Enantioselective Synthesis of \(\alpha\)-Aryl-\(\beta^2\)-Amino-Esters by Cooperative Isothiourea and Brønsted Acid Catalysis

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Dedicated to Professor Steve Davies upon his retirement for his friendship and mentorship

Abstract: The synthesis of \(\alpha\)-aryl-\(\beta^2\)-amino esters through enantioselective aminomethylation of an arylacetic acid ester in high yields and enantioselectivity via cooperative isothiourea and Brønsted acid catalysis is demonstrated. The scope and limitations of this process are explored (25 examples, up to 94\% yield and 96:4 er), with applications to the synthesis of (S)-Venlafaxine·HCl and (S)-Nakinadine B. Mechanistic studies are consistent with a C(1)-ammonium enolate pathway followed rather than an alternative dynamic kinetic resolution process. Control studies indicate that (i) a linear effect between catalyst and product er is observed; (ii) an acyl ammonium ion can be used as a precatalyst; (iii) reversible isothiourea addition to an in situ generated iminium ion leads to an off-cycle intermediate that can be used as a productive precatalyst.

Introduction

\(\beta\)-Amino acids are important functional groups in an abundance of natural products and medicinally relevant compounds. Although less common than their \(\alpha\)-homologues, many naturally occurring compounds contain the \(\beta\)-amino acid motif as a key structural feature.\(^{[1]}\) The incorporation of \(\beta\)-amino acids within bioactive peptides allows access to structures with modulated conformations and properties such as antimicrobial peptides,\(^{[2]}\) while \(\beta\)-amino acid containing oligomers have important applications in the chemistry of unnatural peptides such as foldamers.\(^{[3]}\) Many examples of pharmaceutically active compounds contain a \(\beta\)-amino carbonyl motif,\(^{[4]}\) with \(\alpha\)-aryl-\(\beta^2\)-amino acids representing an important subclass. For example, natural products (S)-Nakinadine B 1 isolated from the marine sponge Amphimedon sp.\(^{[5]}\) and Bishyocamine 2 from Anisodus acutangulus\(^{[6]}\) both contain an \(\alpha\)-aryl-\(\beta^2\)-amino motif (Figure 1a). Biologically active \(\alpha\)-aryl-\(\beta^2\)-amino acid derivatives include amide GDC-0068 3 (ipatasertib), an effective pan-Akt inhibitor,\(^{[7]}\) while amino-alcohol derivative Venlafaxine·HCl 4 is a therapeutically approved treatment for depression.\(^{[8]}\)

Enantioselective routes to \(\beta\)-amino acids and their derivatives therefore represent an important synthetic challenge with a range of methods developed for their synthesis. Until recently, synthetic routes to \(\beta\)-amino acid derivatives typically relied upon the elegant and versatile lithium amide conjugate addition approach developed by Davies,\(^{[9]}\) or the use of chiral auxiliaries for the preparation of \(\beta^2\)-amino acids.\(^{[10,11]}\) Catalytic, enantioselective routes to \(\beta^2\)-amino acid derivatives have been established, and include the use of metal complexes with chiral ligands\(^{[12]}\) or complexes that exhibit metal-centered chirality.\(^{[13]}\) Organocatalytic routes have also been reported, predominantly employing secondary amine Lewis base catalysts and aldehydes to access \(\beta\)-amino aldehydes through enamine intermediates.\(^{[14]}\) Additionally, a thiourea-catalyzed route to enantioenriched nitro-com-

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pounds has been developed that can be effectively reduced to β-amino acids, as have Brønsted acid catalyzed routes that harness the stereodirecting effect of a chiral anion.

In 2015, Chi and co-workers reported an enantioselective NHC-catalyzed route to α-alkyl-β²-amino esters 6 from enals using NHC-precatalyst 7 and hemiaminal ether 5 as a precursor to an in situ generated iminium ion. This method incorporates Brønsted acid activation of amino-ether 5 with the NHC-catalyzed formation of azolium enolates, generating a range of α-alkyl-β²-amino esters in good yields and excellent enantioselectivity (up to 97:3 er). Important to this method was the use of catalytic weak base (NEt₃) that served a dual purpose; firstly to generate the free NHC, but secondly to allow the in situ acid-catalyzed formation of a formyl iminium ion (as its conjugate acid). Despite its synthetic utility, one inherent limitation of this methodology is that the resulting products are restricted to α-alkyl-β¹-amino esters, and limited mechanistic understanding of this process has been developed. Given their importance, the development of a simple and effective enantioselective route to α-aryl-β²-amino esters would be of significant synthetic value.

C(1)-Ammonium enolates are powerful catalytically generated synthetic intermediates that have been widely used in a range of enantioselective C-C and C-X bond forming processes through reaction with suitable electrophilic partners. In recent years the reactivity of C(1)-ammonium enolate intermediates has been significantly broadened through the development of aryl esters as precursors using isothioureas as catalysts. These substrates allow aryloxide promoted catalytic turnover and have been applied to enantioselective [2,3]-sigmatropic rearrangements cooperative catalysis with Pd-, Ir- and Cu-derived electrophiles as well as base free ammonium enolate catalysis. Building upon this work, we proposed that enantioselective aminomethylation of C(1)-ammonium enolates, catalytically generated from chiral isothioureas and arylacetic acid esters, would provide ready access to enantioenriched α-aryl-β²-amino esters.

