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Chiral relay in NHC-mediated asymmetric β-lactam synthesis II; asymmetry from NHCs derived from acyclic 1,2-diamines

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ABSTRACT

The synthesis of a range of imidazolinium salts derived from acyclic 1,2-diamines, and an evaluation of the reactivity and asymmetric induction of the corresponding NHCs as catalysts for the asymmetric synthesis of β-lactams, is reported. An *N*-methyl-substituted NHC derived from (1*R*,2*R*)-1,2-diphenylethanediamine shows optimal reactivity and enantioselectivity in this series, in contrast to that observed with NHCs derived from (1*R*,2*R*)-cyclohexane-1,2-diamine.

1. Introduction

The ability of Lewis bases to promote numerous catalytic asymmetric processes has been investigated extensively over the last decade.[1] Within this area, an array of molecular catalysts have been designed and utilised, with the development of stereochemical models that rationalise the preferred configuration of a given product central to the development of our mechanistic understanding of these reactions. As part of our ongoing studies with regards to the development and understanding of the use of Lewis base catalysts in asymmetric catalysis,[2] in a previous manuscript we reported that N-heterocyclic carbenes (NHCs)[3] derived from (1*R*,2*R*)-cyclohexane-1,2-diamine promote the formal [2+2] cycloaddition of diphenylketene and *N*-tosyl imines,[4,5] with the nature of the N-substituent key to maximising asymmetry in this series due to a chiral relay effect (Fig. 1).[6,7]

Building upon this knowledge, this manuscript explores the consequence of altering the catalyst architecture within this system through the preparation of a range of imidazolinium precatalysts derived from acyclic 1,2-diamines and α-amino acids rather than (1*R*,2*R*)-cyclohexane-1,2-diamine. The trend in enantioselectivity through variation of the N-substituents from *N*-methyl to *N*-benzyl, as well as the consequence of incorporating stereogenic *N*-α-methylbenzyl substituents, is assessed through evaluating their catalytic activity in the formal [2+2] cycloaddition of ketenes and *N*-tosyl imines (Fig. 2).

The conformational effects of ligands derived from both cyclic and acyclic 1,2-diamines and their stereochemical influence on reactions have been widely probed, with the work of North et al.

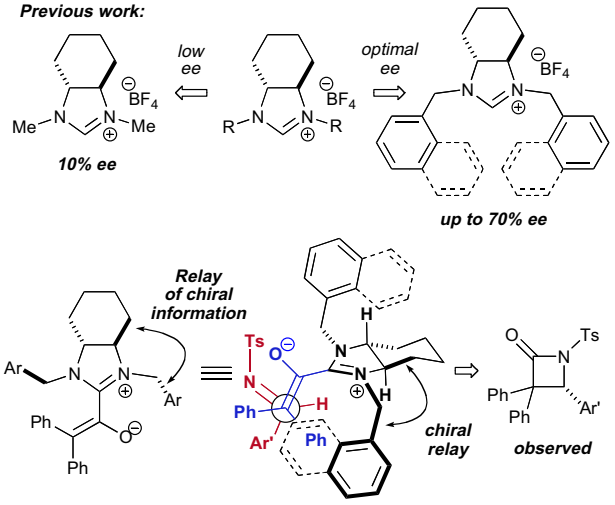

Figure 1. Proposed chiral relay in C_2-symmetric imidazolinium NHC promoted catalysis.

and their studies upon the enantioselectivity of a series of metal-salen complexes being representative.[8] In this study, the use of (1*R*,2*R*)-cyclohexane-1,2-diamine **1** to form the catalyst backbone allowed the Cu-salen complex **3** to only adopt the '*gauche*' conformation **5** due to the constraints of the cyclohexane ring, giving **8** in high ee in the enantioselective phase transfer benzylation of **7**. However, the Cu-salen complex **4** prepared from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine **2** preferred the '*anti*' conformation **6**, resulting in markedly reduced reactivity and enantioselectivity in the benzylation of **7** (Fig. 3).

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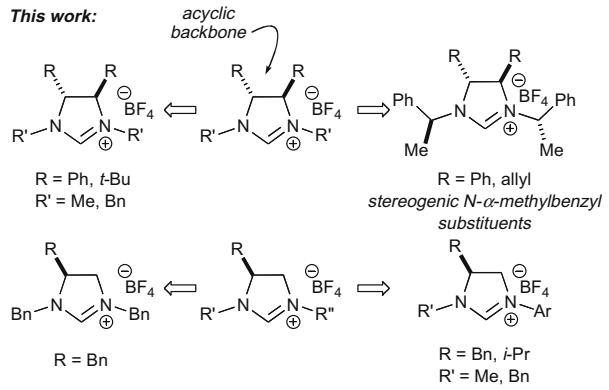


Figure 2. C_2-Symmetric and C_1-symmetric imidazolinium precatalysts derived from acylic 1,2-diamines.

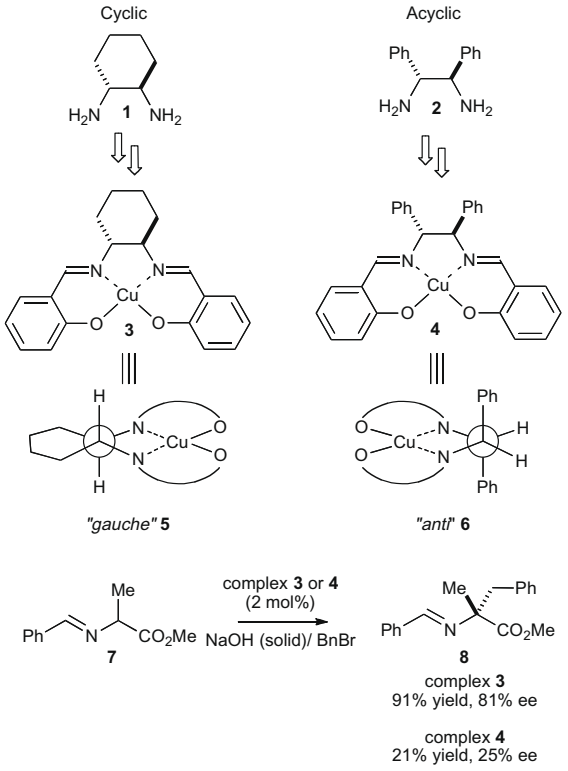


Figure 3. North's proposed '*gauche*' and '*anti*' conformations of metal-Salen complexes and their effect upon enantioselective phase transfer catalysis.

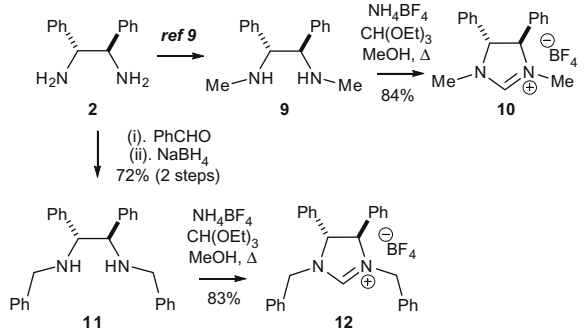
Given this precedent for conformational effects in complexes derived from acyclic and cyclic 1,2-diamines resulting in markedly different reaction enantioselectivities, we were intrigued to discover the effect that such constraints would impose upon the proposed chiral relay mechanism in the NHC-mediated synthesis of β-lactams. We herein report our studies within this area.

2. Results and discussion

2.1. C_2-Symmetric precatalyst synthesis from acyclic 1,2-diamines

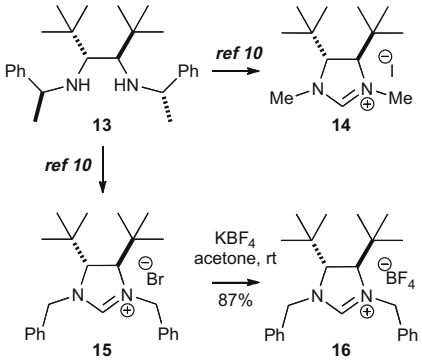
2.1.1. C_2-Symmetric *N*-Me and *N*-Bn substituted imidazolinium salts with 4,5-diphenyl and 4,5-di-*tert*-butyl substituents

Initial studies focused upon the preparation of C_2-symmetric *N*-methyl and *N*-benzyl-substituted imidazolinium precatalysts derived from commercially available (1*R*,2*R*)-1,2-diphenylethanediamine. *N*-Methyl-substituted precatalyst **10** was prepared following modified literature procedures,[9] while the *N*-benzyl-substituted precatalyst **12** was prepared by sequential imine formation, reduction and cyclisation (Scheme 1).



Scheme 1. Preparation of (4*R*,5*R*)-diphenyl *N*-methyl and *N*-benzyl imidazolinium salts **10** and **12**.

To prepare the analogous *N*-methyl- and *N*-benzyl- substituted 4,5-di-*tert*-butyl imidazolinium salts **14** and **15**, the method of Mangeney et al.[10] was followed from **13**,[11] with ion exchange of the bromide salt to the tetrafluoroborate salt generating **16** (Scheme 2). Consistent with the observations of Nolan[12] and Movassaghi,[13] the C(2) proton of imidazolium salt **15** with a coordinating halide counterion shows a C(2)–H resonance at 11.0 ppm in $CDCl_3$, whereas upon ion exchange to a non-coordinating tetrafluoroborate anion **16** the C(2)–H resonance appears at 9.1 ppm in $CDCl_3$.



Scheme 2. Preparation of (4*R*,5*R*)-di-*tert*-butyl *N*-methyl and *N*-benzyl imidazolinium salts **14**, **15** and **16**.

The solid state structures of *N*-methyl precatalyst **10** and *N*-benzyl precatalyst **15** were verified by X-ray crystallographic analysis (Figs. 4 and 5). Notably, in the solid state, the incorporation of diphenyl substituents at C(4) and C(5) within **10** results in a H–C(4)–C(5)–H dihedral angle of 143.1°, while the incorporation of di-*tert*-butyl substituents at C(4) and C(5) results in a H–C(4)–C(5)–H dihedral angle of 113.2°, both markedly different to the approximately antiperiplanar array observed crystallographically in the imidazolinium salts derived from (1*R*,2*R*)-cyclohexane-1,2-diamine that were reported in the previous manuscript. While this large difference in dihedral angle may be partly due to packing effects in the solid state, it also presumably reflects the minimisation of the 1,2-strain between the acyclic skeletal substituents. These effects result in the C(4)- and C(5)-aryl or alkyl substituents of imidazolinium salts derived from acyclic 1,2-diamines disfavouring the '*gauche*' conformation found in the imidazolinium salts derived from (1*R*,2*R*)-cyclohexane-1,2-diamine.

