A General Catalytic Enantioselective Transfer Hydrogenation Reaction of $\beta,\beta$-Disubstituted Nitroalkenes Promoted by a Simple Organocatalyst

Luca Bernardi and Mariafrancesca Fochi

Article

A General Catalytic Enantioselective Transfer Hydrogenation Reaction of $\beta,\beta$-Disubstituted Nitroalkenes Promoted by a Simple Organocatalyst

Luca Bernardi and Mariafrancesca Fochi

Department of Industrial Chemistry “Toso Montanari” and INSTM RU Bologna, Alma Mater Studiorum, University of Bologna, V. Risorgimento 4, 40136 Bologna, Italy; luca.bernardi2@unibo.it (L.B.); mariafrancesca.fochi@unibo.it (M.F.); Tel.: +39-051-209-3653 (L.B.); +39-051-209-3626 (M.F.)

Academic Editors: Alessandro Palmieri and Derek J. McPhee

Received: 28 June 2016; Accepted: 28 July 2016; Published: 30 July 2016

Abstract: Given its synthetic relevance, the catalytic enantioselective reduction of $\beta,\beta$-disubstituted nitroalkenes has received a great deal of attention. Several bio-, metal-, and organo-catalytic methods have been developed, which however are usually applicable to single classes of nitroalkene substrates. In this paper, we present an account of our previous work on this transformation, which implemented with new disclosures and mechanistic insights results in a very general protocol for nitroalkene reductions. The proposed methodology is characterized by (i) a remarkably broad scope encompassing various nitroalkene classes; (ii) Hantzsch esters as convenient (on a preparative scale) hydrogen surrogates; (iii) a simple and commercially available thiourea as catalyst; (iv) user-friendly procedures. Overall, the proposed protocol gives a practical dimension to the catalytic enantioselective reduction of $\beta,\beta$-disubstituted nitroalkenes, offering a useful and general platform for the preparation of nitroalkanes bearing a stereogenic center at the $\beta$-position in a highly enantioenriched form. A transition state model derived from control kinetic experiments combined with literature data is proposed and discussed. This model accounts and justifies the observed experimental results.

Keywords: asymmetric catalysis; Hantzsch ester; H-bond; nitroalkanes; nitroalkenes; organocatalysis; reduction; thiourea; transfer hydrogenation

1. Introduction

The enantioselective reduction of pro-chiral $\beta,\beta$-disubstituted nitroalkenes is a powerful synthetic transformation. It provides a straightforward access to optically active nitroalkanes carrying a configurationally stable stereogenic center at the $\beta$-position of the nitro group. These compounds can be easily converted to broadly useful chiral building blocks (e.g., enantioenriched $\beta$-chiral amines) exploiting the renowned synthetic versatility of the nitro moiety [1–3]. Accordingly, this reaction has received considerable attention from the synthetic chemistry community, leading to several efficient protocols based on different catalytic approaches and encompassing various nitroalkene substrates 1–4, providing access to enantioenriched nitroalkanes 6–9 (Scheme 1).

“Ene”-reductases, mainly of the OYE (Old Yellow Enzyme) family, have been applied to the biocatalytic enantioselective reduction of $\beta$-alkyl-$\beta$-aryl nitroalkenes 1 [4–8]. In fact, $\alpha$-methyl-$\beta$-nitrostyrene is a benchmark substrate for “ene”-reductases and stereocomplementary enzymes, guaranteeing access to both enantiomers of the reduced product, are known [8]. However, variations in the aryl and alkyl moieties of substrates 1 have only been partially addressed. Concurrently, enantioselective metal-catalyzed reductions of $\beta,\beta$-disubstituted nitroalkenes have been developed, employing different chiral complexes based on Cu, Rh, and Ir in hydrosilylation,
transfer hydrogenation, and hydrogenation reactions [9–20]. Protocols featuring very broad substrate scopes encompassing not only a variety of β-alkyl-β-aryl and β,β-dialkyl nitroalkenes 1 [9–16], but also their β-amido [17–19] and β-carbonyl [20] counterparts 2–3 are available. A Lewis base catalyzed hydrosilylation reaction with substrates 2 has also been reported [21].

An alternative strategy to enantioselective reduction that has gained great attention, due to its elegance, simplicity, and practical features (at least on a preparative scale), is the organocatalytic transfer hydrogenation reaction with Hantzsch esters 10 as hydrogen surrogates [22–28]. In this context, exploring the notion of the efficient coordination of the nitro group by double hydrogen bond donors [29–31], thioureas, and related catalysts 5a–f (Scheme 2) have been found to be efficient in the promotion of the enantioselective reduction of β,β-disubstituted nitroalkenes 1, 3, 4 with Hantzsch esters 10 [32–40]. Catalyst 5a, a thiourea resulting from the combination of an N,N-diethyl tert-butylglycinamide residue on one side and an elaborated trans-1,2-cyclohexanediamicine on the other, has been successfully employed in the reaction with nitroalkenes 1 and 3 [32,33]. The related thiourea 5b, keeping the same structural features of 5a but bearing a different amino-acidic component (N,N-dimethylvalinamide), proved instead to be efficient in the reduction of β-trifluoromethyl nitroalkenes 4 [34]. The simpler structure 5c, wherein the cyclohexanediamicine part was replaced by the 3,5-bis(trifluoromethyl)phenyl group, and carrying an alcohol in place of the amide moiety, was applied to substrates 1 and 3 giving results worse than 5a in terms of enantioselectivities [35]. The unrelated paracyclophane catalysts 5d and 5e were also tested in the reaction with a nitroalkene 1, but gave only low enantioselectivity [36]. Conversely, a chiral-at-metal pyrazole-amide double hydrogen bond donor 5f was applied very successfully to the transfer hydrogenation reaction with nitroalkenes 3 [37].