The process would require a cooperative Brønsted acid co-catalyst to generate an iminium ion in situ from an amino ether precursor. This contrasts with the typical necessity to generate the C(1)-ammonium enolate using a chiral tertiary amine in the presence of a stoichiometric Brønsted base. The addition of this auxiliary base is usually considered necessary to neutralize acidic by-products, and to prevent protonation (and thus deactivation) of the Lewis base catalyst. The use of tertiary amine salts as Lewis base catalysts has limited precedent, with DMAP (4-dimethylaminopyridine) salts having been used as acylation catalysts and sub-stoichiometric acid additives used sporadically with other tertiary amine Lewis base catalysts. In previous work we demonstrated the use of an isothiourea hydrochloride salt as a catalyst for C(1)-ammonium enolate generation from N-acyl imidazole precursors (Figure 2a). N-Protonation of the acyl imidazole (acting as a Brønsted base) both activated the substrate to nucleophilic attack and generated free isothiourea for Lewis base catalysis. Taking inspiration from this work, in this manuscript isothiourea hydrochloride salts are used to enable the catalytic enantioselective synthesis of α-aryl-β²-amino esters.

The protocol harnesses Brønsted acid and isothiourea Lewis base catalysis for the catalytic activation of both reaction partners. The Brønsted acid promotes in situ generation of a reactive iminium species from a hemiaminal ether presumably through initial N-protonation, generating the free isothiourea that is required for generation of a C(1)-ammonium enolate (Figure 2b). Comprehensive control studies aimed at understanding the mechanism of this process are consistent with a C(1)-ammonium enolate pathway and highlight the subtle equilibria between species along the productive reaction pathway that lead to off-cycle intermediates.

Results and Discussion

Investigation of Optimal Reaction Conditions

The effective enantioselective construction of α-aryl-β²-amino ester 9 was realized via the benzotetramisole·HCl (BTM·HCl, 5 mol%) catalyzed Mannich addition of pentafluorophenyl ester pronucleophile 8 to hemiaminal ether iminium precursor 5 in THF at room temperature in the presence of 4 Å molecular sieves (MS). Subsequent addition of MeOH gave the isolable methyl ester 9 in excellent yield (81%) and with high enantioselectivity (96:4 er) (Table 1, entry 1). Control experiments indicated that without the hydrochloric acid co-catalyst, yield and enantioselectivity were significantly reduced even after extended reaction time (entry 2). Other halide salts gave high product yield but the er values were lower than for BTM·HCl (entries 3 and 4). Other classes of Brønsted acid co-catalysts again led to high product yield but significantly diminished enantioselectivity compared with halide salts (entries 5–7). Removing molecular sieves led to reduced yield while maintaining product

![Figure 2. a) Precedent for using acyl imidazole and isothiourea·HCl salts in C(1)-ammonium enolate generation. b) Proposed dual-catalytic enantioselective synthesis of α-aryl-β²-amino esters.](image-url)
Table 1: Variation of Reaction Conditions.[a]

| Entry | Variation | Yield [%] | ee [%] |
|-------|-----------|-----------|--------|
| 1     | –         | 83        | 96:4   |
| 2     | without HCl | 40[t] | 72:28 |
| 3     | (R)-BTM-HBr (5 mol%) | 95 | 93:7 |
| 4     | (R)-BTM-HI (5 mol%) | 94 | 89:11 |
| 5     | (R)-BTM-HBF4 (5 mol%) | 89 | 71:29 |
| 6     | (R)-BTM-HOCCF3 (5 mol%) | 95 | 72:28 |
| 7     | (R)-BTM-HOTf (5 mol%) | 88 | 66:34 |
| 8     | without 4 Å MS[b] | 44 | 94:6 |
| 9     | (R)-BTM-HCl (1 mol%) | 55[t] | 91:7 |
| 10    | HyperBTM-HCl (5 mol%) | 61 | 85:15 |
| 11    | Ester = 4-nitrophenyl (OC6H4-NO2) | 75 | 94:6 |
| 12    | CH2Cl2 (0.1 m) | 70 | 87:13 |
| 13    | toluene (0.1 m) | 60 | 95:5 |

[a] The mixture of S (0.3 mmol), 8 (0.2 mmol), (R)-BTM-HCl (5 mol%), and 4 Å molecular sieves (MS, 100 mg) in dry THF (2 mL, 0.1 m) was stirred at rt under a N2 atmosphere for up to 24 hours before treatment with MeOH (0.5 mL) and DMAP (20 mol%) for 4 h. [b] isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Incomplete reaction after 2–3 days before addition of MeOH. [e] Molecular sieves were activated in a furnace at 400°C for 16 h. THF = Tetrahydrofuran. TFOH = Triflic acid. rt = room temperature.

