Isothiourea-catalyzed asymmetric synthesis of β-lactams and β-amino esters from arylacetic acid derivatives and *N*-sulfonyl aldimines

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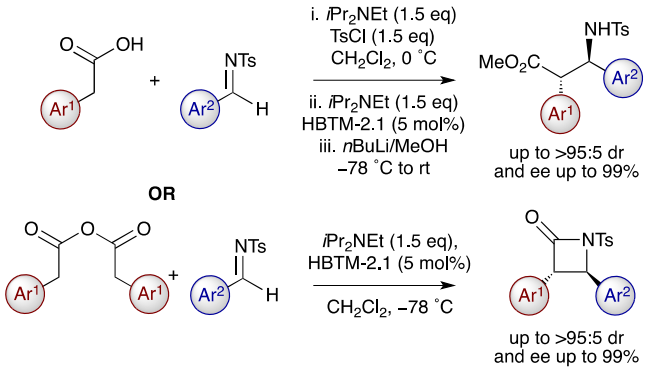


Abstract:

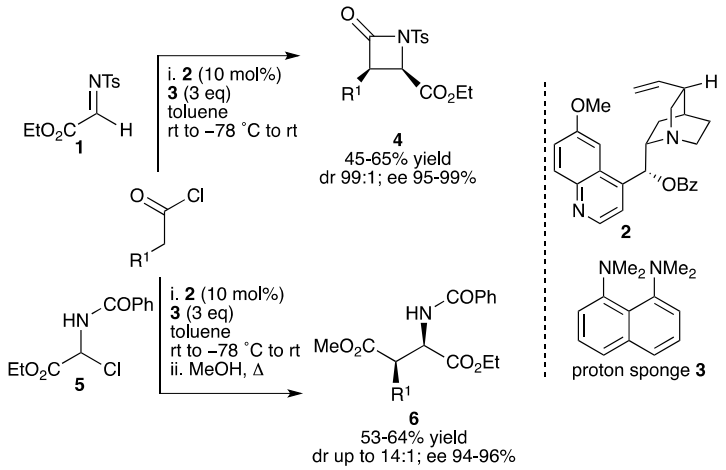
The isothiourea HBTM-2.1 (5 mol%) catalyzes the asymmetric formal [2+2] cycloaddition of both arylacetic acids (following activation with tosyl chloride) and preformed 2-arylacetic anhydrides with *N*-sulfonyl aldimines, generating stereodefined 2,3-diaryl-β-amino esters (after ring-opening) and 3,4-diaryl-*anti*-β-lactams respectively with high diastereocontrol (up to >95:5 dr) and good to excellent enantiocontrol. Deprotection of the *N*-tosyl substituent within the β-lactam framework was possible without racemisation by treatment with SmI_2.

Introduction

The β-lactam motif continues to find great importance in the pharmaceutical and biochemical sciences as well as generating significant interest from the broader synthetic community.[1] Their historically widespread role as antibacterial agents has come under increased pressure due to recent discoveries of bacterial strains resistant to current drugs.[2] This challenge, coupled with their emerging use in non-antibacterial therapeutic areas such as serine protease inhibitors and cholesterol absorption inhibitors,[3] makes the development of synthetic methods to prepare novel β-lactam based scaffolds a valuable endeavor.[1-3]

The most enduring synthetic route to access β-lactams remains the formal [2+2] cycloaddition of ketenes and imines[4] that was first reported by Staudinger in 1907.[5] Chiral auxiliary methods were used historically to control the relative and absolute product configuration within this process.[6] More recent approaches have detailed, amongst others,[7] the use of chiral Lewis base catalysis,[8] with pioneering work within this area initially reported by Lectka and co-workers.[9] Using cinchona alkaloid derivative **2**, a range of *syn*-3,4-disubstituted-β-lactams **4** was accessed in excellent yield (typically >90%) and with superb diastereo- and enantioselectivity (typically >90:10 dr and 99% ee), derived from the use of *in situ* generated mono-substituted ketenes and activated aldimine **1**. An alternative two-step β-lactam formation and ring-opening sequence provided both β-amino amides and esters in moderate yield (typically 40-60%) and with excellent diastereo- and enantioselectivity (dr up to 14:1 and up to 96% ee) (Scheme 1). A variety of related synthetic methods has been investigated, predominantly through Lewis base catalyzed processes involving isolable disubstituted ketenes and imines. For example, Fu has used a planar chiral PPY derivative to selectively generate either *syn*- or *anti*-β-lactams using *N*-tosyl and *N*-triflyl aldimines respectively.[10] Alternatively, NHCs[11] have been used by Ye[12] and ourselves,[13] while Kerrigan[14] has used a chiral phosphine to prepare α,α-disubstituted β-lactams with good to excellent levels of stereocontrol. Despite these

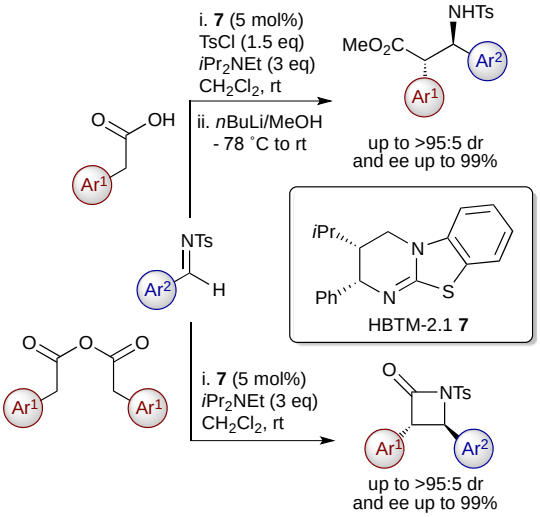
precedents, there remains a clear rationale for the development of synthetic methods directed towards the synthesis of alternative substitution patterns within the β-lactam core, especially if such a process could be rendered both catalytic and asymmetric.



Scheme 1: Lectka's route to β-lactams and β-amino esters

Following their induction as acyl transfer agents by Birman[15] and Okamoto[16] the use of isothioureas as Lewis base catalysts has seen appreciable recent growth, with a range of processes that utilize these catalysts having been developed.[17] Recent work has showcased their use for the generation of ammonium enolates from bench stable carboxylic acids *via in situ* mixed anhydride formation as a convenient alternative to using ketenes. Within this arena, research by Romo and co-workers has demonstrated the versatility of these catalysts in asymmetric *intra*molecular β-lactone formation,[18,19] while our own research has demonstrated this methodology in both *intra*- and *inter*molecular formal [4+2] cycloadditions.[20] Building upon this work and that of Connon and co-workers who performed the functionalization of enolizable anhydrides with a bifunctional squaramide,[21] alternative Lewis base mediated ester enolate equivalents have recently been reported. For example, Chi and co-workers have utilized activated *p*-nitrophenyl esters as azolium enolate precursors,[22] while we have used pre-formed 2-arylacetic anhydrides in ammonium enolate catalyzed cycloadditions.[23, 24] Mindful of these precedents, this manuscript demonstrates the ability of isothioureas to provide facile access to the β-lactam and β-amino ester motifs *via* a formal intermolecular [2+2] cycloaddition between

N-sulfonyl aldimines and ammonium enolates generated using isothiourea catalysis from a carboxylic acid or isolable anhydride (Scheme 2).[25] Although referred to as formal [2+2] cycloadditions in this and the following manuscript, these reactions could also be described as intermolecular enolate-imine cyclizations or Gilman-Speeter type reactions.[26] Notably, this methodology provides access to β-lactams with the distinct 3,4-diaryl *anti*-stereochemical motif,[27,28] in contrast with the organocatalytic methods previously reported that often give the *syn*-diastereoisomer.[9-14]

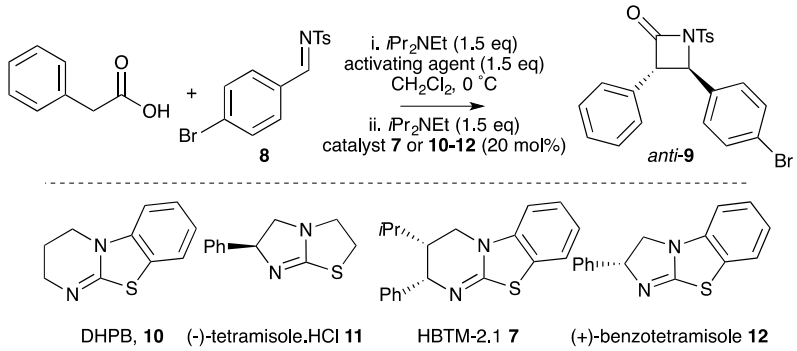


Scheme 2: This work: preparation of β-lactams and β-amino esters

Results and Discussion

Reaction Optimization: Following our previous methodology, initial studies utilized pivaloyl chloride as an *in situ* carboxylic acid activating agent, in tandem with a range of isothiourea catalysts, to promote the formal [2+2] cycloaddition of an ammonium enolate derived from phenylacetic acid and imine **8**. Using achiral isothiourea DHPB **10** and chiral isothioureas **7**, **11** and **12** the diastereoselectivity of this process was uniformly excellent (>95:5 dr *anti*:*syn*, enty 1-4), generating preferentially *anti*-β-lactam **9**, however the yields were variable and the ee at best moderate (66% ee, Table 1, Entry 4). A consistent problem encountered with the use of pivaloyl chloride was the isolation of the β-lactam, with products contaminated with pivalic anhydride that was generated *in situ* (entries 1-5). Furthermore an *i*Pr$_2$NEt base-catalyzed background reaction in the absence of

catalyst was operative under these conditions, leading to a competitive racemic reaction process that leads to erosion of product ee (entry 5). To circumvent these issues associated with the use of pivaloyl chloride, tosyl chloride was screened as an alternative activating agent for the carboxylic acid. Pleasingly, a marked increase in ee was observed, and in the case of benzotetramisole **12** a concurrent increase in isolated yield, while maintaining the excellent levels of diastereoselectivity (entry 7). Further optimization *via* lowering of reaction temperature to 0 °C was successful in increasing product ee at the expense of yield, whereas further reduction to −78 °C was detrimental to both yield and ee (entries 8-9).

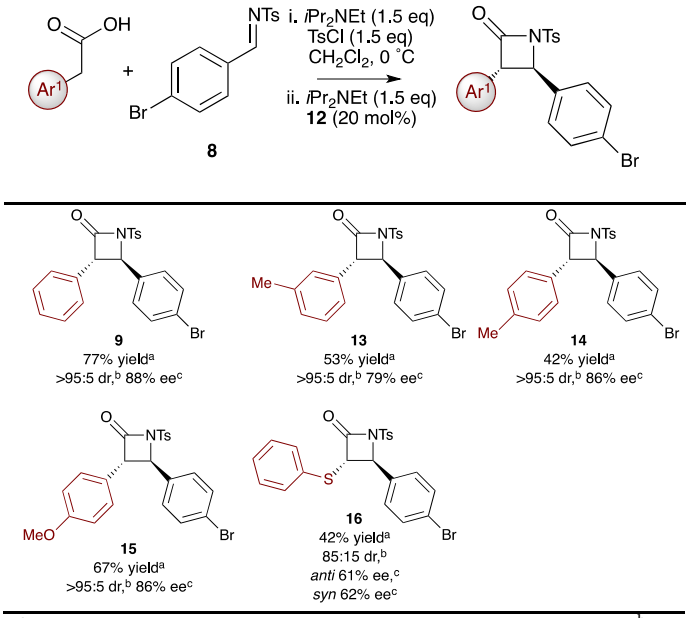


Entry	Catalyst	Activating Agent	T/ °C	Time /h	dr[a] (*anti*:*syn*)	Yield %[b]	ee %[c] (*anti*)
1	**10**	*t*BuCOCl	rt	2	>95:5	67[d]	N/A
2	**7**	*t*BuCOCl	rt	2	>95:5	37[d]	57
3	**11**	*t*BuCOCl	rt	2	>95:5	89[d]	57 (*ent*)
4	**12**	*t*BuCOCl	rt	2	>95:5	67[d]	66
5	**-**	*t*BuCOCl	rt	2	>95:5	39[d]	ND
6	**7**	TsCl	rt	4.5	>95:5	32	72
7	**12**	TsCl	rt	2	>95:5	77	85
8	**12**	**TsCl**	**0**	**5**	**>95:5**	**58**	**93**
9	**12**	TsCl	−78	18	>95:5	17	80

[a] Calculated by inspection of the ^{1}H NMR of the crude reaction mixture. [b] Isolated yield of single diastereoisomer. [c] ee Determined by HLPC analysis on a chiral stationary phase. [d] Yield including pivalic anhydride contaminent.

Table 1: Optimization of reaction conditions.

Applying these conditions to a small selection of arylacetic acids provided the corresponding 3,4-diaryl β-lactams in moderate to good yield (42-77% yield), excellent diastereoselectivity (exclusively >95:5 dr) and in high levels of enantioselectivity (79-88% ee) (Table 2). The relative configuration within β-lactam **9** was assigned *via* a combination of nOe and coupling constant analysis (typically, J = 3.4 Hz),[29] with the absolute configuration assigned by analogy to β-aminoester **17** as *anti*-(3*S*,4*R*).[30] Pleasingly, previous efforts directed towards the catalytic asymmetric synthesis of β-lactams have not provided efficient access to this *anti*-3,4-diaryl structural motif. Additionally, (thiophenyl)acetic acid could also be used in this protocol, generating **16** with moderate diastereo- and enantiocontrol.

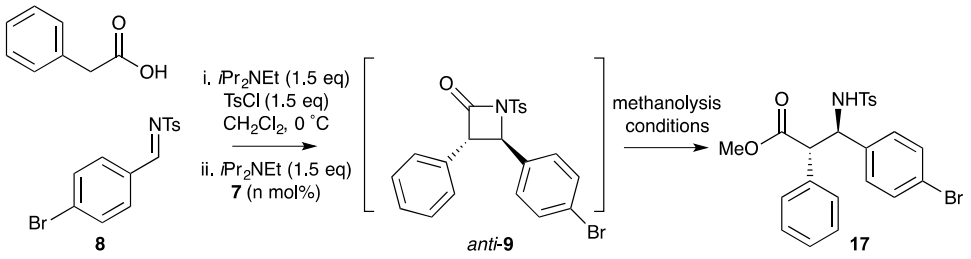


[a] Isolated yield of single *anti*-diastereoisomer (>95:5 dr). [b] Calculated by inspection of the ^{1}H NMR of the crude reaction mixture. [c] ee Determined by HLPC analysis on a chiral stationary phase. [d] Combined yield of separable diastereoisomers.