Herein, we report a general enantioselective transfer hydrogenation reaction of β,β-disubstituted nitroalkenes with tert-butyl Hantzsch ester 10d, catalyzed by the simple and commercially available Jacobsen type thiourea catalyst 5g [41–43] and applicable to all nitroalkene classes 1–4 (Scheme 3). Catalyst 5g, originally developed in the frame of the Strecker reaction, is considerably simpler to synthesize than 5a,b or 5f, the previous most successful structures, that moreover were only applied to some nitroalkene classes (Scheme 2). In this paper, we first detail our previous development of the reaction with β-trifluoromethyl nitroalkenes 4 [39]. Then, providing experimental evidence on the mode of action of catalyst 5g in this transformation, we demonstrate its remarkable tolerance to

**Scheme 1.** Nitroalkene substrates 1–4 employed in catalytic enantioselective reductions, and corresponding nitroalkane products 6–9.
variations in the substituents of the nitroalkene substrate (i.e., \( R_1 \) and \( R_2 \) in Scheme 3). By slightly varying reaction conditions, we show its application to nitroalkenes \( 2 \), \( 1 \) and \( 3 \), ultimately providing a very general and broadly useful protocol for enantioselective transfer hydrogenation reactions of \( \beta,\beta \)-disubstituted nitroalkenes based on a readily available catalyst.

Scheme 2. Organocatalysts \( 5a-f \) employed in transfer hydrogenation reactions of \( \beta,\beta \)-disubstituted nitroalkenes with Hantzsch esters, and their substrate scope.

Scheme 3. A general enantioselective transfer hydrogenation reaction of \( \beta,\beta \)-disubstituted nitroalkenes \( 1-4 \) with Hantzsch ester \( 10d \) catalyzed by the simple thiourea \( 5g \).

2. Results and Discussion

2.1. Optimization and Development of the Transfer Hydrogenation Reaction with \( \beta \)-Trifluoromethyl Nitroalkenes \( 4 \)

We started our investigation by studying the H-bond driven transfer hydrogenation reaction of \( \beta \)-trifluoromethyl nitroalkene \( 4a \) with Hantzsch ester \( 10a \) (Scheme 4) testing various typical H-bond donor catalysts (thioureas, ureas, squaramides, diols, phosphoric acids, etc.).

Even if most catalysts \( 5 \) were able to afford the desired \( \beta \)-trifluoromethyl nitroalkane \( 9a \) with good conversions (Table 1, entries 1–7) only the 1,2-diaminocyclohexane derived amido-thiourea \( 5o \) gave a promising enantioselectivity in the reaction (entry 8). Accordingly, variations in the two thiourea \( N \)-substituents were undertaken exploiting the modularity of this catalyst structure.
Having identified catalyst 5g, the notable outcome of the simpler structure was the superior behavior the good conversions (Table 1, entries 1–7) only the 1,2-diaminocyclohexane derived amido-thiourea catalyst 10a gave a promising enantioselectivity in the reaction (entry 8). Accordingly, variations in the two catalyst combinations afforded promising values of conversion up to 97% and ee up to +77% (Table 1).

Catalyst 5p (entry 9) bearing the same 1,2-diaminocyclohexane moiety as 5o afforded the product with lower conversion and very poor and opposite selectivity, showing that enantioselectivity is driven by the amide portion of the catalyst. Indeed, the simpler amido-thiourea catalyst 5g (entry 10) afforded results even better than 5o.

Whereas the utility of a 1,2-cyclohexanediamine derived catalysts (i.e., 5a, Scheme 2) for the asymmetric reactions of nitroalkenes with Hantzsch esters had been previously reported [32,33], the notable outcome of the simpler structure 5g was an unanticipated yet gratifying result. Having identified catalyst 5g as the optimal, a screening of reaction conditions and Hantzsch esters 10 was undertaken, performing the reactions under more concentrated conditions and at 40 °C, to ensure

Table 1. Catalysts screening 1.

| Entry | Catalyst 5 | Conversion 2 (%) | ee 3 (%) |
|-------|------------|------------------|----------|
| 1     | 5h         | 97               | +12      |
| 2     | 5i         | 80               | −9       |
| 3     | 5j         | >95              | +20      |
| 4     | 5k         | >95              | +5       |
| 5     | 5l         | 60               | −14      |
| 6     | 5m         | >95              | −17      |
| 7     | 5n         | 87               | −24      |
| 8     | 5o         | >95              | +48      |
| 9     | 5p         | 85               | −15      |
| 10    | 5g         | >95              | +77      |

1 Conditions: 4a (0.05 mmol), cat. 5 (10 mol %), toluene (0.5 mL, 0.1 M), 10a (0.06 mmol, 1.2 equiv), RT, 18–24 h;
2 Determined on the crude mixture by 19F-NMR analysis;
3 Determined by chiral stationary phase HPLC.
full conversion (Table 2). The methyl, iso-butyl, and tert-butyl Hantzsch esters 10b–d were tested and compared with 10a (entries 1–4). The tert-butyl derivative 10d outclassed the other dihydropyridines 10a–c in term of enantioinduction, affording 9a in 89% ee and for this reason it was selected for further exploration. The superior behavior the tert-butyl Hantzsch ester 10d compared to other esters, a common feature to many organocatalytic reactions, had been previously rationalized invoking not only increased nonbonding interactions between the Hantzsch ester ring and the catalyst-substrate complex, but also electronic factors related to the boat-like conformation of the tert-butyl Hantzsch ester 10d [23]. However, it is also important to underline that tert-butyl ester 10d features improved solubility in apolar solvents, compared to 10a–c. Next, toluene was confirmed as the most appropriate solvent after a short screening (entries 4–7), and a satisfactory 94% ee value was accomplished by cooling the reaction mixture to −20 °C (entry 8).

