

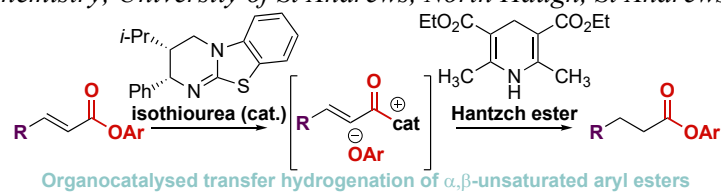
Graphical Abstract

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Isothiourea-catalyzed transfer hydrogenation of α,β -unsaturated *para*-nitrophenyl esters

Jiufeng Wu,^a Claire M. Young,^a and Andrew D. Smith^{a*}

^aEastCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, UK, KY16 9ST



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Jiufeng Wu,^a Claire M. Young,^a and Andrew D. Smith^{a*}

^aEastCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, UK, KY16 9ST

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This manuscript is dedicated to the memory of Professor Jon Williams who was a leader and inspiration in the field of organic chemistry and catalysis.

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ABSTRACT

Abstract: A protocol for the isothiourea-catalysed transfer hydrogenation of α,β -unsaturated *para*-nitrophenyl esters using Hantzsch ester has been developed. Good to excellent yields are observed using α,β -unsaturated aryl esters bearing electron-withdrawing β -substituents. The aryl ester products can either be isolated directly in moderate to excellent yields (7 examples, 16–98%) or converted to the corresponding methyl esters (2 examples, 68–70% yield) or benzyl amides (2 examples, 44–88% yield) after in situ reaction of the hydrogenated ester with the appropriate nucleophile. Preliminary experiments showed that modest enantioinduction (76:24 er) is possible when a chiral isothiourea catalyst was used.

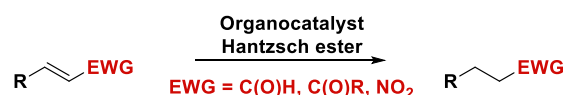
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1. Introduction

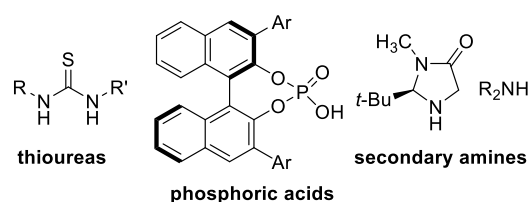
The hydrogenation of carbon-carbon double bonds is an important transformation both in Nature and in synthetic chemistry. The general synthetic approach uses a metal catalyst and hydrogen gas. Although useful, this technique has associated drawbacks, in particular the use of highly flammable hydrogen gas, often at high pressure. The hydrogenation of carbon-carbon double bonds conjugated with electron withdrawing groups (such as carbonyl-containing esters or ketones) can be approached differently due to the polarisation of the target bond. While the presence of this additional functionality can lead to chemoselectivity issues due to multiple reactive sites in the molecule, there are many reported methods that overcome this issue. For example, metal catalysts and hydrogen gas can be used, as demonstrated in Stryker's seminal publication where reactive copper hydride selectively reduces the carbon-carbon double bond of α,β -unsaturated enones.¹ Avoiding the use of hydrogen gas, catalytically generated metal hydrides can be accessed using a range of metals (eg. Cu, Co, Rh) and various reducing agents (eg. borohydrides, silanes).^{2,3,4} Importantly, metal-catalysed hydrogenations have been extended to α,β -unsaturated esters and amides⁵ while the use of chiral ligands allows for the stereoselective reduction of prochiral substrates.⁶ An alternative strategy involves the use of transfer hydrogenation, with significant contributions in this area found from the pioneering work of Williams.⁷

Hantzsch esters, for example **2**, are often considered as NADPH analogues and have found particular prevalence in organocatalysis