Table 2: Variation of acid component.

Although proceeding in excellent diastereo- and good enantioselectivity, this procedure suffers from typically moderate and often variable product yields that were not representative of reaction

conversion. This was rationalized as being due to the instability of the β-lactam products towards chromatographic purification and therefore a range of *in situ* derivatization methods was investigated. In our hands, attempted ring-opening with benzylamine following formation of the β-lactam, or reduction into the corresponding aminoalcohol, both proved unsuccessful. However, *in situ* sodium azide promoted methanolysis[31] provided a reproducible yield of β-amino ester **17** over multiple runs.[32,33] Re-evaluating a range of chiral isothiourea catalysts in this newly developed protocol revealed HBTM 2.1 **7** to provide marginally better levels of enantioselectivity (24% yield, 83% ee) over **12** (30% yield, 74% ee) over the two steps.[34] To improve the yield a further range of methanolysis conditions were screened (Table 3, entries 1-6). Reducing the quantity of sodium azide to 10 mol% had a positive effect on yield with comparable diastereo- and enantioselectivity. Switching to NaOMe/methanol at rt had a detrimental effect on yield but provided product in high ee, while lowering the reaction temperature maintained product ee and led to increased isolated yield (53%) of β-aminoester **17**.[27] Finally, optimum conditions utilized the generation of methoxide *in situ* *via* the addition of *n*BuLi to methanol at −78 °C, which was then added to a solution of the β-lactam, followed by warming to rt over 1 h to effect ring-opening. This procedure led to the formation of β-aminoester **17** in acceptable yield over two steps (62%) and with excellent diastereo- and enantioselectivity (>95:5 dr and 93% ee). Furthermore, under these conditions the catalyst loading could be lowered to 5 mol% without significant erosion of either yield or enantioselectivity (Table 3, Entry 8). The yields obtained over this two-step procedure are acceptable, reproducible and are consistent with the findings of Lectka.[9]



Entry	Methanolysis conditions	T/ °C	Time /h	n mol% (7)	ee (%)[a]	dr[b] (*anti*/*syn*)	Yield %[c]
1	Excess NaN_3/MeOH	rt	1	20	83	>95:5	24
2	NaN_3 (10 mol%)/MeOH	rt	4	20	85	>95:5	66
3	NaOMe/MeOH	rt	2	20	96	>95:5	40
4	NaOMe/MeOH	0	4	20	96	>95:5	53
5	BuLi/MeOH	–78 to rt	1	20	95	>95:5	62
6	BuLi/MeOH	–78 to rt	2.5	20	93	>95:5	65
7	BuLi/MeOH	–78 to rt	2.5	10	95	>95:5	53
8	**BuLi/MeOH**	**–78 to rt**	**2.5**	**5**	**92**	**>95:5**	**65**
9	BuLi/MeOH	–78 to rt	2.5	1	85	>95:5	44

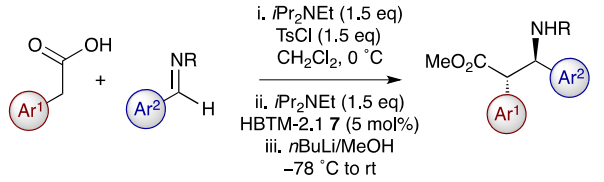
[a] ee Determined by HLPC analysis on a chiral stationary phase. [b] Calculated by inspection of the ^{1}H NMR of the crude reaction mixture. [c] Isolated yield of single *anti*-diastereoisomer (>95:5 dr).

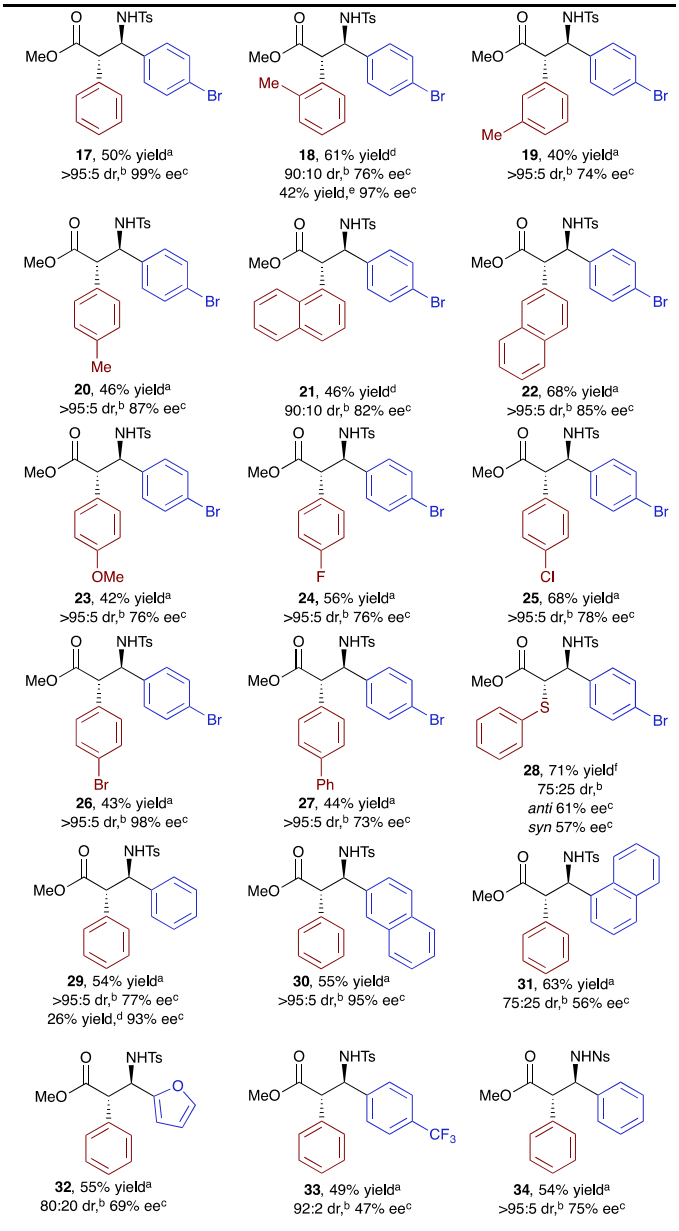
Table 3: Optimization of methanolysis conditions and catalyst loading.

β-Amino Ester Series: Scope and Limitations

A range of arylacetic acids was next tested within this protocol to probe the reaction scope. Tolylacetic acids proceeded with comparable yield (40-61%) to that obtained for the parent phenylacetic acids, albeit in lower ee (74-86% ee) (Table 4). 2-Tolylacetic acid displayed slightly reduced diastereoselectivity (90:10 dr, *anti*:*syn*) as did 1-naphthyl (90:10 dr, *anti*:*syn*) which is thought to be due to steric effects. Arylacetic acids with electron donor (-OMe) and halogen substituents also proved compatible in this process, proceeding with excellent diastereoselectivity (>95:5 dr) in all cases, with good to excellent ee (76-98% ee) and in moderate yield (43-56%). In certain cases the product ee could be increased to near enantiopurity *via* recrystallization of the β-

aminoester products (**18**, **22**) at the expense of isolated yield. Crystallization effects during purification of both **17** (>99% ee) and **26** (98% ee) are postulated to account for the higher than average ee obtained in these cases.





[a] Isolated yield of single *anti*-diastereoisomer (>95:5 dr). [b] Calculated by inspection of the ^{1}H NMR of the crude reaction mixture. [c] ee Determined by HLPC analysis on a chiral stationary phase. [d] Isolated yield of inseparable diastereoisomers. [e]

Isolated yield of single *anti*-diastereoisomer (>95:5 dr) following recrystallization. [f] Combined isolated yield of separable diastereoisomers.

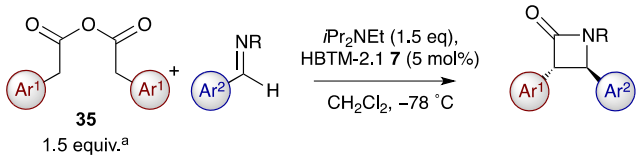
Table 4: Variation of the acid and imine components.

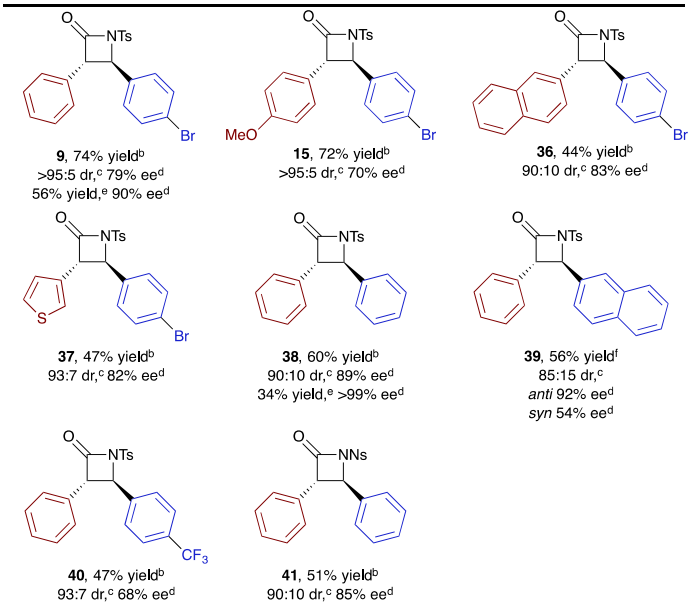
Alternative aryl substituted *N*-sulfonyl aldimines were next evaluated in this methodology (Table 4). Phenyl and 2-naphthyl-substitution were well tolerated giving **29** and **30** in good dr and ee. However, 1-naphthyl and heteroaromatic 2-furyl substituted imine (**31** and **32**) both proceeded with reduced diastereoselectivity, while the incorporation of a strongly electron withdrawing trifluoromethyl unit performed poorly leading to **33** in greatly reduced enantioselectivity. Variation of the *N*-substituent was briefly investigated with an *N*-nosyl imine providing **34** with comparable results to *N*-tosyl substitution, although *N*-Boc or *N*-PMP aldimines failed to provide any β-lactam.

2-Arylacetic anhydrides for β-lactam synthesis:

While this two-step procedure is effective at providing a range of *anti*-2,3-diaryl-β-aminoesters with excellent diastereocontrol and good to excellent enantiocontrol, reproducible access to the corresponding β-lactam motif as the direct reaction product was still desired. Attention therefore turned to simplification of the reaction components with the aim of aiding purification, leading to the consideration of 2-arylacetic anhydrides (**35**) as alternative ammonium enolate precursors. Treatment of benzoic anhydride (Ar^1 = Ph) and aldimine **8** with HBTM 2.1 **7** (5 mol%) and *i*Pr_2NEt (1.5 eq) led to formation of the β-lactam **9** that could be consistently isolated as the major reaction product, albeit in low yield (30%). It was postulated that this low yield was a result of competitive Claisen-type condensation through addition of the ammonium enolate to the phenylacetic anhydride, resulting in incomplete imine consumption and so moderate conversion to β-lactam. Further optimization through dropwise addition of an increased quantity of anhydride (1.5 eq), combined with a lower reaction temperature (–78 °C), improved the yield to 74% with continued excellent diastereoselectivity and reasonable enantioselectivity (>95:5 dr and 79% ee), that following recrystallization could be isolated in 90% ee. Under these conditions a range of both 2-arylacetic

anhydrides and imines were tested, all leading to the isolation of the parent β-lactam in moderate to good yield (44-74% yield) (Table 5). Modification of the anhydride portion allowed the incorporation of a range of aryl and heteroaryl substitution, providing β-lactams **9**, **15**, **36** and **37** with good to excellent diastereo- and enantiocontrol (up to >95:5 dr; ee up to 83%). A selection of other aryl-substituted *N*-sulfonyl aldimines were also tolerated, giving β-lactams in similar yield (47-60% yield) and enantioselectivity (68-92% ee), but with slightly reduced diastereoselectivity (up to 93:7 dr). Importantly, as opposed to the original procedure from the arylacetic acid, the use of a 2-arylacetic anhydride allowed consistent isolation of the β-lactam heterocycle. Additionally, removal of the *N*-tosyl substituent of the parent β-lactam without racemisation was possible by treatment with SmI_2.[35]

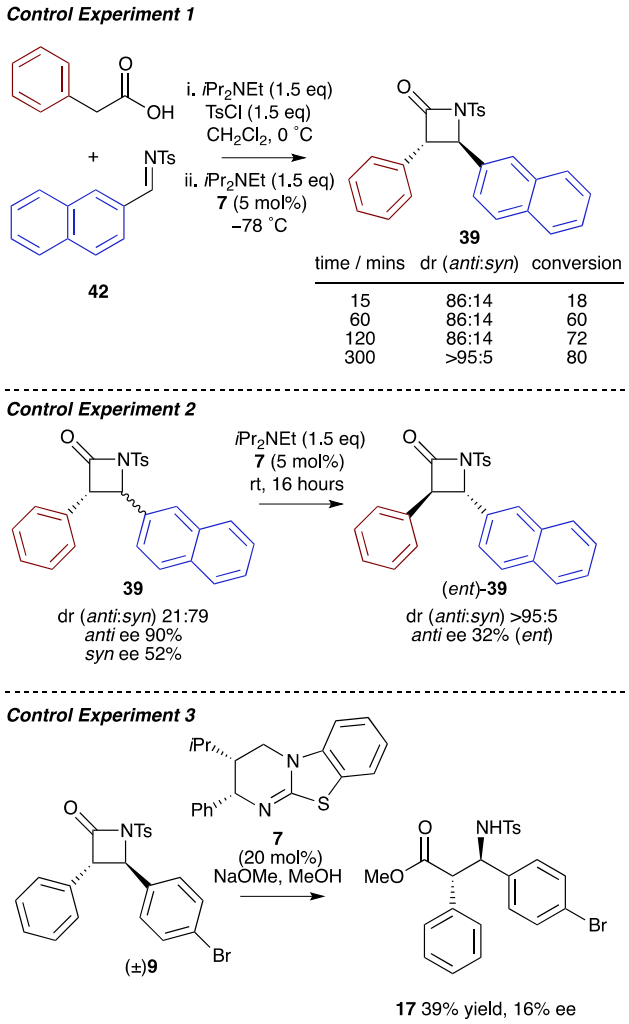




[a] Dropwise addition. [b] Isolated yield of *anti*-diastereoisomer (>95:5 dr). [c] Calculated by inspection of the ^{1}H NMR of the crude reaction mixture. [d] Determined by HLPC analysis on a chiral stationary phase. [e] Isolated yield of single *anti*-diastereoisomer (>95:5 dr) following recrystallization.