### Table 2. Reaction conditions screening 1.

| Entry | 10  | 5 (mol %) | Solvent (M) | T (°C) | Conversion 2 (%) | ee 3 (%) |
|-------|-----|----------|-------------|--------|------------------|---------|
| 1     | 10a | 5g (10)  | toluene (0.625) | 40     | >95              | 77      |
| 2     | 10b | 5g (10)  | toluene (0.625) | 40     | >95              | 69      |
| 3     | 10c | 5g (10)  | toluene (0.625) | 40     | >95              | 70      |
| 4     | 10d | 5g (10)  | toluene (0.625) | 40     | >95              | 89      |
| 5     | 10d | 5g (10)  | CH2Cl2 (0.13) | 40     | 61               | 66      |
| 6     | 10d | 5g (10)  | MTBE (0.13)    | 40     | 60               | 39      |
| 7     | 10d | 5g (10)  | THF (0.13)     | 40     | 60               | 4       |
| 8     | 10d | 5g (10)  | toluene (0.625) | −20    | >95              | 94      |
| 9     | 10d | 5g (10)  | toluene (0.625) | −20    | >95              | 77      |
| 10    | 10d | 5g (10)  | toluene (0.625) | −20    | >95              | 92      |
| 11    | 10d | 5g (10)  | PhCF3 (0.625)  | −20    | >95              | 95      |
| 12    | 10d | 5g (5)   | PhCF3 (0.625)  | −20    | >95              | 92      |
| 13    | 10d | 5g (10)  | PhCF3 (0.3)    | −20    | >95              | 97      |

1 Conditions: 4a (0.05 mmol), cat. 5, solvent, 10 (0.06 mmol, 1.2 equiv), 18–24 h; 2 Determined on the crude mixture by 19F-NMR analysis; 3 Determined by chiral stationary phase HPLC.

A variation of the amide N-substituents in catalyst 5 was then explored, by using the closely related thioareas 5q and 5r in the transfer hydrogenation reaction, at −20 °C in toluene. The N,N-diethyl derivative 5q performed rather poorly, while the N-methyl-N-benzhydryl amide 5r did not give any improvement compared to 5g (entries 9–10). The use of α,α,α-trifluorotoluene as solvent provided slightly better results than toluene, when catalyst 5g was employed (entry 11 vs. entry 8). Unluckily, a lower catalyst loading gave a small decrease in the enantiomeric excess of the product 9a (entry 12). Reverting to 10 mol % loading, slightly better results were achieved by lowering reaction concentration (entry 13).

These conditions, namely catalyst 5g (10 mol%) Hantzsch ester 10d, α,α,α-trifluorotoluene as solvent, and −20 °C as reaction temperature, were applied on a preparative scale (Scheme 5) obtaining product 9a in 94% yield, with a small erosion in the enantioreclectivity compared to the optimization scale reaction (95% instead of 97%).

A study of the scope of the reaction was undertaken (Scheme 6). Similarly to derivative 4a, the reactions with different substrates 4b–h bearing aromatic rings substituted at different positions with either electron donating or electron withdrawing groups furnished a series of β-aryl-β-trifluoro...
nitroalkanes 9b–h with excellent results (>70% yield and >93% ee). Very good yields and enantioselectivities (93%–97% ee) can also be achieved when a 2-naphthyl and two heteroaromatic substituents are collocated in substrates 4i–k. Notably, the optimized reaction conditions could also be applied successfully to substrates 4l and 4m bearing aliphatic chains, which furnished the expected adducts 9l and 9m with very good results. The benefit of using α,α,α-trifluorotoluene as reaction medium with respect to toluene was demonstrated by performing few reactions using toluene as the solvent (Scheme 6, results in brackets): in all the examined cases, the results in terms of enantioselectivity were slightly lower.

Scheme 5. Optimized reaction on preparative scale.

Scheme 6. Scope of the transfer hydrogenation reaction of β-trifluoromethyl nitroalkenes 4.

2.2. Extension of the Transfer Hydrogenation Reaction Catalyzed by 5g to Other Nitroalkenes 1–3

The relevant results obtained in the transfer hydrogenation reaction of β-trifluoromethyl nitroalkenes 4 catalyzed by thiourea 5g prompted us to verify the applicability of the methodology
to other readily accessible β,β-disubstituted nitroolefins such as (E)-1-nitro-2-phenyl-1-propene 1a, β-amino nitroolefines 2a and 2b, and β-nitroacrylate 3a (Figure 1).

Substrates 1a and 3a had been previously studied and organocatalytic protocols based on thioureas are present in the literature (see Scheme 2); on the contrary, prior to our work [40], β-amino nitroolefines 2 were utilized only in asymmetric hydrosilylation [21] or in metal-catalyzed asymmetric hydrogenations [17–19].

To our delight, after carefully adjusting the reaction conditions, thiourea 5g was able to promote the transfer hydrogenation reaction of 2a and 2b in the presence of Hantzsch ester 10d as hydrogen donor, affording the corresponding β-amino nitroalkanes 7a and 7b in 97% and 90% yield respectively, with complete enantioselectivity (ee >99%) regardless of the protecting group installed on the amine function (Scheme 7). Although a higher reaction temperature was required with these substrates 2 compared to the trifluoromethyl derivatives 4, presumably due to stereoelectronic effects rendering amido substrates 2 less reactive than 4, full enantioselectivity was observed even at a lower (5 mol %) catalyst loading.