eanominal ether 5 under the developed conditions (Table 2A). Importantly, arylacetic esters bearing electron-donating (4-dimethylamino-, 4-methoxy- and 4-tolyl) substituents, as well as halogen substituents (4-bromo-, 4-chloro- and 4-fluoro-) and electron-withdrawing substituents (4-trifluoromethyl-) were all tolerated, with α-aryl-β-amino esters 10–16 all obtained with excellent yields (77% to 94%) and enantioselectivity (~95:5 er). The absolute configuration of (S)-13 was determined by single crystal X-ray crystallography, with all other products assigned by analogy.[29] This stereochemical outcome is consistent with the expected configuration at C(2) if this process proceeds through a C(1)-ammonium enolate intermediate.[18] Only the introduction of a 4-nitro-substituent led to the product 17 in reduced yield and enantioselectivity. Further variation of the arylacetic ester showed that incorporation of substituents at both the 3-position (such as 3,4-dimethoxy-, 3-methoxy- and 3-bromo- to give 18–21) and the 2-position (2-methoxy- and 2-bromo- to give 22–23) gave products with consistently high yields and er. Notably, the 2-substitution pattern frequently provides reduced stereoselectivity in related isothiourea-catalyzed methods.[30] β-Amino esters 24 and 25 with 1- and 2-naphthyl substituents were readily prepared, as was heteroaromatic 2-thienyl 26. Beyond aryl acetic acid derivatives, the use of (E)-pent-3-enoic acid pentafluorophenyl ester was also productive, providing 3-alkyl-substituted β-amino ester 27 in excellent er. The consistent yield and enantiocontrol observed with variation in both steric and electronic aryl substitution within the ester component indicate that neither provide a significant bias in this process. Further investigations probed the effect of N-substituents within the hemiaminal ether reaction partner (Table 2B). Halogen- (4-fluoro and 4-bromo) and electron donating (4-methoxy) substituents were readily incorporated within the N-benzyl groups, giving α-aryl-β-amino esters 28–30 in consistent yield and enantioselectivity. The hemiaminal ether derived from diallylamine also worked well in catalysis, giving β-amino ester 31 in 80% yield and 94:6 er.

The limitations of this methodology were also probed (Table 2C). Notably, the N-benzyl-N-methyl and cyclic N-alkyl substituted hemiaminal ether variants 32–34 led to complex product distributions that included <5% product formation in THF. In the case of 32 and 33, the corresponding amides 37 and 38 were isolated in 30–39% yield upon treatment with either BTM-HCl or BTM (5 mol%). The formation of these amides is consistent with preferential N-acylation of the corresponding hemiaminal ether with either the pentafluorophenyl ester or an in situ generated acyl ammonium ion, followed by fragmentation to generate the corresponding amide. This is consistent with observations from Böhme and Sickmüller,[31] who demonstrated the ambident nature of hemiaminal ethers in reactions with acyl halides, with acyl transfer reactions leading to the formation of amides and esters. That this fragmentation pathway is preferred over iminium ion formation when hemiaminal ethers 32–34 presumably reflects the increased nucleophilicity of these species relative to the corresponding N,N-diallyl- or N,N-dibenzy1 substituted hemiaminal ethers that lead to constructive enantioselective aminomethylation. Alternative pathways involving either iminium hydrolysis, or formation of...
an oxonium ion and amine elimination, that subsequently lead to amide formation cannot be ruled out at this stage. Within the ester component, and consistent with common observations using isothiourea catalysis, 3-phenylpropanoate and phenylthioacetate pentafluorophenyl esters led to <5% product, [32] showing that this process complements the NHC-catalyzed protocol developed by Chi and co-workers.[17]

Having demonstrated the scope and limitations of this process, two target compounds, (S)-Venlafaxine·HCl 4 and (S)-Nakinadine B 1,[34] were synthesized to demonstrate the utility of this methodology (Table 2D). Each route began with the preparation of α-aryl-β-amino esters 11 and 9 on a >1 g scale, giving the products in excellent yield and er. For the synthesis of (S)-Venlafaxine·HCl 4, 11 was subjected to hydrogenolysis and reductive amination to give N,N-dimethyl derivative 39 in 83% yield. Double addition of the Grignard reagent derived from 1,5-dibromopentane, followed by recrystallization, afforded the target compound in 99:1 er and 47% overall yield over 5 steps. To prepare (S)-Nakinadine B 1, hydrogenolysis of 9, followed by reductive amination with 13-(pyridin-3-yl)tridecanal gave 40 in 73% yield and 95:5 er, with ester hydrolysis giving 1 in 93:7 er and 44% overall yield over 5 steps. In both cases correlation of the products with literature data served as proof of both structure and configuration.
Mechanistic Investigations