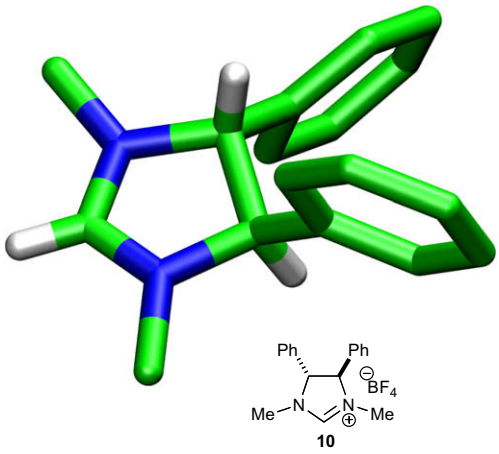


Figure 4. Molecular representation of the X-ray crystal structure of (4*R*,5*R*)-diphenyl *N*-methyl precatalyst **10** (tetrafluoroborate counterion and selected H atoms omitted for clarity).

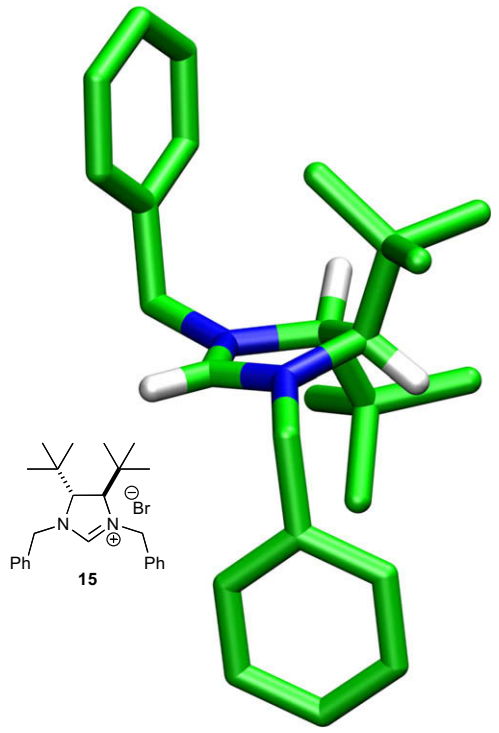
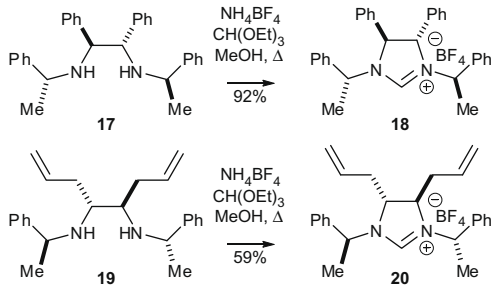


Figure 5. Molecular representation of the X-ray crystal structure of (4*R*,5*R*)-di-*tert*-butyl *N*-benzyl precatalyst **15** (bromide counterion and selected H atoms omitted for clarity).



Scheme 3. Synthesis of C_2 symmetric imidazolinium salts bearing *N*-α-methylbenzyl substituents.

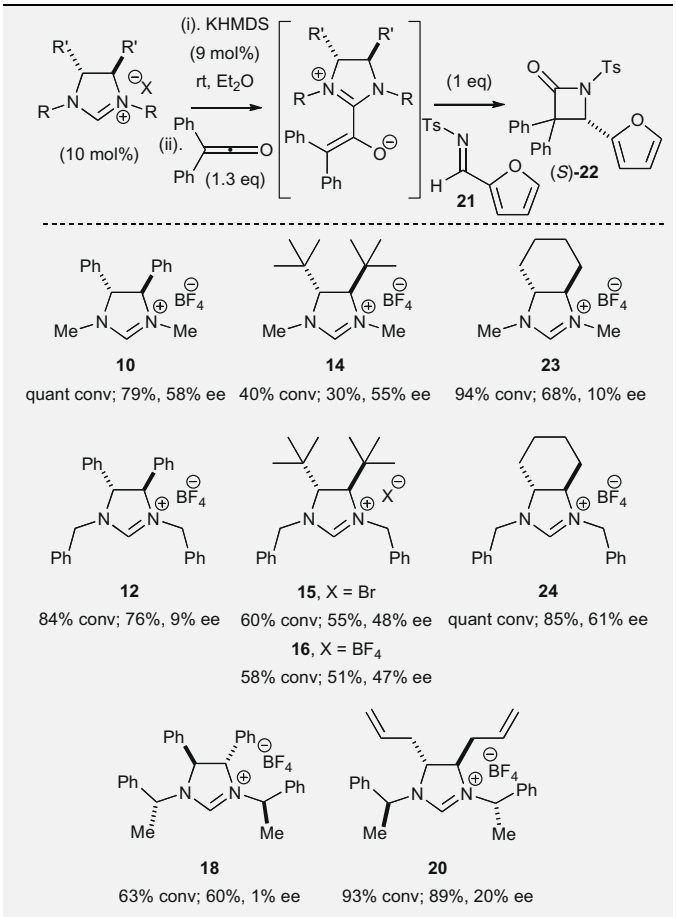
2.1.2. C_2-Symmetric *N*-α-methylbenzyl substituted imidazolinium salts

N-α-Methylbenzyl imidazolinium salts **18** and **20** were next prepared following standard methods from the corresponding acyclic diamines **17** and **19** (Scheme 3).[14,15]

2.2. Probing structure–enantioselectivity relationships in β-lactam formation

These C_2-symmetric imidazolinium salts were subsequently used as precatalysts under standardised conditions (10% precatalyst, 9 mol % KHMDS) to promote the formal [2+2] cycloaddition of diphenylketene and *N*-tosyl imine **21** to generate β-lactam (*S*)-**22**. Their reactivity and enantioselectivity in comparison with those of the *N*-methyl and *N*-benzyl imidazolinium precatalysts **23** and **24** prepared from (1*R*,2*R*)-cyclohexane-1,2-diamine are shown (Table 1). Distinctive trends in reactivity observed within this series indicate that the (4*R*,5*R*)-di-*tert*-butyl-substituted catalysts **14–16** lead to only moderate reaction conversion (30–55%), presumably reflecting poor reactivity due to steric encumbrance. Notably, when using precatalysts **10** and **12** containing a (4*R*,5*R*)-diphenyl backbone, good levels of reaction conversion were observed independent of the N-substituent, although optimal enantioselectivity was observed with *N*-methyl substituents (*N*-methyl, 58% ee, *N*-benzyl, 9% ee). The introduction of N-α-methylbenzylsubstituents led to only moderate enantioselectivity.

Table 1
Asymmetric formal [2+2] cycloadditions using C_2-symmetric imidazolinium precatalysts



All conversions determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. All ees determined by HPLC analysis.

3. Trends in asymmetric induction

In the previous manuscript we described the results consistent with a chiral relay mechanism operating within NHCs derived from (1*R*,2*R*)-cyclohexanediamine, with *N*-benzyl or *N*-1-naphthylmethyl substitution leading to optimal enantioselectivity in β-lactam formation. With C_2-symmetric precatalysts derived from acyclic 1,2-diamines, however, optimal (albeit modest) enantioselectivity and reactivity in the β-lactam formation were observed with 4,5-diphenyl substitution and *N*-methyl substituents. This stereochemical dichotomy presumably reflects a change in the preferred conformation of the stereogenic units within these systems in the intermediate azolium enolate. Using precatalysts derived from (1*R*,2*R*)-1,2-cyclohexanediamine, the C(4)H and C(5)H imidazolidinium substituents are held approximately antiperiplanar, forcing the stereogenic cyclohexane ring substituents to adopt a '*gauche*' conformation due to the conformational constraints of the ring system, and therefore requiring a chiral relay mechanism in order to operate to generate optimal ee. However, with NHC precatalysts derived from acyclic diamines such as (1*R*,2*R*)-1,2-diphenylethanediamine, the stereogenic substituents preferentially adopt an alternative '*anti*' conformation in order to minimise 1,2-steric interactions. This leads to the opposite trend in enantioselectivity within these series, with *N*-methyl substituents leading to optimal ee and reactivity as schematically indicated in Figure 6.

Given these results, a further comparison between the *N*-methyl- and *N*-benzyl-substituted precatalysts in the cyclohexane-fused and diphenyl series was probed, through their use in the formal [2+2] cycloaddition of ethylphenylketene and imine **21** (Scheme 4). Analogous trends to those observed in the formal [2+2] reaction with diphenylketene were observed, with (4*R*,5*R*)-diphenyl *N*-methyl **10** giving the optimal, although only modest, enantioselectivity (33% ee for the major *syn*-diastereoisomer).[16] However, within this series, the use of precatalyst **10** also resulted in a reversal in the absolute configuration of the major *syn*-diastereoisomer **25**, consistent with the sense and levels of asymmetric induction in these reactions being dependent upon both the conformational flexibility of the stereogenic backbone and the nature of the N-substituents.

From all of these results, the NHC derived from *N*-Me precatalyst **10** showed the optimal compromise between reactivity and enantioselectivity, with comparable reactivity and enantioselectivity in the model system to that employing precatalyst **24**. The use of *N*-Me precatalyst **10** to generate β-lactam **28** from diphenylketene and *N*-tosyl imine **27** was also evaluated, requiring high catalyst loadings (20 mol %) to generate **28** in 47% ee at 76% conversion (Scheme 5). Given the modest reactivity of the NHC derived from precatalyst **10** in this system, its reaction generality was not pursued further.

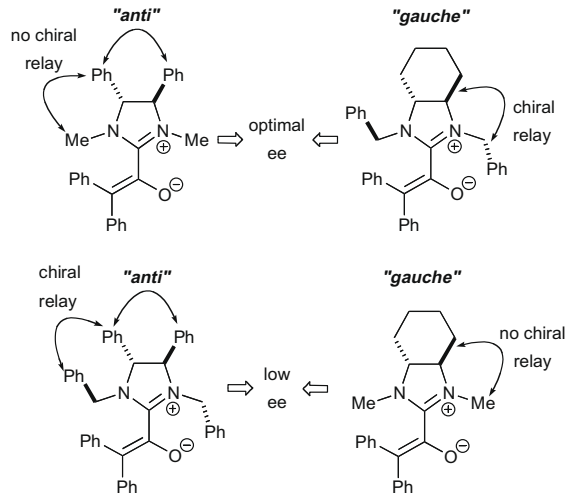
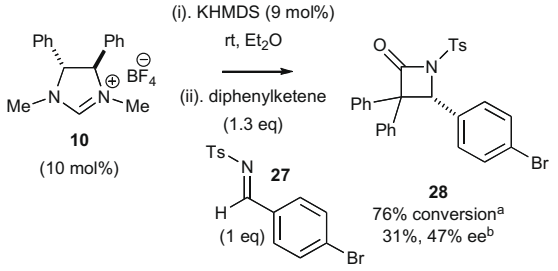


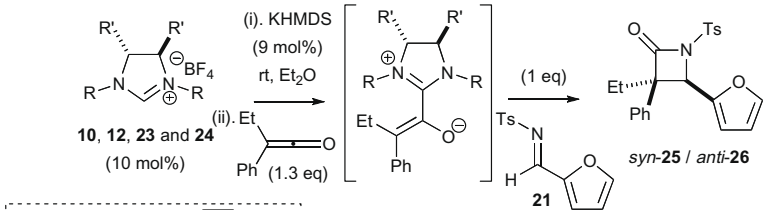
Figure 6. Schematic representations of conformational factors leading to enantiocontrol in C_2-symmetric imidazolidinium promoted β-lactam synthesis.

