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Catalytic Enantioselective Intramolecular Aza-Michael Addition to α,β-Unsaturated Esters

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ABSTRACT

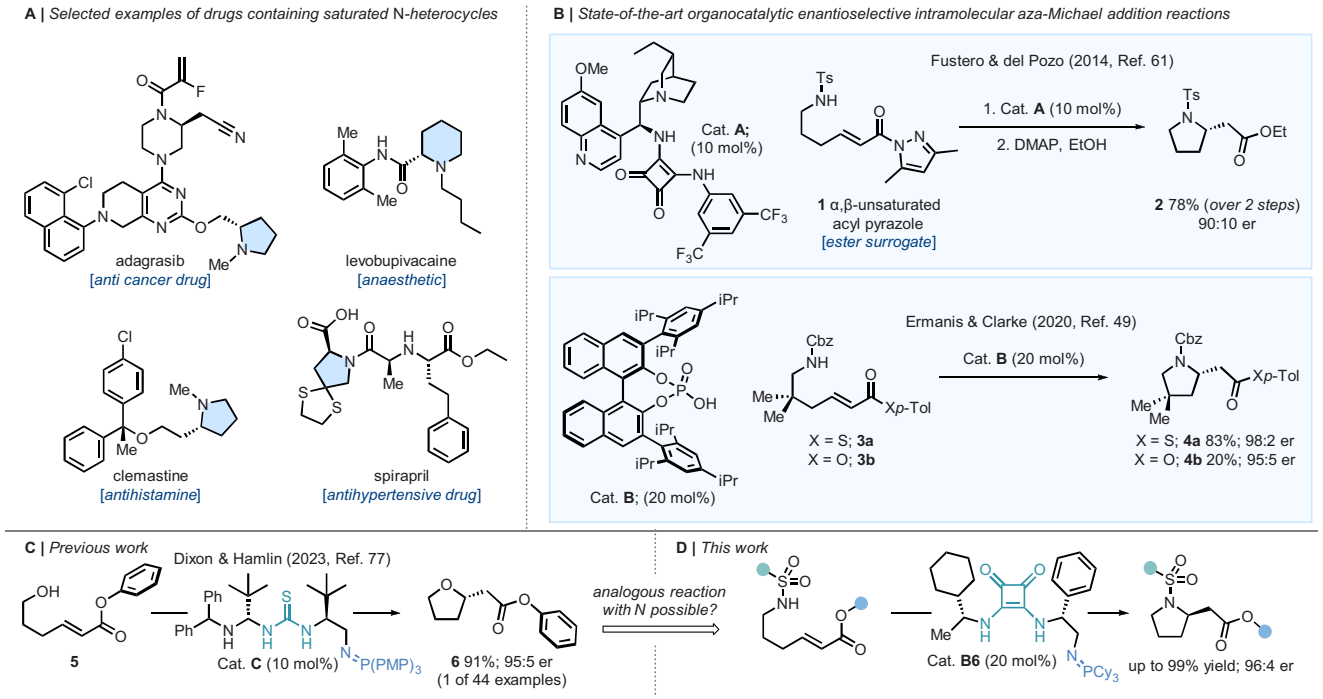
A bifunctional iminophosphorane (BIMP)-catalyzed enantioselective intramolecular aza-Michael reaction of sulfonamides to tethered α,β-unsaturated esters is described. Reactivity toward traditionally challenging ester Michael acceptors is achieved through careful catalyst design, enabling the synthesis of enantioenriched pyrrolidines, piperidines, and indoline derivatives in excellent yields (up to 99%) and enantiomeric ratios (up to 97.5:2.5 er) under operationally simple conditions. The broad reaction scope demonstrates excellent tolerance to variation in the sulfonamide group, the Michael acceptor, and substituents on the tether in between. Furthermore, the synthetic utility of the method is highlighted by gram-scale reactions at reduced catalyst loadings and by downstream derivatization of multiple enantiopure products.