Eager to further verify the capacity of catalyst 5g in inducing enantioselectivity in the reaction of β,β-disubstituted nitroolefin substrates with Hantzsch ester 10d, we moved to investigate substrates 1a and 3a. A short screening of reaction conditions (solvent, dilution, temperature, amount of Hantzsch ester 10d), indicated dichloromethane as a more suitable solvent for these substrates, and 0 and −20 °C as optimal reaction temperatures for 1a and 3a, respectively. Under these newly found conditions, catalyst 5g was indeed able to provide the corresponding nitroalkanes 6a and 8a in high yields and enantioselectivities, as depicted in Scheme 8.

Figure 1. Additional nitroalkenes 1–3 studied.

Scheme 7. Catalytic enantioselective transfer hydrogenation reactions with substrates 2a and 2b.

Scheme 8. Catalytic enantioselective transfer hydrogenation reactions with substrates 1a and 3a.
2.3. Proposed Reaction Model for the Transfer Hydrogenation Reactions Catalyzed by 5g with Nitroalkenes

Keeping the activation of nitro compounds by thioureas as the preliminary reasonable assumption, we aimed at gaining some insights on the mode of action of catalyst 5g in the reactions. We first performed some simple control experiments, comparing in the reaction between 4a and 10d the activity of catalyst 5g vs. simpler achiral thiourea derivatives 5s and 5t (Scheme 9).

The evolution of the reactions was conveniently monitored by \(^{19}\)F-NMR spectroscopy. Whereas thiourea 5s should feature a similar acidity to 5g (pK\(_a\) ca. 12.57 in DMSO [44]), 5t bearing two aryl substituents is considerably more acidic (pK\(_a\) ca. 8.5 in DMSO [44]). Considering only the coordination of the nitro group by the thiourea moiety acting as a general acid catalyst, and neglecting conformational effects, an increase in acidity should roughly correspond to an increase in catalyst activity [45]. However, as shown in Figure 2, catalyst 5g is considerably more efficient in reaction promotion than 5s and 5t. Furthermore, the less acidic 5s was found to be slightly more effective than 5t.

These reactions were found to obey pseudo-second order kinetics according to the following equation [46]:

\[
\ln \left( \frac{[4a]_0 \times ([10d]_0 - [9a])}{[10d]_0 \times ([4a]_0 - [9a])} \right) = ([10d]_0 - [4a]_0) \times k_{\text{obs}}t
\]

where:

\[
[4a]_0 = 0.125 \text{ M};\ [10d]_0 = 0.1875 \text{ M};\ [9a] = (0.125 \times \text{ conversion}) \text{ M}
\]
The straight lines reported in Figure 3 display good correlation coefficients. Their slopes are the rate constant $k_{\text{obs}}$ (in $\text{M}^{-1}\text{h}^{-1}$) for the reactions, from which a more quantitative comparison of the activity displayed by the three catalysts $5g$, $5s$, and $5t$ can be deduced.

![Figure 3. Pseudo-second order rate constants for the three catalysts $5g$, $5s$, and $5t$.](image)

Together with the previously determined mode of action of catalyst $5g$ in the Strecker reaction [41,42], these experiments suggest that the amide moiety of this catalyst effectively participates in the coordination/stabilization of a reaction transition state (TS) leading to the major enantiomer of product 9. The pseudo-second order kinetics followed by the reactions (Figure 3) indicates as a first approximation that interactions prior to TS are not relevant (i.e., Curtin-Hammett control). Thus, it can be surmised that, along with the coordination of the Lewis acidic thiourea moiety to the negatively charged nitro moiety, the amide oxygen acts as a Lewis base in this TS, coordinating the N-H proton of the Hantzsch ester having a positive charge density. Applying the previously determined most stable conformation of catalyst $5g$ [41], these considerations result in the model depicted in Scheme 10. Overall, a dipolar TS is effectively stabilized by the electrostatically complementary functionalities present in the catalyst structure, in a way reminding the mode of action of some macromolecular enzymes [47]. A coordination of both dipole charges (negative at the nitro moiety and positive at the Hantzsch ester) might be more than an exclusive coordination of the negative part of the dipole (nitro moiety), justifying the lower activity offered by “mono-functional” catalysts $5s$ and $5t$.

After TS, an irreversible proton-transfer follows, leading to the products 9 and the pyridine co-product. We have previously demonstrated [40], using an α-substituted nitroalkene giving a pro-chiral nitronate intermediate, that catalyst $5g$ is not able to exert significant stereocontrol in this proton-transfer process [48,49].

![Scheme 10. Transition state model for the reduction of nitroalkenes 4 catalyzed by 5g.](image)
The soundness of this model is confirmed by computational work on the transfer hydrogenation reaction with the related catalyst 5b [34]. In line with the established mode of action of thiourea catalysts in this type of reactions [50], enantioinduction is not due to repulsive interactions between catalysts and substrates, but rather to the good 3D geometrical fit between the polar functionalities of the catalyst and a TS giving the (R)-enantiomer of 9. Apparently, alternative TSs leading to (S)-9 are not matching well the 3D structure of the catalyst, and cannot thus be stabilized/promoted. The tert-butyl moiety serves to control the 3D conformation of the catalyst. Furthermore, catalyst/substrates interactions in this TS are limited to the nitro and N-H groups, the nitroalkene β-substituents do not play an obvious role. Indeed, the reaction with nitroalkenes 4 proved to be applicable with very good results to both aromatic and aliphatic substrates (R in Scheme 10). Besides, these considerations justify the remarkable performances of this catalyst with the different nitroalkenes 1–4, as well as the attack of the hydride to the same pro-chiral face [51] of the nitroolefins, irrespective of the nature of the β-substituents (Scheme 11).