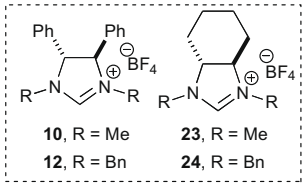


Scheme 5. C_2-symmetric imidazolinium precatalyst **10** in asymmetric β-lactam synthesis. [a] As shown by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] Determined by chiral HPLC analysis.

3.1. Asymmetric imidazolinium precatalyst synthesis from amino acids

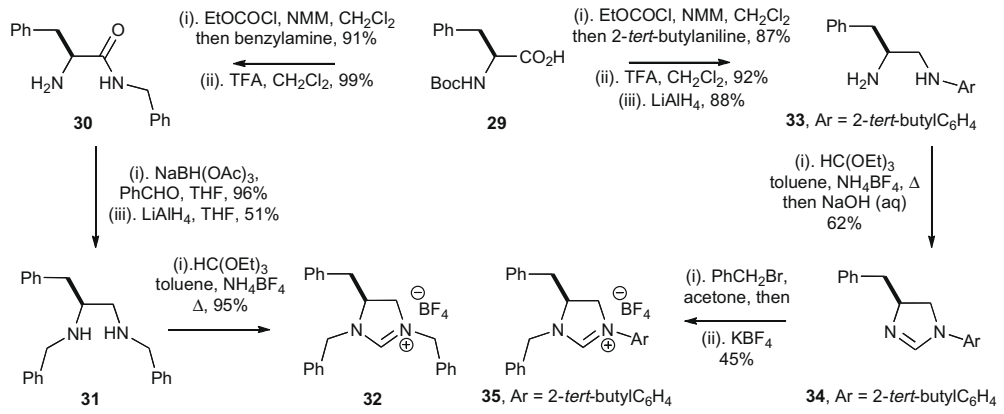
As alternative precatalysts for asymmetric β-lactam formation, we developed a flexible route to imidazolinium salts derived from amino acids. This route was designed to allow both selective and differential incorporation of N-substituents within the imidazolinium framework, as well as allowing the level of asymmetry from a



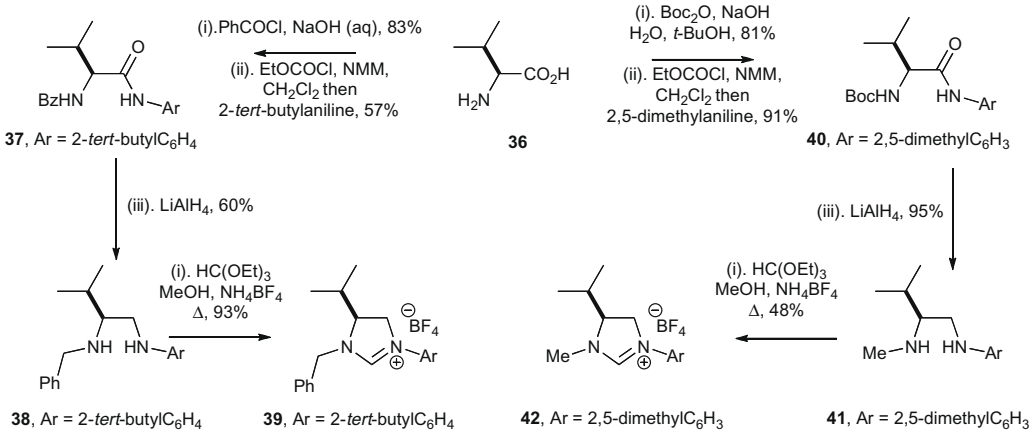


Precatalyst	Conversion[a]	Yield[b]	dr (*syn*:*anti*)[a]	ee (*syn*)[c]
10	quant	49%	68:32	33% (*ent*)
12	75%	48%	60:40	19%
23	64%	27%	74:26	1%
24	quant	55%	65:35	26%

Scheme 4. Comparison of C_2-symmetric imidazolinium precatalysts in asymmetric β-lactam synthesis. [a] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] Isolated yield of diastereoisomeric product mixture after purification. [c] Determined by chiral HPLC analysis.



Scheme 6. Synthesis of imidazolinium salts **32** and **35** from *N*-Boc-phenylalanine.



Scheme 7. Synthesis of imidazolinium salts **39** and **42** from valine.

single stereogenic centre within the catalyst framework to be evaluated. With this hypothesis in mind, *N*-Boc phenylalanine was readily transformed into *N*,*N*-dibenzyl-substituted imidazolinium **32** through sequential amide formation, *N*-Boc deprotection, reductive amination, $LiAlH_4$ reduction and ring closure. Imidazolinium salt **35** containing mixed *N*-aryl-*N*-benzyl substitution was also prepared via a related route, through amide formation, *N*-Boc deprotection, reduction and cyclisation to imidazoline **34** which was N-benzylated to give **35** after anion exchange (Scheme 6).

In a similar fashion, imidazolinium salts **39** and **42** were prepared from valine by sequential N-benzoylation or *N*-Boc formation, followed by amide formation, exhaustive reduction to the corresponding *N*-benzyl and *N*-methyl diamines **38** and **41**, respectively, followed by cyclisation under standard conditions (Scheme 7).

3.2. Catalytic evaluation of imidazolinium precatalysts derived from amino acids

Imidazolinium precatalysts **32**, **35**, **39** and **42** were subsequently evaluated in model β-lactam syntheses using diphenylketene and ethylphenylketene with *N*-tosyl imine **21**. In both series, the incorporation of an *N*-2-*tert*-butylphenyl substituent proved detrimental to both the catalyst activity and enantioselectivity. Valine-derived precatalyst **42** bearing *N*-aryl-*N*-methyl substituents and phenylalanine-derived *N*-benzyl-substituted **32** proved reasonably catalytically active in both cases, although only modest enantio- and diastereoselectivity were observed (Scheme 8). These results are consistent with catalyst reactivity and reaction stereoselectivity being markedly dependent upon the nature of the N-substituents of the catalyst, with a single stereogenic centre within the imidazolinium catalyst architecture leading to only modest enantioselectivity.

4. Conclusion

In conclusion, a range of imidazolinium precatalysts have been prepared from acyclic 1,2-diamines and amino acids and subsequently evaluated in the formal [2+2] cycloaddition of ketenes with *N*-tosyl imines. Optimal enantioselectivity for β-lactam formation in this series was observed when using *N*-methyl-substituted salts derived from (1*R*,2*R*)-1,2-diphenylethanediamine (up to 58% ee). Current studies are focused upon fully probing the mechanisms of this transformation and developing alternative applications of enantiomerically pure NHCs in asymmetric catalysis.

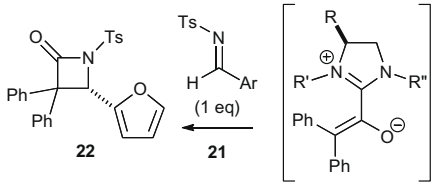
5. Experimental

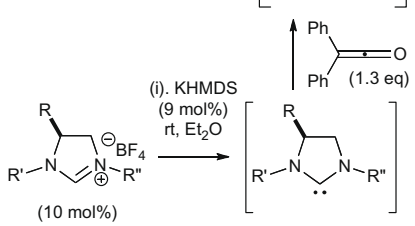
5.1. General experimental procedures

All reactions involving moisture sensitive reagents were performed under an atmosphere of argon using standard vacuum line techniques and with freshly distilled solvents. All glasswares were flame dried and allowed to cool under vacuum.

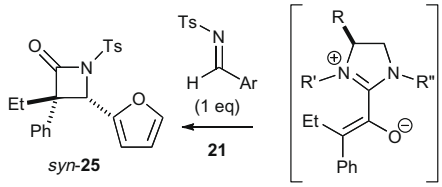
Solvents were dried and purified either by distillation (under an atmosphere of nitrogen as described below) or obtained from a sol-

Precatalyst	Conversion[a]	Yield[b]	ee (22)[c]
32	65%	21%	23%
35	<10%	--	--
39	<10%	--	--
42	49%	37%	31% (*ent*)





32 R, R', R"=Bn
35 R, R'=Bn, R"=2-*t*-BuC_6H_4
39 R=*i*-Pr, R'=Bn, R"=2-*t*-BuC_6H_4
42 R=*i*-Pr, R'=Me, R"=2,5-$(CH_3)_2C_6H_3$



Precatalyst	Conversion[a]	Yield[d]	dr (*syn*:*anti*)[a]	ee (*syn*-25)[c]
32	quant	84%	70:30	30%
35	70%	53%	65:35	4%
39	68%	46%	70:30	0%
42	quant	76%	68:32	3%

Scheme 8. Catalytic evaluation of imidazolinium precatalysts derived from valine and phenylalanine.

vent purification system (MBraun, SPS-800). MeOH was distilled from CaH_2. Petrol refers to the fraction of petroleum ether boiling between 40 °C and 60 °C. All other reagents were used directly as supplied without further purification.

Silica chromatography was carried out using Silica Gel 60 (0.043–0.060 mm) (Merck) in the solvent system stated. Analytical thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (Merck silica Kieselgel 60 F_{254}). TLCs were visualised either by UV fluorescence (254 nm) or by staining with basic $KMnO_4$ solution.

Melting points were recorded on an Electrothermal apparatus and are uncorrected. Microanalyses were carried out on a Carlo Erba CHNS analyser. Infrared spectra were recorded on a Perkin–Elmer Spectrum GX FT-IR spectrometer and analysed either as thin films between NaCl plates (thin film) or KBrs (KBr) as stated. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}) and only structurally significant peaks are quoted.

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz ^1H, 75.4 MHz ^{13}C), a Bruker Avance 400 (400 MHz ^1H, 100 MHz ^{13}C) or a Bruker Avance 500 (500 MHz ^1H, 125 MHz ^{13}C) spectrometer in the deuterated solvent stated. ^{13}C NMR spectra were recorded with proton decoupling. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to residual solvent peaks or to $SiMe_4$ as an internal standard (δ = 0.00). Coupling constants, *J*, are quoted in. The abbreviations s, d, dd, dt, td, q and m denote singlet, doublet, doublet of doublets, doublet of triplets, triplet of doublets, quartet and multiplet, respectively. The abbreviation Ar is used to denote aromatic.

Mass spectrometric (*m*/*z*) data were acquired by electrospray ionisation (ESI) or chemical ionisation (CI), either at the University of St Andrews Mass Spectrometry facility ([M+Na] quoted) or at the EPSRC National Mass Spectrometry Service Centre, Swansea ($[M+H]^+$, $[2M+H]^+$, $[M+Na]^+$ or $[2M+Na]^+$ quoted). At the University of St. Andrews, low and high resolution ESI MS was carried out on a Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, CI MS was carried out on a Micromass Quattro II spectrometer. High resolution ESI was carried out on a Finnigan MAT 900 XLT; a Thermofisher LTQ Orbitrap XL spectrometer was used to obtain high resolution ESI MS for accurate mass determination but also provided fragmentation data for the characterisation of samples. Values are quoted as a ratio of mass to charge in Daltons.