1 | Introduction

Chiral saturated nitrogen heterocycles are ubiquitous in natural products [1–3] and pharmaceuticals [4–7], including the $KRAS^{G12C}$ inhibitor adagrasib [8], the local anaesthetic drug levobupivacaine [9], and the histamine H1 antagonist clemastine [10] (Scheme 1A). A 2024 review reports that 82% of FDA-approved small molecule drugs from 2013 to 2023 contain a nitrogen heterocycle, with piperidines and pyrrolidines ranking as the second and third most prevalent, respectively [4]. In recent years, spirocyclic pyrrolidines and piperidines, for example, the ACE inhibitor spirapril [10] (Scheme 1A), have received increasing attention in the pharmaceutical sector due to their stereochemically defined three-dimensional structures, which often exhibit improved binding to biological targets [11–14]. Consequently, the development of novel catalytic methods for constructing these motifs remains of significant importance [15–17].

Amongst the most direct strategies for the synthesis of enantioenriched saturated *N*-heterocycles [18–39] is the catalytic enantioselective intramolecular aza-Michael reaction (IMAMR) [17]. Although catalytic enantioselective IMAMR processes involving α,β-unsaturated aldehydes [40–43], ketones [44–48], and thioesters [49–51] are well developed, the analogous reaction employing synthetically attractive and more readily accessible α,β-unsaturated esters remains comparatively unexplored [52–59]. This limitation likely arises from the reduced electrophilicity of the ester-based Michael acceptors [60].

State-of-the-art approaches (Scheme 1B) include the catalytic enantioselective IMAMR to more activated α,β-unsaturated pyrazole amides reported by Fustero and del Pozo [61]. However, in order to unmask the corresponding ester product, alcoholysis of the pyrazole amide is required in a subsequent step, resulting in a less atom-efficient process overall. Additionally, Ermanis and



SCHEME 1 | (A) Selected examples of small molecule drugs containing saturated *N*-heterocycles. (B) State-of-the-art organocatalytic enantioselective intramolecular aza-Michael reactions and limitations with respect to α,β-unsaturated ester Michael acceptors. (C) Previous work by our group on catalytic enantioselective intramolecular oxa-Michael reaction to α,β-unsaturated esters and amides. (D) This work.

Clarke disclosed a chiral phosphoric acid-catalysed IMAMR to α,β-unsaturated thioesters [49–51], achieving excellent yields and enantioselectivities. In contrast, applying this catalytic system to the corresponding ester Michael acceptors resulted in a dramatic decrease in yield from 83% to 20%, underscoring both the diminished electrophilicity of α,β-unsaturated esters relative to their aldehyde, ketone, and thioester counterparts, and the ongoing challenge of developing a general catalytic method for this transformation.

Building on recent advances in iminophosphorane catalysis [62–76], in 2023 our group reported a general method for the catalytic enantioselective intramolecular oxa-Michael reaction to α,β-unsaturated esters and amides (Scheme 1C) [77], highlighting the advantages of employing a high-pK_{BH+} bifunctional iminophosphorane (BIMP) catalyst to activate high-pK_a pronucleophiles [63]. The reported findings suggested that an analogous aza-Michael reaction might also be feasible (Scheme 1D). Herein, we describe the catalytic enantioselective IMAMR of suitably protected amine-derived pronucleophiles using highly basic BIMP catalysts and present our findings on the development of this transformation.

2 | Results and Discussion

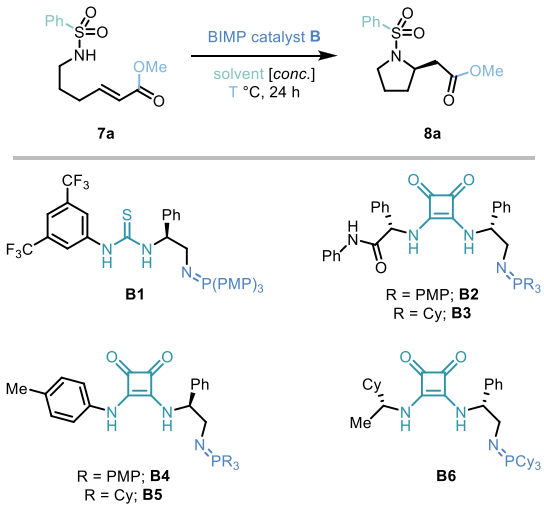
Preliminary studies examining various *N*-protected amines (*N*-Boc, *N*-Ph, *N*-SO_2Ph) led us to focus on the cyclization of sulfonamide model substrate **7a** into enantioenriched pyrrolidine **8a**. Initial evaluation of a small set of BIMP catalysts revealed that thiourea-derived catalyst **B1** promoted the conversion of precursor **7a** to the enantioenriched pyrrolidine **8a** in 66% conversion and 29:71 er (Table 1, entry 1). Modification of the hydrogen bond donor moiety to a squaramide group (catalyst **B2**) afforded similar results (Table 1, entry 2). Improved performance was observed when the phosphine component was replaced with the more electron-rich tricyclohexylphosphine (catalyst **B3**), delivering **8a** in 91% conversion and 75.5:24.5 er (Table 1, entry 3).