Having explored the scope and limitations of this process, further investigations focused on developing a mechanistic understanding. Initial studies attempted to elucidate reaction orders and track any potential intermediates through temporal reaction monitoring using $^{19}$F/$^1$H NMR spectroscopy and $^{19}$F labelled reactants (see SI). However, the heterogeneous nature of the reaction, together with the observation of multiple resonances that could not be fully deconvoluted meant that these investigations were abandoned.[28] Instead, a series of control experiments were performed to give insight to the productive reaction mechanism. At the onset of these investigations, two feasible mechanisms were considered that involved either enantioselective aminomethylation of a C(1)-ammonium enolate, or an alternative dynamic kinetic resolution (DKR) process of a racemic (or scalemic) β-amino pentafluorophenyl ester product. If a DKR were operative, a racemic β-amino pentafluorophenyl ester added to an enantioselective reaction would be predicted to become enantioenriched over the reaction course. To test this hypothesis, racemic β-amino ester 41 was prepared under standard reaction conditions using racemic BTM-HCl (10 mol%). β-Amino ester 41 proved difficult to isolate due to the lability of the pentafluorophenyl ester and so was used directly without purification. Subsequent addition of 2-naphthyl substituted pentafluorophenyl ester 42, enantiopure (R)-BTM-HCl (15 mol%) and 5 allowed potential DKR of the β-amino ester 41 under the reaction conditions to be assessed alongside the enantioselective aminomethylation of 42 (Table 3A). Upon isolation, 2-naphthyl β-amino ester 25 was obtained in 92:8 er and 81% yield, with 9 isolated in 61% yield and racemic form. This is inconsistent with a DKR of the β-amino pentafluorophenyl ester product being operative under catalytically competent conditions, although DKR of a post-aminomethylation acyl ammonium ion (prior to catalyst release by phenoxide) cannot be currently ruled out. Interestingly, while the overall BTM enantiomeric ratio (after second charge of catalyst) is expected to be 80:20, the er of product 25 was 92:8. As a linear correlation between the er of β-amino ester product 9 and catalyst BTM-HCl was observed (Table 3B), the er of 25 was higher than expected. We assume that either partial deactivation or deactivation of racemic-BTM-HCl from the first charge had occurred under the reaction conditions and may account for this discrepancy.

As DKR of the β-amino pentafluorophenyl ester can be excluded, this reaction was proposed to proceed through enantioselective aminomethylation of a C(1)-ammonium enolate intermediate generated from an acyl ammonium ion. To further probe this proposal, catalyst (R)-BTM was acylated with phenylacetyl chloride to give isolable acyl ammonium ion 43. Acyl ammonium ion 43 (5 mol%) was subsequently used as a precatalyst in the reaction process (Table 3C), giving β-amino ester 9 in comparable yield and er (78% yield, 95:5 er) to using (R)-BTM-HCl, indicating that 43 is a competent precatalyst for this transformation. Further studies considered the function of the hemiaminal ether within this process. If a pentafluorophenyl ester is used as an acyl ammonium ion precursor, the pentafluorophenolate formed upon acylation of the isothiourea is typically invoked as the functioning base for C(1)-ammonium enolate formation.[23] However, the reaction using acyl ammonium 43 as precatalyst proceeded without pentafluorophenolate, leading to the conclusion that the hemiaminal ether could function as a Brønsted base to promote deprotonation and C(1)-ammonium enolate formation in this instance. The effect of addition of an amine base upon reaction conversion and product enantioselectivity was therefore investigated (Table 3D). Performing the reaction with one equivalent of BN$_2$NEt (structurally similar to the hemiaminal ether 5) gave β-amino ester product 9 in 87% yield and 96:4 er, while the use of secondary amine BN$_2$NH also gave 9 in high er. However, the use of i-Pr$_2$NEt (a commonly used Brønsted base in tertiary amine Lewis base catalysis) showed a significant reduction in product conversion and reduced product er (22% yield, 89:11 er).

As the addition of dibenzylamine did not lead to significant deviation in er, an alternative iminium ion precursor, tetra-N-benzylmethanediamine 44 was trialed in this process, giving β-amino ester 9 in 47% yield and 93:7 er. The nature of the base present in the reaction is therefore highly significant, presumably effecting both iminium ion and C(1)-ammonium enolate formation through modulation of equilibrium distributions.

Further mechanistic investigations tested the feasibility of an iminium ion intermediate in the reaction process (Table 3E). N,N-Dibenzylinumium ion 45 was prepared from hemiaminal ether 5 using TMSI (trimethylsilyl chloride)[30] and used as a stoichiometric electrophile in a reaction with (R)-BTM and ester 8 in the presence of BN$_2$NEt. β-Amino ester 9 was generated in 65% yield and 92:8 er, consistent with iminium ion 45 being a potential intermediate in this reaction process. Given the known ability of tertiary amines to add reversibly to iminium ions,[30] further consideration led to the possibility of the iminium ion 45 being intercepted in situ by the Lewis base (R)-BTM. Addition of (R)-BTM to N,N-dibenzylinumium chloride 45 showed complex behavior and gave a mixture of products by $^1$H NMR analysis, with aminomethylation of the Lewis base to give 46 tentatively assigned as a significant component.[37] The use of this mixture as a potential precatalyst (20 mol%) gave β-amino ester 9 in 80% yield and 93:7 er upon treatment with pentafluorophenyl ester 8 and hemiaminal ether 5. These control studies indicate that while 46 may be a potential reaction intermediate it is inconsequential to the outcome of the reaction process, presumably due to its reversible formation. The enantiomertasting step of the reaction was next investigated. Aminomethylation of the C(1)-ammonium enolate was proposed to proceed enantioselectively, and the observed product configuration at C(2) is consistent with the known facial bias of the Lewis base catalyst. However, during optimization, variation of the couterion of the (R)-BTM-HX salt led to significant variation in product er, and so further experiments considered the effect of a chiral counterion through use of chiral acid additives. Performing the reaction using either (R)- or (S)-BTM alongside chiral acids 47–49 resulted in enantiocontrol being essentially completely dicated to the isothiourea, though with significant erosion of product er observed compared with the use of (R)-BTM-HCl.
Table 3: Mechanistic Control Studies and Proposed Mechanism for Cooperative Lewis Base and Brønsted Acid Catalysis.
and (Table 3F). To further probe the factors leading to product enantioselectivity, the effect of using a chiral iminium ion was investigated. Using a single enantiomer of (S)-hemiaminal ether 50, and both enantiomers of BTM-HCl, gave β-amino esters 51 and 52 as a single diastereoisomer in each case, consistent with the isothiourea catalyst determining enantioselectivity and overriding any control from the chiral iminium ion (Table 3G).

