BIMP Catalyzed 1,3-Prototropic Shift for the Highly Enantioselective Synthesis of Conjugated Cyclohexenones


Abstract: A bifunctional iminophosphorane (BIMP) catalyzed enantioselective synthesis of α,β-unsaturated cyclohexenones via a facially selective 1,3-prototropic shift of β,γ-unsaturated prochiral isomers, under mild reaction conditions and in short reaction times, on a range of structurally diverse substrates, is reported. α,β-Unsaturated cyclohexenone products formed for downstream derivatisation were obtained in high yields (up to 99%) and consistently high enantioselectivity (up to 99% ee). In-depth studies into the reaction mechanism and origins of enantioselectivity, including multivariate linear regression of TS energy, were carried out computationally on the catalytic system and the obtained data was found to be in good agreement with experimental findings.

Chiral conjugated cyclohexenones are valuable building blocks for synthesis, offering great versatility across a broad spectrum of reactions and applications.[1] A number of organocatalytic approaches have been explored to construct such scaffolds in an enantioselective manner, for example through the desymmetrisation of cyclohexadienones or Robinson annulation.[2] However, a powerful yet underdeveloped approach for their enantioselective synthesis is through the double bond migration of their β,γ-unsaturated prochiral isomers. Such transformations have been found to be catalyzed by a number of small molecule and enzymatic pathways and their reaction kinetics have been well-documented.[3] Until recently, chemocatalytic methods to accomplish this transformation enantioselectively proved elusive.[4] Currently, Deng’s approach to the enantioselective prototropic shift via cooperative Brønsted base / iminium ion catalysis offers the best solution for such a transformation, providing typically excellent yields and good enantioselectivities (Scheme 1A).[5] Despite these attributes, the reaction is limited in scope to allyl / allyl-substituted substrates at both the α- and β-positions and requires extended reaction times of on average 85 hours. Furthermore – and relevant to the current study – the Deng group reported that cinchona derived, bifunctional Brønsted base / H-bond donor catalysts used previously to perform related enantioselective isomerization of butenolides, were unable to effect the transformation, owing to the low acidity of the ketone’s α-proton.[6]

Attracted by the numerous synthetic applications of such an enantioselective transformation, we sought to identify an operationally simple, Brønsted base-catalyzed variant using our highly modular and tuneable bifunctional iminophosphorane (BIMP) superbase catalyst family. BIMP catalysts – like many other bifunctional organocatalysts – combine a Bronsted basic moiety with a hydrogen bond donor group linked through a chiral scaffold (Scheme 1B).[7] They have previously been demonstrated to impart high levels of reactivity and enantiocontrol across a diverse range of reactions including, ketimine nitro-Mannich additions, sulfur-Michael additions, conjugate additions to enone diesters, and – relating to this work – the cascade heptenone isomerization / enantioselective intramolecular Diels-Alder reaction key step of our group’s total synthesis of (−)-himalensine A.[8] It was envisaged that in conjunction with the catalyst’s hydrogen bond donor group, the superbasic iminophosphorane moiety would provide sufficient activation to deprotonate the weakly acidic α-position.[9,10] Kinetic and enantiodetermining reprotonation of the extended enolate would then occur preferentially at the γ-position in an enantioselective manner, to afford the desired cyclohexenone product.[10] Our aim, was to identify a catalyst system that would efficiently deliver excellent levels of enantioselectivity across a wide range of substrates in a short reaction time, and herein we wish to report our findings.

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Supporting information for this article is given via a link at the end of the document.
We began our investigation using Hagemann’s ester-derived β,γ-cyclohexenone 1a (see SI). Guided by our previous work, initially, we investigated for performance a range of 1st generation BIMP catalysts (3a-d) including catalyst 3a used previously in the total synthesis of (−)-himalensine A. Each catalyst provided the product in low to moderate yield (17-53%) with low levels of enantioselectivity (1-14% ee). Notably, more basic P(PMP)₂ derived iminophosphoranes performed with improved catalytic activity in comparison with those derived from PPh₃ (Scheme 2). Accordingly, we turned our attention to P(PMP)₂ derived 2nd generation BIMP catalysts and with catalyst 3e, substrate 1a underwent the 1,3-prototropic shift in decent yield (67%) however enantiocontrol (18% ee) remained poor. Replacing the tert-butyl substituent at stereocentre a with methylnaphthyl group – to provide catalyst 3f – unfortunately led to almost complete loss of reactivity and offered no improvement in enantioselectivity. Consequently, the performance of catalyst 3g, 3e's diastereomer, was investigated which interestingly led to a significant uplift in both enantioselectivity (85% ee) and yield (97%). Two configurationally related catalysts, 3h and 3i, possessing phenyl and methylnaphthyl groups at stereocentre b respectively were synthesized and their performance investigated. Impressively, methylnaphthyl containing catalyst 3i resulted in the formation of 2a in near quantitative yield after 24 hours and 99% ee.

