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# Isothiourea-catalyzed formal enantioselective conjugate addition of benzophenone imines to $\beta$-fluorinated $\alpha, \beta$-unsaturated esters $\dagger$ 

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#### Abstract

The isothiourea-catalyzed formal enantioselective conjugate addition of 2-hydroxybenzophenone imine derivatives to $\alpha, \beta$-unsaturated paranitrophenyl esters has been developed. Investigations of the scope and limitations of this procedure showed that $\beta$-electron withdrawing substituents within the $\alpha, \beta$-unsaturated ester component are required for good product yield, giving rise to a range of $\beta$-imino ester and amide derivatives in moderate to good isolated yields with excellent enantioselectivity ( 20 examples, up to $81 \%$ yield and $97: 3 \mathrm{er}$ ).


The development of methods for the enantioselective synthesis of $\beta$-amino acid derivatives ${ }^{1 a}$ is of widespread importance due to the prevalence of this structural motif in natural products and medicinally relevant compounds. ${ }^{1}$ Among the synthetic methods that have been developed for the preparation of $\beta$-amino acid derivatives, arguably the most simple and elegant involves the asymmetric conjugate addition of an ammonia equivalent to an $\alpha, \beta$-unsaturated carbonyl motif. As an example of this approach, the conjugate addition of enantiomerically pure lithium amide derivatives to $\alpha, \beta$-unsaturated esters has been developed and exploited extensively by Davies and coworkers. Conjugate addition of lithium $N$-benzyl $-N-\alpha-$ methylbenzylamide to an $\alpha, \beta$-unsaturated ester gives the corresponding $\beta$-amino ester with high diastereoselectivity ( $>95: 5$ dr ), with N -deprotection through hydrogenolysis giving the corresponding $\beta$-amino ester derivatives (Scheme 1a). ${ }^{2}$

Over the last two decades, several enantioselective organocatalytic approaches to amine conjugate addition have been introduced. To date, these successful approaches rely upon enals, ${ }^{3}$ enones, ${ }^{4} \mathrm{~N}$-acyl pyrazoles, ${ }^{5}$ and nitro-olefins ${ }^{6}$ as Michael acceptors, with the use of bifunctional thiourea ${ }^{4 a, 5 b, 7,8 a-c, e}$ or squaramide ${ }^{4,5,8 a, b, e}$ organocatalysts, or Lewis basic pyrrolidines ${ }^{3,8}$ commonplace. Catalytic enantioselective amine conjugate additions to $\alpha, \beta$-unsaturated esters are rare, reflecting the recognized

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Scheme 1 Synthesis of $\beta$-amino ester derivatives.
recalcitrance of $\alpha, \beta$-unsaturated esters as Michael acceptors (Scheme 1b). To date, the current state-of-the-art organocatalytic approach is represented by Seidel and co-workers, ${ }^{9}$ demonstration of the conjugate addition of cyclic secondary amines to $\beta$ -alkyl- $\alpha, \beta$-unsaturated benzyl esters using a selenourea-thiourea catalyst 1 (Scheme 1c). Although limited to $\beta$-alkyl substituted Michael acceptors, this impressive methodology was applicable to a range of cyclic amines and the kinetic resolution of $( \pm)$-cyclic 2-arylamines.

Our approach to enantioselective amine conjugate addition focused upon the use of imines as nucleophiles. The conjugate addition of (diphenylmethylene)amine to $\alpha, \beta$-unsaturated esters, nitriles and ketones in racemic form has been demonstrated by de Meijere et al. MeOH was optimal as a solvent and


Scheme 2 Previous imine conjugate additions and this work.
a basic additive (such as $\mathrm{NEt}_{3}$ ) led to effective product formation (Scheme 2a). ${ }^{10}$ In 2018, Alemán and co-workers successfully demonstrated an enantioselective aza-Michael addition of nucleophilic imines to enals using secondary amine catalyst 2 (Scheme 2b). ${ }^{11}$ Trapping of the resultant $\beta$-imino aldehydes with a phosphorane gave the corresponding $\delta$-imino esters in good yield and enantioselectivity. Notably, 2-hydroxybenzophenone imines showed increased reactivity and enantioselectivity compared with the parent benzophenone imine, attributed to an increase in acidity of the imine proton caused by intramolecular hydrogen bonding. ${ }^{12,13}$ In previous work, we and others have demonstrated a range of enantioselective Michael-addition processes of in situ generated $\alpha, \beta$-unsaturated acyl ammonium species. ${ }^{14,15}$ Building on these precedents, we report herein the formal isothiourea-catalyzed enantioselective addition of 2-hydroxybenzophenone imines to $\beta$-fluorinated $\alpha, \beta$-unsaturated paranitrophenyl esters via an $\alpha, \beta$-unsaturated acyl ammonium intermediate, giving products in up to 98:2 er (Scheme 2c).