a. Organocatalytic hydrogenation of enals, enones and nitroalkenes



Classes of organocatalyst



b. List's enantioselective, organocatalytic transfer hydrogenation

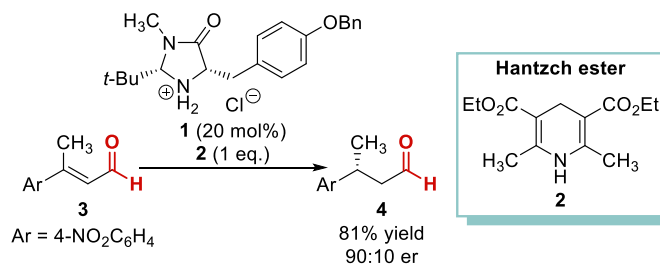


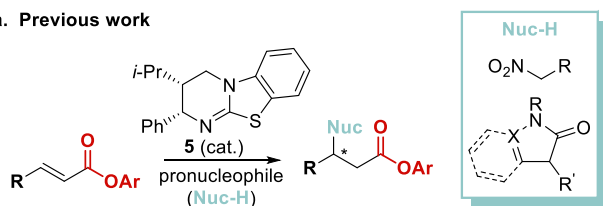
Figure 1: Organocatalytic transfer hydrogenations

for conjugate reductions (Figure 1a).^{8,9} Important classes of organocatalysts used in tandem with this class of reagent include

thioureas, phosphoric acids and Lewis bases, for example secondary amines.⁹ An early example of Lewis base catalysed hydrogen transfer was reported by List in 2004 (Figure 1b).¹⁰ *N,N*-Dibenzylamine was shown to catalyse the reduction of enals under mild reaction conditions using Hantzsch ester **2** as the reducing agent and significantly showed that the reaction could proceed enantioselectively when a chiral catalyst **1** was used giving aldehyde **4** in 81% yield and 90:10 er. Further developments followed this initial proof of concept using the same principle for the enantioselective hydrogenation of enals,¹¹ enones¹² and nitroalkenes.¹³

Despite these advances, to the best of our knowledge the organocatalysed transfer hydrogenation of α,β -unsaturated esters has not been demonstrated to date. To allow such a process to proceed, we proposed the use of catalytically generated α,β -unsaturated acyl isothiuronium intermediates. In early reports of catalysis via α,β -unsaturated acyl isothiuronium species, cyclisation products were required to allow catalyst turnover.¹⁴ In recent publications, we have demonstrated that apposite choice of electron deficient aryl esters can facilitate addition of carbon nucleophiles to α,β -unsaturated acyl isothiuronium intermediates, with catalyst release promoted by the aryl oxide initially derived from the acylating agent (Figure 2a).¹⁵ Building upon this work, in this manuscript we demonstrate the organocatalytic transfer hydrogenation of α,β -unsaturated aryl esters using isothiurea catalysis (Figure 2b).

a. Previous work



b. This work

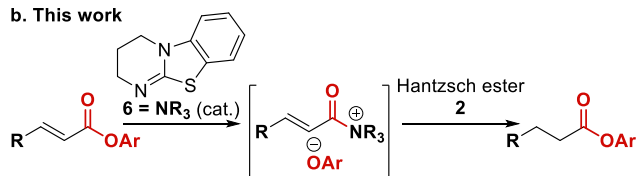
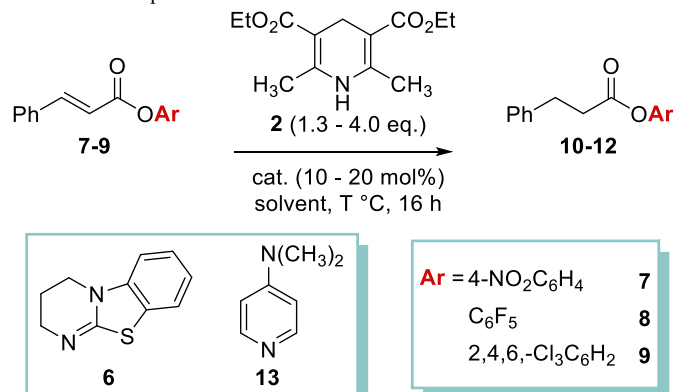


Figure 2: Reactivity of α,β -unsaturated acyl ammonium intermediates

At the onset of these studies, α,β -unsaturated *para*-nitrophenyl (PNP) ester **7** was proposed as a model substrate on which to perform reaction optimisation (Table 1). Using Hantzsch ester **2** as the formal hydrogen source and DHPB **6** as Lewis base catalyst in CH_2Cl_2 at 40°C , no conversion to hydrogenated product **10** was observed (Entry 1). Increasing reaction temperature was next probed, with solvents of higher boiling point used to facilitate this. Pleasingly, around 30% conversion to **10** was observed in CHCl_3 (60°C) and THF (66°C) (Entries 2 and 3). Moving to benzene allowed the reaction to be performed at 80°C and resulted in 63% conversion (Entry 4). In an effort to increase conversion, increasing equivalents of **2** were used. Moving to 2 equivalents gave **10** in improved 75% yield but increasing further to 4 equivalents led to low 42% conversion that was ascribed to the heterogeneous nature of the reaction mixture (Entries 5 and 6). Performing the reaction with archetypal Lewis base catalyst DMAP **13** led to no conversion, while increasing the loading of DHPB **6** to 20% gave an increased conversion of 80% (Entries 7 and 8). As a control, performing the reaction in the absence of **6** again led to no conversion to product (Entry 9). A further control reaction was performed to determine if catalyst deactivation was occurring through direct reaction between **2** and **6**, however