Squaramide catalysts **B4** and **B5** both achieved full conversion, providing **8a** in 25:75 and 21:79 er, respectively (Table 1, entries 4 and 5), with the superior performance of **B5** attributed to the incorporation of the tricyclohexylphosphine unit. Increasing the steric bulk around the additional stereocentre adjacent to the squaramide (catalyst **B6**) further enhanced the enantioselectivity to 83.5:16.5 er (Table 1, entry 6).

Following systematic optimization of solvent, temperature, concentration and catalyst loading (Table 1, entries 7–10, see Supporting Information for full details of optimisation), we were pleased to find that substrate **7a** underwent full conversion to **8a** with 93.5:6.5 er with catalyst **B6** (20 mol%) when the reaction was conducted in tetrahydropyran (THP) at a concentration of 0.1 M and a temperature of −22°C (Table 1, entry 10).

With the optimized conditions in hand, we next explored the scope of the reaction (Scheme 2). We first examined the influence of ring size and the alkoxy substituent of the Michael acceptor. Encouragingly, pyrrolidine precursors **7b** and **7c,** bearing ethyl and *tert*-butyl ester Michael acceptors, respectively, were converted to pyrrolidines **8b** and **8c** with good levels of enantiocontrol (>90:10 er). Although **8b** was obtained in excellent yield (96%), the more sterically demanding and less electrophilic *tert*-butyl ester [60] delivered **8c** in a more modest 26% yield.

TABLE 1 | Selected experiments for the optimization of the catalytic enantioselective intramolecular aza-Michael reaction to α,β-unsaturated esters.



entry	cat. (loading)	solvent (conc.)	T (°C)	conv. (%)[a]	er[b]
1	**B1** (10 mol%)	THF [0.5 M]	rt	66	29:71
2	**B2** (10 mol%)	THF [0.5 M]	rt	65	66.5:33.5
3	**B3** (10 mol%)	THF [0.5 M]	rt	91	75.5:24.5
4	**B4** (10 mol%)	THF [0.5 M]	rt	>99	25:75
5	**B5** (10 mol%)	THF [0.5 M]	rt	>99	21:79
6	**B6** (10 mol%)	THF [0.5 M]	rt	>99	83.5:16.5
7	**B6** (10 mol%)	1,4-dioxane [0.5 M]	rt	>99	87.5:12.5
8	**B6** (5 mol%)	1,4-dioxane [0.5 M]	rt	78	86.5:13.5
9	**B6** (10 mol%)	THP [0.5 M]	rt	>99	85:15
10	**B6** (20 mol%)	THP [0.1 M]	−22	>99 (92)[c]	93.5:6.5

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture.
[b]Determined by HPLC on a chiral stationary phase.
[c]Isolated yield.

We were also pleased to find that pyrrolidine precursor **7d**, bearing a tertiary amide Michael acceptor, underwent cyclization to furnish the corresponding enantioenriched pyrrolidine in 82% yield and 97.5:2.5 er. An extended reaction time of 7 days was, however, required to compensate for the reduced reactivity of the unsaturated amide [60].

Changing the ring size from five- to six-membered (**7e**) required an elevated reaction temperature (room temperature) to achieve >90% yield of **8e**; however, this resulted in a notable decrease in enantioselectivity (68.5:31.5 er). Finally, the reaction was readily performed on a 150 mg scale, affording enantioenriched pyrrolidine **8a** in 98% yield with a slight improvement in enantiomeric ratio to 94.5:5.5 er.