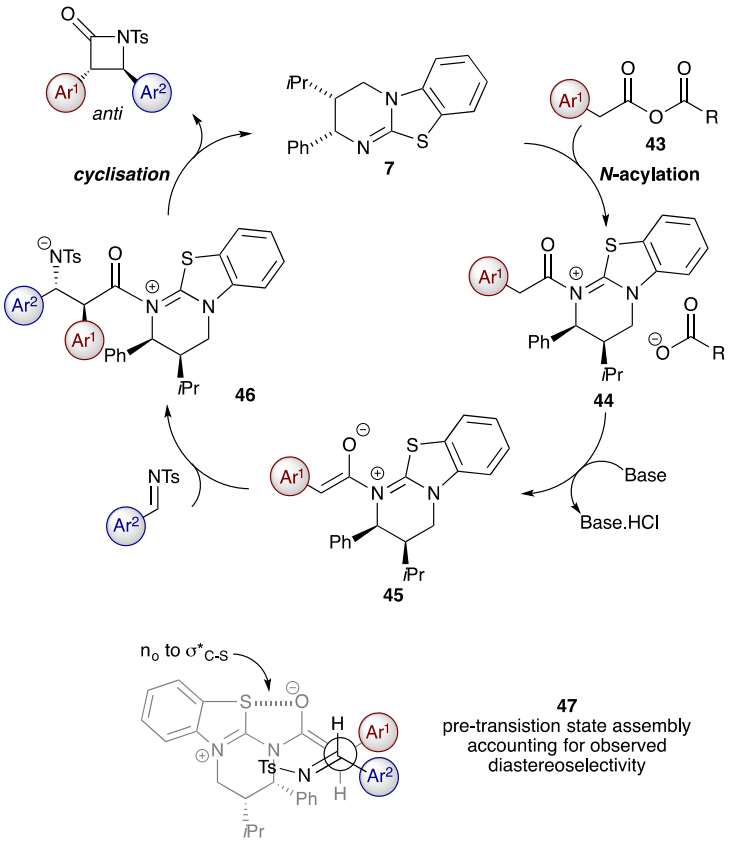
Table 5: Variation of the acid and imine components in reaction from a preformed homo-anhydride.

Control Studies: When using the pre-made isolable arylacetic anhydrides as ammonium enolate precursors, slightly reduced diastereocontrol was observed in formation of the β-lactam products when compared with the analogous example in the β-amino ester series accessed directly from the parent acid. This observation prompted us to investigate the possibility of *in situ* product epimerization leading to enhanced diastereocontrol. To test this hypothesis, the diastereoselectivity of this process was monitored with time using phenylacetic acid and imine **42** (Scheme 3, Control Experiment 1). After short reaction times and modest conversion a dr of *ca.* 85:15 was observed, but after prolonged exposure to the reaction conditions enhanced diastereocontrol was observed (dr 95:5), consistent with *in situ* epimerization. Also, an isolated example of β-lactam **39** (dr *anti*:*syn* 21:79; *anti* 90% ee; *syn* 52% ee) was treated at rt with *i*Pr_2NEt (1.5 eq), HBTM-2.1 **7** (5 mol%) in CH_2Cl_2, generating (*ent*)-*anti*-**39** (>95:5 dr, 32% ee) in quantitative yield (Scheme 3, Control Experiment 2).[36] This is consistent with the *syn*-diastereoisomer having preferentially the (3*S*,4*S*)-configuration, and with *in situ* epimerization generating *ent*-**39** preferentially. Under identical experimental conditions, a sample of *anti*-**39** (>95:5 dr, 90% ee) showed no change in dr or ee, consistent with no epimerization of the *anti*-β-lactam under the reaction conditions. Finally, given that the isothiourea catalyzed ring-opening kinetic resolution of (±)-*syn*-β-lactams has been recently reported by Birman *et al*.[37] we were mindful of such an effect operating within our own system. Control investigations indicated the potential for a moderate, but not significant, resolution effect during the ring-opening methanolysis step, as treatment of (±)-**9** with HBTM-2.1 **7** and NaOMe in MeOH gave β-amino ester **17** (dr >95:5) in 16% ee (Scheme 3, Control Experiment 3).[38]



Scheme 3: Control experiments.

Consistent with our previous reports we propose a catalytic cycle that proceeds *via* generation of an acyl ammonium species from either mixed- or *homo*-anhydride **43** (Scheme 4). Deprotonation to generate the (*Z*)-enolate **45**, followed by addition to the imine furnishes intermediate **46**. Intramolecular cyclization to provide the β-lactam with concurrent catalyst regeneration completes the cycle. The selective formation of the *anti*-β-lactam is postulated by the pre-transition state assembly **47** depicted below. High facial selectivity towards the *Re* face of enolate **45** is controlled by the axial orientation of the phenyl group, with a potential $n_o \rightarrow \sigma^*_{C\text{-}S}$ stabilizing interaction or electrostatic stabilization rigidifying this arrangement.[39] Addition of this enolate to the *Re* face of the imine, occupying a staggered arrangement about the forming C-C bond, would account for the observed *anti* selectivity.



Scheme 4: Proposed catalytic cycle and pre-transition state assembly

In conclusion, isothioureas catalyze the highly diastereo- and enantioselective formation of β-lactams and β-amino esters from arylacetic anhydrides or arylacetic acids and *N*-sulfonyl imines (typically >90:10 dr). Good to excellent enantioselectivity (up to >99% ee) is typically observed in the formation of the β-amino esters, with reduced enantioselectivity but higher isolated product yields observed in formation of β-lactams from arylacetic anhydrides.

Experimental

1.1 General Information

All reactions were performed in open flask conditions with bench grade solvents. All reagents were obtained from commercial sources and were used without further purification. Rt (rt) refers to 20□25 °C, with temperatures of 0 °C and □78 °C obtained using ice/water and CO_2(s)/acetone baths respectively. ^{1}H NMR spectra were acquired at either 300, 400, or 500 MHz, ^{13}C{^{1}H} NMR spectra were acquired at either 75, 100, or 125 MHz, and ^{19}F{^{1}H} NMR spectra were acquired at either 282, 376, or 471 MHz. Chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak, coupling constants, *J*, are quoted in Hertz (Hz). NMR peak assignments were

confirmed using 2D ^{1}H COSY, 2D ^{1}H NOESY, 2D ^{1}H-^{13}C HMBC and 2D ^{1}H-^{13}C HSQC where necessary. Infra-red spectra were recorded as thin films using an ATR accessory. Mass spectrometry (*m/z*) data were acquired using either electrospray ionisation (ESI), electron impact (EI), chemical ionisation (CI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionisation (APCI) or nanospray ionisation (NSI) using a TOF mass analyser. Optical rotations were recorded with a path length of 1 dm and concentrations, *c*, are quoted in g/100 mL. All chiral HPLC traces were compared with an authentic racemic trace prepared using racemic **7** or DHPB **10**.

1.2 General Experimental Procedures

General Procedure A: *Asymmetric Formal [2+2] Cycloaddition of Aryl Acetic Acids and Imines*

To a stirred solution of the appropriate carboxylic acid (1 eq) in dichloromethane (0.2 M) at 0 °C, tosyl chloride (1.5 eq) and *i*Pr_2NEt (1.5 eq) were added. The solution was stirred at 0 °C for 20 min. The isothiourea catalyst **12** (20 mol%) and the imine (1 eq) were added followed by *i*Pr_2NEt (1.5 eq). The solution was then stirred at rt for 5 h, quenched using 1 M HCl (0.2 M), extracted (3 × EtOAc) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by column chromatography under the stated conditions to give the β-lactam product.

General Procedure B: *Asymmetric Formal [2+2] Cycloaddition of Aryl Acetic Acids and Imines With In Situ Ring-opening*

To a stirred solution of the carboxylic acid (1 eq) in dichloromethane (0.2 M) at 0 °C, tosyl chloride (1.5 eq) and *i*Pr_2NEt (1.5 eq) were added. The solution was stirred at 0 °C for 20 min. The isothiourea catalyst, **7** (5 mol%) and the imine (1 eq) were added followed by *i*Pr_2NEt (1.5 eq). The solution was then stirred at rt for 5 h. *n*BuLi (2.5 M) solution in hexanes (55 eq) was added to methanol (0.2 M) at −78°C and this solution was added by canula to the reaction mixture. After 1 hour, the reaction was quenched using water (0.2 M), extracted (3 × EtOAc) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* followed by purification by column chromatography under the stated conditions to give the β-amino ester product.

General Procedure C: *Asymmetric Formal [2+2] Cycloaddition of Homoanhydrides and Imines*

To a stirred solution of the imine (1 eq) in dichloromethane (0.2 M) at −78 °C, tosyl the isothiourea catalyst **7** (5 mol%) and *i*Pr_2NEt (1.25 eq) were added followed by the anhydride (1.5 eq) as a solution in dichloromethane (0.25 M) dropwise (2.3 mLh^{-1}) *via* syringe pump. The solution was then warmed to rt and stirred for a further 30 min, quenched using 1 M HCl (0.2 M), extracted (3 × EtOAc)

and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* followed by purification by column chromatography under the stated conditions to give the β-lactam product.

1.3 Starting Materials

Isothiourea catalysts

DHPB, (±)-HBTM-2.1 (±)-**7**, (2*S*,3*R*)-HBTM-2.1 **7** and (+)-benzotetramisole **12** were synthesized according to literature procedures.[15, 20d]

N-Sulfonylaldimines

(*E*)-*N*-(4-bromobenzylidene)-4-methylbenzenesulfonamide **8**, (*E*)-4-methyl-*N*-(naphthalen-2-ylmethylene)benzenesulfonamide **42**, (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide **S1**, (*E*)-*N*-(4-methoxybenzylidene)-4-methylbenzenesulfonamide **S2**, (*E*)-4-methyl-*N*-(4-(trifluoromethyl)benzylidene)benzenesulfonamide **S3**, (*E*)-*N*-(furan-2-ylmethylene)-4-methylbenzenesulfonamide **S4**, (*E*)-4-methyl-*N*-(naphthalen-1-ylmethylene)benzenesulfonamide **S5** and (*E*)-*N*-benzylidene-4-nitrobenzenesulfonamide **S6** were all synthesized following literature procedures.[13, 40]

Anhydrides

2-phenylacetic anhydride **35**, 2-(4-methoxyphenyl)acetic anhydride **S7**, 2-(naphthalen-2-yl)acetic anhydride **S8** and 2-(thiophen-2-yl)acetic anhydride **S9** were all synthesized following literature procedures.[23]

1.4 Experimental Procedures

(3S,4R)-4-(4-Bromophenyl)-3-phenyl-1-tosylazetidin-2-one **9**

The title compound was prepared according to General Procedure A from phenyl acetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **12** (10 mg, 20 mol%, 0.04 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (5:95-10:90 EtOAc:Petrol) to afford the β-lactam **9** as a white solid (52.7 mg, 58%); mp 60-64 °C; $[a]_D^{22}$ −2.3 (*c* 1.0 in CH_2Cl_2); chiral HPLC analysis, Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, rt), t_R minor: 19.4 min, t_R major: 21.0 min, 93% ee; ν_{max} (KBr)/cm^{-1} 1797 (C=O), 1369 (C-N), 1172 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.48 (3H, s, SO_2ArCH_3), 4.22 (1H, d, *J* 3.4, C(3)*H*), 4.92 (1H, d, *J* 3.4, C(4)*H*), 7.04 (2H, m, Ar*H*), 7.18 (2H, m, Ar*H*), 7.32 (5H, m, Ar*H*), 7.47 (2H, m, Ar*H*), 7.75 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (SO_2ArCCH_3), 64.4. (*C*(3)), 65.1 (*C*(4)), 123.4 (*C*Br), 127.3 (*Ph*), 127.6 (*Ph*), 128.1 (*Ph*), 128.6 (Ar*C*), 129.3 (Ar*C*), 130.0 (Ar*C*), 132.2 (*Ph*), 132.5

(C_{ipso}), 135.2 (C_{ipso}), 135.6 (C_{ipso}), 145.6 (*C*Me), 165.2 (*C*(2)); *m/z* (NSI^+) 475($[M+NH_4]^+$, 100%); HRMS (NSI+) *m/z* $[M+NH_4]^+$ calculated for $C_{22}H_{22}BrN_2O_3S^+$ 473.0528; found 473.0539 (−0.2 ppm).

(3S,4R)-4-(4-Bromophenyl)-3-(m-tolyl)-1-tosylazetidin-2-one **13**

The title compound was prepared according to General Procedure A from *m*-tolylacetic acid (30.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **12** (10 mg, 20 mol%, 0.04 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (10:90 EtOAc:Petrol) to afford the β-lactam **13** as a white solid (50.2 mg, 53%); mp 130-134 °C; $[a]_D^{22}$ −2.6 (*c* 1.0 in CH_2Cl_2); chiral HPLC analysis, Chiralcel OD-H (20% *i*PrOH:hexane, flow rate 0.25 mL min^{-1}, 211 nm, rt), t_R minor: 45.0 min, t_R major: 51.5 min, 79% ee; ν_{max} (KBr)/cm^{-1} 1806 (C=O), 1370 (C-N), 1172 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.25 (3H, s, NSO_2ArCH_3), 2.47 (3H, s, C(3)ArCH_3) 4.15 (1H, d, *J* 3.4, C(3)*H*) 4.87 (1H, d, *J* 3.4, C(4)*H*), 6.72 (1H, s, Ar*H*), 6.80 (1H, d, *J* 7.7, Ar*H*), 6.71 (1H, d, *J* 7.7, Ar*H*), 7.18 (3H, m, Ar*H*), 7.33 (2H, d, *J* 8.3, Ar*H*), 7.46 (2H, d, *J* 8.4, Ar*H*), 7.76 (2H, d, *J* 8.3, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (NSO_2ArCH_3), 21.9 (C(3)ArCH_3), 64.8 (*C*(3)), 65.3 (*C*(4)), 123.3 (ArC(4)Br), 124.7 (Ar*C*), 127.7 (Ar*C*), 127.8 (Ar*C*), 128.3 (Ar*C*), 129.2 (Ar*C*), 129.5 (Ar*C*), 130.2 (C_{ipso}), 132.3 (Ar*C*), 132.6 (Ar*C*), 135.4 (C_{ipso}), 135.8 (C_{ipso}), 139.3 (C_{ipso}), 145.7 ($NSO_2ArC(4)CH_3$), 165.5 (*C*(2)); *m/z* (NSI^+) 489 ($[M+NH_4]^+$, 100%); HRMS (NSI+) *m/z* $[M+NH_4]^+$ calculated for $C_{23}H_{24}BrN_2O_3S^+$ 487.0683; found 487.0686 (−0.5 ppm).

