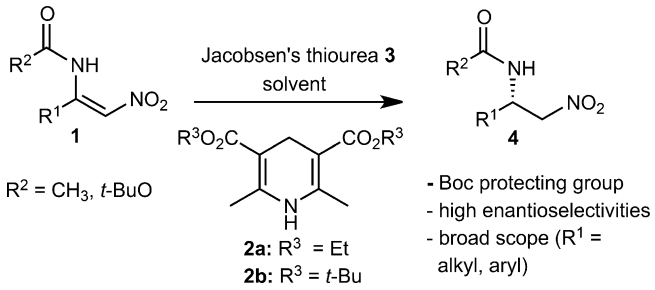
Scheme 2. Asymmetric hydrogenation of β-acylamino nitroalkenes: (i) $[Rh(COD)TangPhos]BF_4$ (1 mol%), H_2 (5 atm), TFE, room temperature, 20 h. (ii) $[Ir(COD)Cl]_2$/(*R*,*R*)-f-spiroPhos (0.5 mol%), H_2 (20 atm), CH_2Cl_2, 80 °C, 12 h. (iii) $(Rh(NBD)_2BF_4$/ligand/substrate ratio 1:1.1:100, CH_2Cl_2, H_2 (50 atm)/room temperature, 24 h.

gands complex employing 50 atm H_2 as very recently reported by Hu, Dong and Zhang [Scheme 2, (iii)].[16]

While direct hydrogenation uses a pressure of H_2 gas, transfer hydrogenation refers to the addition of hydrogen to a molecule from a non-H_2 hydrogen source. This synthetic technique is an attractive alternative to direct hydrogenation, since it does not require pressurised H_2 gas nor elaborate experimental set-ups.

Recently, many organocatalysts were extensively used in asymmetric transfer hydrogenation processes, especially using Hantzsch esters as readily available and easy to handle hydrogen donors.[17] Chiral phosphoric acids[18] are the most used organocatalysts for this type of reaction, even if the NH-containing organocatalysts have recently emerged in the asymmetric catalytic transfer hydrogenation of nitroolefins (C=C bond),[19] α,β-unsaturated aldehydes,[20] and conjugated olefins of steroids.[21]

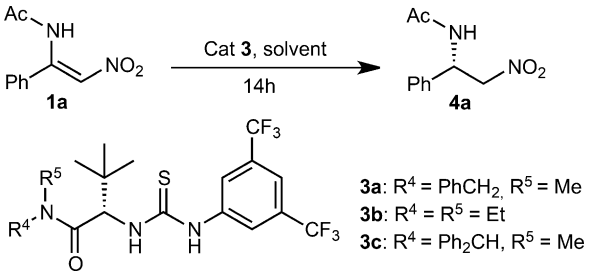
Following our recent study in this field,[19c] herein we report on the catalytic asymmetric transfer hydrogenation reaction of readily accessible β-amino nitroolefins **1** with Hantzsch esters **2**, using a simple and commercially available Jacobsen thiourea catalyst **3** (Scheme 3). Compared to previous work (Scheme 1 and Scheme 2), this protocol furnishes with a metal-free procedure not only β-amino nitroalkanes bearing an acyl moiety at the amine, but also the corresponding compounds with a synthetically more useful Boc[22] protecting group. Furthermore, the products **4** bearing both β-aryl and β-alkyl substituents are obtained with very high enantioselectivities in all cases.



Scheme 3. Catalytic asymmetric transfer hydrogenation of β-amino nitroolefins **1** with Hantzsch esters **2**.

We started our studies by testing the transfer hydrogenation reaction between (*Z*)-*N*-(2-nitro-1-phenylvinyl)acetamide **1a**[23] with ethyl Hantzsch ester **2a** as hydrogen donor in *p*-xylene at 60 °C. Screening of a few different thiourea catalysts immediately pointed to the Jacobsen derivative **3a**[24] since the desired β-amino nitroalkanes **4a** was obtained in quantitative conversion and 94% *ee* (Table 1, entry 1). Moving to the *tert*-butyl Hantzsch ester **2b** the *ee* increased to 98% (entry 2).[25] Then, a short solvent screening (entries 4–6) indicated toluene (0.3 M) as the most suitable solvent. A lower catalyst loading (compare entries 4, 7 and 8) gave a slight decrease in the enantioselectivity of the product **4a**. We observed that when the reaction temperature was decreased from 60 to 40 °C, the conversion remained excellent while enantioselectivity reached perfect values (compare entries 4 and 9). A further lowering to 20 °C gave a small decrease in the conversion of **1a** (compare entries 9 and 10).