heating a stoichiometric mixture of **2** and **6** in benzene at 80°C led to no reaction. Alternative aryl esters **8** and **9**, that have been successfully employed as α,β -unsaturated acyl isothiuronium precursors, were also tested but no product conversion was observed (Entries 10 and 11). Taking the conditions in Entry 8 as optimal, **10** was isolated in 60% yield (Entry 9) but it was noted that some hydrolysis of both the starting material and ester products was occurring.

Table 1: Scope of isolated amides



Entry	Ester	Solvent	T / °C	Cat. (mol%)	2 (equiv)	Yield / % ^a
1	7	CH_2Cl_2	40	6 (10)	1.3	0
2	7	CHCl_3	60	6 (10)	1.3	32
3	7	THF	66	6 (10)	1.3	29
4	7	Benzene	80	6 (10)	1.3	63
5	7	Benzene	80	6 (10)	2.0	75
6	7	Benzene	80	6 (10)	4.0	42
7	7	Benzene	80	13 (10)	2.0	0
8	7	Benzene	80	6 (20)	2.0	80(60) ^b
9	7	Benzene	80	-	2.0	0
10	8	Benzene	80	6 (20)	2.0	0
11	9	Benzene	80	6 (20)	2.0	0

^a Determined by ^1H NMR analysis of the crude material. ^b isolated yield

The scope and limitations of this process under the developed conditions was explored. Despite high conversion of starting material for a range of substrates (all > 80%), the isolated yields were variable (16–89%) and highly substrate dependent (Figure 3). First, variation of β -substituent (R') was explored. Substrates substituted with an electron-withdrawing group were suitable for the reaction. Ester **14** was formed in only 16% yield. Pleasingly, **15** could be isolated in good 64% yield from β -methyl substituted starting material. Trifluoromethyl substituted **16** was isolated in excellent 89% and notably, the reaction was not limited to the *p*-nitrophenyl ester, with 2,4,6-trichlorophenyl (TCP) ester **17** isolated in good 67% yield. Significantly, a disubstituted substrate could be successfully used, giving chiral ester **18** in 73% isolated yield. Some limitations were also observed with β,β -dimethyl substituted variant **19** and β -isopropyl **20** giving no conversion, presumably indicative of the requirement for an electron withdrawing β -substituent within the substrate for effective reduction. α -Methyl **21** also led to no conversion despite the expected high reactivity of the terminal alkene but is consistent with past observations that α -substituted α,β -unsaturated esters are typically unreactive in isothiurea catalysis.