(3S,4R)-4-(4-Bromophenyl)-3-(p-tolyl)-1-tosylazetidin-2-one **14**

The title compound was prepared according to General Procedure A from *p*-tolylacetic acid (30.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **12** (10 mg, 20 mol%, 0.04 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (5:95 EtOAc:Petrol) to afford the β-lactam **14** as a white solid (39.3 mg, 42%); mp 40-44 °C; $[a]_D^{22}$ −2.5 (*c* 1.0 in CH_2Cl_2); chiral HPLC analysis, Chiralcel OD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, rt), t_R major: 13.6 min, t_R minor: 16.1 min, 86% ee; ν_{max} (KBr)/cm^{-1} 1795 (C=O), 1368 (C-N), 1158 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s, C(3)ArCH_3), 2.47 (3H, s, NSO_2ArCH_3), 4.17 (1H, d, *J* 3.4, C(3)*H*), 4.87 (1H, d, *J* 3.4, C(4)*H*), 6.90 (2H, d, *J* 8.2, C(3)ArC(2)*H*), 7.10 (2H, d, *J* 8.2, C(3)ArC(3)*H*), 7.15 (2H, d, *J* 8.3, SO_2ArC(2)*H*), 7.31 (2H, d, *J* 8.6, C(4)ArC(2)*H*), 7.46 (2H, d, *J* 8.5, C(4)ArC(3)*H*), 7.73 (2H, d, *J* 8.3, SO_2ArC(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (C(3)ArCH_3), 21.9 (NSO_2ArCH_3), 64.3 (*C*(3)), 65.4 (*C*(4)), 123.1 (C(4)Ar*C*(4)), 127.3 (Ar*C*), 127.7 (C(3)Ar*C*(2)), 128.2

($NSO_2ArC(2)$), 129.6 (C_{ipso}), 130.0 (Ar*C*), 130.1 (Ar*C*), 132.3 (C(4)Ar*C*(3)), 135.3 (C(3)Ar*C*(1)), 135.7 ($SO_2ArC(1)$), 138.8 (C(3)Ar*C*(4)), 145.7 ($SO_2ArC(4)$), 165.4 (*C*(2)); *m/z* (NSI^+) 489 ($[M+NH_4]^+$, 100%); HRMS (NSI+) $C_{23}H_{24}BrN_2O_3S^+$ ($[M+NH_4]^+$), requires 487.0682; found 487.0686 (−0.7 ppm).

(3S,4R)-4-(4-Bromophenyl)-3-(4-methoxyphenyl)-1-tosylazetidin-2-one **15**

The title compound was prepared according to General Procedure A from *p*-methoxyphenylacetic acid (33.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **12** (10 mg, 20 mol%, 0.04 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to afford the β-lactam **15** as a white solid (62.0 mg, 67%); mp 32-36 °C; $[a]_D^{22}$ −30.0 (*c* 1.0 in CH_2Cl_2); chiral HPLC analysis, Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, rt), t_R minor: 33.4 min, t_R major: 42.0 min, 86% ee; ν_{max} (film)/cm^{-1} 1792 (C=O), 1514, 1167 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.47 (3H, s, NSO_2ArCH_3), 3.77 (3H, s, OCH_3), 4.19 (1H, d, *J* 3.4, C(3)*H*), 4.85 (1H, d, *J* 3.4, C(4)*H*), 6.01 (2H, d *J* 8.8, Ar*H*), 6.93 (2H, d *J* 8.5, Ar*H*), 7.15 (2H, d, *J* 8.3, Ar*H*), 7.31 (2H, m, Ar*H*), 7.45 (2H, d, *J* 8.5, Ar*H*), 7.73 (2H, d, *J* 8.3, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.9 (NSO_2ArCH_3), 55.5 (OCH_3), 64.1 (*C*(3)), 65.6 (*C*(4)), 114.8 (Ar*C*), 123.2, (C_{ipso}), 124.6 (C_{ipso}), 127.7 (Ar*C*), 128.2 (Ar*C*), 128.6 (Ar*C*), 130.1 (Ar*C*), 132.3 (Ar*C*), 135.4 (C_{ipso}), 135.7 (C_{ipso}), 145.7 ($NSO_2ArC(4)CH_3$), 159.8 (C(3)Ar*C*(4)OMe), 165.7 (*C*(2)); *m/z* (NSI^+) 505 ($[M+NH_4]^+$, 100%); HRMS (NSI+) *m/z* $[M+H]^+$ calculated for $C_{23}H_{21}BrNO_4S^+$ 486.0368; found 486.0369 (−0.2 ppm).

*(3S,4S)-4-(4-Bromophenyl)-3-(phenylthio)-1-tosylazetidin-2-one **16***

The title compound was prepared according to General Procedure A from (phenylthio)acetic acid (33.6 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **12** (10 mg, 20 mol%, 0.04 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (10:90 EtOAc:Petrol) to afford the β-lactam **16** as a white solid (40.7 mg, 42% as a mixture of *syn:anti* 85:15); *Anti*: isolated white solid (8.3 mg, 14%); mp 78-84 °C; $[a]_D^{22}$ +7.0 (*c* 0.1 in $CHCl_3$); chiral HPLC analysis, Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R major: 16.1 min, t_R minor: 20.8 min, 61% ee; ν_{max} (film)/cm^{-1} 1790 (C=O), 1366 (C-N), 1170 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.46 (3H, s, NSO_2ArCH_3), 4.11 (1H, d, *J* 3.2, C(3)*H*), 4.70 (1H, d, *J* 3.2, C(4)*H*), 7.12-7.24 (2H, m, Ar*H*), 7.21-7.30 (5H, m, Ar*H*), 7.42-7.47 (4H, m, Ar*H*), 7.57-7.59 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.9 (NSO_2ArCH_3), 61.5 (*C*(3)), 63.6 (*C*(4)), 123.5

(*C*Br), 127.9 (*Ph*), 128.1 (*Ph*), 128.6 (Ar*C*), 129.3 (Ar*C*), 129.6 (Ar*C*), 130.1 (Ar*C*), 132.3 (Ar*C*), 134.5 (Ar*C*), 134.5 (C_{ipso}), 135.3 (C_{ipso}), 145.6 (*C*Me), 163.2 (C(2)); *m/z* (ESI^+) 512 ($[M+Na]^+$, 100%); HRMS (NSI+) *m/z* $[M+Na]^+$ calculated for $C_{22}H_{18}BrNO_3S_2^+$ 509.9798; found 509.9804 (−1.1 ppm). *Syn*: from mixture of diastereoisomers, selected data δ_H (400 MHz, $CDCl_3$) 2.49 (3H, s, NSO_2ArCH_3), 4.79 (2H, d, *J* 6.4, C*H*), 5.35 (2H, d, *J* 6.1, C*H*), 6.99-7.02 (2H, m, Ar*H*), 7.71-7.76 (2H, m, Ar*H*); chiral HPLC analysis, Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211nm, 24°C), t_R major: 25.9 min, t_R major: 33.6 min, 62% ee.

(2S,3R)-Methyl-3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-phenylpropanoate **17**

The title compound was prepared according to General Procedure B from phenylacetic acid (27 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 55 eq, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **17** as a white solid (49.0 mg, 50%); mp 156-159 °C; $[a]_D^{22}$ −24.3 (*c* 1 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R minor: 29.0 min, t_R major: 42.7 min, 99% ee; ν_{max} (film)/cm^{-1} 3237 (NH), 1740 (C=O), 1331 (R-SO_2N), 1153 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.35 (3H, s, ArCH_3), 3.61 (3H, s, OCH_3), 3.92 (1H, d, *J* 6.45, C(2)*H*), 4.80 (1H, dd, *J* 8.82, 6.53, C(3)*H*), 5.98 (1H, d, *J* 8.64, N*H*), 6.89-6.91 (2H, m, C(3)ArC(2)*H*), 7.01 (2H, d, *J* 7.95, C(3)$NHSO_2$ArC(3)*H*), 7.13-7.16 (2H, m, Ar*H*), 7.20-7.23 (5H, m, Ar*H*), 7.33 (2H, d, *J* 8.29, C(3)$NHSO_2$Ar(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (Ar*C*H_3), 52.6 (O*C*H_3), 57.5 (*C*(2)), 60.6 (*C*(3)), 121.7 (Ar*C*Br), 127.0 (C(3)$NHSO_2$Ar*C*(2)), 128.1 (Ar*C*), 128.6 (Ar*C*), 128.7 (Ar*C*), 128.9 (C(3)Ar*C*(2)), 129.3 (C(3)$NHSO_2$Ar*C*(3)), 131.5 (Ar*C*), 134.5 (C(2)Ar*C*(1)), 137.5 (C(3)$NHSO_2$Ar*C*(1)), 137.8 (C(3)Ar*C*(1)), 143.1 (C(3)$NHSO_2$Ar*C*(4)), 172.2 (*C*(1)); *m/z* (NSI^+) 507 ($[M+NH4]^+$, 100%); HRMS (NSI+) *m/z* $[M+H]^+$ calculated for $C_{23}H_{23}BrNO_4S^+$ 488.0523; found 488.0526 (−0.5 ppm).

(2S,3R)-Methyl-3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(o-tolyl)propanoate **18**

The title compound was prepared according to General Procedure B from *o*-tolylacetic acid (150 mg, 1.0 mmol), tosyl chloride (286.5 mg, 1.50 mmol), 2 portions of *i*Pr_2NEt (260 μL, 1.50 mmol), **7** (15.5 mg, 5 mol%, 0.05 mmol), *n*BuLi (2.5 M) solution in hexanes (0.5 mL, 55 mmol), imine **8** (354.0 mg, 1.0 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **18** as a white solid (304.5 mg, 61%); mp 124-128 °C; $[a]_D^{22}$ −17.2 (*c* 0.25 in $CHCl_3$); chiral HPLC analysis,

ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R minor: 16.7 min, t_R major: 24.2 min, 76% ee; ν_{max} (film)/cm^{-1} 3246.2 (NH), 1746 (C=O), 1163 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, C(2)ArCH_3), 2.34 (3H, s, C(3)NHSO_2ArCH_3), 3.59 (3H, s, OCH_3), 4.20 (1H, d, *J* 6.8 Hz, C(2)*H*), 4.76 (1H, dd, *J* 8.7, 6.8, C(3)*H*), 6.30 (1H, d, *J* 8.8, N*H*), 6.93-6.96 (2H, m, C(3)ArC(2)*H*), 6.99-7.02 (3H, m, Ar*H*), 7.07-7.09 (2H, m, C(2)ArC(4)*H* & C(2)ArC(5)*H*), 7.19-7.21 (2H, m, C(3)ArC(3)*H*), 7.26-7.28 (1H, m, C(2)ArC(6)*H*), 7.33 (2H, d, *J* 8.3, C(3)NHSO_2ArC(2)*H*); δ_C (100 MHz, $CDCl_3$) 19.7 (C(2)ArC(2)*C*H_3), 21.6 (C(3)NHSO_2Ar*C*H_3), 52.5 (*C*H_3O), 52.9 (*C*(2)), 59.5 (*C*(3)), 121.6 (*C*Br), 126.5 (C(3)NHSO_2Ar*C*(2)), 126.9 (C(2)Ar*C*(4)), 127.8 (C(2)Ar*C*(6)), 128.0 (C(2)Ar*C*(5)), 128.7 (C(3)Ar*C*(2)), 129.3 (Ar*C*), 130.9 (Ar*C*), 132.9 (C(3)Ar*C*(3)), 133.0 (C(2)Ar*C*(1)), 135.9 (C(2)Ar*C*(2)), 137.4 (C(3)Ar*C*(1)), 138.0 (C(3)NHSO_2Ar*C*(1)), 143.0 (C(3)NHSO_2Ar*C*(4)), 172.6 (*C*(1)); *m/z* (NSI^+) 521 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) *m/z* $[M+H]^+$ calculated for $C_{24}H_{25}BrNO_4S^+$ 502.0682; found 502.0682 (−0.0 ppm). This was recrystallised from CH_2Cl_2/Petrol to give the β-lactam as a white solid (209.7 mg, 42%); mp 116-120 ˚C; $[a]_D^{22}$ −12.0° (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R minor: 16.7 min, t_R major: 24.2 min, 97% ee.

*(2S,3R)-Methyl 3-(4-methylphenylsulfonamido)-3-phenyl-2-(m-tolyl)propanoate **19***

The title compound was prepared according to General Procedure B from *m*-tolylacetic acid (30 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **19** as a white solid (40.7 mg, 40%); mp 124-130 °C; $[a]_D^{22}$ −25.0 (*c* 0.1 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R minor: 39.9 min, t_R major: 42.8 min, 74% ee; ν_{max} (film)/cm^{-1} 3248.1 (NH), 1736 (C=O), 1159 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.23 (3H, s, C(2)ArC(3)CH_3), 2.34 (3H, s, C(3)NHSO_2ArCH_3), 3.60 (3H, s, OCH_3), 3.90 (1H, d, *J* 6.6, C(2)*H*), 4.79 (1H, dd, *J* 8.9, 6.7, C(3)*H*), 6.14 (1H, d, *J* 8.9, N*H*), 6.91-6.93 (4H, m, Ar*H*), 7.00 (3H, d, *J* 7.9, Ar*H*), 7.07 (1H, t, *J* 7.9, C(2)ArC(3)*H*), 7.22 (2H, d, *J* 8.5, Ar*H*), 7.32 (2H, d, *J* 8.3, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.5 (C(2)ArC(3)*C*H_3), 21.6 (C(3)NHSO_2Ar*C*H_3), 52.6 (O*C*H_3), 57.4 (C(2)), 60.6 (C(3)), 121.6 (*C*Br), 125.6 (C(3)Ar*C*(2)), 126.9 (Ar*C*), 128.7 (2×Ar*C*), 128.8 (Ar*C*), 129.2 (Ar*C*), 129.3 (Ar*C*), 131.4 (Ar*C*), 134.4 (C(2)Ar*C*(1)), 137.6 (C(3)NHSO_2Ar*C*(1)), 138.0 (C(3)Ar*C*(1)), 138.5 (C(2)Ar*C*(3)), 143.0 (C(3)NHSO_2Ar*C*(4)), 172.3 (*C*(1)); *m/z* (NSI^+) 214 (100%), 519 ($[M+NH_4]^+$, 40%); HRMS (NSI^+) *m/z* $[M+H]^+$ calculated for $C_{24}H_{25}BrNO_4S^+$ 502.0681; found 502.0682 (−0.2 ppm).