Based on these experiments, the reaction is proposed to proceed via cooperative Lewis base and Brønsted acid catalytic cycles (Table 3H). Reversible proton transfer from (R)-BTM-HCl to the hemiaminal ether generates the free isothiourea catalyst (for the Lewis base cycle) and the N-protonated hemiaminal ether for the Brønsted acid cycle. In the Brønsted acid cycle, proton transfer generates I, with subsequent formation of the iminium ion chloride salt II. In the Lewis base cycle, (R)-BTM can undergo reversible addition to the iminium ion II to give an aminoethylated catalyst III as an off-cycle intermediate that is inconsequential to the outcome of the reaction.[38] For the constructive formation of the β-amino ester, N-acylation of (R)-BTM with the pentafluorophenol ester generates an acyl ammonium pentafluorophenolate ion pair IV. Subsequent deprotonation generates the (Z)-C-(1)-ammonium enolate V, with a key 1,5-O=S contact.[39] that can be classified as either a chalcogen-chalcogen interaction[40,41] or chalcogen bond (n O to s2,π).[42] providing a conformational bias and ensuring coplanarity between the 1,5-O- and S-atoms. Enantioselective aminomethylation proceeds preferentially through reaction of the Re-face of the C(1)-ammonium enolate with the iminium ion II, leading to intermediate VI. Subsequent reaction with the pentafluorophenol generated in situ leads to the desired β-aminoo ester and regenerates the isothiourea Lewis base and Brønsted acid catalysts.

**Conclusion**

The development of an operationally simple, scalable and effective approach to the synthesis of α-aryl-β-amino esters via cooperative isothiourea tertiary amine Lewis base and Brønsted acid catalysis has been described. The utility of the method was demonstrated through an extensive substrate scope and the total synthesis of (S)-Venlafaxine-HCl 4 and (S)-Nakindine B I. Mechanistic investigations support a C(1)-ammonium enolate pathway rather than a DKR of an α-aryl-β-amino pentafluorophenyl ester. Control studies indicate that (i) a linear effect between catalyst and product er is observed; (ii) an acyl ammonium ion can be used as a precatalyst; (iii) reversible isothiourea addition to an in situ generated iminium ion leads to an off-cycle intermediate that is inconsequential to the outcome of the reaction. Ongoing work within this laboratory is exploring alternative cooperative catalytic procedures.[43]

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** aminomethylation · cooperative catalysis · isothiourea · mechanistic studies · α-aryl-β-amino acid