Table 1. Selected optimisation results.[a]



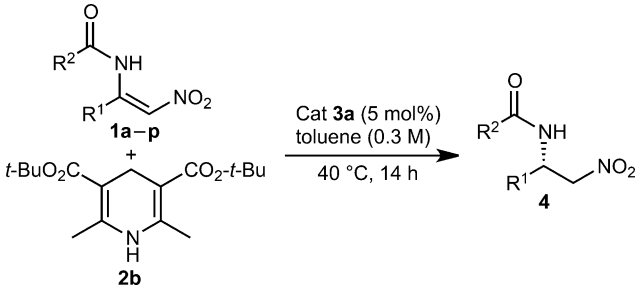
Entry	2	Solvent (M)	*T* [°C]	3 (mol%)	Conv. [%][b]	*ee* [%][c]
1	**a**	*p*-xylene (0.1)	60	**3a** (10)	99	94
2	**b**	*p*-xylene (0.1)	60	**3a** (10)	85	98
3	**b**	*p*-xylene (0.3)	60	**3a** (5)	>99	97
4	**b**	toluene (0.3)	60	**3a** (5)	>99	98
5	**b**	$PhCF_3$ (0.3)	60	**3a** (5)	>99	96
6	**b**	DCM (0.3)	40[d]	**3a** (5)	97	96
7	**b**	toluene (0.3)	60	**3a** (2.5)	96	90
8	**b**	toluene (0.3)	60	**3a** (1)	94	90
9	**b**	toluene (0.3)	40	**3a** (5)	>99	>99
10	**b**	toluene (0.3)	20	**3a** (5)	97	>99
11	**b**	toluene (0.3)	40	**3b** (5)	99	94
12	**b**	toluene (0.3)	40	**3c** (5)	99	96

[a] *Reaction conditions:* **1a** (0.05 mmol), cat. **3** (x mol%), solvent, **2** (0.06 mmol), 14 h.
[b] Determined on the crude mixture by ^{1}H NMR analysis.
[c] Determined by chiral stationary phase HPLC.
[d] Reaction performed at 20 °C: conv. 97%, *ee* = 97%

Using these conditions, catalysts **3b** and **3c**, closely related to **3a** but varying in the amide *N*-substituents,[24] were applied to the reaction. Both the *N*,*N*-diethyl derivative **3b** and the *N*-methyl-*N*-benzhydryl amide **3c** did not give any improvement compared to **3a** (compare entries 9, 11 and 12).

These conditions were taken as optimal to study the scope of the reaction (Table 2). Similar to derivative **1a**, the reactions with different substrates **1b–e** bearing aromatic rings substituted with either electron-donating or electron-withdrawing groups and a 2-naphthyl substituent afforded a series of β-acylamino nitroalkanes **4b–e** with excellent results (90–94% yield and 97 to >99% *ee*, entries 2–5). Notably, under the optimised reaction conditions *tert*-butyl (*Z*)-(2-nitro-1-phenylvinyl)carbamate **1f** led to the corresponding β-amino nitroalkane **4f** bearing the

Table 2. Scope of the reaction.[a]



Entry	1	R^1	R^2	4	Yield[b] [%]	*ee*[c] [%]
1	**a**	Ph	CH_3	**a**	97	>99
2	**b**	4-$MeOC_6H_4$	CH_3	**b**	91	>99
3	**c**	4-ClC_6H_4	CH_3	**c**	90	97
4	**d**	4-FC_6H_4	CH_3	**d**	94	97
5	**e**	2-naphthyl	CH_3	**e**	91	99
6	**f**	Ph	*t*-BuO	**f**	90	>99
7[d]	**f**	Ph	*t*-BuO	**f**	86	>99
8[e]	**g**	*n*-Pent	*t*-BuO	**g**	91	98
9[e]	**h**	*i*-Bu	*t*-BuO	**h**	60	96
10[e]	**i**	*c*-Hex	*t*-BuO	**i**	88	98
11[e]	**j**	*i*-Pr	*t*-BuO	**j**	91	93
12[e]	**k**	Et	*t*-BuO	**k**	92	97
13	**l**	2-furyl	*t*-BuO	**l**	71	>99
14	**m**	4-$CF_3C_6H_4$	*t*-BuO	**m**	86	>99
15[f]	**n**	4-$NO_2C_6H_4$	*t*-BuO	**n**	93	96
16	**o**	4-MeC_6H_4	*t*-BuO	**o**	86	97
17	**p**	3-MeC_6H_4	*t*-BuO	**p**	75	>99
18	**q**	2-MeC_6H_4	*t*-BuO	**q**	40	98

