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# Isothiourea-catalyzed formal enantioselective conjugate addition of benzophenone imines to β-fluorinated α,β-unsaturated esters†

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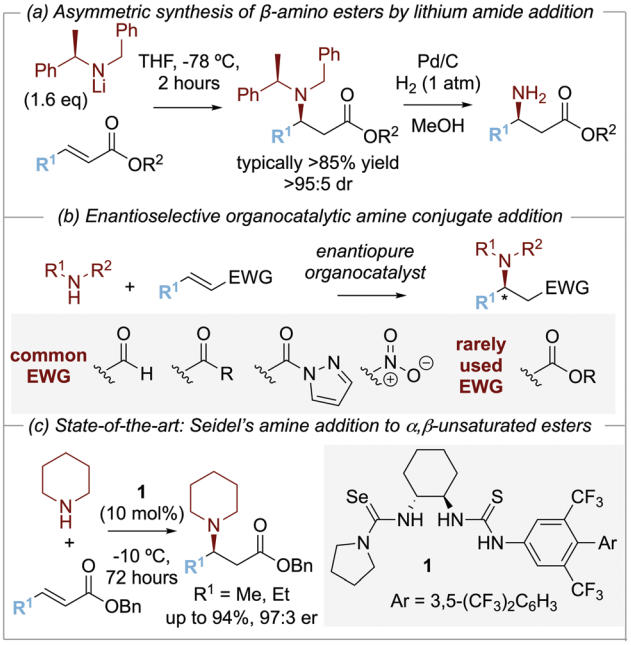
**The isothiourea-catalyzed formal enantioselective conjugate addition of 2-hydroxybenzophenone imine derivatives to α,β-unsaturated *para*-nitrophenyl esters has been developed. Investigations of the scope and limitations of this procedure showed that β-electron withdrawing substituents within the α,β-unsaturated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

The development of methods for the enantioselective synthesis of β-amino acid derivatives[1a] 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 β-amino acid derivatives, arguably the most simple and elegant involves the asymmetric conjugate addition of an ammonia equivalent to an α,β-unsaturated carbonyl motif. As an example of this approach, the conjugate addition of enantiomerically pure lithium amide derivatives to α,β-unsaturated esters has been developed and exploited extensively by Davies and co-workers. Conjugate addition of lithium *N*-benzyl-*N*-α-methylbenzylamide to an α,β-unsaturated ester gives the corresponding β-amino ester with high diastereoselectivity (>95 : 5 dr), with N-deprotection through hydrogenolysis giving the corresponding β-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] *N*-acyl pyrazoles,[5] and nitro-olefins[6] as Michael acceptors, with the use of bifunctional thiourea[4a,5b,7,8a–c,e] or squaramide[4,5c,8a,b,e] organocatalysts, or Lewis basic pyrrolidines[3,8] commonplace. Catalytic enantioselective amine conjugate additions to α,β-unsaturated esters are rare, reflecting the recognized recalcitrance of α,β-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 β-alkyl-α,β-unsaturated benzyl esters using a selenourea-thiourea catalyst **1** (Scheme 1c). Although limited to β-alkyl substituted Michael acceptors, this impressive methodology was applicable to a range of cyclic amines and the kinetic resolution of (±)-cyclic 2-arylamines.




Scheme 1 Synthesis of β-amino ester derivatives.

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

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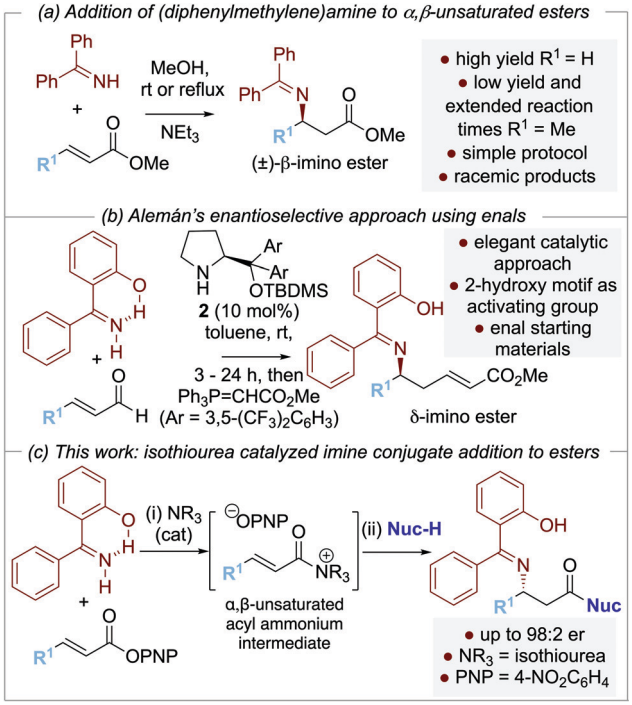
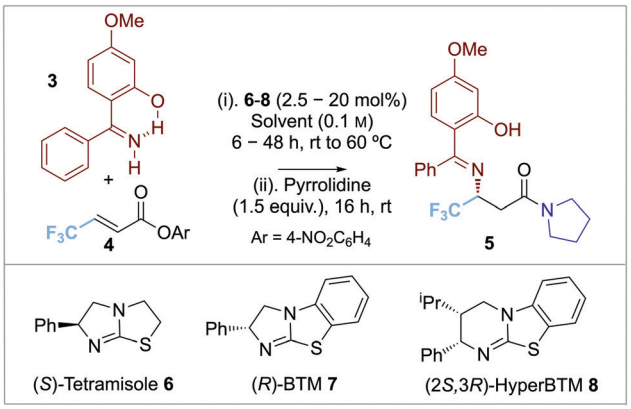