With optimal catalyst and conditions identified, the scope of the enantioselective prototropic shift was investigated (Scheme 3A). Wide variation to the ether substituent was well-tolerated with high yields and enantioselectivities (>95% ee) being obtained for products 2b-e. Almost complete enantiocontrol and conversion to O-TBS protected product 2f was witnessed even upon scale up to 1.5 g. Furthermore, unprotected alcohol 1g was a viable substrate providing 2g in good yield and 85% ee. We sought to apply our method to the synthesis of a key building block in the construction of both (−)-reserpine and (−)-penitrem D, achieved by Stork and co-workers and Smith et. al. respectively (Scheme 3B). Isomerization substrate 1h was synthesized in a single step using methodology developed by Hilt, and smoothly underwent the 1,3-prototropic shift to afford 2h in 64% yield and 92% ee removing a total of 4 steps from 2h's previously reported synthesis.

In further exploration of the reaction scope we looked at the effect of pendant-heteroatom variance on reactivity and selectivity (Scheme 3A). N-Boc protected amines 2i and 2j were found to perform particularly well in the 1,3-prototropic shift with both high yields and enantioselectivities being obtained in both cases. We turned our attention to more complex amine-based functionalities to introduce further structural diversity. Accordingly, hydrazine and hydroxylamine functionalized substrates 1k and 1l were synthesized. Both compounds underwent the 1,3-prototropic shift in high yield and excellent enantioselectivity. Heterocyclic appendages incorporated into the starting material, for example, an indole substituent attached at the 5-position (2m), performed consistently. Introduction of an amido furan moiety was easily achieved and subjection to the standard reaction conditions afforded 2n and 2o in high yield and 99% and 97% ee, respectively. Pleasingly bis-phenylated substrate 1p performed equally well with the product 2p being obtained in 76% yield and impressive 94% ee.

A significant drop in reactivity was encountered with substrate 1q. Based on a previous study by Whalen and co-workers it was more than likely that the rate-limiting step of the prototropic shift would show Brønsted base strength dependence. Thus, to further augment Brønsted base strength we surveyed a range of iminophosphoranes whilst maintaining the chiral H-bond donor scaffold (see SI). A significant uplift in reactivity with a tributlyphosphate-derived iminophosphorane was observed although the conversion was poor over the standard reaction time and the selectivity decreased significantly (20% yield, 87% ee).

Pleasantly, switching the hydrogen bond donor motif to a urea group provided the uplift in reactivity we desired. After re-optimization of the reaction conditions we were able to perform the 1,3-prototropic shift on substrate 1q to afford 2q in 62% yield and impressive 97% ee. Having successfully re-tuned the BIMP catalyst for enhanced performance we proceeded to expand the reaction scope with a selection of challenging substrates (Scheme 3C). Bis-propyl substrate 1r underwent the prototropic shift in 50% yield and 97% ee. Replacement of the β-substituent with a phenyl group (1s) allowed smooth conversion to its chiral counterpart (2s) in 63% yield and 95% ee. Enhancing the electron density on the phenyl ring by introducing a para-methoxy group had little effect on reactivity (1t) and the desired product could be obtained in good yield and excellent enantioselectivity.