[1] F. Kudo, A. Miyanaga, T. Eguchi, *Nat. Prod. Rep.* 2014, 31, 1056.
[2] For review of peptides containing β-amino acids, see: a) C. Cabrele, T. Martinek, O. Reiser, L. Berliss, *J. Med. Chem.* 2014, 57, 9718; For a recent review of antimicrobial peptides, see: b) H. X. Luong, T. T. Thanh, T. H. Tran, *Life Sci.* 2020, 260, 118407.
[3] R. P. Cheng, S. H. Hellman, W. F. DeGrado, *Chem. Rev.* 2001, 101, 3219.
[4] For a discussion of the synthesis and biology of β-amino acids see: *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), Wiley-VCH, New York, 1997.
[5] T. Nishi, T. Kubota, J. Fromont, T. Sasaki, J. Kobayashi, *Tetrahedron* 2008, 64, 3127.
[6] C.-A. Geng, Y.-B. Ma, J.-J. Chen, *Chin. Chem. Lett.* 2013, 24, 236.
[7] a) J. F. Blake, R. Xu, J. R. Benešík, D. Xiao, N. C. Kallan, S. Schlachter, I. S. Mitchell, K. L. Spencer, A. L. Banka, E. M. Wallace, S. L. Glor, M. Martinson, R. D. Woessner, G. P. A. Vigers, B. J. Brandhuber, J. Liang, B. S. Safina, J. Li, B. Zhang, C. Chabot, S. Do, L. Lee, J. Oeh, D. Sampath, B. R. Lee, K. Lin, B. M. Liederer, N. J. Skelton, *J. Med. Chem.* 2012, 55, 8110; For selected syntheses of the core β-amino acid see: b) J.-H. Jian, C.-L. Hsu, J.-F. Syu, T.-S. Kuo, M.-K. Tsai, P.-Y. Wu, H.-L. Wu, *J. Org. Chem.* 2018, 83, 12184; c) T. Remarchuk, S. Babu, J. Stults, A. Zanotti-Gerosa, S. Roseblade, S. Yang, P. Huang, C. Sha, Y. Wang, *Org. Process Res. Dev.* 2014, 18, 155.
[8] a) G. E. M. Husbands, J. P. Yardley, E. A. Muth, U.S. Patent 4, 535,186, 1985; b) J. P. Yardley, G. E. M. Husbands, G. Stack, J. Butch, J. Bickels, J. A. Moyer, E. A. Muth, T. Andree, H. Fletcher III, M. N. G. James, A. R. Sileocek, *J. Med. Chem.* 1990, 33, 2899; c) A. T. Harvey, R. L. Rudolph, S. H. Preskorn, *Arch. Gen. Psychiatry* 2000, 57, 503.
[9] For reviews see: a) S. G. Davies, A. D. Smith, P. D. Price, *Tetrahedron: Asymmetry* 2005, 16, 2833; b) S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Tetrahedron: Asymmetry* 2012, 23, 1111.
[10] For selected examples, see: a) A. Tessier, N. Lahmar, J. Pytkowicz, T. Brigaud, *J. Org. Chem.* 2008, 73, 3970; b) J. E. Beddow, S. G. Davies, A. D. Smith, A. J. Russell, *Chem. Commun.* 2004, 2778.
[11] For a recent review of β-amino acid syntheses, see: H. Noda, M. Shibasaki, *Eur. J. Org. Chem.* 2020, 2350.
[12] a) M. P. Sibi, K. Patil, *Angew. Chem. Int. Ed.* 2004, 43, 1235; *Angew. Chem.* 2004, 116, 1255; b) H. M. L. Davies, C. Venkataramani, *Angew. Chem. Int. Ed.* 2002, 41, 2197; *Angew. Chem.* 2002, 114, 2301; c) A. Duursma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* 2003, 125, 3700; d) X. Lian, L. Lin, K. Fu, B. Ma, X. Liu, X. Feng, *Chem. Sci.* 2017, 8, 1238.
[13] a) J. Gong, S.-W. Li, S. Qurban, Q. Kang, *Eur. J. Org. Chem.* 2017, 3584; b) L. Feng, X. Dai, E. Meggers, L. Gong, *Chem.*
Asian J. Chem. 2017, 12, 963; c) C. Wang, Y. Zheng, H. Huo, P. Röse, L. Zhang, K. Harms, G. Hilt, E. Meggers, Chem. Eur. J. 2015, 21, 7355.

[14] a) Y. Chi, S. H. Gellman, J. Am. Chem. Soc. 2006, 128, 6804; b) Y. Chi, E. P. English, W. C. Pomerantz, W. S. Fleming, L. A. Joyce, L. R. Alexander, W. S. Fleming, E. A. Hopkins, S. H. Gellman, J. Am. Chem. Soc. 2009, 131, 6050; c) S. Liu, S. Gellman, J. Org. Chem. 2020, 85, 1718; d) Y. You, L. Zhang, L. Cui, X. Mi, S. Luo, Angew. Chem. Int. Ed. 2017, 56, 13814; Angew. Chem. 2017, 129, 14002.

[15] N. J. A. Martin, X. Cheng, B. List, J. Am. Chem. Soc. 2008, 130, 13862.

[16] a) C. D. Gheewala, B. E. Collins, T. H. Lambert, Science 2016, 357, 961; b) Z. Kang, Y. Wang, D. Zhang, R. Wu, X. Xu, W. H. Hu, J. Am. Chem. Soc. 2019, 141, 1473.

[17] J. Xu, X. Chen, M. Wang, P. Zheng, B. A. Song, Y. R. Chi, Angew. Chem. Int. Ed. 2015, 54, 5161; Angew. Chem. 2015, 127, 5290.

[18] For reviews, see: a) S. France, D. J. Guerin, S. J. Miller, T. Lectka, Angew. Chem. Int. Ed. 2004, 43, 6214; For a review of transition metal mediated catalysis in combination with C(1)-ammonium enolate intermediates, see: e) G. J. Knox, L. S. Hutchings-Goetz, C. M. Pearson, T. N. Snaddon, Top. Curr. Chem. 2018, 378, 16.

[19] For reviews of isocoumarins in catalysis see: a) J. Merad, J.-M. Pons, O. Chazel, C. Bressy, Eur. J. Org. Chem. 2016, 5519; c) D. G. Stark, L. C. Morrill, D. G. Stark, J. E. Taylor, S. R. Smith, J. A. Squires, A. C. D’Hollander, C. Simal, P. Shapland, T. J. C. O’Riordan, A. D. Smith, Org. Biomol. Chem. 2014, 12, 9016; d) D. G. Stark, L. C. Morrill, D. B. Cordes, A. M. Z. Slawin, T. J. C. O’Riordan, A. D. Smith, Chem. Asian J. 2016, 11, 395.

[20] For selected examples see: a) D. Belmesri, L. C. Morrill, C. Simal, A. M. Z. Slawin, A. D. Smith, J. Am. Chem. Soc. 2011, 133, 2714; b) L. C. Morrill, D. G. Stark, J. E. Taylor, S. R. Smith, J. A. Squires, A. C. D’Hollander, C. Simal, P. Shapland, T. J. C. O’Riordan, A. D. Smith, Org. Biomol. Chem. 2014, 12, 9016; c) D. G. Stark, L. C. Morrill, D. B. Cordes, A. M. Z. Slawin, T. J. C. O’Riordan, A. D. Smith, Chem. Asian J. 2016, 11, 395.