Scheme 2 Previous imine conjugate additions and this work.

a basic additive (such as $NEt_3$) 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 β-imino aldehydes with a phosphorane gave the corresponding δ-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 α,β-unsaturated acyl ammonium species.[14,15] Building on these precedents, we report herein the formal isothiourea-catalyzed enantioselective addition of 2-hydroxybenzophenone imines to β-fluorinated α,β-unsaturated *para*-nitrophenyl esters *via* an α,β-unsaturated acyl ammonium intermediate, giving products in up to 98 : 2 er (Scheme 2c).

Preliminary investigations used β-$CF_3$-substituted α,β-unsaturated *para*-nitrophenyl ester **4** (1.0 equiv.) in toluene as standard. Given the moderate reactivity of α,β-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 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 (~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




| Entry | Catalyst (mol%) | Temp. (°C) | Solvent | 3 : 4 | Yield[a] (%) | er[b] |
|---|---|---|---|---|---|---|
| 1[c] | **6** (10) | rt | Toluene | 1 : 2 | 50 | 12 : 88 |
| 2[c] | **7** (10) | rt | Toluene | 1 : 2 | 54 | 96 : 4 |
| 3[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[c] | **7** (20) | rt | $Et_2O$ | 1 : 2 | 30 | 96 : 4 |
| 13[c] | **7** (20) | rt | $CH_2Cl_2$ | 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 $^1$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] Ar = 4-$NO_2C_6H_4$. [d] Isolated yield. [e] Ar = 2,4,6-$Cl_3C_6H_2$. [f] Ar = $C_6F_5$. [g] Ar = 3,5-$(CF_3)_2C_6H_3$.

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 °C or 60 °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 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 electron-donating 4-MeO- (**5**, 70% yield) to 4-Me (**9**, 49% yield), 4-H (**11**, 36% yield) and electron-withdrawing 4-Br substituent (**10**, 24% yield) all with >96 : 4 er. This is consistent with increasing

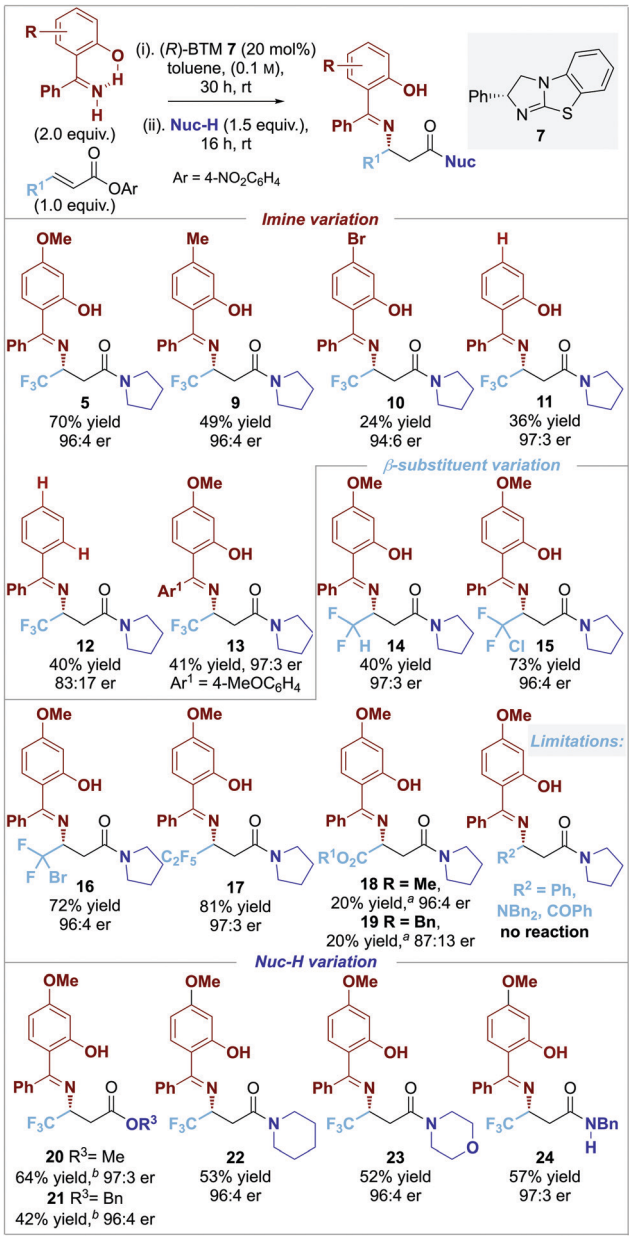
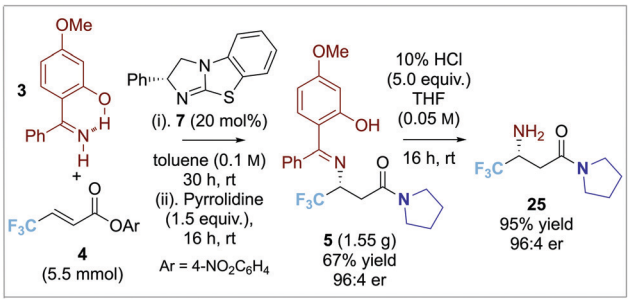