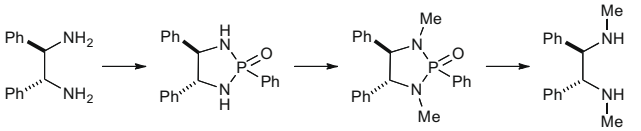
Temperatures of 0 °C were obtained using an ice/water bath and of −78 °C were obtained using a dry ice/acetone bath.

Crystallographic data (excluding structure factors) for compounds **10** and **15** have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 761457 and 761458, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

An authentic sample of diamine **17** was kindly provided by Professor Nigel Simpkins.

5.2. Synthesis of NHC precatalysts 10, 12, 14, 15, 16, 18 and 20

5.2.1. (1*R*,2*R*)-*N*,*N*′-Dimethyl-1,2-diphenylethane-1,2-diamine 9

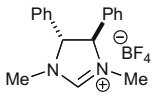


Following the procedure outlined by Wills et al.,[9] (*R*,*R*)-1,2-diphenylethane-1,2-diamine **2** (0.500 g, 2.36 mmol) was dissolved in CH_2Cl_2 (25 mL) and triethylamine (0.660 mL, 4.71 mmol) was added and the mixture was cooled to 0 °C. Phenylphosphonic dichloride (0.330 mL, 2.36 mmol) was added dropwise over 30 min before being left to stir overnight. The reaction was quenched by the addition of H_2O (15 mL) and the separated organics were dried ($MgSO_4$), filtered and concentrated in vacuo to furnish the phosphacycle as a colourless solid (0.647 g, 82%); mp 186–187 °C; $[\alpha]_D^{20} = +74.4$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr disc)/cm^{-1} 3199 (N–H), 3029 (N–H), 2888 (C–H), 1171 (P═O), 1124 (C–N), 748 and 696; δ_H (300 MHz, $CDCl_3$) 8.07–8.00 (2H, m, Ar*H*), 7.53–7.44 (3H, m, Ar*H*), 7.28–7.23 (7H, m, Ar*H*), 7.19-7.15 (3H, m, Ar*H*), 4.65 (1H, dd, *J* 8.8, 1.9, C_6H_5CH), 4.51 (1H, app d, *J* 8.8, C_6H_5CH), 3.36 (1H, d, *J* 15.0, N*H*) and 3.26 (1H, d, *J* 8.9, N*H*); δ_C (75 MHz, $CDCl_3$) 139.7 (J_{PC} 11.1), 139.6 (J_{PC} 7.3), 134.0 (J_{PC} 160.4), 132.4 (J_{PC} 10.3), 131.8 (J_{PC} 2.9), 127.3 (J_{PC} 23.4), 128.6, 128.5, 128.4, 128.3, 68.7 (J_{PC} 3.6) and 65.8 (J_{PC} 4.5); δ_P (121 MHz, $CDCl_3$) 26.8 (s); *m*/*z* (ESI^+) 367.2 (100, $M+H^+$+$MeOH^+$), 335.1 (72, $M+H^+$); HRMS (ESI^+) $C_{20}H_{20}N_2OP$ requires 335.1308, found 335.1312 (+1.3 ppm).

The phosphacycle (0.619 g, 1.85 mmol) was dissolved in THF (25 mL) and cooled to 0 °C. ^{n}BuLi (2.5 M solution in hexanes, 1.49 mL, 3.73 mmol) was added dropwise and the resultant orange solution was stirred for 1 h before dropwise addition of methyl iodide (0.230 mL, 3.73 mmol). After 1.5 h at room temperature, the reaction was quenched by the addition of H_2O (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined

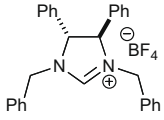
organics were dried ($MgSO_4$) and concentrated in vacuo to give the methylated phosphacycle as a colourless sticky foam (0.610 g, 91%); $[\alpha]_D^{20} = +27.2$ (*c* 1.0, $CHCl_3$); ν_{max} (film)/cm^{-1} 3061, 2925, 2855 (C–H), 1151 (P=O), 741 and 697; δ_H (400 MHz, $CDCl_3$) 7.94–7.85 (2H, m, Ar*H*), 7.50–7.41 (3H, m, Ar*H*), 7.23–7.16 (6H, m, Ar*H*), 7.15–7.06 (2H, m, Ar*H*), 7.05–7.00 (2H, m, Ar*H*), 4.16 (1H, d, *J* 8.7, C_6H_5CH), 4.02 (1H, d, *J* 8.5, C_6H_5CH), 2.34 (3H, d, *J* 10.6, NCH_3) and 2.10 (3H, d, *J* 9.8, NCH_3); δ_C (100 MHz, $CDCl_3$) 137.8, 137.1, 132.8, 131.8, 130.9, 128.6, 128.5, 128.5, 128.2, 128.2, 128.0, 127.6, 73.4, 71.8, 29.9 and 29.8; δ_P (121 MHz, $CDCl_3$) 32.3 (s).

To a solution of methylated phosphacycle (0.649 g, 1.79 mmol) in methanol (6.5 mL) was added 4 M HCl in dioxane (1.02 mL) and the mixture was stirred at reflux for 24 h. The pale orange solution was cooled to room temperature and concentrated in vacuo to give a light brown solid which was recrystallised from *iso*-propyl alcohol to give the diamine hydrochloride salt as a colourless solid. The solid was dissolved in saturated aqueous K_2CO_3 solution and extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over K_2CO_3, filtered and concentrated in vacuo to give **9** as a colourless solid (0.25 g, 59%) with spectroscopic data in accordance with the literature.[17] Mp 48–49 °C; {lit.[17] mp 50–51 °C}; $[\alpha]_D^{20} = +19.3$ (*c* 1.0, $CHCl_3$); {lit.[17] = +20.0 (*c* 0.01, $CHCl_3$)}; δ_H (300 MHz, $CDCl_3$) 7.28–7.17 (6H, m, Ar*H*), 7.14–7.08 (4H, m, Ar*H*), 3.62 (2H, s, C_6H_5CH), and 2.33 (6H, s, NCH_3).



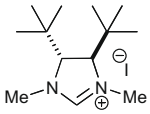
5.2.2. (4*R*,5*R*)-1,3-Dimethyl-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate 10

A mixture of diamine **9** (0.252 g, 1.05 mmol), triethyl orthoformate (0.87 mL, 5.24 mmol), ammonium tetrafluoroborate (0.110 g, 1.05 mmol) and methanol (0.44 mL) was stirred at 110 °C for 16 h. Upon cooling to room temperature, the residue was redissolved in methanol and diethyl ether was added dropwise to induce precipitation of **10** as a pale yellow solid (0.298 g, 84%) with spectroscopic data in accordance with the literature.[18] Mp 204–206 °C; {lit.[18] mp 223–224 °C}; $[\alpha]_D^{20} = +251$ (*c* 0.6, $CHCl_3$); {lit.[18] +253 (*c* 0.59, $CHCl_3$)}; δ_H (300 MHz, $CDCl_3$) 8.62 (1H, s, NC*H*N), 7.50–7.44 (6H, m, Ar*H*), 7.32–7.27 (4H, m, Ar*H*), 4.87 (2H, C_6H_5CH) and 3.12 (6H, NCH_3).



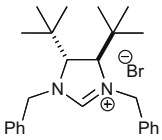
5.2.3. (4*R*,5*R*)-1,3-Dibenzyl-4,5-diphenyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate 12

A mixture of (1*R*,2*R*)-*N*,*N*′-dibenzyl-1,2-diphenylethane-1,2-diamine **11** (prepared according to the protocols of Kobayashi et al.,[19] 1.05 g, 2.68 mmol), triethyl orthoformate (0.89 mL, 5.35 mmol) and ammonium tetrafluoroborate (0.28 g, 2.7 mmol) in methanol (10 mL) was heated at 110 °C for 5 h before concentration in vacuo gave tetrafluoroborate salt **12** as a colourless solid (1.09 g, 83%). Mp 147–149 °C; $[\alpha]_D^{20} = +147$ (*c* 0.25 in $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 3422, 3033, 1638 (C=N), 1456, 1196, 1084 (C–N), 1030 (C–N) and 702; δ_H (300 MHz, $CDCl_3$) 9.27 (1H, s, NC*H*N), 7.40–7.33 (6H, m, Ar*H*), 7.30–7.22 (6H, m, Ar*H*), 7.20–7.14 (4H, m, Ar*H*), 7.07–6.99 (4H, m, Ar*H*), 5.13 (2H, d, *J* 14.6, $PhCH_AH_B$), 4.53 (2H, s, PHC*H*N) and 4.12 (2H, d, *J* 14.6, $PhCH_AH_B$); δ_C (75 MHz, $CDCl_3$) 158.1, 134.7, 131.9, 130.0, 129.9, 129.2, 129.1, 129.0, 127.3, 72.0 and 50.6; *m*/*z* HRMS (ESI^+): $C_{29}H_{27}N_2^+$ requires 403.2169, found 403.2159 (−2.4 ppm).



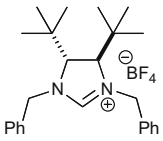
5.2.4. (4*R*,5*R*)-4,5-Di-*tert*-butyl-1,3-dimethyl-4,5-dihydro-1*H*-imidazol-3-ium iodide 14

Compound **14** was prepared according to the protocols of Mangeney et al.[10] Mp 258–262 °C; {lit.[10] mp 270–271 °C}, $[\alpha]_D^{20} = -63.1$ (*c* 0.42, $CHCl_3$); {lit.[10] $[\alpha]_D^{20} = -54.4$ (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 9.97 (1H, s, NC*H*N), 3.43 (6H, s, CH_3), 3.39 (2H, s, NC*H*) and 1.00 (18H, s, $C(CH_3)_3$).



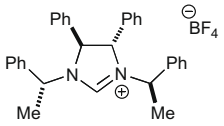
5.2.5. (4*R*,5*R*)-1,3-Dibenzyl-4,5-di-*tert*-butyl-4,5-dihydro-1*H*-imidazol-3-ium bromide 15

Compound **15** was prepared according to the protocols of Mangeney et al.[10] Mp 235–240 °C; {lit.[10] mp 249–250 °C}; $[\alpha]_D^{20} = -82.8$ (*c* 1.09 in $CHCl_3$); {lit.[10] $[\alpha]_D^{20} = -114.3$ (*c* 1.6 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 11.12 (1H, s, N=C*H*–N), 7.55–7.52 (4H, m, Ar*H*) 7.40–7.37 (6H, m, Ar*H*), 5.52 (2H, d, *J* 14.3 Hz, CH_2), 4.45 (2H, d, *J* 14.3 Hz, CH_2), 3.36 (2H, s, NC*H*) and 0.69 (18H, s, $C(CH_3)_3$).