Variation of the sulfonyl group was broadly tolerated, with both electron-rich and electron-deficient heteroaromatic substituents proving compatible under the reaction conditions. Substrates bearing benzyl, pyridine, furan, thiophene, and isoxazole-derived sulfonyl groups (**7f-7j**) underwent smooth cyclization to furnish products **8f-8j** in moderate to excellent yields (58%–99%) and with consistently high levels of enantiocontrol (>90:10 er). We next examined more sterically demanding aromatic groups. Encouragingly, increasingly hindered aromatic groups were also well tolerated (**7k-7m**), affording pyrrolidines **8k-8m** without substantial loss in efficiency or selectivity.

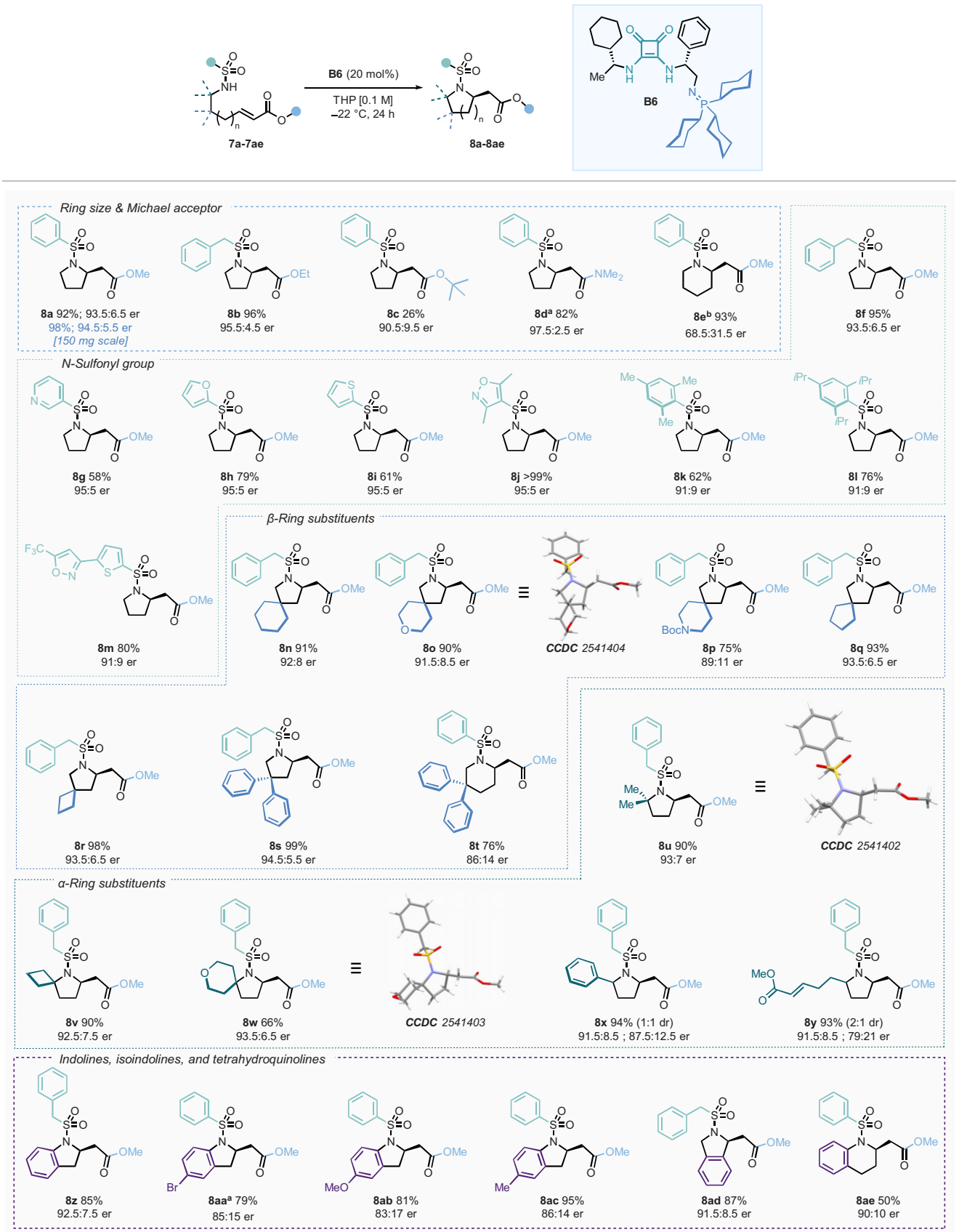
After examining the variation of the Michael acceptor and sulfonyl group, we next explored the effect of substitution along the amine tether. Precursors **7n-7p**, bearing cyclohexane, tetrahydropyran, and *N*-Boc piperidine substituents at the β-position relative to the amine, underwent efficient cyclization to furnish the corresponding spiropyrrolidines **8n-8p** in good yields (75%–91%). High levels of enantiocontrol were maintained for substrates **8n** and **8o** (>90:10 er), whilst spiropyrrolidine **8p** containing the *N*-Boc piperidine unit was obtained with a slightly diminished enantiomeric ratio (89:11 er). Single-crystal x-ray diffraction (SCXRD) analysis of a recrystallised sample of **8o** established the absolute stereochemical configuration of the major enantiomer as (*R*) [78].