![Scheme 11](image-url)

**Scheme 11.** Attack of the hydride to the same pro-chiral face of 1–4 according to the TS model.

### 3. Materials and Methods

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. CH2Cl2 for the catalytic reactions was filtered on a plug of basic alumina before use. Hantzsch esters 10a–c [52,53] and 10d [40] were prepared following literature procedures. Chiral thiourea 5g was prepared as reported in the literature, or purchased from commercial sources [41–43]. (E)-1-Nitro-2-phenyl-1-propene 1a [4], β-acylamino nitroolefins and β-1-butyloxy carbonylamino nitroolefins 2 [40], ethyl Z-3-nitro-2-phenylacrylate 3a [33], and trifluoromethylated nitroalkenes 4 [54], were prepared following literature procedures.

(S)-(1-Nitropropan-2-yl)benzene 6a: in a screw cap 1.5 mL vial, to a solution of (E)-1-nitro-2-phenyl-1-propene 1a (24.5 mg, 0.15 mmol) in dichloromethane (0.3 mL, 0.5 M), catalyst 5g (7.6 mg, 0.015 mmol, 0.1 equiv) and Hantzsch ester 10d (69.5 mg, 0.225 mmol, 1.5 equiv) were sequentially added at 0 °C. The vial was saturated with nitrogen and closed with the cap, then the reaction mixture was stirred for 70 h at 0 °C. The resulting mixture was directly purified by column chromatography eluting with diethyl ether/ hexane 1:15 (v/v), to afford the title compound in quantitative yield (24.6 mg). The enantiomeric excess of 6a was determined by CSP HPLC analysis (Chiralcel OJ-H, flow = 0.75 mL/min, eluent: n-hexane/1-PrOH 90:10, λ = 234 nm, t_maj = 20.2 min, t_min = 22.2 min). The obtained spectroscopic data were in accord with those previously published [32].
Asymmetric transfer hydrogenation β-amino nitroalkanes 2: in a screw cap round bottom vial, to a stirred solution of 2 (0.15 mmol), toluene (510 µL, 0.3 M), catalyst 5g (3.9 mg, 0.0075 mmol, 0.05 equiv), and Hantzsch ester 10d (56 mg, 0.18 mmol, 1.2 equiv) were added. The vial was saturated with nitrogen and closed with the cap. The reaction mixture was stirred for 14 h at 40 °C. The resulting mixture was purified by column chromatography to afford product 7. The spectroscopic data have been previously published [40].

(S)-N-(2-Nitro-1-phenylethyl)acetamide 7a: the title compound was prepared according to the above procedure and purified by silica gel chromatography (elucent ethyl acetate/petroleum ether 4:1). White solid; Yield 97%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; n-hexane/2-propanol 9:1; 0.75 mL/min; λ = 254 nm; tR (major) = 35.3 min; tR (minor) = 42.8 min; ee >99%.

tert-Butyl (S)-(2-nitro-1-phenylethyl)carbamate 7b: the title compound was prepared according to the above procedure and purified by silica gel chromatography (elucent CH2Cl2/petroleum ether 6:1). White solid; Yield 90%. The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; n-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm; tR (major) = 22.6 min; tR (minor) = 25.7 min; ee >99%.

Asymmetric transfer hydrogenation of β-trifluoromethyl nitroalkanes 4: in a screw cap round bottom vial, to a solution of nitroalkene 4 (0.15 mmol) in trifluorotoluene (0.5 mL, 0.3 M), catalyst 5g (7.6 mg, 0.015 mmol, 0.1 equiv), and Hantzsch ester 10d (56 mg, 0.18 mmol, 1.2 equiv) were added at −20 °C. The reaction mixture was stirred for 24 h at −20 °C. The resulting mixture was purified by column chromatography eluting with diethyl ether/n-hexane 2:50 (v/v), to afford the trifluoromethyl nitroalkane 9.

(R)-1,1,1-Trifluoro-2-phenyl-3-nitropropane 9a: in a screw cap round bottom vial, to a solution of nitroalkene 4a (870 mg, 4.0 mmol) in trifluorotoluene (12 mL, 0.3 M), catalyst 5g (202 mg, 0.4 mmol, 0.1 equiv) and Hantzsch ester 10d (1.51 g, 4.8 mmol, 1.2 equiv) were added at −20 °C. The reaction mixture was stirred for 24 h at −20 °C. The resulting mixture was purified by column chromatography eluting with diethyl ether/n-hexane 2:50 (v/v), to afford the trifluoromethyl nitroalkane 9a. The obtained spectroscopic data were in accordance with those previously published [39]. Yield: 94% (823 mg); pale yellow oil; The enantiomeric excess was determined by CSP HPLC analysis using a Daicel Chiralcel OJH column; n-hexane/2-propanol 9:1; 0.75 mL/min, λ = 254 nm, tR (major) = 24.4 min; tR (minor) = 31.0 min; ee 95%.