[21] H. Böhm, A. Sickmüller, Chem. Ber. 1977, 110, 208.

[22] The lack of reactivity observed for 35 was proposed to be a result of lower acidity of the c-alkyl acyl ammonium intermediate and so a range of Brønsted bases and acids additives were tested to try to promote the transformation. However, no reactivity could be observed. See supporting information for details.

[23] For selected other syntheses of venlafaxine see: a) C. V. Basappa Kavitha, K. S. Rangappa, Bioorg. Med. Chem. Lett. 2004, 14, 3279; b) S. P. Chavan, D. A. Khoobragade, M. Thakkar, U. R. Kalkote, Synth. Commun. 2007, 37, 3901; c) M. Saravanan, B. Satyanarayana, P. P. Reddy, Org. Process Res. Dev. 2011, 15, 1392; For selected enantioselective syntheses see: d) H. M. L. Davies, A. Ni, Chem. Commun. 2006, 3110; e) S. P. Chavan, K. P. Pawar, S. Garai, RSC Adv. 2014, 4, 44688; f) K. F. Chin, X. Ye, Y. Li, R. Lee, A. M. Kabylida, D. Locw, X. Zhang, E. C. X. Ang, C.-H. Tan, ACS Catal. 2020, 10, 2684.

[24] For other synthetic routes to Nakinadine B see: a) S. G. Davies, J. A. Lee, P. M. Roberts, R. S. Shah, J. E. Thomson, Chem. Commun. 2012, 48, 9236; b) Y. Garg, S. K. Pandey, RSC Adv. 2016, 6, 25913; For other asymmetric syntheses of Nakinadine derivatives see: c) S. G. Davies, A. M. Fletcher, R. S. Shah, P. M. Roberts, J. E. Thomson, J. Org. Chem. 2015, 80, 4017.

[25] D. Kaiser, V. Tona, C. R. Gonçalves, S. Shaaban, A. Oppedisano, N. Maulide, Angew. Chem. Int. Ed. 2019, 58, 14639; Angew. Chem. 2019, 131, 14781.

[26] For selected examples see: a) H. Böhm, M. Haake, Chem. Ber. 1967, 705, 147; b) A. R. Katritzky, C. V. Hughes, S. Rachwal, J. Heterocycl. Chem. 1989, 26, 1579; c) D. Schärer, V. Jindra, A. O. Bringhen, U. Burger, Helv. Chim. Acta 1991, 74, 1817; d) N. Allefeld, B. Neumann, H.-G. Stammeler, G.-V. Rosenthaler, N. Ignat’ev, B. Hoge, Chem. Eur. J. 2014, 20, 7736.

[27] Addition of (R)-BTM to N,N-dibenzylliminium chloride 45 in CDCl3, gave a mixture of products with amonothymethylated 46 a significant reaction product that was characterised in situ. This mixture was used as a stock solution in subsequent reaction processes (see SI for further information). As a linear correlation between catalyst and product er is observed, it seems unlikely that 46 can act as a direct enantioselective aminomethylating reagent with a BTM-derived C(1)-ammonium enolate.
For selected examples that highlight the importance of off-cycle intermediates in enantioselective organocatalysis see: a) J. Burés, A. Armstrong, D. G. Blackmond, Pure Appl. Chem. 2013, 85, 1919; b) D. D. Ford, D. Lehnherr, C. R. Kennedy, E. N. Jacobsen, J. Am. Chem. Soc. 2016, 138, 7866.

For discussions of the importance of 1,5-S···O interactions in isothiourea catalysis: a) V. B. Birman, X. Li, Z. Han, Org. Lett. 2007, 9, 37; b) P. Liu, X. Yang, V. B. Birman, K. N. Houk, Org. Lett. 2012, 14, 3268; c) M. E. Abbasov, B. M. Hudson, D. J. Tantillo, D. Romo, J. Am. Chem. Soc. 2014, 136, 4492; d) E. R. T. Robinson, D. M. Walden, C. Fallan, M. D. Greenhalgh, P. H.-Y. Cheong, A. D. Smith, Chem. Sci. 2016, 7, 6919; e) M. D. Greenhalgh, S. M. Smith, D. M. Walden, E. T. Taylor, Z. Brice, E. R. T. Robinson, C. Fallan, D. B. Cordes, A. M. Z. Slawin, H. C. Richardson, M. A. Grove, P. H.-Y. Cheong, A. D. Smith, Angew. Chem. Int. Ed. 2018, 57, 3200; Angew. Chem. 2018, 130, 3254; f) D.-J. Barrios Antúnez, M. D. Greenhalgh, A. C. Brueckner, D. M. Walden, P. Elias-Rodríguez, P. Roberts, B. G. Young, T. H. West, A. M. Z. Slawin, P. H.-Y. Cheong, A. D. Smith, Chem. Sci. 2019, 10, 6162; g) C. M. Young, A. Elmi, D. J. Pascoe, R. K. Morris, C. McLaughlin, A. M. Woods, A. B. Frost, A. de la Houplière, K. B. Ling, T. K. Smith, A. M. Z. Slawin, P. H. Willoughby, S. L. Cockroft, A. D. Smith, Angew. Chem. Int. Ed. 2020, 59, 3705; Angew. Chem. 2020, 132, 3734; for use of S···O interactions in asymmetric synthesis: h) Y. Nagao, S. Miyamoto, M. Miyamoto, H. Takeshige, K. Hayashi, S. Sano, M. Shiro, K. Yamaguchi, Y. Sci, J. Am. Chem. Soc. 2006, 128, 9722; for examples of S···O interactions in medicinal chemistry: i) B. R. Beno, K.-S. Yeung, M. D. Bartberger, L. D. Pennington, N. A. Meanwell, J. Med. Chem. 2015, 58, 4383; for a discussion on the origin of chalcogen-bonding interactions: j) D. I. Pascoe, K. B. Ling, S. L. Cockroft, J. Am. Chem. Soc. 2017, 139, 15160; For an excellent short overview see: k) M. Breugst, J. J. Koenig, Eur. J. Org. Chem. 2020, 5473.