Preliminary investigations used $\beta-\mathrm{CF}_{3}$-substituted $\alpha, \beta$ unsaturated para-nitrophenyl ester 4 (1.0 equiv.) in toluene as standard. Given the moderate reactivity of $\alpha, \beta$-unsaturated acyl ammonium ions, imine 3 ( 2.0 equiv.) bearing an electron donor 4 -OMe-substituent was postulated to enhance nucleophilicity (Table 1). Attempted isolation of the para-nitrophenyl ester product led to low and irreproducible product yields, so addition of pyrrolidine to give the isolable amide 5 was adopted. Screening of isothiourea catalysts 6-8 ( $10 \mathrm{~mol} \%$ ) at $1: 2$ substrate ratio of ester 4: imine 3 (entries 1-3) showed that tetramisole 6 and BTM 7 gave promising product yield ( $\sim 50 \%$ ) whereas HyperBTM 8 showed poor catalytic activity ( $<10 \%$ yield). Excellent enantioselectivity (96:4 er) was observed using BTM 7. Altering the

Table 1 Reaction optimisation
(S)-Tetramisole 6

| Entry | Catalyst (mol\%) | Temp. $\left({ }^{\circ} \mathrm{C}\right)$ | Solvent | 3:4 | Yield ${ }^{a}$ (\%) |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| $1{ }^{\text {c }}$ | 6 (10) | rt | Toluene | 1:2 | 50 | 12:88 |
| $2^{\text {c }}$ | 7 (10) | rt | Toluene | $1: 2$ | 54 | 96:4 |
| $3{ }^{\text {c }}$ | 8 (10) | rt | Toluene | 1:2 | $<10$ | 68:32 |
| $4^{c}$ | 7(10) | rt | Toluene | 1:1.5 | 42 | 95:5 |
| $5^{c}$ | 7 (10) | rt | Toluene | $1.5: 1$ | 38 | 97:3 |
| $6^{c}$ | 7 (10) | 40 | Toluene | 1:2 | 52 | 94:6 |
| $7^{c}$ | 7 (10) | 60 | Toluene | $1: 2$ | 47 | 91:9 |
| $8^{c}$ | 7 (2.5) | rt | Toluene | $1: 2$ | <10 | 91:9 |
| $9^{c}$ | 7 (5.0) | rt | Toluene | 1:2 | 18 | 96:4 |
| $10^{c}$ | 7 (20) | rt | Toluene | 1:2 | $71^{d}$ | 96:4 |
| $11^{c}$ | 7 (20) | rt | THF | 1:2 | 31 | 96:4 |
| $12^{\text {c }}$ | 7 (20) | rt | $\mathrm{Et}_{2} \mathrm{O}$ | 1:2 | 30 | 96:4 |
| $13^{\text {c }}$ | 7 (20) | rt | $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ | 1:2 | 37 | 96:4 |
| $14^{e}$ | 7 (20) | rt | Toluene | 1:2 | 31 | 98:2 |
| $15^{f}$ | 7 (20) | rt | Toluene | 1:2 | 42 | 96:4 |
| $16^{g}$ | 7 (20) | rt | Toluene | 1:2 | 36 | 96:4 |

${ }^{a}$ Using ${ }^{1} \mathrm{H}$ NMR spectroscopic analysis and 1,3,5-trimethoxybenzene as internal standard. ${ }^{b}$ Ratio of $(R):(S)$ enantiomers determined by HPLC analysis on a chiral stationary phase. ${ }^{c} \mathrm{Ar}=4-\mathrm{NO}_{2} \mathrm{C}_{6} \mathrm{H}_{4} .{ }^{d}$ Isolated yield. ${ }^{e} \mathrm{Ar}=2,4,6-\mathrm{Cl}_{3} \mathrm{C}_{6} \mathrm{H}_{2} .{ }^{f} \mathrm{Ar}=\mathrm{C}_{6} \mathrm{~F}_{5} .{ }^{g} \mathrm{Ar}=3,5-\left(\mathrm{CF}_{3}\right)_{2} \mathrm{C}_{6} \mathrm{H}_{3}$.
reaction stoichiometry (entries 4 and 5) led to reduced product yield. A detrimental effect on product enantioselectivity (91:9 er) was observed when the reaction temperature was increased to $40{ }^{\circ} \mathrm{C}$ or $60{ }^{\circ} \mathrm{C}$ (entries 6 and 7). Lowering the catalyst loading showed a significant decrease in product yield and enantioselectivity (entries 8 and 9), while using $20 \mathrm{~mol} \%$ BTM 7 gave increased yield (71\% yield, 96:4 er, entry 10). Screening of a alternative solvents gave high product enantioselectivity but reduced yields (entries 11-13). Further optimisation probed the effectiveness of alternative electron-deficient aryl esters. Comparison of para-nitrophenyl with 2,4,6-trichlorophenyl, pentafluorophenyl, and 3,5-bis(trifluoromethyl)phenyl esters (entries 14-16) showed that excellent enantioselectivities were observed in each case (up to 98:2 er), with the para-nitrophenyl ester leading to the best product yield (71\%).