*(2S,3R)-Methyl 3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(p-tolyl)propanoate **20***

The title compound was prepared according to General Procedure B from *p*-tolylacetic acid (30 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **20** as a white solid (45.8 mg, 46%); mp 163-168 °C; $[a]_D^{22}$ −26.0 (*c* 0.25 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C), t_R major: 33.9 min, t_R minor: 38.3 min, 87% ee; ν_{max} (film)/cm^{-1} 3252 (NH), 1736 (C=O), 1352.1 (R-SO_2N), 1159.2 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.28 (3H, s, C(2)ArC*H*$_3$), 2.35 (3H, s, C(3)NHSO_2ArC*H*$_3$), 3.59 (3H, s, OC*H*$_3$), 3.89 (1H, d, *J* 6.5, C(2)*H*), 4.77 (1H, dd, *J* 8.8, 6.5, C(3)*H*), 6.03 (1H, d, *J* 8.8, N*H*), 6.91 (2H, d, *J* 8.4, C(3)ArC(2)*H*), 6.99-7.02 (6H, m, Ar*H*), 7.22 (2H, d, *J* 8.5, C(3)ArC(3)*H*), 7.33 (2H, d, *J* 8.3, C(3)NHSO_2ArC(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (C(2)Ar*C*H_3), 21.6 (C(3)NHSO_2Ar*C*H_3), 52.5 (O*C*H_3), 57.1 (*C*(2)), 60.6 (*C*(3)), 121.6 (Ar*C*Br), 127.0 (C(3)NHSO_2Ar*C*(2)), 128.8 (C(3)Ar*C*(2)), 128.4 (Ar*C*), 129.3 (C(3)NHSO_2Ar*C*(3)), 129.6 (Ar*C*), 131.4 (C(2)Ar*C*(1)), 131.5 (C(3)Ar*C*(3)), 137.6 (C(3)NHSO_2Ar*C*(1)), 137.9 (C(2)Ar*C*(4)), 138.0 (C(3)Ar*C*(1)), 143.0 (C(3)NHSO_2Ar*C*(4)), 172.4 (*C*(1)); *m/z* (NSI^+) 519 ($[M+NH_4]^+$, 45%), 526 (100%); HRMS (NSI^+) *m/z* $[M+H]^+$ calculated for $C_{24}H_{25}BrNO_4S^+$ 502.0681; found 502.0682 (−0.2 ppm).

*(2S,3R)-Methyl 3-(4-bromophenyl)-3-(4-2-(naphthalene-1-yl)propanoate **21***

The title compound was prepared according to General Procedure B from 1-naphthylacetic acid (37.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **21** as a white solid (49.8 mg, 46%); mp 122-128°C; $[a]_D^{22}$ −12.2 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 270 nm, 30 °C), t_R major: 24.9 min, t_R minor: 30.6 min, 82% ee; ν_{max} (film)/cm^{-1} 3244.3 (NH), 1736 (C=O), 1331 (R-SO_2N), 1157 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.24 (3H, s, ArC*H*$_3$), 3.57 (3H, s, OC*H*$_3$), 4.82 (1H, d, *J* 4.7, C(2)*H*), 4.86-4.89 (1H, m, C(3)*H*), 6.47 (1H, d, *J* 8.7, N*H*), 6.74 (2H, d, *J* 8.0, C(3)NHSO_2ArC(3)*H*), 7.07-7.10 (2H, m, C(3)NHSO_2ArC(2)*H*), 7.21-7.25 (2H, m, C(3)ArC(2)*H*), 7.27-7.37 (4H, m, Ar*H*), 7.46-7.58 (2H, m, Ar*H*), 7.69 (1H, d, *J* 7.9, Ar*H*), 7.79-7.82 (1H, m, Ar*H*), 7.90 (1H, d, *J* 8.4, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.5 (Ar*C*H_3), 52.2 (*C*(2)), 52.6 (O*C*H_3), 58.7 (*C*(3)), 121.8 (*C*Br), 121.82 (Ar*C*),

125.4 (Ar*C*), 125.9 (Ar*C*), 126.1 (Ar*C*), 126.4 (C(3)NHSO$_2$Ar*C*(2)), 127.1 (Ar*C*)), 128.5 (C(3)Ar*C*(2)), 128.9 (Ar*C*), 129.0 (C(3)NHSO$_2$Ar*C*(3)), 129.5 (Ar*C*), 130. 2 (C_{ipso}), 130.7 (C_{ipso}), 131.75 (Ar*C*), 134.2 (C_{ipso}), 136.9 (C(3)NHSO$_2$Ar*C*(1)), 139.0 (C(3)Ar*C*(1)), 142.6 (Ar*C*(4)CH$_3$), 172.8 (*C*(1)); *m/z* (NSI$^+$) 555 ([M+NH$_4$]$^+$, 45%), 562 (100%); HRMS (NSI$^+$) *m/z* [M+H]$^+$ calculated for $C_{27}H_{25}BrNO_4S^+$ 538.0680; found 538.0682 (−0.4 ppm).

(2S,3R)-Methyl 3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(naphthalen-2-yl)propanoate ***22***

The title compound was prepared according to General Procedure B from 2-naphthylacetic acid (186.0 mg, 1.0 mmol), tosyl chloride (286.5 mg, 1.50 mmol), 2 portions of *i*Pr$_2$NEt (260 μL, 1.50 mmol), **7** (15.5 mg, 5 mol%, 0.05 mmol), *n*BuLi (2.5 M) solution in hexanes (0.5 mL, 55 mmol), imine **8** (354.0 mg, 1.0 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **22** as a white solid (368.5 mg, 68%); mp 164-170 °C; $[a]_D^{22}$ −35.8 (*c* 0.25 in CHCl$_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 220 nm, 30 °C), t_R major: 24.0 min, t_R minor: 27.7 min, 85% ee; ν_{max} (film)/cm^{-1} 3210 (NH), 1711 (C=O), 1337 (R-SO$_2$N), 1163 (R-SO$_2$N); δ_H (400 MHz, CDCl$_3$) 2.17 (3H, s, ArC*H$_3$*), 3.61 (3H, s, OC*H$_3$*), 4.13 (1H, d, *J* 6.0, C(2)*H*), 4.87 (1H, dd, *J* 9.0, 5.9, C(3)*H*), 6.23 (1H, d, *J* 9.0, N*H*), 6.72 (2H, d, *J* 7.9, C(3)NHSO$_2$ARC(3)*H*), 7.04-7.07 (2H, m, C(3)ArC(2)*H*), 7.20-7.23 (3H, m, Ar*H*), 7.26-7.29 (2H, m, C(3)ArC(3)*H*), 7.46-7.49 (2H, m, Ar*H*), 7.56 (1H, d, *J* 1.2, C(2)ArC(3)*H*), 7.60-7.63 (1H, m, Ar*H*), 7.67-7.70 (1H, m, Ar*H*), 7.74-7.77 (1H, m, Ar*H*); δ_C (100 MHz, CDCl$_3$) 21.5 (Ar*C*H$_3$), 52.6 (O*C*H$_3$), 57.3 (*C*(2)), 60.6 (*C*(3)), 121.8 (*C*Br), 126.0 (Ar*C*), 126.5 (2×Ar*C*), 126.6 (C(3)NHSO$_2$Ar*C*(2)), 127.6 (C(2)Ar*C*(3)), 127.7 (Ar*C*), 128.1 (Ar*C*), 128.6 (C(3)Ar*C*(2)), 128.7 (C(3)Ar*C*(2)), 129.1 (C(3)NHSO$_2$Ar*C*(3)), 131.6 (C(3)Ar*C*(3)), 131.9 (C(2)Ar*C*(2)), 132.9 (C_{ipso}), 133.2 (C_{ipso}), 137.2 (C(3)NHSO$_2$Ar*C*(1)), 138.3 (C(3)Ar*C*(1)), 142.9 (Ar*C*(4)CH$_3$), 172.2 (*C*(1)); HRMS (NSI$^+$) *m/z* [M+NH$_4$]$^+$ calculated for $C_{27}H_{28}BrN_2O_4S^+$ 555.0945; found 555.0948 (−0.5 ppm). This was recrystallised from CH$_2$Cl$_2$/Petrol to give the β-lactam as a white solid (222.2 mg, 41%); mp 106-112 °C; $[a]_D^{22}$ −39.0° (*c* 0.5 in CHCl$_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 220 nm, 30 °C), t_R major: 24.0 min, t_R minor: 27.7 min, 91% ee.

(2S,3R)-Methyl 3-(4-bromophenyl)-2-(4-methoxyphenyl)-3-(4-methylphenylsulfonamido)propanoate ***23***

The title compound was prepared according to General Procedure B from *p*-methoxyphenylacetic acid (33.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr$_2$NEt (52 μL, 0.30

mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **23** as a white solid (43.2 mg, 42%); mp 168-172 °C; $[a]_D^{22}$ −27.6 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 220 nm, 30 °C), t_R major: 24.1 min, t_R minor: 27.1 min, 76% ee; ν_{max} (film)/cm^{-1} 3254 (NH), 1734 (C=O), 1157 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.35 (3H, s, ArCH_3), 3.60 (3H, s, C(1)(O)OCH_3), 3.76 (3H, s, ArOCH_3), 3.86 (1H, d, *J* 6.66, C(2)*H*), 4.73-4.77 (1H, dd, *J* 8.79, 6.49, C(3)*H*), 5.97-5.99 (1H, d, *J* 8.89, N*H*), 6.69 (2H, d, *J* 8.79, C(2)ArC(2)*H*), 6.89 (2H, d, *J* 8.62, C(3)ArC(2)*H*), 6.99-7.01 (2H, m, C(3)$NHSO_2$ArC(3)*H*), 7.04 (2H, d, *J* 8.81, C(2)ArC(3)*H*), 7.21 (2H, d, *J* 8.52, C(3)ArC(3)*H*), 7.32-7.34 (2H, m, C(3)$NHSO_2$ArC(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (Ar*C*H_3), 52.5 (C(1)(O)O*C*H_3), 55.3 (ArO*C*H_3), 56.6 (C(2)), 60.7 (C(3)), 114.2 (C(2)Ar*C*(2)), 121.6 (*C*Br), 126.5 (C(2)Ar*C*(1)), 127.0 (C(3)$NHSO_2$Ar*C*(2)), 128.7 (C(3)Ar*C*(2)), 129.3 (Ar*C*), 129.6 (Ar*C*), 131.5 (C(3)Ar*C*(3)), 137.6 (C(3)$NHSO_2$Ar*C*(1)), 137.9 (C(3)Ar*C*(1)), 143.0 (Ar*C*(4)CH_3), 159.4 (Ar*C*(4)OCH_3), 172.5 (*C*(1)); *m/z* (NSI^+) 535 ($[M+NH_4]^+$, 90%), 542 (100%); HRMS (NSI^+) *m/z* $[M+H]^+$ calculated for $C_{24}H_{25}BrNO_5S^+$ 518.0630; found 518.0631 (−0.3 ppm).

*(2S,3R)-Methyl 3-(4-bromophenyl)-2-(4-fluorophenyl)-3-(4-methylphenylsulfonamido)propanoate **24***

The title compound was prepared according to General Procedure B from 4-fluorophenylacetic acid (30.8 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **24** as a white solid (56.5 mg, 56%); mp 138-144 °C; $[a]_D^{22}$ −22.2 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, Chiralcel OD-H (20% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C), t_R minor: 17.8 min, t_R major: 22.4 min, 76% ee; ν_{max} (film)/cm^{-1} 3273 (NH), 1719 (C=O), 1153 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.35 (3H, s, ArCH_3), 3.61 (3H, s, OCH_3), 3.91 (1H, d, *J* 6.6, C(2)*H*), 4.75 (1H, dd, *J* 8.8, 6.8, C(3)*H*), 6.05 (1H, d, *J* 9.0, N*H*), 6.85 (2H, t, *J* 8.6, C(2)ArC(3)*H*), 6.90 (2H, d, *J* 8.4, C(3)ArC(2)*H*), 7.02 (2H, d, *J* 8.0, C(3)$NHSO_2$ArC(3)*H*), 7.10 (2H, dd, *J* 8.6, 5.3, C(2)ARC(2)*H*), 7.23 (2H, d, *J* 8.4, C(3)ArC(3)*H*), 7.34 (2H, d, *J* 8.2, $NHSO_2$ARC(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.5 (Ar*C*H_3), 52.7 (O*C*H_3), 56.6 (*C*(2)), 60.7 (*C*(3)), 115.8 (d, *J* 21.3, C(2)Ar*C*(3)), 121.8 (*C*Br), 126.9 (C(3)$NHSO_2$Ar*C*(2)), 128.6 (C(3)Ar*C*(2)), 129.4 (C(3)$NHSO_2$Ar*C*(3)), 130.2 (d, *J* 7.5, C(2)Ar*C*(2)), 130.3 (d, *J* 3.8, C(2)Ar*C*(1)), 131.6 (C(3)Ar*C*(3)), 137.5 (C(3)Ar*C*1)), 137.7 (C(3)$NHSO_2$*C*(1)), 143.3 (Ar*C*(4)CH_3), 162.5 (d, *J* 246.3, Ar*C*F), 172.1 (*C*(1)); δ_F (470 MHz, $CDCl_3$) −114.3 (Ar*F*); *m/z*

(NSI$^+$) 524 ([M+NH$_4$]$^+$, 100%); HRMS (NSI$^+$) *m/z* [M+H]$^+$ calculated for $C_{23}H_{22}BrFNO_4S^+$ 506.0430; found 506.0431 (−0.3 ppm).