Variation of the ring size at the β-position was also well tolerated, with five- and four-membered ring containing substrates **7q** and **7r** smoothly cyclizing to afford spiropyrrolidines **8q** and **8r** in excellent yields and with high levels of enantiocontrol (>90:10 er). Gratifyingly, pyrrolidine and piperidine precursors **7s** and **7t** bearing a bulky *gem*-diphenyl substituent at the β-position underwent smooth cyclization to deliver pyrrolidine **8s** in 99% yield and 94.5:5.5 er, and piperidine **8t** in 76% yield and 86:14 er. Notably, enantioenriched piperidine **8t** could also be formed at −22°C in 76% yield, enabling improved enantioselectivity (86:14 er) relative to its unsubstituted analogue **8e**, likely due to a reduced kinetic barrier to cyclization [79].

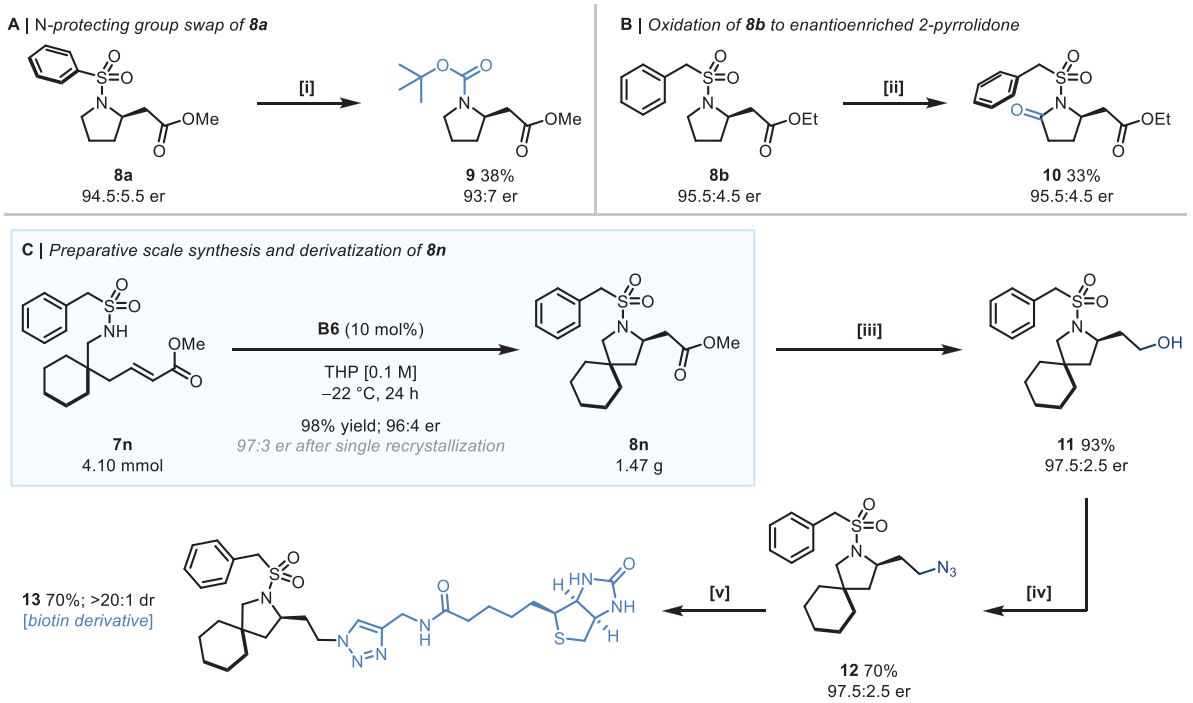
The effects of introducing substituents in the α-position relative to the amine were next examined. Pyrrolidine precursor **7u** bearing a *gem*-dimethyl group underwent smooth conversion to **8u** in 90% yield and 93:7 er. Replacing this substituent with a cyclobutyl group (**7v**) also afforded **8v** in excellent yield (90%) and enantioselectivity (92.5:7.5 er), whilst tetrahydropyran-substituted precursor **7w** delivered **8w** in good yield (66%), and with good enantiocontrol (93.5:6.5 er). SCXRD analysis of **8u** and **8w** confirmed the absolute stereochemical configuration of both products as (*R*) [78].