Kinetic studies on the asymmetric transfer hydrogenation of β-trifluoromethyl nitroalkene 4a: in a screw cap round bottom vial, to a solution of nitroalkene 4a (21.8 mg, 0.1 mmol), toluene (800 µL, 0.125 M), catalyst 5 (0.01 mmol, 0.1 equiv), and Hantzsch ester 10d (46.4 g, 0.15 mmol, 1.5 equiv) were added at 0 °C. The mixture was stirred at the same temperature. The reaction evolution was followed by sampling the mixture with a Pasteur pipette, followed by immediate dilution in CDCl3, followed by 19F-NMR analysis: product 9a: −69 ppm (d, J = 8.5 Hz, 3F); nitroalkene 4a: −67 ppm (s, 3F).

4. Conclusions

To summarize, we have presented a very general methodology for organocatalytic enantioselective transfer hydrogenation reactions of β,β-disubstituted nitroalkenes, making use of a simple thiourea catalyst, and Hantzsch esters as convenient hydrogen donors. It is the first time that a single catalyst can be used with all nitroalkene substrate classes; previous reports [32–37] were all focused on specific catalysts tailored for specific substrates. Some kinetic studies confirmed the generally accepted mode of action of this type of catalysts, allowing us to put forward a reasonable transition state model accounting for the remarkable substrate generality. We envision this synthetic platform might be useful for further synthetic applications and other studies related to thiourea based on catalytic asymmetric transformations [55].

Acknowledgments: We acknowledge financial support from the University of Bologna (RFO program). We are grateful to our co-workers involved in the previous development of the reaction with nitroalkenes 2 and 4, whose
names can be found in the reference section, and to Giacomo Foli for preliminary results with nitroalkenes 1a and 3a. Takashi Ooi is gratefully acknowledged for suggesting to use of a thiourea like 5s in the kinetic studies.

**Author Contributions:** M.F. conceived the project. L.B. and M.F. designed and performed the experiments, analyzed the data, and wrote the paper.

**Conflicts of Interest:** The authors declare no conflict of interest.

**References**

1. Ono, N. *The Nitro Group in Organic Synthesis;* John Wiley & Sons: New York, NY, USA, 2001.

2. Ballini, R.; Gabrielli, S.; Palmieri, A.; Petrini, M. Nitroalkanes as key compounds for the synthesis of amino derivatives. *Curr. Org. Chem.* 2011, 15, 1482–1506. [CrossRef]

3. Ballini, R.; Petrini, M. The nitro to carbonyl conversion (Nef reaction): New perspectives for a classical transformation. *Adv. Synth. Catal.* 2015, 357, 2371–2402. [CrossRef]

4. Ohta, H.; Kobayashi, N.; Ozaki, K. Asymmetric reduction of nitro olefins by fermenting bakers’ yeast. *J. Org. Chem.* 1989, 54, 1802–1804. [CrossRef]

5. Hall, M.; Stueckler, C.; Kroutil, W.; Macheroux, P.; Faber, K. Asymmetric bioreduction of activated alkenes using cloned 12-oxophytodienoate reductase isoenzymes OPF-1 and OPF-3 from lycopersicon esculentum (tomato): A striking change of stereoselectivity. *Angew. Chem. Int. Ed.* 2007, 46, 3934–3937. [CrossRef] [PubMed]

6. Toogood, H.S.; Scrutton, N.S. New developments in ‘ene’-reductase catalyzed biological hydrogenations. *Curr. Opin. Chem. Biol.* 2014, 19, 107–115. [CrossRef] [PubMed]

7. Fryszkowska, A.; Fisher, K.; Gardiner, J.M.; Stephens, G.M. Highly enantioselective reduction of β,β-disubstituted aromatic nitroalkenes catalyzed by *clostridium sporogenes.* *J. Org. Chem.* 2008, 73, 4295–4298. [CrossRef] [PubMed]

8. Bertolotti, M.; Brenna, E.; Crotti, M.; Gatti, F.G.; Monti, D.; Parmeggiani, F.; Santangelo, S. Substrate scope evaluation of the enantioselective reduction of β-alkyl-β-arylnitroalkenes by old yellow enzymes 1–3 for organic synthesis applications. *ChemCatChem* 2016, 8, 577–583. [CrossRef]

9. Czekelius, C.; Carreira, E.M. Catalytic enantioselective conjugate reduction of β,β-disubstituted nitroalkenes. *Angew. Chem. Int. Ed.* 2003, 42, 4793–4795. [CrossRef] [PubMed]

10. Czekelius, C.; Carreira, E.M. Enantioselective reduction of nitroalkene mixtures by in situ equilibration. *Org. Process Res. Dev.* 2007, 11, 633–636. [CrossRef]

11. Soltani, O.; Ariger, M.A.; Carreira, E.M. Transfer hydrogenation in water: Enantioselective, catalytic reduction of (E)-β,β-disubstituted nitroalkenes. *Org. Lett.* 2009, 11, 4196–4198. [CrossRef] [PubMed]

12. Li, S.; Huang, K.; Zhang, J.; Wu, W.; Zhang, X. Rh-catalyzed highly enantioselective hydrogenation of nitroalkenes under basic conditions. *Chem. Eur. J.* 2013, 19, 10840–10844. [CrossRef] [PubMed]

13. Zhao, Q.; Li, S.; Huang, K.; Wang, R.; Zhang, X. A novel chiral bisphosphine-thiourea ligand for asymmetric hydrogenation of β,β-disubstituted nitroalkenes. *Org. Lett.* 2013, 15, 4014–4017. [CrossRef] [PubMed]

14. Yu, Y.-B.; Cheng, L.; Li, Y.-P.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. Enantioselective iridium-catalyzed hydrogenation of β,β-disubstituted nitroalkenes. *Chem. Commun.* 2016, 52, 4812–4815. [CrossRef] [PubMed]