5.2.6. (4*R*,5*R*)-1,3-Dibenzyl-4,5-di-*tert*-butyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate 16

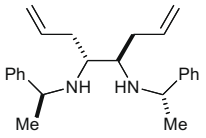
To a suspension of bromide salt **15** (60.0 mg, 0.135 mmol) in acetone (1 mL) was added potassium tetrafluoroborate (500 mg). The resultant suspension was stirred at room temperature for 1 h and concentrated in vacuo. The salt was reconstituted in CH_2Cl_2 (5 mL), washed with a saturated solution of potassium tetrafluoroborate (3 × 5 mL) and concentrated in vacuo to yield tetrafluoroborate salt **16** as a colourless solid (53.1 mg, 87%); mp 127–130 °C; $[\alpha]_D^{20} = -155.2$ (*c* 0.53, $CHCl_3$); ν_{max} (KBr disk)/cm^{-1} 2960 (N–CH_2), 1632 (N=C), 1474 (CH_3), 1375 ($C(CH_3)_3$), 1207 (C–N), 765 and 705; δ_H (300 MHz, $CDCl_3$) 9.05 (1H, s, NC*H*N), 7.44–7.37 (10H, m, Ar*H*), 5.18 (2H, d, *J* 14.4, CH_2), 4.50 (2H, d, *J* 14.4, CH_2), 3.41 (2H, s, C*H*) and 0.72 (18H, s, $C(CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 158.9, 132.6, 130.0, 129.5, 129.5, 70.0, 54.0, 35.8 and 26.5; *m*/*z* HRMS (ESI^-): $C_{25}H_{35}N_2^+$ requires 363.2795, found 363.2784 (−3.0 ppm).



5.2.7. (4*S*,5*S*)-4,5-Diphenyl-1,3-bis((*R*)-1-phenylethyl)-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate 18

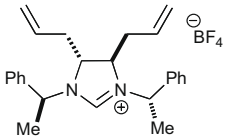
A suspension of diamine **17** (500 mg, 1.19 mmol) and ammonium tetrafluoroborate (125 mg, 1.19 mmol) in neat triethyl orthoformate (0.99 mL, 5.94 mmol) was stirred at 80 °C for 2 days before cooling to room temperature. Upon addition of a small volume of diethyl ether, the crude product precipitated, which was purified via recrystallisation (EtOAc/MeOH/hexane) to yield **18** as a colourless solid (567 mg, 92%) with spectroscopic data in accordance with the literature.[20] Mp 196–197 °C; $[\alpha]_D^{20} = -216$ (*c* 0.98, $CHCl_3$);

{lit.[20] $[\alpha]_D^{20} = -174$ (*c* 0.54, $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 9.18 (1H, s, NC*H*N), 7.38–7.31 (12H, m, Ar*H*), 7.21–7.19 (4H, m, Ar*H*), 6.95–6.93 (4H, m, Ar*H*), 4.45 (2H, s, PhC*H*N), 4.38 (2H, q, *J* 6.8, PhC*H*Me) and 1.99 (6H, d, *J* 6.8, CH_3).



5.2.8. (4*R*,5*R*)-N^4,N^5-Bis((*S*)-1-phenylethyl)octa-1,7-diene-4,5-diamine 19

Compound **19** was prepared according to the protocols of Savoia et al.[14]

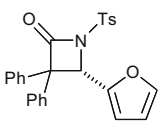


5.2.9. (4*R*,5*R*)-4,5-Diallyl-1,3-bis((*S*)-1-phenylethyl)-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate 20

A mixture of diamine **19** (100 mg, 0.287 mol), triethyl orthoformate (213 mg, 1.43 mol) and ammonium tetrafluoroborate (30.1 mg, 0.287 mol) was heated to 80 °C and stirred for 4.5 h. The reaction mixture was concentrated in vacuo and the remaining triethyl orthoformate was removed via silica chromatography (MeOH/CH_2Cl_2 1:9) to yield the pure product **20** as a dark brown oil (76.5 mg, 59%); $[\alpha]_D^{20} = -33.1$ (*c* 1.1, $CHCl_3$); ν_{max} (thin film) 2982, 1634 (N=C), 1456, 1386, 1271 and 705; δ_H (400 MHz, $CDCl_3$) 9.04 (1H, s, NC*H*N), 7.46–7.33 (10H, m, Ar*H*), 5.28 (2H, ddt, *J* 17.1, 10.1, 7.1, 2 × CH_2CH=CH_2), 5.06 (2H, dd, *J* 10.1, 1.1, CH=CH_AH_B), 4.87 (2H, dd, *J* 17.1, 1.1, CH=H_AH_B), 4.81 (2H, q, *J* 7.1, C*H*CH_3), 3.48 (2H, q, *J* 7.1, NC*H*CH_2), 2.20–2.14 (4H, m, NCHCH_2) and 1.96 (6H, d, *J* 6.8, CH_3); δ_C (75 MHz, $CDCl_3$) 152.7, 138.5, 130.0, 129.8, 129.5, 126.6, 121.9, 63.0, 57.4, 35.7 and 20.7; *m*/*z* HRMS (ESI^-) $C_{25}H_{35}N_2^+$, requires 359.2482, found 359.2472 (−2.7 ppm).

5.3. Enantioselective synthesis of β-lactam (*S*)-22 by NHC precatalysts 10, 14, 12, 14, 16, 18 and 20

General procedure: A 0.50 M solution of KHMDS in toluene (9 mol %) was added to a suspension of chiral imidazolinium salt (10 mol %) in Et_2O (1.5 mL) under a nitrogen atmosphere and the mixture was stirred for 30 min at room temperature. A solution of diphenylketene (1.3 equiv) in Et_2O (1.5 mL) was added, followed by the imine (1.0 equiv) as a solid, and the reaction mixture was stirred at room temperature for 16 h before concentration in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with 0.1 M HCl(aq) (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo to yield the crude product as an orange oil.



5.3.1. Table 1 entry 1: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

The β-lactam (*S*)-**22** was obtained using diphenylketene (101 mg, 0.521 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (100 mg, 0.401 mmol) with chiral imidazolinium salt **10** (13.6 mg, 0.040 mmol) and a 0.50 M solution of KHMDS in toluene (0.07 mL, 0.036 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 10:90 then CH_2Cl_2/petrol/EtOAc 50:45:5) to give β-lactam (*S*)-**22** as a pale yellow solid (140 mg, 79%) with spectroscopic data in accordance with the literature.[5] Mp 160 °C; {lit.[5] mp 160 °C}; $[\alpha]_D^{20} = +31.2$ (*c* 1.00, $CHCl_3$, 58% ee); {lit.[5] $[\alpha]_D^{20} = +32.6$ (*c* 1.00, $CHCl_3$, 61% ee); HPLC analysis: 58% ee (Daicel CHIRALCEL OD-H column, eluent: hexane/*i*-PrOH 90:10, flow 1 mL min^{-1}, wavelength 254 nm, retention times: 9.29 min (major, *S*) and 12.21 min (minor, *R*)); δ_H (300 MHz, $CDCl_3$); 7.72 (2H, d, *J* 8.4, SO_2Ar*H*), 7.44–7.23 (8H, m, Ar*H*), 7.17–7.03 (4H, m, Ar*H*), 7.00–6.98 (1H, m, furyl*H*), 6.18–6.13 (2H, m, furyl*H*), 5.76 (1H, s, NTsC*H*) and 2.42 (3H, s, CH_3).

5.3.2. Table 1 entry 2: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

The β-lactam (*S*)-**22** was obtained using diphenylketene (101 mg, 0.521 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (100 mg, 0.401 mmol) with chiral imidazolinium salt **14** (13.6 mg, 0.040 mmol) and a 0.50 M solution of KHMDS in toluene (0.07 mL, 0.036 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 10:90 then CH_2Cl_2/petrol/EtOAc 50:45:5) to give β-lactam (*S*)-**22** as a pale yellow solid (53.4 mg, 30%) with spectroscopic data in accordance with the literature[5] and as described above. HPLC analysis: 55% ee.

5.3.3. Table 1 entry 3: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

Prepared from imidazolinium salt **23** as described in a previous publication.[6]

5.3.4. Table 1 entry 4: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

The β-lactam (*S*)-**22** was obtained using diphenylketene (97.4 mg, 0.501 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (96.1 mg, 0.386 mmol) with chiral imidazolinium salt **12** (18.9 mg, 0.039 mmol) and a 0.50 M solution of KHMDS in toluene (0.07 mL, 0.035 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 10:90 then CH_2Cl_2/petrol/EtOAc 50:45:5) to give β-lactam (*S*)-**22** as a pale yellow solid (130 mg, 76%) with spectroscopic data in accordance with the literature[5] and as described above. HPLC analysis: 9% ee.

5.3.5. Table 1 entry 5: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

The β-lactam (*S*)-**22** was obtained using diphenylketene (101 mg, 0.521 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (100 mg, 0.401 mmol) with chiral imidazolinium salt **15** (17.8 mg, 0.040 mmol) and a 0.50 M solution of KHMDS in toluene (0.07 mL, 0.036 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 10:90 then CH_2Cl_2/petrol/EtOAc 50:45:5) to give β-lactam (*S*)-**22** as a pale yellow solid (97.9 mg, 55%) with spectroscopic data in accordance with the literature[5] and as described above. HPLC analysis: 48% ee.

5.3.6. Table 1 entry 6: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

The β-lactam (*S*)-**22** was obtained using diphenylketene (101 mg, 0.521 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (100 mg, 0.401 mmol) with chiral imidazolinium salt **16** (18.1 mg, 0.040 mmol) and a 0.50 M solution of KHMDS in toluene (0.07 mL, 0.036 mmol) following the above-mentioned general procedure. The crude product was purified by silica

chromatography (EtOAc/petrol 10:90 then CH_2Cl_2/petrol/EtOAc 50:45:5) to give β-lactam (*S*)-**22** as a pale yellow solid (90.1 mg, 51%) with spectroscopic data in accordance with the literature[5] and as described above. HPLC analysis: 47% ee.

5.3.7. Table 1 entry 7: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

This compound was prepared from imidazolinium salt **24** as described in a previous publication.[6]

5.3.8. Table 1 entry 8: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

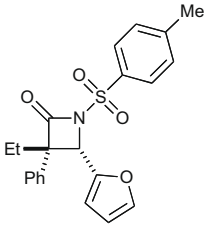
The β-lactam (*S*)-**22** was obtained using diphenylketene (101 mg, 0.521 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (100 mg, 0.401 mmol) with chiral imidazolinium salt **18** (20.8 mg, 0.040 mmol) and a 0.50 M solution of KHMDS in toluene (0.07 mL, 0.036 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 10:90 then CH_2Cl_2/petrol/EtOAc 50:45:5) to give β-lactam (*S*)-**22** as a pale yellow solid (106 mg, 60%) with spectroscopic data in accordance with the literature[5] and as described above. HPLC analysis: 1% ee.

5.3.9. Table 1 entry 9: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

The β-lactam (*S*)-**22** was obtained using diphenylketene (101 mg, 0.521 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (100 mg, 0.401 mmol) with chiral imidazolinium salt **20** (17.9 mg, 0.040 mmol) and a 0.50 M solution of KHMDS in toluene (0.07 mL, 0.036 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 10:90 then CH_2Cl_2/petrol/EtOAc 50:45:5) to give β-lactam (*S*)-**22** as a pale yellow solid (159 mg, 89%) with spectroscopic data in accordance with the literature[5] and as described above. HPLC analysis: 20% ee.