Racemic substrate **7x**, bearing a phenyl substituent α to the nitrogen, was converted to **8x** (and epi-**8x**) in 94% yield as a 1:1 mixture of inseparable diastereomers, each formed with high enantioselectivity. Unfortunately, the difference in reaction rates between the two enantiomers of the starting material was insufficient to enable an effective kinetic resolution of **7x** using this catalyst system. Similarly, desymmetrization precursor **7y** afforded pyrrolidine **8y** (and epi-**8y**) in 93% yield as a 2:1 mixture of inseparable diastereomers. Although the major diastereomer was formed with good enantiocontrol (91.5:8.5 er), the small difference in reaction rates leading to the two diastereomers precluded the development of an efficient desymmetrization process.

With general reactivity established, we envisioned extending this methodology to a different substrate class incorporating an aromatic ring within the tether, thereby providing access to enantiomerically enriched benzannulated nitrogen heterocycles. Indoline precursor **7z** was converted to **8z** in 85% yield and with good enantiocontrol (92.5:7.5 er). Substituents on the aromatic ring were also well tolerated. Precursors **7aa** (*p*-Br), **7ab** (*p*-OMe), and **7ac** (*p*-Me) furnished products **8aa**-**8ac** in good yields (79%-95%). The electron-deficient *para*-bromo aniline **7aa** required



SCHEME 2 | Scope of BIMP catalysed enantioselective intramolecular aza-Michael addition to α,β-unsaturated esters; reactions were carried out on a 0.1 mmol scale; all yields refer to isolated yields; er were determined by HPLC analysis on a chiral stationary phase; dr were determined by crude ^{1}H NMR analysis; variations from standard conditions: [a]7 days; [b]room temperature.



SCHEME 3 | (A) *N*-protecting group swap of **8a**. (B) Oxidation of **8b** to enantioenriched 2-pyrrolidone. (C) Preparative scale synthesis and derivatization of **8n**. All yields refer to isolated yields; er were determined by HPLC or SFC analysis on a chiral stationary phase; dr were determined by crude ^{1}H NMR analysis. (i) Mg (25 equiv.), MeOH (0.05 M), ultrasound, 1 h; *then* Boc_2O (1.5 equiv.), NEt_3 (3 equiv.), DMAP (20 mol%), CH_2Cl_2 (0.05 M), 16 h. (ii) ketoABNO (25 mol%), *m*CPBA (4.3 equiv.), MeCN (0.1 M) r.t., 20 h. (iii) $LiAlH_4$ (2 equiv.), THF (0.1 M), 0°C, 15 min. (iv) PPh_3 (1.5 equiv.), DIAD (1.5 equiv.), DPPA (1.5 equiv.), THF (0.1 M), r.t., 17 h. (v) (3a*S*,4*S*,6a*R*)-Hexahydro-2-oxo-*N*-2-propyn-1-yl-1*H*-thieno[3,4-*d*]imidazole-4-pentanamide (1 equiv.), sodium ascorbate (25 mol%), $CuSO_4.5H_2O$ (10 mol%), H_2O/THF 1/1 (0.175 M), r.t., 20 h.

an extended reaction time of 7 days and delivered slightly lower enantioselectivity than the unsubstituted analogues (>83:17 er).