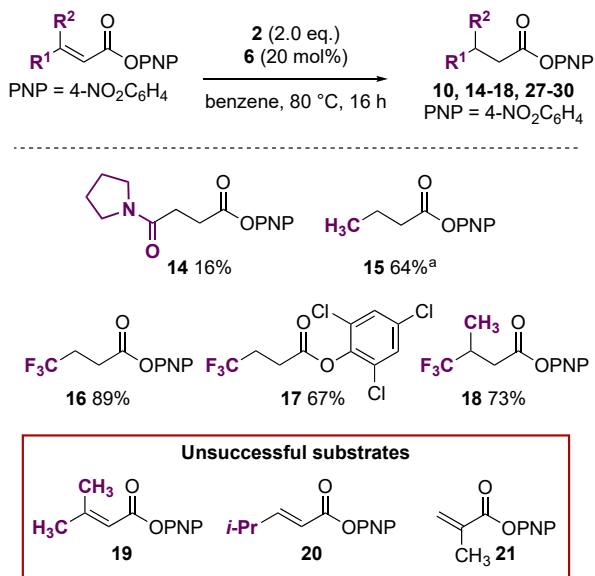


Figure 3: Scope of isolated esters. All yields given are isolated yields after flash column chromatography. The inconsistent isolated yields of *p*-nitrophenyl esters was proposed to be a result of both hydrolysis of the starting esters and ester products, as well as the instability of the product esters to column chromatography. Therefore, for further exploration of the scope, addition of coupling agent (EDCI) and benzylamine after the hydrogen transfer was complete gave stable amide products **22** and **23** (Figure 4). Using this protocol, β -aryl ester substrates containing electron withdrawing substituents could be used, leading to the formation of amides **23** and **24** in excellent to moderate yields (88% and 44%, respectively). Substrates with β -aryl substituents bearing electron-donating groups **24** and **25** as well as β -furyl **26**, led to no product formation consistent with the requirement for an electron withdrawing β -substituent observed previously (Figure 4).

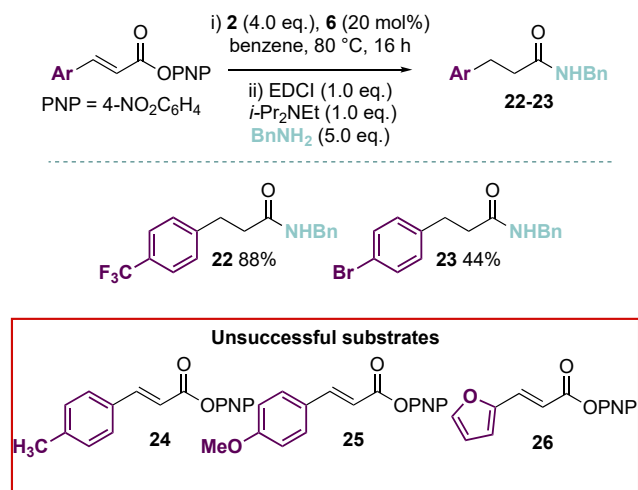


Figure 4: Scope of amides from in situ derivatisation. All yields given are isolated yields after flash column chromatography.

Despite promising results, the use of benzene as solvent was recognised as non-ideal due to its toxicity. Toluene is generally accepted as a safer alternative to benzene, in terms of both environmental impact and human toxicity.¹⁶ While no reactivity was observed using toluene at 80 °C, further optimisation showed that upon heating to reflux good conversion to product was observed, allowing the isolation of model compound **10** in 55% yield (Figure 5). Using this protocol, substrates with electron-withdrawing β -substituents

were well tolerated, giving **14** and **27** in good 55 and 59% yields. Pleasingly, **15** was isolated in excellent 98% yield, while both PNP and TCP esters could be used to give trifluoromethyl examples **16** and **17** in 78% and 67% yields respectively. Again, a disubstituted substrate could be successfully used, giving chiral ester **18** in 70% yield. The scope of β -aryl substituents was also explored, with **28** formed in 59% yield. As an alternative approach to in situ derivatisation, a selection of examples was treated with methanol after completion of the transfer hydrogenation, leading to the formation of methyl esters **29** and **30** in very good yields (68% and 70%, respectively).

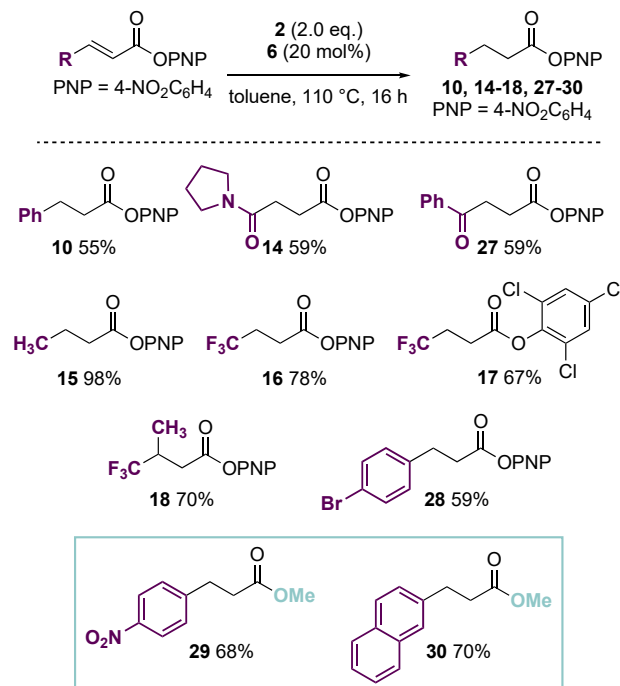
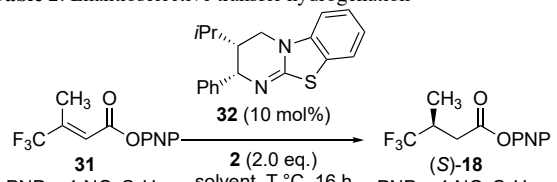


Figure 5: Scope of isolated *para*-nitrophenyl esters and methyl esters from in situ derivatisation. All yields given are isolated yields after flash column chromatography.