Fig. 1 0.10 mmol scale. Isolated product yield; er determined by HPLC analysis on a chiral stationary phase; [a] 40 °C for step i; [b] DMAP 20 mol% in step ii.

electron density within the imine component leading to increased product yield. Interestingly, comparing the yield and er of products **11** and **12** 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 electron-donating 4-MeO substituent led to product **13** in reduced yield but maintained high product er. Variation of the β-substituent within the α,β-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 ($CF_2H$) and polyhalogenated

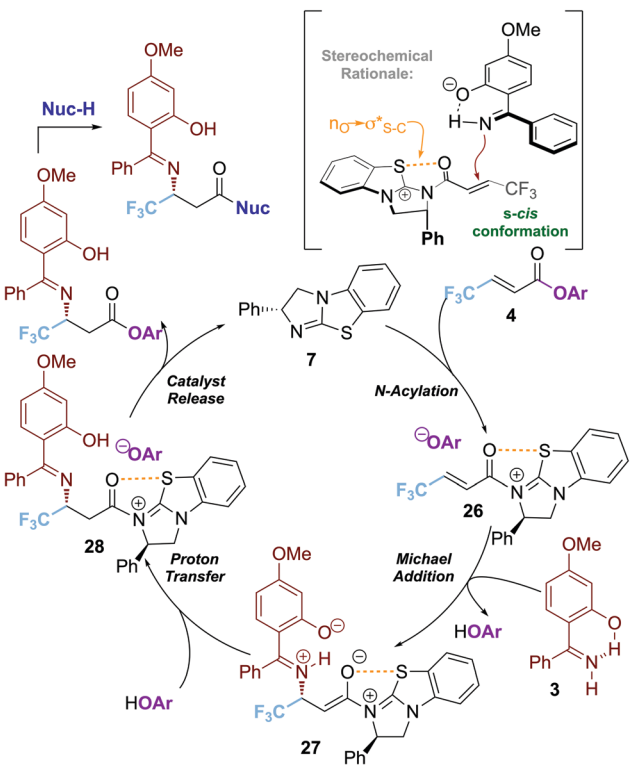



Scheme 3 Gram scale synthesis of product **5**.

substituents ($CF_2Cl$, $CF_2Br$, and $C_2F_5$) led to products **14–17** in up to excellent yields with high enantioselectivity (40% to 81%; >96 : 4 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 (≥96 : 4 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 β-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 α,β-unsaturated ester **1a** generates the key α,β-unsaturated acyl isothiouronium ion pair **26**.




Scheme 4 Proposed reaction mechanism.

An intramolecular chalcogen 1,5-S···O interaction ($n_O \rightarrow \sigma^*_{S\text{-}C}$)[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 α,β-unsaturated acyl isothiouronium **26** *anti*- to the stereodirecting phenyl substituent of the isothiourea catalyst generates the ammonium enolate intermediate **27**. Proton transfer generates the β-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 α,β-unsaturated esters using the isothiourea BTM as an organocatalyst gives enantioenriched β-imino amides in modest to good yield (20–81%) and excellent enantioselectivity (typically >95 : 5 er).[19]

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## Conflicts of interest

There are no conflicts of interests to declare.

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