[a] *Reaction conditions:* **1** (0.15 mmol), cat. **3a** (0.075 mmol, 5 mol%), **2b** (0.18 mmol), 40 °C, 14 h.
[b] Pure product **4**, isolated by chromatography on silica gel.
[c] Determined by chiral stationary phase HPLC.
[d] On a 2.0 mmol scale.
[e] Reaction performed at 60 °C.
[f] Reaction performed at 20 °C.

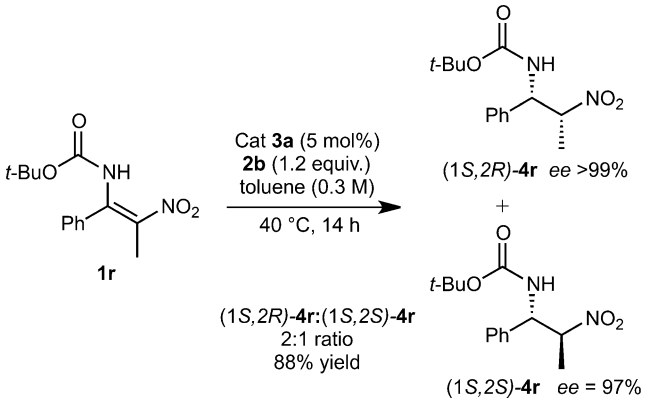
Boc protecting group in 90% yield, and with complete enantioselectivity (entry 6). The transfer hydrogenation of **1f** could also be performed on a larger scale (2 mmol, Table 1, entry 7) although with a small erosion in the yield (compare entries 6 and 7). It was also very pleasing to observe that the reaction could be applied successfully to substrates **1g–k** bearing aliphatic chain groups, which furnished the expected *N*-Boc protected products **4g–k** with excellent results (entries 8–12).

A heteroaromatic substituent in substrate **1l** was also well tolerated by the catalytic system, as well as substrates **1m–o** bearing aromatic rings substituted with either electron-donating or electron-withdrawing groups, the corresponding *N*-Boc adducts **4l–o** being produced with very good yields and enantioselectivities (96 to >99% *ee*, entries 13–16).

To evaluate the influence of the substitution pattern on the benzene ring, Boc-protected β-amino nitroalkanes **1o–q** with a methyl group placed in each position on the aromatic ring, were tested. Derivatives **4o–q** could be obtained in 86–40% yields and with very good enantioselectivities (entries 16–18). Yields followed the order *para* > *meta* > *ortho*, indicating a (not dramatic) sensitivity of the reaction to steric factors. Enantioselectivities remained always very high.

The absolute configuration of products **4** was determined to be *S* by comparison with literature data (CSP-HPLC retention time and optical rotation $[\alpha]_D$ value) for compounds **4a**,[15] **4f**,[26,10c] **4i**,[26,10c] **4h**,[26] **4k**[27] and **4q**[28] (for details, see the Supporting Information).

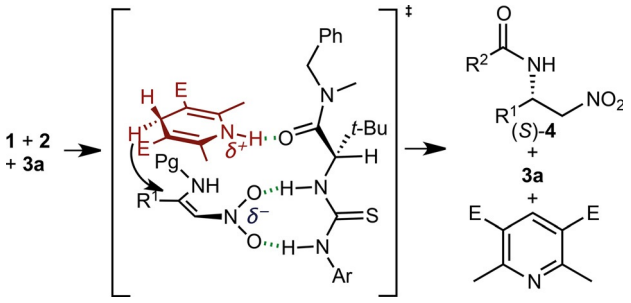
tert-Butyl (*Z*)-(2-nitro-1-phenylprop-1-en-1-yl)carbamate **1r** was subjected to the optimised reaction conditions affording a mixture of two nearly enantiopure diasteroisomers (1*S*,2*R*)-**4r** and (1*S*,2*S*)-**4r** in a 2:1 ratio in 88% yield (Scheme 4).[29]



Scheme 4.