(2S,3R)-Methyl 3-(4-bromophenyl)-2-(4-chlorophenyl)-3-(4-methylphenylsulfonamido)propanoate ***25***

The title compound was prepared according to General Procedure B from 4-chlorophenylacetic acid (34.1mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr$_2$NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **25** as a white solid (71.3 mg, 68%); mp 120-124 °C; $[a]_D^{22}$ −27.2 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R major: 15.6 min, t_R minor: 17.7 min, 78% ee; ν_{max} (film)/cm^{-1} 3304 (NH), 3258 (NH), 1736 (C=O), 1719 (C=O), 1153 (R-SO_2N), 1090 (C-Cl); δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s, C*H*$_3$), 3.60 (3H, s, C*H*$_3$OC(1)), 3.91 (1H, d, *J* 6.4, C(2)*H*), 4.74 (1H, dd, *J* 9.2, 6.4, C(3)*H*), 6.13 (1H, d, *J* 9.1, N*H*), 6.90-6.96 (2H, m, C(3)CC*H*), 6.99-7.08 (4H, m, Ar*H*), 7.09-7.15 (2H, m, C(2)CC*H*), 7.23-7.29 (2H, m, C*H*CBr), 7.30-7.36 (2H, m, SO_2CC*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (*C*H$_3$), 52.4 (*C*H$_3$C(1)), 56.3 (*C*(2)), 60.2 (*C*(3)), 121.5 (*C*Br), 126.7 (SO_2CAr*C*), 128.4 (C(3)CAr*C*H), 128.8 (Ar*C*), 129.2 (C(2)C*C*H), 129.6 (Ar*C*), 131.5 (Ar*C*CBr), 132.7 (C(2)Ar*C*), 133.9 (Ar*C*Cl), 137.1 (SO_2*C*), 137.4 (C(3)Ar*C*), 143.0 (Ar*C*CH$_3$), 171.6 (C(1)(O)); *m/z* (NSI$^+$) 522 ([M+NH$_4$]$^+$, 50%), 546 (100%); HRMS (NSI$^+$) *m/z* [M+H]$^+$ calculated for $C_{23}H_{22}BrClNO_4S^+$ 522.0134; found 522.0136 (−0.4 ppm).

(2S,3R)-Methyl 2,3-bis(4-bromophenyl)-3-(4-methylphenylsulfonamido)propanoate ***26***

The title compound was prepared according to General Procedure B from 4-bromophenylacetic acid (43.0 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr$_2$NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **26** as a white solid (49.6 mg, 43%); mp 168-172 °C; $[a]_D^{22}$ −28.0 (*c* 1.0 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 220 nm, 30 °C), t_R major: 15.7 min, t_R minor: 18.5 min, 98% ee; ν_{max} (film)/cm^{-1} 3368 (NH), 3298 (NH), 1719 (C=O), 1709 (C=O), 1339 (R-SO_2N), 1155 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, ArC*H*$_3$), 3.59 (3H, s, OC*H*$_3$), 3.90 (1H, d, *J* 6.3, C(2)*H*), 4.73 (1H, dd, *J* 9.1, 6.3, C(3)*H*), 6.09 (1H, d, *J* 9.1, N*H*), 6.94-6.96 (2H, m, C(3)ArC(2)*H*), 6.99-7.01 (2H, m, C(2)ArC(2)*H*), 7.02-7.05 (2H, m, Ar*H*), 7.24-7.26 (1H, m, Ar*H*), 7.27-7.29 (3H, m, Ar*H*), 7.31-7.33 (2H, m, C(3)NHSO_2ArC(2)*H*); δ_C (100 MHz,

$CDCl_3$) 21.7 (Ar*C*H_3), 52.7 (O*C*H_3), 56.7 (*C*(2)), 60.5 (*C*(3)), 121.9 (C(3)Ar*C*(4)Br), 122.4 (C(2)Ar*C*(4)Br), 126.8 (C(3)$NHSO_2$Ar*C*(2)), 128.6 (C(3)Ar*C*(2)), 129.4 (C(2)Ar*C*(2)), 130.1 (C(3)$NHSO_2$Ar*C*(3)), 131.7 (C(3)Ar*C*(3)), 131.9 (C(2)Ar*C*(3)), 133.6 (C(2)Ar*C*(1)), 137.4 (C(3)$NHSO_2$Ar*C*(1)), 137.7 (C(3)Ar*C*(1)), 143.4 (Ar*C*(4)CH_3), 171.9 (*C*(1)); *m/z* (NSI^+) 582 ($[M+NH_4]^+$, 35%), 589 (100%); HRMS (NSI^+) *m/z* $[M+H]^+$ calculated for $C_{23}H_{22}Br_2NO_4S^+$ 565.9630; found 565.9631 (−0.1 ppm).

*(2S,3R)-Methyl 2-([1,1'-biphenyl]-4-yl)-3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)propanoate **27***

The title compound was prepared according to General Procedure B from biphenylacetic acid (42.4 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **27** as a white solid (49.7 mg, 44%); mp 148-154 °C; $[a]_D^{22}$ −45.5 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 220 nm, 30 °C), t_R major: 39.4 min, t_R minor: 50.3 min, 73% ee; ν_{max} (film)/cm^{-1} 3306 (NH), 1719 (C=O), 1153 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.20 (3H, s, ArCH_3), 3.63 (3H, s, OCH_3), 4.00 (1H, d, *J* 6.5, C(2)*H*), 4.84 (1H, dd, *J* 9.1, 6.5, C(3)*H*), 6.23 (1H, d, *J* 9.1, N*H*), 6.93-7.01 (4H, m, Ar*H*), 7.16-7.22 (2H, m, C(3)$NHSO_2$ArC(3)*H*), 7.22-7.26 (2H, m, C(3)ArC(3)*H*), 7.31-7.36 (3H, m, Ar*H*), 7.36-7.48 (4H, m, Ar*H*), 7.50-7.57 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (Ar*C*H_3), 52.6 (O*C*H_3), 57.1 (*C*(2)), 60.7 (*C*(3)), 121.2 (*C*Br), 127.0 ($NHSO_2$Ar*C*(2)), 127.2 (Ar*C*), 127.4 (Ar*C*), 127.7 (Ar*C*), 128.7 (Ar*C*), 128.9 (Ar*C*), 129.0 (Ar*C*), 129.2 ($NHSO_2$Ar*C*(3)), 131.5 (C(3)Ar*C*(3)), 133.5 (C_{ipso}), 137.6 (C(3)$NHSO_2$Ar*C*(1)), 138.0 (C(3)Ar*C*(1)), 140.2 (C(2)Ar*C*(1)), 140.8 (C_{ipso}), 143.1 (Ar*C*(4)CH_3), 172.3 (*C*(1)); *m/z* (NSI^+) 581 ($[M+NH_4]^+$, 70%), 588 (100%); HRMS (NSI^+) *m/z* $[M+H]^+$ calculated for $C_{29}H_{27}BrNO_4S^+$ 564.0838; found 564.0839 (−0.1 ppm).

*(2S,3S)-Methyl 3-(4-bromophenyl)-3-(4-methylphenylsulfonamido)-2-(phenylthio)propanoate **28***

The title compound was prepared according to General Procedure B from (phenylthio)acetic acid (33.6 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **8** (70.8 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **28** as a white solid and a mixture of diastereoisomers (73.8 mg, 71%); *Anti*: isolated white solid (8.3 mg, 14%); mp 120-124 °C; $[a]_D^{22}$ +6.0 (*c* 0.2 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H

(20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 220 nm, 30 °C), t_R major: 20.4 min, t_R minor: 24.7 min, 61% ee; ν_{max} (film)/cm^{-1} 3289 (NH), 1711 (C=O), 1339 (R-SO_2N), 1159 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.37 (3H, s, ArCH_3), 3.52 (3H, s, OCH_3), 3.85 (1H, d, *J* 5.3, C(2)*H*), 4.82 (1H, dd, *J* 8.8, 5.3, C(3)*H*), 6.18 (1H, d, *J* 8.8, N*H*), 6.90 (2H, d, *J* 8.4, C(3)ArC(2)*H*), 7.10-7.15 (2H, m, C(3)NHSO_2ArC(3)*H*), 7.25-7.31 (7H, m, Ar*H*), 7.53-7.55 (2H, m, C(3)NHSO_2ArC(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (Ar*C*H_3), 52.7 (O*C*H_3), 56.8 (*C*(2)), 58.7 (*C*(3)), 122.2 (*C*Br), 127.3 (C(3)NHSO_2Ar*C*(3)), 128.6 (C(3)Ar*C*(2)), 128.8 (Ar*C*), 129.4 (C(3)NHSO_2Ar*C*(2)), 129.5 (Ar*C*), 131.7 (C(3)Ar*C*(3)), 132.8, SAr*C*(1)), 133.3 (Ar*C*), 136.8 (C(3)Ar*C*(1), 137.6 (SO_2Ar*C*(1)), 143.5 (Ar*C*(4)CH_3), 170.9 (*C*(1)); *m/z* (NSI^+) 537 ($[M+NH_4]^+$, 75%), 544 (100%); HRMS (NSI^+) *m/z* $[M+Na]^+$ calculated for $C_{23}H_{22}BrNO_4S_2Na^+$ 542.0060; found 542.0066 (−1.1 ppm). *Syn*: isolated as a colourless oil (6.2 mg, 8%), selected data: δ_H (400 MHz, $CDCl_3$) 2.41 (3H, s, ArCH_3), 3.50 (3H, s, OCH_3), 3.80 (1H, d, *J* 9.1, C(2)*H*), 4.55-4.58 (1H, m, C(3)*H*), 5.70-5.75 (1H, m, N*H*), 6.97-7.00 (2H, m, C(3)ArC(2)*H*), 7.13-7.16 (2H, m, C(3)NHSO_2ArC(3)*H*), 7.22-7.24 (2H, m, C(3)ArC(3)*H*), 7.32-7.43 (5H, m, Ar*H*), 7.43-7.46 (2H, m, C(3)NHSO_2ArC(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.7 (Ar*C*H_3), 52.6 (O*C*H_3), 56.9 (*C*(2)), 57.3 (*C*(3)), 122.5 (*C*Br), 127.4 (C(3)NHSO_2Ar*C*(2)), 129.2 (Ar*C*), 129.5 (C(3)NHSO_2Ar*C*(3)), 129.5 (Ar*C*), 129.9 (C(3)Ar*C*(2)), 130.8 (SAr*C*(1)), 131.4 (C(3)Ar*C*(3)), 134.0 (Ar*C*), 135.7 (C(3)Ar*C*(1)), 136.9 (SO_2Ar*C*(1)), 143.7 (Ar*C*(4)CH_3),169.1 (*C*(1)); $[a]_D^{22}$ −7.0 (*c* 0.1 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 220nm, 30°C), t_R major: 30.6 min, t_R minor: 38.4 min, 57% ee.

(2R,3S)-Methyl 3-(4-methylphenylsulfonamido)-2,3-diphenylpropanoate ***29***

The title compound was prepared according to General Procedure B from phenylacetic acid (136.0 mg, 1.0 mmol), tosyl chloride (286.5 mg, 1.50 mmol), 2 portions of *i*Pr_2NEt (260 μL, 1.50 mmol), **7** (15.5 mg, 5 mol%, 0.05 mmol), *n*BuLi (2.5 M) solution in hexanes (0.5 mL, 55 mmol), imine **S1** (259.5 mg, 1.0 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **29** as a white solid (219.3 mg, 54%); mp 162-165 °C; $[a]_D^{22}$ −25.6 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (10% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C), t_R minor: 61.7min, t_R major: 82.0 min, 77% ee; ν_{max} (film)/cm^{-1} 3283 (NH), 1715 (C=O), 1159 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.30 (3H, s, ArCH_3), 3.59 (3H, s, OCH_3), 3.97 (1H, d, *J* 6.5, C(2)*H*), 4.85 (1H, dd, *J* 9.1, 6.5, C(3)*H*), 6.01 (1H, d, *J* 9.1, N*H*), 6.98 (2H, d, *J* 8.0, C(3)NHSO_2ArC(3)*H*), 7.00-7.03 (2H, m, Ar*H*), 7.10 (3H, m, Ar*H*), 7.16-7.20 (5H, m, Ar*H*), 7.34-7.36 (2H, m, C(3)NHSO_2ArC(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.5 (Ar*C*H_3), 52.5 (O*C*H_3), 57.8 (*C*(2)), 61.2 (*C*(3)), 126.8 (Ar*C*), 127.0

(C(3)NHSO$_2$Ar*C*(2)), 127.6 (Ar*C*), 127.9 (Ar*C*), 128.4 (Ar*C*), 128.6 (Ar*C*), 128.8 (Ar*C*), 129.2 (C(3)NHSO$_2$Ar*C*(3)), 134.9 (C(2)Ar*C*(1)), 138.8 (C(3)NHSO$_2$*C*(1)), 142.8 (Ar*C*(4)CH$_3$), 151.1 (C(3)Ar*C*(1)), 172.4 (*C*(1)); *m/z* (NSI$^+$) 427 ([M+NH$_4$]$^+$, 100%); HRMS (NSI$^+$) *m/z* [M+H]$^+$ calculated for $C_{23}H_{24}NO_4S^+$ 410.1422; found 410.1421 (+0.4 ppm). This was recrystallised from CH_2Cl_2/Petrol to give the β-lactam as a white solid (105.6 mg, 26%); mp 168-172 ˚C; $[a]_D^{22}$ −30.8° (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (10% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C), t_R minor: 61.7min, t_R major: 82.0 min, 93% ee.