For a review of 1.5-chalcogen bonding interactions in organo-selenium chemistry, see: a) A. J. Mukherjee, S. S. Zade, H. B. Singh, R. B. Sunoj, Chem. Rev. 2010, 110, 4357; For selected examples in catalysis, see: b) K. Fujita, M. Iwaoka, S. Tomoda, Chem. Lett. 1994, 23, 923; c) K. Fujita, K. Murata, M. Iwaoka, S. Tomoda, J. Chem. Soc. Chem. Commun. 1995, 1641; d) K. Fujita, K. Murata, M. Iwaoka, S. Tomoda, Tetrahedron Lett. 1995, 36, 5219; e) T. Wirth, Angew. Chem. Int. Ed. Engl. 1995, 34, 1726; Angew. Chem. 1995, 107, 1872; f) S.-I. Fukuzawa, K. Takahashi, H. Kato, H. Yamazaki, J. Org. Chem. 1997, 62, 7711; g) T. Wirth, S. Häuptli, M. Leuenberger, Tetrahedron: Asymmetry 1998, 9, 547; h) M. Tiecco, L. Testaferri, C. Santì, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, Tetrahedron: Asymmetry 2000, 11, 4645; i) M. Tiecco, L. Testaferri, C. Santì, C. Tomassini, F. Marini, L. Bagnoli, A. Temperini, Chem. Eur. J. 2002, 8, 1118; j) D. M. Browne, O. Niyomura, T. Wirth, Org. Lett. 2007, 9, 3169; k) Y. Kawamata, T. Hashimoto, K. Maruoka, J. Am. Chem. Soc. 2016, 138, 5206.

For an early theoretical investigation of chalcogen bonding, see: a) C. Bleibholder, R. Gleiter, D. B. Herz, H. Köppel, Inorg. Chem. 2007, 46, 2249; For a recent review, see: b) R. Gleiter, G. Haberhauer, D. B. Werz, F. Rominger, C. Bleibholder, Chem. Rev. 2018, 118, 2010; For a recent perspective see: c) S. Kolb, G. A. Oliver, D. B. Werz, Angew. Chem. Int. Ed. 2020, 59, 22306; Angew. Chem. 2020, 132, 22490.

For examples of chalcogen bonding catalysis see: a) S. Benz, J. Lópex-Andarias, J. Mareda, N. Sakai, S. Matile, Angew. Chem. Int. Ed. 2017, 56, 812; Angew. Chem. 2017, 129, 850; b) P. Wonner, L. Vogel, M. Ducer, L. Gomes, F. Kneip, B. Mallick, D. B. Werz, S. M. Huber, Angew. Chem. Int. Ed. 2017, 56, 12009; Angew. Chem. 2017, 129, 12172; c) P. Wonner, L. Vogel, F. Kniep, S. M. Huber, Chem. Eur. J. 2017, 23, 16972; d) P. Wonner, A. Dreger, L. Vogel, E. Engelage, S. M. Huber, Angew. Chem. Int. Ed. 2019, 58, 16923; Angew. Chem. 2019, 131, 17079; e) W. Wang, H. Zhu, S. Liu, Z. Zhao, L. Zhang, J. Hao, Y. Wang, J. Am. Chem. Soc. 2019, 141, 9175; f) W. Wang, H. Zhu, L. Feng, Q. Yu, J. Hao, R. Zhu, Y. Wang, J. Am. Chem. Soc. 2020, 142, 3117.

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Enantioselective Synthesis of α-Aryl-β-hydroxyamino-Esters by Cooperative Isothiourea and Brønsted Acid Catalysis

An operationally simple and effective catalytic enantioselective approach to α-aryl-β-hydroxyamino esters is demonstrated and applied to the synthesis of (S)-Venlafaxine·HCl and (S)-Nakinadine B. Mechanistic investigations support a C(1)-ammonium enolate pathway with reversible isothiourea addition to an in situ generated iminium ion leading to an off-cycle intermediate that can be used as a productive precatalyst.