Extensive mechanistic studies of the role of chiral thiourea catalysts related to **3a**, using kinetic, spectroscopic and computational work, have previously been performed, establishing its more stable conformations and mode of action.[24a] Building upon these studies and in line with our previous hypothesis[19c] and related calculation results,[19d] a tentative reaction model for the transfer hydrogenation reaction of β-amino nitroalkenes can be reasonably put forward (Scheme 5). This model implies the stabilisation of the transition state of the reaction by coordination of the nitro group of nitroalkenes by the thiourea moiety, while the amide oxygen coordinates the Hantzsch ester at its NH proton, positively charged during the hydride-transfer step. A subsequent irreversible proton transfer step leads to the (*S*)-adducts **4** and the pyridine derivative with concomitant catalyst release.

The very high enantioselectivities obtained with the catalyst **3a** with both the previously reported[19c] β-trifluoromethyl and the present β-amino nitroolefins remarks the reliability of this model and the good geo-



Scheme 5. Tentative reaction model.

metrical fit between the electrostatically complementary functionalities of the catalyst and a transition state leading to (*S*)-products. Moreover, the results reported in Scheme 4 suggest that while the stereochemistry of the conjugate addition of the hydride is controlled very efficiently by the catalyst, there is little, if any, stereocontrol over the ensuing proton-transfer step(s) to the prochiral carbon of the nitronate.[30] The two diastereomers at the stereogenic centre α to the nitro group are in fact generated in nearly equimolar amounts.[31]

In summary, we have developed a highly enantioselective organocatalytic transfer hydrogenation of β-acylamino and β-*tert*-butyloxycarbonylamino nitroolefins **1** with a simple thiourea catalyst and Hantzsch esters **2** as hydrogen source for the direct access to enantiomerically pure β-amino nitroalkanes.

Experimental Section

General Procedure for the Asymmetric Transfer Hydrogenation

In a screw-cap, round-bottom vial, catalyst **3a** (3.9 mg, 0.0075 mmol, 0.05 equiv.) and Hantzsch ester **2b** (56 mg, 0.18 mmol, 1.2 equiv.) were added to a stirred solution of **1** (0.15 mmol) in toluene (510 μL, 0.3 M). The vial was saturated with nitrogen and closed with the cap. The reaction mixture was stirred for 14 h at 40 °C (Pg = Ac) or for 18 h at 40 °C (Pg = Boc, R^1 = aromatic) or for 24 h at 60 °C (Pg = Boc, R^1 = aliphatic). The resulting mixture was purified by column chromatography to afford product **4**.