5.4. General procedures for the synthesis of β-lactams 58–65 by NHC precatalyst 10

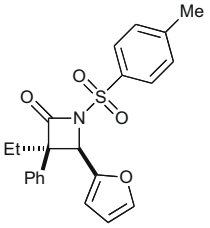
A 0.50 M solution of KHMDS in toluene (0.07 mL, 0.036 mmol, 9 mol %) was added to a suspension of chiral imidazolinium salt (10 mol %) in Et_2O (1.5 mL) under nitrogen atmosphere and the mixture was stirred for 30 min at room temperature. A solution of ethylphenylketene (76 mg, 0.521 mmol, 1.3 equiv) in Et_2O (1.5 mL) was added, followed by the imine (100 mg, 0.401 mmol, 1.0 equiv) as a solid, and the reaction mixture was stirred at room temperature for 16 h before concentration in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with 0.1 M HCl(aq) (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo to yield the crude product as an orange oil. The crude product was purified by silica chromatography, (Et_2O/petrol 10:90 then Et_2O/petrol 30:70) to give *syn*-**25** as a colourless solid.



***(3S,4S) syn*-25**

5.4.1. Scheme 4: entry 1: (3*S*,4*S*)-3-ethyl-4-(furan-2-yl)-3-phenyl-1-tosylazetidin-2-one (3*S*,4*S*)-25

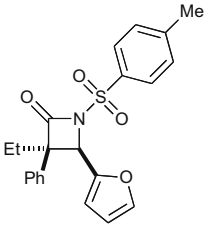
The β-lactam (3*S*,4*S*)-**25** was prepared according to the above-mentioned general procedure using chiral imidazolinium salt **10** (13.5 mg, 0.040 mmol) to give (3*S*,4*S*)-**25** as a colourless solid (77.8 mg, 49%) and as a diastereomeric mixture (dr *syn*:*anti* 68:32) with spectroscopic data in accordance with the literature.[4] (3*R*,4*R*)-**60** mp 158-162 °C; {lit.[4] mp 117–118 °C}; $[\alpha]_D^{20} = -30.0$ (*c* 0.1, CH_2Cl_2, 33% ee); {lit.[4] $[\alpha]_D^{20} = -45.2$ (*c* 0.5, CH_2Cl_2, 83% ee}; HPLC analysis: 33% ee (Daicel CHIRALCEL AD-H column, eluent: hexane/^{i}PrOH 90:10, flow 1 mL min^{-1}, wavelength 254 nm, retention times: 13.6 min (minor, *R*,*R*) and 15.3 min (major, *S*,*S*)); δ_H (300 MHz, $CDCl_3$); 7.68 (2H, d, *J* 8.4, Ar*H*), 7.19–7.15 (5H, m, Ar*H*), 7.04–6.99 (3H, m, 2 × Ar*H*, 1 × furyl*H*), 6.13–6.10 (2H, m, furyl*H*), 5.12 (1H, s, TsNC*H*), 2.43 (3H, s, ArCH_3), 2.11 (2H, q, *J* 7.4, CH_2) and 0.90 (3H, t, *J* 7.4, CH_2CH_3).



***(3R,4R) syn*-25**

5.4.2. Scheme 4: entry 2: (3*R*,4*R*)-3-ethyl-4-(furan-2-yl)-3-phenyl-1-tosylazetidin-2-one (3*R*,4*R*)-25

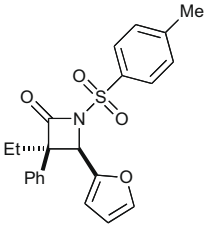
The β-lactam (3*R*,4*R*)-**25** was prepared according to the above-mentioned general procedure using chiral imidazolinium salt **12** (19.6 mg, 0.040 mmol) to give (3*S*,4*S*)-**25** as a colourless solid (76.2 mg, 48%) and as a diastereomeric mixture (dr *syn*:*anti* 60:40) with spectroscopic data in accordance with the literature[4] and as described above. HPLC analysis: 19% ee.



***(3R,4R) syn*-25**

5.4.3. Scheme 4: entry 3: (3*R*,4*R*)-3-ethyl-4-(furan-2-yl)-3-phenyl-1-tosylazetidin-2-one (3*R*,4*R*)-25

The β-lactam (3*R*,4*R*)-**25** was prepared according to the above-mentioned general procedure using chiral imidazolinium salt **23** (9.6 mg, 0.040 mmol) to give (3*S*,4*S*)-**25** as a colourless solid (42.0 mg, 48%) and as a diastereomeric mixture (dr *syn*:*anti* 74:26) with spectroscopic data in accordance with the literature[4] and as described above. HPLC analysis: 1% ee.

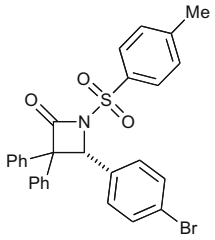


***(3R,4R) syn*-25**

5.4.4. Scheme 4: entry 4: (3*R*,4*R*)-3-ethyl-4-(furan-2-yl)-3-phenyl-1-tosylazetidin-2-one (3*R*,4*R*)-25

The β-lactam (3*R*,4*R*)-**25** was prepared as described in a previous manuscript.[6]

5.5. Reaction generality with NHC precatalyst 10



A 0.50 M solution of KHMDS in toluene (0.11 mL, 0.056 mmol) was added to a suspension of chiral imidazolinium salt **10** (20.0 mg, 0.059 mmol) in Et_2O (1.5 mL) under a nitrogen atmosphere and the mixture was stirred for 30 min at room temperature. A solution of ethylphenylketene (104 mg, 0.384 mmol) in Et_2O (1.5 mL) was added, followed by the imine (100 mg, 0.296 mmol) as a solid, and the reaction mixture was stirred at room temperature for 16 h before concentration in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with 0.1 M HCl(aq) (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo to yield the crude product as an orange oil. The crude product was purified by silica chromatography, (EtOAc/petrol 10:90 then CH_2Cl_2/EtOAc/petrol 50:5:45) to give *syn*-**25** as a colourless solid (49 mg, 31%) with spectroscopic data in accordance with the literature.[5] Mp 170–174 °C; {lit.[5] mp 214–215 °C}; $[\alpha]_D^{20} = +17.6$ (*c* 1.0, $CHCl_3$, 57% ee); {lit.[5] $[\alpha]_D^{20} = +21.8$ (*c* 1.0, $CHCl_3$, 57% ee)}; HPLC analysis: 47% ee (Daicel CHIRALCEL OD-H column, eluent: hexane/^{i}PrOH 90:10, flow: 1 mL/min, wavelength: 254 nm, retention times: 10.1 min (major, *R*) and 26.5 min (minor, *S*)); δ_H (300 MHz, $CDCl_3$); 7.80–7.69 (2H, m, Ar*H*), 7.35–7.28 (7H, m, Ar*H*), 7.26–7.20 (2H, m, Ar*H*), 7.17–7.02 (3H, m, Ar*H*), 6.90–6.82 (2H, m, Ar*H*), 6.79 (2H, d, *J* 7.9, Ar*H*), 5.69 (1H, s, NC*H*) and 2.43 (3H, s, ArCH_3).

5.6. Synthesis of NHC precatalysts 32, 35, 39 and 42

5.6.1. General procedure A: amide coupling via mixed anhydride

N-Methylmorpholine (1 equiv) and ethyl chloroformate (1 equiv) were added to a solution of carboxylic acid (1 equiv) in CH_2Cl_2 over 10 min at 0 °C followed by the dropwise addition of amine (1 equiv) over 10 min. The reaction mixture was stirred at ambient temperature for 12 h and the reaction was then quenched with water and the mixture was extracted with CH_2Cl_2 (×3). The organic extracts were combined, washed with 1 M HCl, saturated $NaHCO_3$(aq), and dried ($MgSO_4$), filtered and concentrated in vacuo. Further purification was achieved by trituration with ice-cold pentane.

5.6.2. General procedure B: deprotection of BOC protecting group

At first TFA (9.5 equiv) was added dropwise to a solution of the carbamate (1 equiv) in CH_2Cl_2 at ambient temperature and the mixture was allowed to stir for 12 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2. The organic extracts were washed in 1 M NaOH(aq), saturated NaCl(aq), and dried ($MgSO_4$), filtered and concentrated in vacuo.

5.6.3. General procedure C: amide reduction

A solution of $LiAlH_4$ in THF (2.5 equiv) was added dropwise to a stirred solution of the amide (1 equiv) in THF at ambient temperature under nitrogen atmosphere. The reaction mixture was refluxed at 80 °C for 96 h and then the reaction was quenched with Et_2O followed by sequential dropwise addition of water (1 mL g^{-1} of $LiAlH_4$), 40% KOH solution (1 mL g^{-1} of $LiAlH_4$) and water (3 mL g^{-1} $LiAlH_4$). The reaction mixture was allowed to stir for a few min before the addition of excess $MgSO_4$ and then left to stir for 1 h. The reaction mixture was filtered through Celite and the filtrate was washed with Et_2O. The organic extracts were combined and concentrated in vacuo.

5.6.4. General procedure D: diamine cyclisation

A suspension of the diamine (1 equiv), NH_4BF_4 (1 equiv), $CH(OEt)_3$ (5 equiv) in toluene was heated to 80 °C for 12 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2. The organics were washed in 0.1 M NaOH(aq), saturated NaCl(aq), and dried ($MgSO_4$), filtered and concentrated in vacuo.

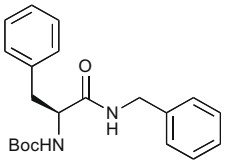
5.6.5. General procedure E: alkylation of amidine

Benzyl bromide (1 equiv) was added to a solution of amidine (1 equiv) in acetone at ambient temperature under a nitrogen atmosphere. The reaction mixture was refluxed at 75 °C for 12 h and then concentrated in vacuo. The residue was redissolved in acetone. Next, KBF_4 (1.2 equiv) was added and the mixture was stirred for 1 h at ambient temperature and thereafter concentrated in vacuo. The residue was taken into CH_2Cl_2, washed with saturated NaCl(aq), dried ($MgSO_4$), filtered and concentrated in vacuo.

5.6.6. General procedure F: reductive amination

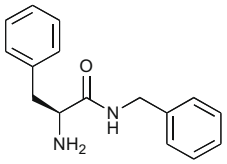
$NaBH(OAc)_3$ (1.5 equiv) was added to a solution of amine (1 equiv) and aldehyde (1 equiv) in THF. The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 12 h and thereafter washed in 1 M NaOH(aq), saturated NaCl(aq), and dried ($MgSO_4$), filtered and concentrated in vacuo.