The scope and limitations of the developed process was explored through variation of the nucleophilic imine reaction component (Fig. 1). Variation of the electronic bias of the 4 -aryl substituent within the imine component showed that decreased product yield was observed upon changing from an electrondonating $4-\mathrm{MeO}-(5,70 \%$ yield) to $4-\mathrm{Me}(9,49 \%$ yield), $4-\mathrm{H}(11$, $36 \%$ yield) and electron-withdrawing $4-\mathrm{Br}$ substituent (10, $24 \%$ yield) all with $>96: 4 \mathrm{er}$. This is consistent with increasing


Fig. $1 \quad 0.10 \mathrm{mmol}$ scale. Isolated product yield; er determined by HPLC analysis on a chiral stationary phase; [a] $40^{\circ} \mathrm{C}$ for step i; [b] DMAP $20 \mathrm{~mol} \%$ in step ii.
electron density within the imine component leading to increased product yield. Interestingly, comparing the yield and er of products $\mathbf{1 1}$ and $\mathbf{1 2}$ indicates that the 2-hydroxy-substituent within the imine is essential for high product er, but does not affect product yield. The incorporation of an additional electrondonating $4-\mathrm{MeO}$ substituent led to product 13 in reduced yield but maintained high product er. Variation of the $\beta$-substituent within the $\alpha, \beta$-unsaturated ester indicated that the incorporation of polyhalogenated or ester electron-withdrawing groups was necessary for reactivity as alkyl, aryl, ketone and amide substituted acceptors gave no significant product formation. For example, the introduction of halogenated $\left(\mathrm{CF}_{2} \mathrm{H}\right)$ and polyhalogenated


Scheme 3 Gram scale synthesis of product 5 .
substituents $\left(\mathrm{CF}_{2} \mathrm{Cl}, \mathrm{CF}_{2} \mathrm{Br}\right.$, and $\left.\mathrm{C}_{2} \mathrm{~F}_{5}\right)$ led to products $\mathbf{1 4 - 1 7}$ in up to excellent yields with high enantioselectivity ( $40 \%$ to $81 \%$; $>96: 4 \mathrm{er}$ ), while the incorporation of ester substituents gave 18-19 in poor 20\% product yield in up to $96: 4$ er. Variation of the post catalysis nucleophilic component (Nuc-H) to incorporate alcohols as well as cyclic secondary and acyclic primary amines gave a range of ester and amide products 20-24 in good yield ( $42 \%$ to $64 \%$ ) and excellent enantioselectivity ( $\geq 96: 4 \mathrm{er}$ ).

To further demonstrate the synthetic utility of this transformation, it was applied to the gram-scale synthesis of product 5 with consistent yield and enantioselectivity ( $67 \%$, 96:4 er, Scheme 3). Hydrolysis gave the free $\beta$-amino amide product 26 in high yield and enantioselectivity ( $95 \%$, $96: 4$ er). ${ }^{16}$

A proposed mechanism of this transformation is shown in Scheme 4. Reversible acylation of the isothiourea with the $\alpha, \beta$-unsaturated ester 1a generates the key $\alpha, \beta$-unsaturated acyl isothiouronium ion pair 26.


Scheme 4 Proposed reaction mechanism.

An intramolecular chalcogen 1,5-S $\cdots \mathrm{O}$ interaction $\left(\mathrm{n}_{\mathrm{O}} \rightarrow \sigma^{*}{ }_{\mathrm{S}-\mathrm{C}}\right)^{17}$ provides a plausible stabilising effect and conformational lock. Hydrogen bonding between the 2-hydroxy-substituent and the imine N serves to conformationally restrict this functionality and facilitate deprotonation. ${ }^{11-13}$ Subsequent conjugate addition to the $s$-cis conformation of the $\alpha, \beta$-unsaturated acyl isothiouronium 26 anti- to the stereodirecting phenyl substituent of the isothiourea catalyst generates the ammonium enolate intermediate 27. Proton transfer generates the $\beta$-imino acyl isothiouronium intermediate 28, with catalyst turnover facilitated by the aryloxide counterion to form the product and release the isothiourea catalyst BTM $7 .{ }^{18}$

In summary, enantioselective organocatalytic conjugate addition of 2-hydroxybenzophenone imines to $\alpha, \beta$-unsaturated esters using the isothiourea BTM as an organocatalyst gives enantioenriched $\beta$-imino amides in modest to good yield (20$81 \%$ ) and excellent enantioselectivity (typically $>95: 5 \mathrm{er}$ ). ${ }^{19}$

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## Conflicts of interest

There are no conflicts of interests to declare.

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