Acknowledgements

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

References

[1] N. Ono, *The Nitro Group in Organic Synthesis*, John Wiley & Sons, New York, **2001**.
[2] a) E. Forestim, G. Palmieri, M. Petrini, R. Profeta, *Org. Biomol. Chem.* **2003**, *1*, 4275–4281; b) R. Ballini, M. Petrini, *Tetrahedron* **2004**, *60*, 1017–1047.
[3] a) D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724–2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627; b) J. Wu, D. Wang, F. Wu, B. Wan, *J. Org. Chem.* **2013**, *78*, 5611–5617; c) C. A. Sandoval, T. Ohkuma, K. Muniz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490–13503; d) H. Ooka, N. Arai, K. Azuma, N. Kurono, T. Ohkuma, *J. Org. Chem.* **2008**, *73*, 9084–9093.
[4] B. Shen, J. N. Johnston, *Org. Lett.* **2008**, *10*, 4397–4400.
[5] a) F. A. Davis, Y. Zhang, D. Li, *Tetrahedron Lett.* **2007**, *48*, 7838–7840; b) M. E. Flanagan, T. A. Blumenkopf, W. H. Brissette, M. F. Brown, J. M. Casavant, C. Shang-Poa, J. L. Doty, E. A. Elliott, M. B. Fisher, M. Hines, C. Kent, E. M. Kudlacz, B. M. Lillie, K. S. Magnuson, S. P. McCurdy, M. J. Munchhof, B. D. Perry, P. S. Sawyer, T. J. Strelevitz, C. Subramanyam, J. Sun, D. A. Whipple, P. S. Changelian, *J. Med. Chem.* **2010**, *53*, 8468–8484.
[6] G. Deray, C. Bagnis, R. Brouard, J. Necciari, A. F. Leenhardt, F. Raymond, A. Baumelou, *Clin. Drug Investig.* **1998**, *16*, 319–328.
[7] J.-J. Shie, J.-M. Fang, S.-Y. Wang, K.-C. Tsai, Y.-S. E. Cheng, A.-S. Yang, S.-C. Hsiao, C.-Y. Su, C.-H. Wong, *J. Am. Chem. Soc.* **2007**, *129*, 11892–11893.
[8] W. Binder, J. S. Walker, *Br. J. Pharmacol.* **1998**, *124*, 647–654.
[9] a) B. Westermann, *Angew. Chem.* **2003**, *115*, 161–163; *Angew. Chem. Int. Ed.* **2003**, *42*, 151–153; b) E. Marques-Lopez, P. Merino, T. Tejero, R. P. Herrera, *Eur. J. Org. Chem.* **2009**, 2401–2420; c) A. Noble, J. C. Anderson, *Chem. Rev.* **2013**, *113*, 2887–2939; d) H. Pellissier, *Recent Developments in Asymmetric Organocatalysis*, RSC Catalysis Series, **2010**, Chapter 3, pp 123–149; e) A. M. F. Phillips, *Recent Advances on the Organocatalytic Asymmetric Aza-Henry Reaction*, in: *Current Organocatalysis*, **2016**, Vol. 3, (Ed: B. K. Banik), DOI: 10.2174/2213337202666150908210627.
[10] a) L. Wang, S. Shirakawa, K. Maruoka, *Angew. Chem.* **2011**, *123*, 5439–5442; *Angew. Chem. Int. Ed.* **2011**, *50*, 5327–5330; b) D. Uraguchi, D. Nakashima, T. Ooi, *J. Am. Chem. Soc.* **2009**, *131*, 7242–7243; c) L. Lykke, D. Monge, M. Nielsen, K. A. Jorgensen, *Chem. Eur. J.* **2010**, *16*, 13330–13334; d) J. Wang, H. Li, L. Zu, W. Wang, *Org. Lett.* **2006**, *8*, 1391–1394.
[11] T. Mukaiyama, H. Ishikawa, H. Koshino, Y. Hayashi, *Chem. Eur. J.* **2013**, *19*, 17789–17800.
[12] X.-W. Liu, Y. Yan, Y.-Q. Wang, C. Wang, J. Sun, *Chem. Eur. J.* **2012**, *18*, 9204–9207.
[13] For the hydrogenation of nitroalkenes see: a) S. Li, K. Huang, B. Cao, J. Zhang, W. Wu, X. Zhang, *Angew. Chem.* **2012**, *124*, 8701–8704; *Angew. Chem. Int. Ed.* **2012**, *51*, 8573–8576; b) Q. Zhao, S. Li, K. Huang, R. Wang, X. Zhang, *Org. Lett.* **2013**, *15*, 4014–4017; c) S. Li, K. Huang, J. Zhang, W. Wu, X. Zhang, *Chem. Eur. J.* **2013**, *19*, 10840–10844. For transfer hydrogenation and conjugate addition, see: d) C. Czekelius, E. M. Carreira, *Angew. Chem.* **2003**, *115*, 4941–4943; *Angew. Chem. Int. Ed.* **2003**, *42*, 4793–4795; e) C. Czekelius, E. M. Carreira, *Org. Lett.* **2004**, *6*, 4575–4577; f) C. Czekelius, E. M. Carreira, *Org. Process Res. Dev.* **2007**, *11*,