*(2S,3R)-Methyl 3-(4-methylphenylsulfonamido)-3-(naphthalen-2-yl)-2-phenylpropanoate **30***

The title compound was prepared according to General Procedure B from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr$_2$NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **42** (61.9 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **30** as a white solid (50.3 mg, 55%) as a white solid; mp 164-170 °C; $[a]_D^{22}$ −24.4 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R minor: 18.5 min, t_R major: 21.2 min, 95% ee; ν_{max} (film)/cm^{-1} 3258 (NH), 1722 (C=O), 1165 (R-SO$_2$N); δ_H (400 MHz, $CDCl_3$) 2.08 (3H, s, ArC*H*$_3$), 3.61 (3H, s, OC*H*$_3$), 4.09 (1H, d, *J* 6.7, C(2)*H*), 5.03 (1H, dd, *J* 9.2, 6.7, C(3)*H*), 6.18 (1H, d, *J* 9.2, N*H*), 6.77-6.80 (2H, m, Ar*H*), 7.04-7.26 (5H, m, Ar*H*), 7.27-7.37 (4H, m, Ar*H*), 7.39-7.43 (2H, m, Ar*H*), 7.52-7.64 (2H, m, Ar*H*), 7.69-7.72 (1H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (Ar*C*H$_3$), 52.5 (O*C*H$_3$), 57.7 (*C*(2)), 61.3 (*C*(3)), 124.3 (Ar*C*), 126.1 (Ar*C*), 126.2 (Ar*C*), 126.6 (Ar*C*), 126.9 (Ar*C*), 127.5 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.3 (Ar*C*), 128.7 (Ar*C*), 128.8 (Ar*C*), 129.1 (Ar*C*), 132.7 (*C$_{ipso}$*), 132.9 (*C$_{ipso}$*), 134.8 (*C$_{ipso}$*), 135.6 (*C$_{ipso}$*), 137.6 (*C$_{ipso}$*), 142.8 (Ar*C*(4)CH$_3$), 172.5 (*C*(1)); *m/z* (NSI$^+$) 477 ([M+NH$_4$]$^+$, 80%), 482 (100%); HRMS (NSI$^+$) *m/z* [M+Na]$^+$ calculated for $C_{27}H_{25}NO_4SNa^+$ 482.1387; found 482.1397 (−2.0 ppm).

*(2S,3R)-Methyl 3-(4-methylphenylsulfonamido)-3-(naphthalen-1-yl)-2-phenylpropanoate **31***

The title compound was prepared according to General Procedure B from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr$_2$NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **S5** (61.9 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **31** as a white solid (57.6 mg, 63%); mp 122-128 °C; $[a]_D^{22}$ −30.4 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 0.4 mL min^{-1}, 211 nm, 30 °C), t_R minor: 80.1 min, t_R major:

101.2 min, 56% ee; ν_{max} (film)/cm^{-1} 3287 (NH), 1721 (C=O), 1161 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.21 (3H, s, ArCH_3), 3.53 (3H, s, OCH_3), 4.23 (1H, d, *J* 5.0, C(2)*H*), 5.62 (1H, dd, *J* 9.2, 5.0, C(3)*H*), 6.63 (1H, d, *J* 9.0, N*H*), 6.72-6.86 (2H, m, Ar*H*), 7.15-7.25 (6H, m, Ar*H*), 7.30-7.38 (3H, m, Ar*H*), 7.48 (1H, ddd, *J* 8.0, 6.8, 1.2, Ar*H*), 7.56 (1H, ddd, *J* 8.5, 6.8, 1.5, Ar*H*), 7.64 (1H, d, *J* 8.1, Ar*H*), 7.75-7.83 (1H, m, Ar*H*), 8.00 (1H, d, *J* 8.5, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.3 (Ar*C*H_3), 52.5 (O*C*H_3), 57.6 (*C*(2)), 61.3 (*C*(3)), 124.3 (Ar*C*), 126.2 (Ar*C*), 126.3 (Ar*C*), 126.6 (Ar*C*), 126.9 (Ar*C*), 127.6 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.3 (Ar*C*), 128.7 (Ar*C*), 128.8 (Ar*C*), 129.1 (Ar*C*), 132.7 (*C*$_{ipso}$), 133.0 (*C*$_{ipso}$), 134.8 (*C*$_{ipso}$), 135.7 (*C*$_{ipso}$), 137.6 (*C*$_{ipso}$), 142.8 (Ar*C*(4)CH_3), 172.5 (*C*(1)); *m/z* (NSI$^+$) 477 ([M+NH_4]$^+$, 80%), 482 (100%); HRMS (NSI$^+$) *m/z* [M+Na]$^+$ calculated for $C_{27}H_{25}NO_4SNa^+$ 482.1387; found 482.1397 (−2.0 ppm).

*(2S,3R)-Methyl 3-(furan-2-yl)-3-(4-methylphenylsulfonamido)-2-phenylpropanoate **32***

The title compound was prepared according to General Procedure B from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **S4** (53.6 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **32** as a white solid (43.7 mg, 55%); mp 154-160 °C; $[a]_D^{22}$ −4.6 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, Chiralcel OJ-H (10% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C), t_R major: 45.3 min, t_R minor: 53.9 min, 69% ee; ν_{max} (film)/cm^{-1} 3264 (NH), 1726 (C=O), 1163 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, ArCH_3), 3.65 (3H, s, OCH_3), 4.12 (1H, d, *J* 7.1, C(2)*H*), 4.97 (1H, dd, *J* 9.7, 7.1, C(3)*H*), 5.66 (1H, d, *J* 9.8, N*H*), 5.84 (1H, d, *J* 3.3, C(3)ArC(3)*H*), 6.04 (1H, dd, *J* 3.2, 1.8, C(3)ArC(4)*H*), 7.09 (2H, d, *J* 8.0, $NHSO_2$ArC(3)*H*), 7.13 (3H, dd, *J* 9.3, 1.2, Ar*H*), 7.20 (3H dd, *J* 4.8,2.4, Ar*H*), 7.46 (2H, d, *J* 8.2, SO_2ArC(2)*H*); δ_C (100 MHz, $CDCl_3$) 21.6 (Ar*C*H_3), 52.5 (O*C*H_3), 55.0 (*C*(2)), 55.4 (*C*(3)), 108.4 (Ar*C*), 110.4 (Ar*C*), 127.0 (Ar*C*), 128.0 (Ar*C*), 128.6 (C(3)$NHSO_2$Ar*C*(3)), 128.7 (C(2)Ar*C*(1)), 129.4 (C(3)$NHSO_2$Ar*C*(1)), 134.4 (Ar*C*), 137.7 (C(3)$NHSO_2$Ar*C*(1)), 142.0 (C(3)$NHSO_2$Ar*C*(4)), 143.0 (Ar*C*(4)CH_3), 151.1 (C(3)Ar*C*(1)), 172.0 (*C*(1)); *m/z* (NSI$^+$) 229 (100%), 417 ([M+NH_4]$^+$, 55%); HRMS (NSI$^+$) *m/z* [M+H]$^+$ calculated for $C_{21}H_{22}NO_5S^+$ 400.1209; found 400.1213 (−1.0 ppm).

*(2S,3R)-Methyl 3-(4-methylphenylsulfonamido)-2-phenyl-3-(4-(trifluoromethyl)phenyl)propanoate **33***

The title compound was prepared according to General Procedure B from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **S3** (65.5 mg,

0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **33** as a white solid (46.4 mg, 49%); mp 118-124 °C; $[a]_D^{22}$ −17.6 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R minor: 15.9 min, t_R major: 20.9 min, 47% ee; ν_{max} (film)/cm^{-1} 3237 (NH), 1742 (C=O), 1323 (R-SO_2N), 1161 (R-SO_2N), 1117 (CF_3); δ_H (400 MHz, $CDCl_3$) 2.28 (3H, s, ArCH_3), 3.64 (3H,s, OCH_3), 3.96 (1H, d, *J* 7.3, C(2)*H*), 4.94 (1H, dd, *J* 9.1, 7.3, (C(3)*H*), 6.34 (1H, d, *J* 9.1, N*H*), 6.95 (2H, d *J* 8.3, C(3)NHSO_2ArC(3)*H*), 7.07-7.10 (2H, m, Ar*H*), 7.16-7.19 (5H, m, Ar*H*), 7.29-7.34 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (Ar*C*H_3), 52.7 (O*C*H_3), 57.6 (*C*(2)), 60.8 (*C*(3)), 124.0 (q, *J* 271.3, CF_3), 125.2 (q, *J* 5, C(3)Ar*C*(3)), 126.9 (Ar*C*), 127.6 (Ar*C*), 128.2 (Ar*C*), 128.6 (Ar*C*), 128.9 (Ar*C*), 129.3 (Ar*C*), 129.7 (q, *J* 36.6, C(3)Ar*C*(4)CF_3), 134.3 (C(2)Ar*C*(1)), 137.4 (C(3)NHSO_2Ar*C*(1)), 142.4 (C(3)Ar*C*(1)), 143.2 (C(3)NHSO_2Ar*C*(4)CH_3), 172.2 (*C*(1)); δ_F (470 MHz, $CDCl_3$) −63.2 (C*F*$_3$); *m/z* (NSI^+) 495 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) *m/z* $[M+H]^+$ calculated $C_{24}H_{23}F_3NO_4S^+$ 478.1289; found 478.1294 (−1.1 ppm).

*(2S,3R)-Methyl 3-(4-nitrophenylsulfonamido)-2,3-diphenylpropanoate **34***

The title compound was prepared according to General Procedure B from phenylacetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr_2NEt (52 μL, 0.30 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *n*BuLi (2.5 M) solution in hexanes (0.1 mL, 11 mmol), imine **S6** (58.1 mg, 0.20 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-aminoester **34** as a white solid (47.4 mg, 54%); mp 158-162 °C; $[a]_D^{22}$ −20.8 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 0.5 mL min^{-1}, 211 nm, 30 °C), t_R minor: 63.7 min, t_R major: 106.7 min, 75% ee; ν_{max} (film)/cm^{-1} 3240 (NH), 1740 (C=O), 1390 (NO_2), 1323 (RSO_2N), 1161 (RSO_2N); δ_H (400 MHz, $CDCl_3$) 3.60 (s, 3H, OCH_3), 4.02 (1H, d, *J* 5.4, C(2)*H*), 4.86 (1H, dd, *J* 9.2, 5.4, C(3)*H*), 6.59 (1H, d, *J* 9.2, N*H*), 7.09-7.12 (3H, m, Ar*H*), 7.14-7.23 (7H, m, Ar*H*), 7.58 (2H, d, *J* 8.8, NHSO_2ArC(2)*H*), 7.98 (2H, d, *J* 8.8, NHSO_2ArC(3)*H*); δ_C (125 MHz, $CDCl_3$) 52.6 (O*C*H_3), 57.1 (*C*(2)), 61.7 (*C*(3)), 123.8 (NHSO_2Ar*C*(3)), 126.7 (Ar*C*), 128.0 (Ar*C*), 128.1 (Ar*C*), 128.2 (Ar*C*), 128.3 (Ar*C*), 128.7 (Ar*C*), 129.0 (NHSOAr*C*(2)), 134.8 (NHSO_2Ar*C*(1)), 138.5 (C_{ipso}), 146.5 (C_{ipso}), 149.4 (*C*NO_2), 172.6 (*C*(1)); *m/z* (NSI^+) 458 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) *m/z* $[M+NH_4]^+$ calculated for $C_{22}H_{24}N_3O_6S^+$ 458.1382; found 458.1380 (+0.4 ppm).

*(3S,4R)-4-(4-Bromophenyl)-3-(2-napthylene)-1-tosylazetidin-2-one **36***

The title compound was prepared according to General Procedure C from imine **8** (70.8 mg, 0.20 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *i*Pr_2NEt (43.0 μL, 0.25 mmol), 2-naphthoic anhydride (106.4 mg, 0.30 mmol) and purified by chromatography (10:90 EtOAc:Petrol) to give β-lactam **36** as a white solid (44.4 mg, 44%); mp 120-126 °C; $[a]_D^{22}$ −63.0 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 221 nm, 30 °C), t_R minor: 22.2 min, t_R major: 28.4 min, 83% ee; ν_{max} (KBr)/cm^{-1} 1774 (C=O), 1374 (C-N), 1173 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.50 (3H, s, NSO_2ArCH_3), 4.39 (1H, d, *J* 3.4, C(3)*H*), 4.98 (1H, d, *J* 3.3, C(4)*H*), 7.07 (1H, dd, *J* 8.5, 1.9, Ar*H*), 7.21 (2H, d, *J* 8.3, Ar*H*), 7.35 (2H, m, Ar*H*), 7.47-7.53 (5H, m, Ar*H*), 7.69-7.72 (1H, m, Ar*H*), 7.77-7.83 (4H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (NSO_2ArCH_3), 64.5 (*C*(3)), 66.8 (*C*(4)), 123.3 (Ar*C*, *C*Br), 126.7 (2×Ar*C*), 126.9 (Ar*C*), 127.5 (Ar*C*), 127.8 (Ar*C*), 127.9 (Ar*C*), 128.2 (Ar*C*), 128.6 (Ar*C*), 129.2 (Ar*C*), 129.4 (C(3)$NHSO_2$Ar*C*(2)), 130.0 (Ar*C*), 133.0 (C_{ipso}), 133.2 (C_{ipso}), 133.3 (C_{ipso}), 135.9 (C_{ipso}), 145.5 ($NSO_2ArC(4)CH_3$), 165.4 (*C*(2)); *m/z* (NSI^+) 524 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) *m/z* $[M+NH_4]^+$ calculated for $C_{26}H_{24}BrN_2O_3S^+$ 523.0674; found 523.0686 (−2.2 ppm).

(3S,4R)-4-(4-Bromophenyl)-3-(thiophen-3-yl)-1-tosylazetidin-2-one ***37***

The title compound was prepared according to General Procedure C from imine **8** (70.8 mg, 0.20 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *i*Pr_2Net (43.0 μL, 0.25 mmol), anhydride **S9** (79.9 mg, 0.30 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-lactam **37** as a white solid (43.5 mg, 47%); mp 104-106 °C; $[a]_D^{22}$ +20.0 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 220 nm, 30 °C), t_R minor: 26.6 min, t_R major: 34.1 min, 82% ee; ν_{max} (film)/cm^{-1} 3109 (thiophene CH), 1792 (C=O), 1487 (C-N), 1373 (R-SO_2N), 1173 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.47 (3H, s, NSO_2ArCH_3), 4.29 (1H, d, *J* 3.3, C(3)*H*), 4.87 (1H, d, *J* 3.3, C(4)*H*), 6.76 (1H, dd, *J* 5.0, 1.3, C(3)Ar*H*), 7.08 (1H, dt, *J* 1.8, 0.9, C(3)Ar*H*), 7.16-7.18 (2H, m, Ar*H*), 7.31-7.34 (3H, m, Ar*H*), 7.46-7.48 (2H, m, Ar*H*), 7.72-7.74 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.9 (NSO_2ArCH_3), 60.1 (*C*(3)), 64.9 (*C*(4)), 123.4 (C(3)Ar*C*), 125.8 (C(3)Ar*C*), 127.6 (Ar*C*), 127.7 (Ar*C*), 128.2 (Ar*C*), 130.1 (Ar*C*), 132.1 (C_{ipso}), 135.2 (C_{ipso}), 135.5 (C_{ipso}), 145.8 ($NSO_2ArC(4)CH_3$), 164.9 (*C*(2)), 185.4 (C_{ipso}); *m/z* (NSI^+) 579 ($[M+NH_4]^+$, 85%), 481 (100%); HRMS (NSI^+) *m/z* $[M+NH_4]^+$ calculated for $C_{20}H_{17}BrNO_3S_2^+$ 461.9830; found 461.9828 (+0.5 ppm).