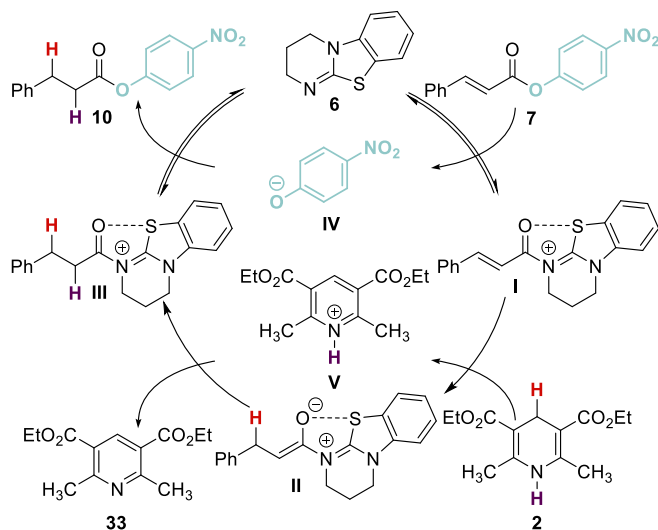
The successful formation of chiral ester **18**, provided the attractive prospect of performing the transfer hydrogenation enantioselectively. Use of chiral isothioureia **31** in toluene at reflux led to **18** in 74% yield but with limited stereocontrol (56:44 er, Table 2, Entry 1).¹⁷ Reduction of the temperature and performing the reaction in both toluene and benzene at 80 °C was next investigated. In toluene, a lower isolated product yield was obtained (49%) but with an increase in er observed (63:37 er) (Entry 2). In benzene a higher yield (70%) and slightly increased er (71:29 er) was observed (Entry 1). Lowering the reaction temperature to 60 °C in benzene gave an increase in er (75:25) but led to a significant decrease in yield (40%) (Entry 4). Although this demonstrates proof of concept for the enantioselective transfer hydrogenation protocol, the high temperature required was concluded to be incompatible with high enantioselectivity so no further experiments were performed.

Table 2: Enantioselective transfer hydrogenation


Entry	Solvent	T / °C	Yield % ^a	er ^b
1	Toluene	110	74	56:44
2	Toluene	80	49	63:37
3	Benzene	80	70	71:29
4	Benzene	60	40	75:25

^a Isolated yield after flash column chromatography. ^b Enantiomeric ratio determined by HPLC analysis on a chiral stationary phase.

Consistent with previous studies,^{15a,18} the reaction is proposed to proceed via acylation of catalyst **6** by ester **7** to form α,β -unsaturated acyl isothiuronium **I**, which along with intermediates **II** and **III** contains a stabilising intramolecular 1,5-O...S interaction.¹⁹ Hydride transfer from **2** leads to intermediate **II** which can subsequently be protonated to give acyl isothiuronium **III**. Formally, the Hantzsch ester serves as the source for this proton via pyridinium **V** but involvement of 4-nitrophenol, the conjugate acid of aryl oxide **IV**, in this proton transfer is also possible and cannot be ruled out. Subsequent reaction of intermediate **III** with aryl oxide **IV** leads to the formation of the ester product **10** and release of catalyst **6**.

**Scheme 1:** Proposed catalytic cycle.

In conclusion, an isothiurea catalysed transfer hydrogenation of α,β -unsaturated aryl esters has been developed. The reaction proceeds well in both benzene and toluene giving aryl ester products in moderate to excellent yields (7 examples, 16–98%) as well as methyl esters (2 examples, 38–70% yield) and benzyl amides (2 examples, 44–88% yield) after in situ reaction of the hydrogenated ester with the appropriate nucleophile. Preliminary experiments showed that enantioinduction was possible when a chiral isothiurea catalyst was used however, the observed enantioselectivity (75:25 er) was only modest.

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20. The research data underpinning this publication can be found at: DOI: 10.17630/b25b27ef-dca3-4590-b92d-221c243dde43

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.