5.6.7. (*S*)-*tert*-Butyl 1-(benzylamino)-1-oxo-3-phenylpropan-2-ylcarbamate



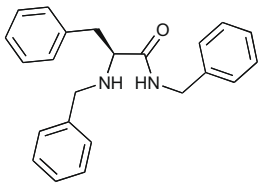
Following general procedure A, *N*-methylmorpholine (4.00 mL, 37.7 mmol), ethyl chloroformate (3.79 g, 37.7 mmol), benzylamine (4.04 g, 37.7 mmol), Boc-L-phenylalanine (10.0 g, 37.7 mmol) in CH_2Cl_2 (145 mL), gave, after trituration with pentane, the amide product (12.1 g, 91%) as a colourless solid with spectroscopic data in accordance with the literature.[21] Mp 129–130 °C; {lit.[21] 136–137 °C}; $[\alpha]_D^{20} = -2.3$ (*c* 1.05, MeOH); {lit.[21] $[\alpha]_D^{20} = -1.8$ (*c* 1.00, MeOH); δ_H (400 MHz; $CDCl_3$) 7.23–7.17 (8H, m, Ar*H*), 7.05–7.00 (2H, m, Ar*H*), 5.98–5.87 (1H, m, CHN*H*CO_2), 5.02–4.86 (1H, m, CON*H*CH_2), 4.33–4.23 (3H, m, CH_2CH(CO)NH, ArCH_2NH), 3.08–2.96 (2H, m, ArCH_2), 1.48 (6H, s, O-*t*-Bu) and 1.33 (3H, s, O-*t*-Bu).

5.6.8. (*S*)-2-Amino-*N*-benzyl-3-phenylpropanamide 30



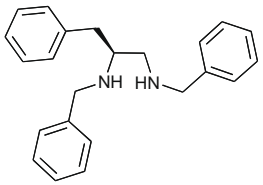
To a solution of (*S*)-*tert*-butyl-1-(benzylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (8.00 g, 22.6 mmol) in CH_2Cl_2 (16 mL) was added TFA (16 mL, 0.23 mol) to give amide **41** (5.75 g, 99%) as a colourless solid with spectroscopic data in accordance with the literature.[22] Mp 62–64 °C; {lit.[22] 61–68 °C); $[\alpha]_D^{20} = -76.2$ (*c* 1.05, $CHCl_3$); {lit.[22] $[\alpha]_D^{20} = -69.0$ (*c* 1.00, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 7.51 (1H, br s, CON*H*CH_2), 7.27–7.14 (10H, m, Ar*H*), 4.43–4.33 (2H, m, PhC*H*$_2$NH), 3.59 (1H, dd, *J* 9.2, 4.1, COC*H*(NH_2)CH_2), 3.23 (1H, dd, *J* 13.7, 4.1, PhC*H*$_2$), 2.68 (1H, dd, *J* 13.7, 9.2, PhC*H*$_2$) and 1.27 (2H, br s, N*H*$_2$).

5.6.9. (*S*)-*N*-Benzyl-2-(benzylamino)-3-phenylpropanamide



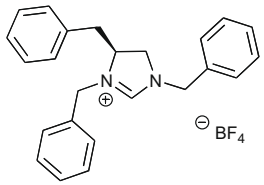
Following general procedure F, $NaBH(OAc)_3$ (2.09 g, 9.84 mmol), (*S*)-2-amino-*N*-benzyl-3-phenylpropanamide **30** and benzaldehyde (1.04 g, 9.84 mmol) in THF gave the amino amide (3.25 g, 96%) as a yellow oil with spectroscopic data in accordance with the literature.[23] $[\alpha]_D^{20} = -73.7$ (*c* 0.54, $CHCl_3$); {lit.[23] $[\alpha]_D^{20} = -69.4$ (*c* 0.50, $CHCl_3$)} δ_H (400 MHz; $CDCl_3$) 7.61–7.57 (1H, m, CON*H*CH_2), 7.35–7.10 (13H, m, Ph*H*), 7.01–6.98 (2H, m, Ph*H*), 4.50–4.40 (2H, m, PhC*H*$_2$NHCO), 3.67 (1H, ABq, *J* 13.3, PhC*H*$_A$H$_B$NH), 3.54 (1H, ABq, *J* 13.3, PhCH$_A$*H*$_B$NH), 3.44 (1H, dd, *J* 9.4, 4.2, PhCH$_2$C*H*), 3.25 (1H, ABX, J_{AB} 13.8, J_{AX} 4.2, PhC*H*$_A$H$_B$CH-), 2.78 (1H, ABX, J_{BA} 13.8, J_{BX} 9.4, PhC*H*$_A$H$_B$CH) and 1.58 (1H, s, N*H*).

5.6.10. (*S*)-N^1,N^2-Dibenzyl-3-phenylpropane-1,2-diamine 31

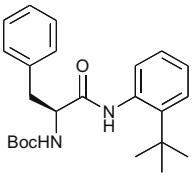


Following general procedure C, $LiAlH_4$ (14 mL, 28.3 mmol) and (*S*)-*N*-benzyl-2-(benzylamino)-3-phenylpropanamide in THF gave after chromatography (2% MeOH/CH_2Cl_2) the diamine **31** (1.57 g, 51%) as a yellow oil. $[\alpha]_D^{20} = +14.1$ (*c* 1.07, CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 3310 (N–H), 3026, 2923, 2852, 1603, 1494, 1453, 1122 and 741; δ_H (400 MHz, $CDCl_3$) 7.33–7.15 (15H, m, Ph*H*), 3.81–3.65 (4H, m, PhC*H*$_2$NH), 2.97–2.85 (2H, m, PhC*H*$_2$, PhCH$_2$C*H*), 2.74–2.68 (2H, m, PhC*H*$_2$, BnNHC*H*$_2$), 2.52 (1H, dd, *J* 11.9, 7.1, BnNHC*H*$_2$) and 1.70 (2H, s, N*H*); δ_C (100 MHz, $CDCl_3$) 141.1, 141.0, 139.7, 129.8, 128.8, 128.8 (2C), 128.5, 127.3, 126.6, 58.5, 54.3, 52.4, 51.7 and 39.8; *m/z* ES(+) 224.11 (44, [M−PhCH$_2$NH]$^+$) and 331.13 (100, [M+H]$^+$); HRMS (ES+) $C_{23}H_{27}N_2$ requires 331.2174, found 331.2166 (−2.4 ppm).

5.6.11. (*S*)-1,3,4-Tribenzyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate 32

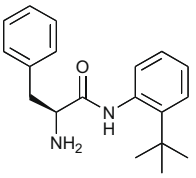


Following general procedure D, (*S*)-N^1,N^2-dibenzyl-3-phenylpropane-1,2-diamine **31** (1.53 g, 4.66 mmol), NH_4BF_4 (0.49 g, 4.66 mmol), $CH(OEt)_3$ (3.45 g, 23.3 mmol) in toluene (25 mL), gave after trituration with petrol, the imidazolinium salt **32** (2.08 g, 95%) as a yellow oil. $[\alpha]_D^{20} = +16.8$ (*c* 0.53, MeOH); ν_{max} (thin film)/cm^{-1} 3398, 3066, 2931, 1650, 1456, 1207, 1060, 744 and 703; δ_H (400 MHz, $CDCl_3$) 8.53 (1H, s, NC*H*N), 7.44–7.20 (13H, m, Ph*H*), 6.96 (2H, dd, *J* 6.4, 2.8, Ph*H*), 5.00 (1H, ABq, *J* 14.8, PhC*H*$_A$H$_B$NH), 4.69–4.61 (1H, m, PhC*H*$_A$H$_B$NH), 4.53 (1H, ABq, *J* 14.8, PhC*H*$_A$H$_B$NH) 4.27–4.19 (1H, m, PhC*H*$_A$H$_B$C*H*–), 3.61 (1H, ABX t, *J* 11.5, PhC*H*$_A$H$_B$CH), 3.45–3.40 (1H, m, PhC*H*$_A$H$_B$CH), 3.15 (1H, ABX, J_{AB} 13.9, J_{AX} 4.8, NC*H*$_A$H$_B$CH) and 2.85 (1H, ABX, J_{BA} 13.9, J_{BX} 8.9, NCH$_A$*H*$_B$CH); δ_C (100 MHz, $CDCl_3$); 157.7, 134.3, 132.4 (2C), 129.5, 129.4, 129.2 (2C), 129.1, 128.9, 128.8, 128.7, 127.5, 60.4, 52.4, 52.2, 50.4, and 37.4; *m/z* ES(+) 251.15 (8, [M−PhCH$_2$−BF$_4$]$^+$), 341.20 (100, [M−BF$_4$]$^+$), 460.27 (2, [M+MeOH]$^+$; HRMS (ES+) $C_{24}H_{25}N_2^+$ requires 341.2012, found 341.2006 (−1.8 ppm).



5.6.12. (*S*)-*tert*-Butyl 1-(2-*tert*-butylphenylamino)-1-oxo-3-phenylpropan-2-yl-carbamate

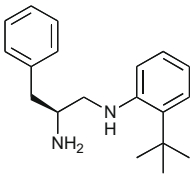
Following general procedure A, *N*-methylmorpholine (4.00 mL, 37.7 mmol), ethyl chloroformate (3.79 g, 37.7 mmol), 2-*tert*-butylaniline (5.63 g, 37.7 mmol), Boc-L-phenylalanine (10.0 g, 37.7 mmol) and CH_2Cl_2 (145 mL), gave after trituration with pentane, the amide product as a colourless solid (9.76 g, 87%). Mp 98-100 °C; $[\alpha]_D^{20} = -21.6$ (*c* 0.99, MeOH); ν_{max} (KBr)/cm^{-1} 3300 (N–H), 3249, 2969, 1685 (C=O), 1655 (aryl C=C), 1528, 1366, 1250 (C–O), 1173 and 757; δ_H (300 MHz, DMSO-d_6) 9.21 (1H, s, ArN*H*), 7.40–7.26 (5H, m, Ph*H*), 7.26–7.15 (4H, m, Ar*H*), 7.00–6.96 (1H, m, CO_2N*H*), 4.40 (1H, td, *J* 9.7, 4.5, BzC*H*), 3.10 (1H, ABX, J_{AB}13.8, J_{AX} 4.5, PhC*H*$_A$H$_B$), 2.85 (1H, ABX, J_{BA}13.8, J_{BX} 9.7, PhCH$_A$*H*$_B$–), 1.32 (9H, s, OC(C*H*$_3$)$_3$) and 1.29 (9H, C(C*H*$_3$)$_3$); δ_C (100 MHz; DMSO-d_6) 171.5, 155.3, 145.8, 138.1, 135.8, 130.5, 129.2, 128.0, 126.6, 126.4, 126.3, 126.2, 78.1, 56.1, 36.9, 34.5, 30.6 and 28.0; *m/z* ES(+) 297.20 (18, [M−*t*-BuOCO+H]$^+$), 341.19 (47, [M−*t*-Bu+H]$^+$), 397.25 (100, [M+H]$^+$) and 419.23 (10, [M+Na]$^+$); HRMS (ES+) $C_{24}H_{33}O_3N_2^+$ requires 397.2486, found 397.2487 (+0.3 ppm).