(3S,4R)-4,3-Diphenyl-1-tosylazetidin-2-one ***38***

The title compound was prepared according to General Procedure C from imine **S1** (338.0 mg, 1.0 mmol), **7** (15.5 mg, 5 mol%, 0.05 mmol), *i*Pr_2NEt (215 μL, 1.25 mmol), benzoic anhydride **35** (381.0 mg, 1.5 mmol) and purified by chromatography (10:90 EtOAc:Petrol) to give β-lactam **38** as a white solid (228.7 mg, 60%); chiral HPLC analysis, Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R major: 14.8 min, t_R minor: 19.6 min, 89% ee; δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, CH_3), 4.27 (1H, d, *J* 3.4, C(3)*H*), 4.98 (1H, d, *J* 3.4, C(4)*H*), 7.06 (2H, m, Ph*H*), 7.26-7.34 (10H, m, Ph*H*), 7.71 (2H, m, Ph*H*). All NMR data was in accordance to the literature.[27a] This was recrystallised from CH_2Cl_2/Petrol to give the β-lactam as a white solid (129.5 mg, 34%); mp 91-98 °C {lit.**Error! Bookmark not defined.** mp 123-124 °C}; $[a]_D^{22}$ +35.6 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, Chiralcel OD-H (10% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 254 nm, 30 °C), t_R major: 14.8 min, t_R minor: 19.6 min, >99% ee.

(3S,4R)-4-(Naphthalene-2-yl)-3-phenyl-1-tosylazetidin-2-one ***39***

The title compound was prepared according to General Procedure C from imine **42** (61.9 mg, 0.20 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *i*Pr_2NEt (43.0 μL, 0.25 mmol), benzoic anhydride **35** (76.2 mg, 0.30 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-lactam **39** as a white solid (47.8 mg, 56%); mp 38-44 °C; $[a]_D^{22}$ −8.8 (*c* 0.25 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R major: 19.3 min, t_R minor: 41.5 min, 92% ee; ν_{max} (film)/cm^{-1} 2920, 1792 (C=O), 1456 (C-N), 1364 (R-SO_2N), 1166 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.41 (3H, s, NSO_2ArCH_3), 4.36 (1H, d, *J* 3.0, C(3)*H*), 5.16 (1H, d, *J* 3.0, C(4)*H*), 7.11-7.14 (2H, m, Ar*H*), 7.16-7.24 (2H, m, Ar*H*), 7.31-7.35 (3H, m, Ar*H*), 7.48-7.57 (2H, m, Ar*H*), 7.69- 7.72 (3H, m, Ar*H*), 7.72-7.76 (2H, m, Ar*H*), 7.80 (1H, d, *J* 8.5, Ar*H*), 7.82-7.89 (1H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 21.8 (NSO_2ArCH_3), 64.5 (*C*(3)), 66.2 (*C*(4)), 123.3 (Ar*C*), 126.7 (Ar*C*), 126.9 (Ar*C*), 127.0 (Ar*C*), 127.4 (Ar*C*), 127.8 (Ar*C*), 127.9 (Ar*C*), 128.2 (Ar*C*), 128.6 (Ar*C*), 129.2 (Ar*C*), 129.4 (Ar*C*), 130.0 (Ar*C*), 133.0 (C_{ipso}), 133.1 (C_{ipso}), 133.3 (C_{ipso}), 133.6 (C_{ipso}), 135.8 (C(3)Ar*C*(1)), 145.5 ($NSO_2ArC(4)CH_3$), 165.5 (*C*(2)); *m/z* (NSI^+) 445 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) *m/z* $[M+NH_4]^+$ calculated for $C_{26}H_{25}N_2O_3S^+$ 445.1578; found 445.1580 (–0.5 ppm). *Syn*: from mixture of diastereoisomers, selected data δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, NSO_2ArCH_3), 5.04 (1H, *J* 6.8, C*H*), 5.65 (1H, *J* 6.9, C*H*); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R major: 18.1 min, t_R minor: 25.6 min, 54% ee.

*(3S,4R)-3-Phenyl-1-tosyl-4-(4-(trifluoromethyl)phenyl)azetidin-2-one **40***

The title compound was prepared according to General Procedure C from imine **S3** (65.5 mg, 0.20 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *i*Pr_2NEt (43.0 μL, 0.25 mmol), benzoic anhydride **35** (76.2 mg, 0.30 mmol) and purified by chromatography (20:80 EtOAc:Petrol) to give β-lactam **40** as a white gum (41.9 mg, 47%); $[a]_D^{22}$ +17.2 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, Chiralcel OD-H (5% *i*PrOH:hexane, flow rate 0.25 mL min^{-1}, 211 nm, 30 °C), t_R minor: 82.7 min, t_R major: 90.2 min, 68% ee; ν_{max} (film)/cm^{-1} 1796 (C=O), 1323 (R-SO_2N), 1167 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 2.47 (3H, s, NSO_2ArCH_3), 4.25 (1H, d, *J* 3.4, C(3)*H*), 5.00 (1H, d, *J* 3.4, C(4)*H*), 6.98-7.08 (2H, m, Ar*H*), 7.29-7.37 (5H, m, Ar*H*), 7.40-7.43 (2H, m, Ar*H*), 7.55-7.63 (2H, m, Ar*H*), 7.73-7.76 (2H, m, Ar*H*); δ_F (282 MHz, CDCl3) 62.7 (CF_3); δ_C (100 MHz, $CDCl_3$) 21.9 (NSO_2ArCH_3), 64.6 (*C*(3)), 65.0 (*C*(4)), 123.9 (q, *J* 217, *C*F_3), 126.2 (q, *J* 3, C(4)Ar*C*(3)), 126.9 (Ar*C*), 127.4 (Ar*C*), 127.7 (Ar*C*), 128.8 (Ar*C*), 129.5 (Ar*C*), 130.2 (Ar*C*), 131.5 (q, *J* 26, C(4)Ar*C*(4)CF_3), 132.5 (C_{ipso}), 135.5 (C_{ipso}), 140.3 (C(4)Ar*C*(1)), 145.9 ($NSO_2ArC(4)CH_3$), 165.1 (*C*(1)); *m/z* (NSI^+) 463 ($[M+NH_4]^+$, 100%); HRMS (NSI^+) *m/z* $[M+NH_4]^+$ calculated for $C_{23}H_{19}BF_3NO_3S^+$ 446.1031; found 446.1032 (−0.3 ppm).

*(3S,4R)-1-((4-Nitrophenyl)sulfonyl)-3,4-diphenylazetidin-2-one **41***

The title compound was prepared according to General Procedure C from imine **S6** (58.1 mg, 0.20 mmol), **7** (3.1 mg, 5 mol%, 0.01 mmol), *i*Pr_2NEt (43.0 μL, 0.25 mmol), benzoic anhydride **35** (72.6 mg, 0.30 mmol) and purified by chromatography (10:90 EtOAc:Petrol) to give β-lactam **41** as a white solid (41.6 mg, 51%). mp 108-114 °C; $[a]_D^{22}$ −2.1 (*c* 0.9 in $CHCl_3$); chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R minor: 28.3 min, t_R major: 32.6 min, 85% ee; ν_{max} (KBr)/cm^{-1} 1797 (C=O), 1529 (NO_2), 1379 (C-N), 1176 (R-SO_2N); δ_H (400 MHz, $CDCl_3$) 4.42 (1H, d, *J* 3.45, C(3)*H*), 5.12 (1H, d, *J* 3.43, C(4)*H*), 7.17-7.20 (2H, m, Ar*H*), 7.24-7.25 (1H, m, Ar*H*), 7.32-7.40 (7H, m, Ar*H*), 7.92-7.97 (2H, m, $NSO_2ArC(2)H$), 8.27-8.29 (2H, m, $NSO_2ArC(3)H$); δ_C (100 MHz, $CDCl_3$) 64.2 (*C*(3)), 66.3 (*C*(4)), 124.3 ($NSO_2ArC(3)$), 126.8 (Ar*C*), 127.0 (Ar*C*), 128.6 (Ar*C*), 128.8 ($NSO_2ArC(2)$), 129.1 (Ar*C*), 129.3 (Ar*C*), 129.6 (Ar*C*), 132.2 (C(4)Ar*C*(1)), 135.0 (C(3)Ar*C*(1)), 144.1 ($NSO_2ArC(1)$), 150.7 ($NSO_2ArC(4)$), 164.8 (*C*(2));

m/z (APCI$^+$) 409 ([M+H]$^+$,100%); HRMS (APCI$^+$) *m/z* [M+H]$^+$ calculated for $C_{21}H_{17}N_2O_5S^+$ 409.0851; found 409.0853(−0.4 ppm).

Detosylation reaction

*(3S,4R)-4-(4-Bromophenyl)-3-phenylazetidin-2-one **S10***

Using a modified version of the procedure by Lectka *et al.*[41] *N*-tosylazetidinone **9** (54.1 mg, 0.12 mmol, 1 eq) was stirred in THF (1 mL) at rt and ~0.1 M SmI_2 in THF (7.80 mL, 0.72 mmol, 6 eq) was added dropwise until the colour remained consistent. The reaction mixture was stirred for 5 min, quenched with $NaHCO_3$ (5 mL), extracted (3 × EtOAc), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a yellow oil. Following purification by column chromatography (40:60 EtOAc:Petrol) β-lactam **S10** was isolated as a colourless oil (14.6 mg, 48%). $[a]_D^{22}$ −55.6 (*c* 0.5 in $CHCl_3$); chiral HPLC analysis, Chiralcel OD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211nm, 25°C), t_R major: 29.2 min, t_R minor: 38.9 min, 90% ee; ν_{max} (film)/cm^{-1} 3263 (NH), 1751 (C=O); δ_H (400 MHz, $CDCl_3$) 4.17 (1H, d, *J* 2.40, C(3)*H*), 4.65 (1H, d, *J* 2.40, C(4)*H*), 6.34 (1H, br s, N*H*), 7.28-7.32 (4H, m, Ar*H*), 7.34-7.39 (2H, m, Ar*H*), 7.53-7.55 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 59.8 (*C*(3)), 66.4 (*C*(4)), 122.5 (*C*Br), 127.4 (Ar*C*), 127.5 (Ar*C*), 128.1 (Ar*C*), 129.2 (Ar*C*), 132.3 (Ar*C*), 134.5 (C_{ipso}), 138.7 (C_{ipso}), 168.8 (*C*(2)); *m/z* (NSI$^+$) 324 (100%), 319 ([M+NH$_4$]$^+$, 85%); HRMS (NSI$^+$) *m/z* [M+H]$^+$ calculated for $C_{15}H_{13}BrNO^+$ 302.0178; found 302.0175 (+1.0 ppm).

Control Experiments

Control Experiment 1

β-Lactam **39** was prepared according to General Procedure A from phenyl acetic acid (27.2 mg, 0.20 mmol), tosyl chloride (57.3 mg, 0.30 mmol), 2 portions of *i*Pr$_2$NEt (52 μL, 0.30 mmol), **12** (10 mg, 20 mol%, 0.04 mmol) and imine **42** (70.8 mg, 0.20 mmol). The reaction was monitored over time using ^{1}H NMR for changes in the diastereomeric ratio. The results are shown in table Scheme 3.

Control Experiment 2

A sample of β-lactam **39** (3.3 mg, 0.007 mmol) with of a known dr (*anti:syn* 21:79) and ees (*anti* 90%, *syn* 52%) was dissolved in CH_2Cl_2 (1 mL) and treated with *i*Pr$_2$NEt (100 μL, 0.6 mmol) and **7** (3.1 mg, 0.01 mmol). The reaction was stirred at rt for 3 h, quenched with 1M HCl, extracted (3×CH_2Cl_2), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (dr >95:5) with

identical spectroscopic data as previously reported; chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R minor: 19.3 min, t_R major: 41.5 min, 32% ee.

Control Experiment 3

To a stirred solution of phenylacetic acid (27.2 mg, 1 eq, 0.20 mmol) in CH_2Cl_2 (1 mL) at 0 °C, tosyl chloride (57.3 mg, 1.5 eq, 0.30 mmol) and *i*Pr_2NEt (52 μL, 1.5 eq, 0.30 mmol) were added. The solution was stirred at 0 °C for 20 min. The achiral isothiourea catalyst, **10** (7.6 mg, 20 mol%, 0.04 mmol) and imine **8** (70.8 mg, 1 eq, 0.20 mmol) were added followed by $^{i}Pr_2$NEt (52 μL, 1.5 eq, 0.30 mmol). The solution was then stirred at rt for 1 h before quenching with 1M HCl, extracted (3×EtOAc), drying the combined organic layers ($MgSO_4$) and concentrating *in vacuo*. The resulting residue was redissolved in CH_2Cl_2 (1 mL) and treated with **7** (12.3 mg, 20 mol%), NaOMe (23.0 mg, 2 eq, 0.40 mmol) and methanol (1 mL). The reaction mixture was stirred for 1 hour at rt before being quenched with water (1 mL), extracted (3×EtOAc), the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Following purification by column chromatography (20:80 EtOAc:Petrol), **17** was obtained as a white solid (38.5 mg, 39%) with identical spectroscopic data as reported previously; chiral HPLC analysis, ChiralPak AD-H (20% *i*PrOH:hexane, flow rate 1.0 mL min^{-1}, 211 nm, 30 °C), t_R minor: 29.0 min, t_R major: 42.7 min, 16% ee.

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Supporting Information: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra and HPLC traces of all products. CIF file giving X-ray crystallographic data for *anti*-**17**. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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