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\text{Scheme 2: Catalytic Optimization}^{[4]} \text{ Reactions were carried out with 0.065 mmol of 1a. Enantiomeric excess (ee) was determined by HPLC analysis on chiral stationary phase. [5] NMR yield. [6] Reaction was carried out with 0.28 mmol of substrate.}
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As the product cyclohexenones are rich in functionality we were keen to demonstrate their downstream derivatisation and synthetic potential (Scheme 4A). This was realized through the removal of 2f’s TBS group and activation of the free alcohol through tosylation in high yield, to provide 4a in 99% enantiopurity. The tosylate could then be used to introduce further functionality. Formation of azide 4b occurred rapidly at 45 °C in modest but unoptimised yield, however, the enantiopurity was maintained. Similarly, base-mediated reaction of thiophenol with 4a resulted in the formation of enantioenriched thioether 4c. The free alcohol could also be transformed into xanthate 4d and subsequent treatment with tributyl tin hydride and AIBN provided us with the enantiopure cyclic thionolactone 4e from which the absolute configuration could be obtained through single crystal X-ray diffraction analysis. Prolonged heating of 2n effected an intramolecular Diels-Alder reaction to afford the stereochemically congested tricyclic scaffold 4f with high ee (Scheme 4B).

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Having succeeded in the development of an enantioselective Bønnsted base catalyzed 1,3-prototropic shift, we then turned our investigation to the mechanistic pathway and origins of enantioselectivity using in-depth computational analysis. Transition structures (TSs) were located for substrate 1a undergoing successive α-deprotonation and γ-reprotonation by BIMP catalyst 3i, resulting in the Gibbs energy profile shown in Figure 1. The reprotonation TSs are higher in energy, making this the rate- and enantio-determining step. Along this reaction coordinate the bifunctional catalyst engages the substrate oxygen with a dual H-bonding interaction from both thiourea N-H protons. Consistent with experimental observations, the (S)-enantiomer is favored in this step by 2.2 kcal/mol, equivalent to a computed ee value of 95%. Computations also predict that α-deprotonation will occur reversibly, consistent with deuterium exchange between labelled and unlabelled.
The catalyst:dienolate ion-pair can reversibly dissociate prior to the irreversible protonation taking place. We performed a systematic conformational analysis of competing TSs, including varied substrate ring conformations and rotations about single bonds. In the preferred TSs, the thiourea binds the substrate oxygen while the iminophosphorane participates as proton acceptor and then donor. Alternative modes of N-H proton transfer from the catalyst to substrate from the (thio)urea were much higher in energy and are not expected to contribute to the observed reactivity (see SI). We located 112 different TS conformers and used statistical modeling to identify the most important structural features that influence their stability. Multivariate linear regression was performed to predict the conformational energy ($R^2$ 0.85 (train), 0.80 (test), 0.80 (5-fold CV)), from which the statistically significant geometric features, automatically selected during model construction, are shown in the SI.

The substrate conformation is decisive in terms of enantioselectivity. The more favorable (S)-TS has less torsional strain and less 1,3-allylic strain. As shown in Figure 2 the (R)-TS has greater eclipsing interactions in the ring and, due to the orientation of the alkoxy group, greater A$_{1,3}$-strain. Indeed, the computed substrate distortion energy is 1.6 kcal/mol greater in this TS, which is disfavored (ΔG$^\ddagger$) by 2.2 kcal/mol overall.

In summary, we have uncovered a new Brønsted base catalyzed 1,3-prototropic shift for the synthesis of enantioenriched, functionalized cyclohexenones using our BIMP family of catalysts and have investigated the mechanistic pathway and origins of enantioselectivity in detail using DFT. The isomerization was found to proceed in high yield within a short time frame and demonstrates impressive levels of enantioselectivity across a range of functionally interesting substrates which could be further derivatized to introduce more diversity and functionality. The catalyst itself has been shown to be versatile enough to overcome reactivity issues through the...
modification of its Brostad base strength, whilst maintaining good enantiocontrol; a design feature we hope to exploit in other challenging synthetic transformations.

Acknowledgements

J. G. is grateful to the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1) for a studentship, generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB and Vertex. L. S. also thanks the MINECO (CTQ2017-87529-R) for financial support. Dr. Heyao Shi is also thanked for X-ray structure determination of compound 4e, and Dr. Amber L. Thompson and Dr. Kirsten E. Christensen (Oxford Chemical Crystallography) for X-ray mentoring.

Keywords: chiral cyclohexenone • prototopic shift • BIMP catalysis • enantioselective • superbase


4a could not be synthesized directly via the prototopic shift owing to the lability of the pendant tosyl group.