15. Tang, Y.; Xiang, J.; Cun, L.; Wang, Y.; Zhu, J.; Liao, J.; Deng, J. Chemoselective and enantioselective transfer hydrogenation of β,β-disubstituted nitroalkenes catalyzed by a water-insoluble chiral diamine-rhodium complex in water. *Tetrahedron Asymmetry* 2010, 21, 1900–1905. [CrossRef]

16. Li, S.; Huang, K.; Cao, B.; Zhang, J.; Wu, W.; Zhang, X. Highly enantioselective hydrogenation of β,β-disubstituted nitroalkenes. *Angew. Chem. Int. Ed.* 2012, 51, 8573–8576. [CrossRef] [PubMed]

17. Li, P.; Zhou, M.; Zhao, Q.; Wu, W.; Hu, X.; Dong, X.-Q.; Zhang, X. Synthesis of chiral β-aminonitroalkanes via rhodium-catalyzed asymmetric hydrogenation. *Org. Lett.* 2016, 18, 40–43. [CrossRef] [PubMed]

18. Yan, Q.; Liu, M.; Kong, D.; Zi, G.; Hou, G. Highly efficient iridium-catalyzed asymmetric hydrogenation of β-acylaminonitroolefins. *Chem. Commun.* 2014, 50, 12870–12872. [CrossRef] [PubMed]

19. Zhou, M.; Dong, D.; Zhu, B.; Geng, H.; Wang, Y.; Zhang, X. Rhodium-catalyzed enantioselective hydrogenation of β-acylamino nitroolefins: A new approach to chiral β-aminonitroalkanes. *Org. Lett.* 2013, 15, 5524–5527. [CrossRef] [PubMed]

20. Li, S.; Xiao, T.; Li, D.; Zhang, X. First iridium-catalyzed highly enantioselective hydrogenation of β-nitroacrylates. *Org. Lett.* 2015, 17, 3782–3785. [CrossRef] [PubMed]
21. Liu, X.-W.; Yan, Y.; Wang, Y.-Q.; Wang, C.; Sun, J. Highly enantioselective reduction of β-amino nitroolefins with a simple N-sulfinyl urea as bifunctional catalyst. Chem. Eur. J. 2012, 18, 9204–9207. [CrossRef] [PubMed]
22. Wang, D.; Astruc, D. The golden age of transfer hydrogenation. Chem. Rev. 2015, 115, 6621–6686. [CrossRef] [PubMed]
23. Ouellet, S.G.; Walij, A.M.; MacMillan, D.W.C. Enantioselective organocatalytic transfer hydrogenation reactions using Hantzsch esters. Acc. Chem. Res. 2007, 40, 1327–1339. [CrossRef] [PubMed]
24. Rossi, S.; Benaglia, M.; Massolo, E.; Raimondi, L. Organocatalytic strategies for enantioselective metal-free reductions. Catal. Sci. Technol. 2014, 4, 2708–2723. [CrossRef]
25. Zheng, C.; You, S.-L. Transfer hydrogenation with Hantzsch esters and related organic hydride donors. Chem. Soc. Rev. 2012, 41, 2498–2518. [CrossRef] [PubMed]
26. Herrera, R.P. Organocatalytic transfer hydrogenation and hydrosylylation reactions. Top. Curr. Chem. 2016, 374, 29. [CrossRef]
27. Rueping, M.; Dufour, J.; Schoepke, S.J. Advances in catalytic metal-free reductions: From bio-inspired concepts to applications in the organocatalytic synthesis of pharmaceuticals and natural products. Green Chem. 2011, 13, 1084–1105. [CrossRef]
28. Bernardi, L.; Fochi, M.; Comes Franchini, M.; Ricci, A. Bioinspired organocatalytic asymmetric reactions. Org. Biomol. Chem. 2012, 10, 2911–2922. [CrossRef] [PubMed]
29. Taylor, M.S.; Jacobsen, E.N. Asymmetric catalysis by chiral hydrogen-bond donors. Bull. Chem. Soc. Jpn. 2008, 81, 785–795. [CrossRef]
30. Miyabe, H.; Takemoto, Y. Discovery and application of asymmetric reaction by multi-functional thioureas. Bull. Chem. Soc. Jpn. 2012, 85, 1724–1727. [CrossRef] [PubMed]
31. Zhang, Z.; Schreiner, P.R. (Thio)urea organocatalysis—What can be learnt from anion recognition? Chem. Soc. Rev. 2009, 38, 1187–1198. [CrossRef] [PubMed]
32. Martin, N.J.A.; Ozores, L.; List, B. Organocatalytic asymmetric transfer hydrogenation of nitroolefins. J. Am. Chem. Soc. 2007, 129, 8976–8977. [CrossRef] [PubMed]
33. Martin, N.J.A.; Cheng, X.; List, B. Organocatalytic asymmetric transfer hydrogenation of β-nitroacrylates: Accessing β2-amino acids. J. Am. Chem. Soc. 2008, 130, 13862–13863. [CrossRef] [PubMed]
34. Massolo, E.; Benaglia, M.; Orlandi, M.; Rossi, S.; Celentano, G. Enantioselective organocatalytic reduction of β-trifluoromethyl nitroalkenes: An efficient strategy for the synthesis of chiral β-trifluoromethyl amines. Chem. Eur. J. 2015, 21, 3589–3595. [CrossRef] [PubMed]
35. Schneider, J.F.; Lauber, M.B.; Muhr, V.; Kratzer, D.; Paradies, J. Readily available hydrogen bond catalysts for the asymmetric transfer hydrogenation of nitroolefins. Org. Biomol. Chem. 2011, 9, 4323–4327. [CrossRef] [PubMed]
36. Schneider, J.F.; Falk, F.C.; Fröhlich, R.; Paradies, J. Planar-chiral thioureas as hydrogen-bond catalysts. Eur. J. Org. Chem. 2010, 2265–2269. [CrossRef]
37. Chen, L.-A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. Asymmetric catalysis with an inert chiral-metal iridium complex. J. Am. Chem. Soc. 2013, 135, 10598–10601. [CrossRef] [PubMed]
38. Anderson, J.C.; Koovits, P.J. An enantioselective tandem reduction/nitro-Mannich reaction of nitroalkenes using a simple thiourea organocatalyst. Chem. Sci. 2013, 4, 2897–2901. [CrossRef]
39. Martinelli, E.; Vicini, A.C.; Mancinelli, M.; Mazzanti, A.; Zani, P.; Bernardi, L.; Fochi, M. Catalytic highly enantioselective transfer hydrogenation of β-trifluoromethyl nitroalkenes. An easy and general entry to optically active β-trifluoromethyl amines. Chem. Commun. 2015, 51, 658–660. [CrossRef] [PubMed]
40. Ferraro, A.; Bernardi, L.; Fochi, M. Organocatalytic enantioselective transfer hydrogenation of β-amino nitroalkenes. Adv. Synth. Catal. 2016, 358, 1561–1565. [CrossRef]
41. Zuend, S.J.; Jacobsen, E.N. Mechanism of amido-thiourea catalyzed enantioselective imine hydrocyanation: Transition state stabilization via multiple non-covalent interactions. J. Am. Chem. Soc. 2009, 131, 15358–15374. [CrossRef] [PubMed]
42. Zuend, S.J.; Coughlin, M.P.; Lalonde, M.P.; Jacobsen, E.N. Scaleable catalytic asymmetric Strecker syntheses of unnatural α-amino acids. Nature 2009, 461, 968–971. [CrossRef] [PubMed]
43. CAS 959979-30-7, Sigma-Aldrich code 693316. [CrossRef] [PubMed]
44. Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K.M.; Schreiner, P.R. (Thio)urea organocatalyst equilibrium acidities in DMSO. Org. Lett. 2012, 14, 1724–1727. [CrossRef] [PubMed]
45. Jensen, K.H.; Sigman, M.S. Systematically probing the effect of catalyst acidity in a hydrogen-bond-catalyzed enantioselective reaction. *Angew. Chem. Int. Ed.* **2007**, *47*, 4748–4750. [CrossRef] [PubMed]