633–636; g) O. Soltani, M. A. Ariger, E. M. Carreira, *Org. Lett.* **2009**, *11*, 4196–4198.
[14] M. Zhou, D. Dong, B. Zhu, H. Geng, Y. Wang, X. Zhang, *Org. Lett.* **2013**, *15*, 5524–5527.
[15] Q. Yan, M. Liu, D. Kong, G. Zi, G. Hou, *Chem. Commun.* **2014**, *50*, 12870–12872.
[16] P. Li, M. Zhou, Q. Zhao, W. Wu, X. Hu, X.-Q. Dong, X. Zhang, *Org. Lett.* **2016**, *18*, 40–43.
[17] a) D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621–6686; b) S. G. Ouellet, A. M. Walji, D. W. C. MacMillan, *Acc. Chem. Res.* **2007**, *40*, 1327–1339; c) S. L. You, *Chem. Asian J.* **2007**, *2*, 820–827; d) S. J. Connon, *Org. Biomol. Chem.* **2007**, *5*, 3407–3417; e) S. Rossi, M. Benaglia, E. Massolo, L. Raimondi, *Catal. Sci. Technol.* **2014**, *4*, 2708–2723; f) L. Bernardi, M. Fochi, M. Comes Franchini, A. Ricci, *Org. Biomol. Chem.* **2012**, *10*, 2911–2922; g) C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498–2518.
[18] D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047–9153.
[19] a) N. J. A. Martin, X. Cheng, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 13862–13863; b) N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 8976–8977; c) E. Martinelli, A. C. Vicini, M. Mancinelli, A. Mazzanti, P. Zani, L. Bernardi, M. Fochi, *Chem. Commun.* **2015**, *51*, 658–660; d) E. Massolo, M. Benaglia, M. Orlandi, S. Rossi, G. Celentano, *Chem. Eur. J.* **2015**, *21*, 3589–3595; e) J. F. Schneider, F. C. Falk, R. Fröhlich, J. Paradies, *Eur. J. Org. Chem.* **2010**, 2265–2269; f) J. F. Schneider, M. B. Lauber, V. Muhr, D. Kratzer, J. Paradies, *Org. Biomol. Chem.* **2011**, *9*, 4323–4327; g) J. C. Anderson, P. J. Koovits, *Chem. Sci.* **2013**, *4*, 2897–2901; h) L.-A. Chen, W. Xu, B. Huang, J. Ma, L. Wang, J. Xi, K. Harms, L. Gong, E. Meggers, *J. Am. Chem. Soc.* **2013**, *135*, 10598–10601.
[20] C. Ebner, A. Pfaltz, *Tetrahedron* **2011**, *67*, 10287–10290.
[21] D. B. Ramachary, R. Sakthidevi, P. S. Reddy, *RSC Adv.* **2013**, *3*, 13497–13506.
[22] a) A. Isidro-Llobet, M. Álvarez, F. Albericio, *Chem. Rev.* **2009**, *109*, 2455–2504; b) G. Theodoridis, *Tetrahedron* **2000**, *56*, 2339–2358.
[23] β-Acylamino nitroolefins were obtained by amination of β-nitroolefins followed by protection of the obtained β-nitroenamines following literature procedures, see: S. Seko, I. Komoto, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2975–2976 and ref.[14]
[24] a) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358–15374; b) S. J. Zuend, M. P. Coughlin, M. P. Lalonde, E. N. Jacobsen, *Nature* **2009**, *461*, 968–970.
[25] For a tentative rationalisation of the superior behaviour of *tert*-butyl Hantzsch ester **2b** in organocatalytic asymmetric reactions, see ref.[17b] It must also be noted that *tert*-butyl ester **2b** features improved solubility in apolar solvents, compared to **2a**.
[26] C. Palomo, M. Oiarbide, A. Laso, R. López, *J. Am. Chem. Soc.* **2005**, *127*, 17622–17623.
[27] F. Fini, V. Sgarzani, D. Pettersen, R. P. Herrera, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, *117*, 8189–8192; *Angew. Chem. Int. Ed.* **2005**, *44*, 7975–7978.
[28] C. Palomo, M. Oiarbide, R. Halder, A. Laso, R. López, *Angew. Chem.* **2006**, *118*, 123–126; *Angew. Chem. Int. Ed.* **2006**, *45*, 117–120.
[29] For enantioselective hydrogenation of α,β-disubstituted nitroalkenes see: S. Li, K. Huangb, X. Zhang, *Chem. Commun.* **2014**, *50*, 8878–8881.
[30] For our recent study on nitro-nitronate tautomerisation processes in organocatalytic reactions, see: S. Romanini, E. Galletti, L. Caruana, A. Mazzanti, F. Himo, S. Santoro, M. Fochi, L. Bernardi, *Chem. Eur. J.* **2015**, *21*, 17578.
[31] As suggested by one of the referees (*E*)-(2-nitroprop-1-en-1-yl)benzene was reacted under the optimised reaction conditions obtaining the corresponding (2-nitropropyl)benzene in a racemic form confirming that there is no stereocontrol over the proton transfer step(s) to the prochiral carbon of the nitronate. The two enantiomers at the stereogenic centre α-to the nitro group of (2-nitropropyl)benzene are in fact generated in equimolar amounts.