The reactivity of isoindoline precursor **7ad** was subsequently examined, affording **8ad** in good yield (87%) whilst maintaining high enantioselectivity (91.5:8.5 er). Finally, sulfonyl-protected aniline **7ae** was converted to tetrahydroquinoline **8ae** in 50% yield - consistent with the lower reactivity observed for other six-membered ring precursors - whilst delivering a pleasing 90:10 er.

Having established a broad substrate scope, we next investigated the synthetic utility of the methodology by evaluating its scalability and derivatization of enantioenriched products. Removal of the sulfonyl group in pyrrolidine **8a** was accomplished by sonication with magnesium in methanol. The resulting intermediate was subsequently protected with Boc_2O to afford enantioenriched *N*-Boc-protected pyrrolidine **9** in 38% yield, without erosion of enantiomeric ratio (Scheme 3A). In addition, ethyl-ester containing **8b** was oxidised to the corresponding lactam **10** in 33% yield using a 9-azabicyclo[3,3,1]nonan-3-one-9-oxyl (ketoABNO)/*m*CPBA-mediated oxidation protocol developed by Lin et al. (Scheme 3B) [80].

Finally, we were pleased to find that reducing the catalyst loading to 10 mol% enabled the conversion of spiropyrrolidine precursor **7n** to enantioenriched spiropyrrolidine **8n** on a 1.5 g scale in 98% yield and 96:4 er (Scheme 3C). The enantiomeric ratio was further improved to 97:3 er following a single recrystallization from hexane. The enantioenriched material was then transformed into the corresponding azide **12** in 65% yield over two steps without loss of optical purity. This sequence involved the reduction of the ester to alcohol **11** using $LiAlH_4$, followed by a Mitsunobu reaction with diphenylphosphoryl azide. The resulting azide underwent a copper-catalysed [3+2] cycloaddition with biotin-derived alkyne (3a*S*,4*S*,6a*R*)-hexahydro-2-oxo-*N*-2-propyn-1-yl-1*H*-thieno[3,4-*d*]imidazole-4-pentanamide, furnishing biotin derivative **13** in 70% yield and with excellent diastereoselectivity (>20:1 dr).

3 | Conclusion

In conclusion, we have developed the first general catalytic enantioselective intramolecular aza-Michael reaction of α,β-unsaturated esters without the need for preactivation strategies. Through careful modification of a modular bifunctional iminophosphorane catalyst and extensive reaction optimisation, we achieved high yields (up to 99%) and enantioselectivities (up to 97.5:2.5 er) across a broad scope of 31 substrates, demonstrating the robustness and synthetic utility of the method. Notably, this protocol is operationally simple: all reactions were performed under air with technical-grade solvents, underscoring the tolerance of the reaction to trace moisture. The reaction is readily scalable to a 1.5 g scale with reduced catalyst loading, delivering improved yield (98%) and enantiomeric ratio (96:4 er; 97:3 er after a single recrystallization). This practical and efficient

method provides streamlined access to highly enantioenriched nitrogen-containing heterocycles, particularly pyrrolidines and spiropyrrolidines, which are valuable scaffolds in pharmaceutical chemistry [4] and natural product synthesis [1]. Efforts to expand the range of enantioselective transformations amenable to BIMP catalysis are ongoing in our laboratory, and the results will be reported in due course.

Author Contributions

Evan G. W. Rutter: investigation, methodology, formal analysis, and writing – original draft, review and editing. **Cameron J. MacRae:** investigation, methodology, and formal analysis. **Haoran Xiong:** methodology, investigation, and formal analysis. **Daniel Rozsar:** investigation, methodology, formal analysis, supervision, and conceptualization. **Katherine F. P. Clarke:** data curation and formal analysis. **Darren J. Dixon:** conceptualization, supervision, project management, and writing – original draft, review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

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78. Deposition Numbers 2541404 (for **8o**), 2541402 (for **8u**), 2541403 (for **8w**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: ange72927-sup-0001-SuppMat.pdf.