46. Cornish-Bowden, A. *Fundamentals of Enzyme Kinetics*; Portland Press: London, UK, 1995.

47. Warshel, A.; Sharma, P.K.; Kato, M.; Xiang, Y.; Liu, H.; Olsson, M.H.M. Electrostatic basis for enzyme catalysis. *Chem. Rev.* **2006**, *106*, 3210–3235. [CrossRef] [PubMed]

48. Romanini, S.; Galletti, E.; Caruana, L.; Mazzanti, A.; Himo, F.; Santoro, S.; Fochi, M.; Bernardi, L. Catalytic asymmetric reactions of 4-substituted indoles with nitroethene: A direct entry to Ergot alkaloid structures. *Chem. Eur. J.* **2015**, *21*, 17578–17582. [CrossRef] [PubMed]

49. Liu, C.; Han, P.; Wu, X.; Tang, M. The mechanism investigation of chiral phosphoric acid-catalyzed Friedel-Crafts reactions—How the chiral phosphoric acid regains the proton. *Comp. Theor. Chem.* **2014**, *1050*, 39–45. [CrossRef]

50. Knowles, R.R.; Jacobsen, E.N. Attractive noncovalent interactions in asymmetric catalysis: Links between enzymes and small molecule catalysts. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678–20685. [CrossRef] [PubMed]

51. It should be noted that the Re-Si descriptors for the pro-chiral face of nitroalkenes 1–4 are not relevant to this discussion, since they are related to the CIP priorities of the substituents.

52. Leutbecher, H.; Greiner, G.; Amann, R.; Stolz, A.; Beifuss, U.; Conrad, J. Laccase-catalyzed phenol oxidation. Rapid assignment of ring-proton deficient polycyclic benzofuran regioisomers by experimental $^1$H-$^13$C long-range coupling constants and DFT-predicted product formation. *Org. Biomol. Chem.* **2011**, *9*, 2667–2673. [CrossRef] [PubMed]

53. Roomi, M.W. Porphyria-inducing activity of a series of pyridine and dihydropyridine compounds. Investigation in a cell culture system. *J. Med. Chem.* **1975**, *18*, 457–460. [CrossRef] [PubMed]

54. Gao, J.-R.; Wu, H.; Xiang, B.; Yu, W.-B.; Han, L.; Jia, Y.-X. Highly enantioselective construction of trifluoromethylated all-carbon quaternary stereocenters via nickel-catalyzed Friedel-Crafts alkylation reaction. *J. Am. Chem. Soc.* **2013**, *135*, 2983–2986. [CrossRef] [PubMed]

55. Foli, G.; Sasso D’Elia, C.; Fochi, M.; Bernardi, L. Reversible modulation of the activity of thiourea catalysts with anions: A simple approach to switchable asymmetric catalysis. *RSC Adv.* **2016**, *6*, 66490–66494. [CrossRef]

**Sample Availability:** Samples of the compounds 7b and 9a are available from the authors.

© 2016 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).