5.6.13. (*S*)-2-Amino-*N*-(2-*tert*-butylphenyl)-3-phenylpropanamide

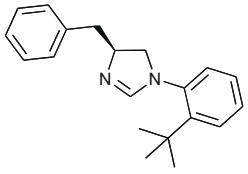
At first, TFA (10.0 mL, 0.131 mol) was added to a mixture of (*S*)-*tert*-butyl-1-(2-*tert*-butylphenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (5.00 g, 12.6 mmol) in CH_2Cl_2 (40 mL) and the mixture was stirred for 12 h. The mixture was concentrated in vacuo, the residue was redissolved in CH_2Cl_2, then the organic fraction was washed sequentially with 1 M NaOH(aq) (100 mL) and brine (100 mL) then dried ($MgSO_4$) to afford the deprotected monoamide as an amber oil (3.83 g, 92%). The product was used without further purification. $[\alpha]_D^{20} = -113.4$ (*c* 1.29, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3778, 3313 (N–H), 2966, 2874, 1681 (C=O), 1515, 1296 and 755; δ_H (400 MHz; $CDCl_3$) 9.65 (1H, s, CON*H*), 7.88 (1H, dd, *J* 8.0, 1.4, ArH), 7.30–7.14 (8H, m, ArH), 7.04–7.00 (1H, m, ArH), 3.71 (1H, dd, *J* 9.4, 3.8, COC*H*), 3.31 (1H, dd, *J* 13.8, 3.8, PhCH_AH_B), 2.78 (1H, dd, *J* 13.8, 9.4, PhCH_AH_B), 1.43 (2H, s, NH_2) and 1.30 (9H, s, C(CH_3)$_3$); δ_C (100 MHz; $CDCl_3$) 171.9, 140.6, 137.7, 135.5, 129.4, 128.8, 127.0, 126.8, 126.4, 125.1, 125.0, 56.8, 40.6, 34.4 and 30.4; *m/z* ES(+) 297.20 (35, $[M+H]^+$), 319.18 (2, $[M+Na]^+$), 593.38 (100, $[2\,M+H]^+$) and 615.36 (22, $[2M+H]^+$); HRMS (ES+) $C_{19}H_{23}ON_2^+$ requires 297.1961, found 297.1958 (−1.1 ppm).

5.6.14. (*S*)-N^1-(2-*tert*-Butylphenyl)-3-phenylpropane-1,2-diamine 33



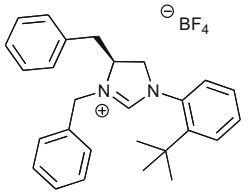
Following general procedure C, $LiAlH_4$ (20.3 mL, 40.5 mmol) and (*S*)-2-amino-*N*-(2-*tert*-butylphenyl)-3-phenylpropanamide (2.00 g, 6.75 mmol) in THF gave the diamine **34** (1.83 g, 88%) as a pale yellow solid. Mp 55–57 °C; $[\alpha]_D^{20} = +19.8$ (*c* 1.06, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3415 (N–H), 3384, 2962 (C–H), 2929, 2902, 1598, 1573, 1507, 1449, 752 and 704; δ_H (400 MHz; $CDCl_3$) 7.35–7.22 (6H, m, Ar*H*), 7.12 (1H, ddd, *J* 8.1, 7.4, 1.3, NHArC(5)*H*), 6.69 (1H, td, 7.4, 1.3, NHArC(3)*H*), 6.63 (1H, dd, *J* 8.1, 1.3, NHArC(6)*H*), 4.67 (1H, br s, ArN*H*), 3.40–3.32 (2H, m, C*H*(NH_2), ArNHCH_AH_B), 3.02–2.96 (1H, m, ArNHCH_AH_B), 2.97 (1H, dd, *J* 13.4, 5.2, PhCH_AH_B), 2.64 (1H, dd, *J* 13.4, 5.2, PhCH_AH_B), 1.45 (9H, s, –C(CH_3)$_3$) and 1.23 (2H, br s –NH_2); δ_C (100 MHz; $CDCl_3$) 146.7, 138.9, 133.6, 129.3, 128.6, 127.1, 126.5, 126.2, 116.9, 111.7, 52.3, 50.1, 43.3, 34.3 and 29.9; *m/z* ES(+) 283.13 (100%, $[M+H]^+$); HRMS (ES+) $C_{19}H_{27}N_2$ requires 283.2174, found 283.2181 (+2.4 ppm).

5.6.15. (*S*)-4-Benzyl-1-(2-*tert*-butylphenyl)-4,5-dihydro-1*H*-imidazole 34



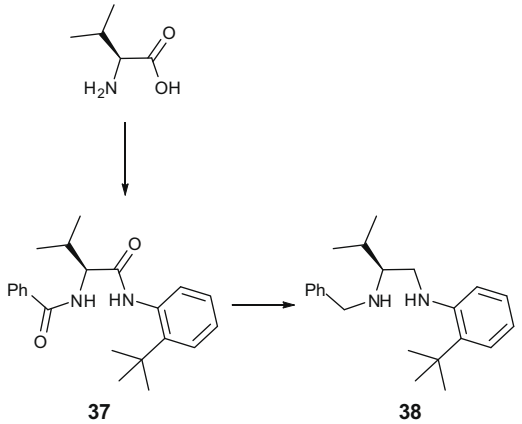
Following general procedure D, (*S*)-N^1-(2-*tert*-butylphenyl)-3-phenylpropane-1,2-diamine **33** (0.800 g, 2.83 mmol), NH_4BF_4 (0.297 g, 2.83 mmol), $CH(OEt)_3$ (2.4 mL, 14.2 mmol) in toluene (8.5 mL) gave after chromatography (2% MeOH/CH_2Cl_2) the amidine **34** (0.513 g, 62%) as a yellow oil. $[\alpha]_D^{20} = -30.6$ (*c* 1.01, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2961, 2869, 1677, 1602, 1489, 1442, 1091, 1055, 759 and 701; δ_H (400 MHz; $CDCl_3$) 7.38 (1H, dd, *J* 7.9, 1.6, Ar*H*), 7.27–7.12 (7H, m, Ar*H*), 6.90 (1H, d, *J* 1.5, N=C*H*), 6.80 (1H, dd, *J* 7.6, 1.6, NHArC(6)*H*), 4.47 (1H, dtdd, *J* 9.5, 8.3, 5.6, 1.6, PhCH_2C*H*), 3.61 (1H, t, *J* 9.5, PhCH_2–), 3.30 (1H, dd, *J* 9.5, 8.3, PhCH_AH_B), 3.13 (1H, ABX, J_{AB} 13.7, J_{AX} 5.6, NCH_AH_B), 2.81 (1H, ABX, J_{BA} 13.7, J_{BX} 8.3, NCH_AH_B) and 1.32 (9H, s, C(CH_3)$_3$); δ_C (100 MHz; $CDCl_3$) 158.0, 149.0, 139.9, 137.9, 130.1, 130.0, 129.7, 129.1, 128.2, 128.1, 127.0, 66.0, 59.6, 41.9, 36.0 and 32.0; *m/z* ES(+) 293.20 (100, $[M+H]^+$) and 311.21 (5, $[M+H_2O+H]^+$); HRMS (ES+) $C_{20}H_{25}N_2^+$ requires 293.2012, found 293.2005 (−2.5 ppm).

5.6.16. Bis((*S*)-3,4-dibenzyl-1-(2-*tert*-butylphenyl)-4,5-dihydro-1*H*-imidazol-3-ium) tetrafluoroborate 35



Following general procedure E, benzyl bromide (0.117 g, 0.683 mmol), (*S*)-4-benzyl-1-(2-*tert*-butylphenyl)-4,5-dihydro-1*H*-imidazole **34** (0.200 g, 0.683 mmol) in acetone (0.4 mL) gave the crude product **35**. The product mixture was treated with KBF_4 (0.103 g, 0.982 mmol) and gave after chromatography (EtOAc/petrol, 1:1) the imidazolinium salt **35** (0.144 g, 45%) as a pale brown solid. Mp 129–130 °C; $[\alpha]_D^{20} = +3.9$ (*c* 1.03, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2967, 1637, 1498, 1256, 1084, 765 and 703; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, s, NC*H*N), 7.47–7.29 (12H, m, Ar-*H*), 7.19–7.17 (2H, m, ArC(6)*H*, NArC(5)*H*), 5.01 (1H, ABq, *J* 14.3, PhCH_AH_BN), 4.80 (1H, ABq, *J* 14.3 PhCH_AH_BN), 4.75–4.69 (1H, m, PhCH_2C*H*), 4.23 (1H, ABX t, *J* 11.2, PhCH_AH_B), 4.00 (1H, ABX, J_{BA} 11.2, J_{BX} 8.5, PhCH_AH_B), 3.43 (1H, ABX, J_{AB} 13.6, J_{AX} 5.3, NCH_AH_BCH), 3.14 (1H, ABX, J_{BA} 13.6, J_{BX} 9.5, NCH_AH_BCH) and 1.33 (9H, s, C(CH_3)$_3$); δ_C (100 MHz; $CDCl_3$) 158.6, 146.8, 134.4, 134.0, 132.3, 130.5, 130.2, 129.5, 129.4, 129.3, 129.2, 129.1, 128.5, 128.3, 127.7, 61.5, 59.5, 50.7, 37.3, 35.7 and 32.0; *m/z* ES(+) 383.25 (100, $[M]^+$); HRMS (ES+) $C_{27}H_{31}N_2$ requires 383.2482, found 383.2479 (−0.7 ppm).

5.6.17. (*S*)-N^2-Benzyl-N^1-(2-*tert*-butylphenyl)-3-methylbutane-1,2-diamine 38

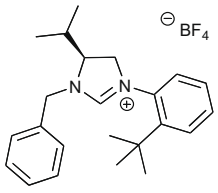


37 38

L-Valine (6.57 g, 56.1 mmol) and NaOH (2.34 g) were dissolved in H_2O (17 mL). Next, Et_2O (90 mL) was added, and the mixture was cooled to 0 °C and stirred rapidly. Benzoyl chloride (6.58 mL,

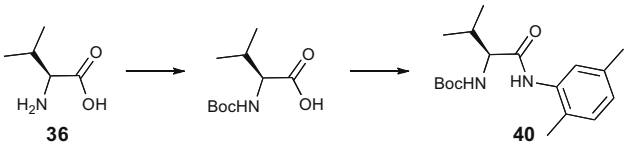
56.6 mmol) and a solution of NaOH (2.34 g) in H_2O (6 mL) were added alternatively portionwise over 90 min, then the mixture was warmed to ambient temperature over 16 h. The mixture was then concentrated to half volume in vacuo before concd HCl (5 mL) was added to induce precipitation of the product. The product was collected by filtration and washed with Et_2O (100 mL) and dried. The product was obtained as a colourless solid (10.3 g, 83%), which was used without further purification. A suspension of *N*-benzoylvaline (1.50 g, 6.78 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and *N*-methylmorpholine (0.75 mL, 6.78 mmol) was added before the dropwise addition of ethyl chloroformate (0.67 mL, 6.78 mmol). After 20 min, 2-*tert*-butylaniline (1.06 mL, 6.78 mmol) was added to the suspension. The mixture was warmed to ambient temperature over 16 h then the reaction was quenched with H_2O (30 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed successively with 4% $NaHCO_3$(aq) (30 mL) and 1 M HCl(aq) (30 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo. The product was triturated with pentane (20 mL) to obtain the product **37** as a colourless solid (1.36 g, 53%) which was used without further purification. To a suspension of diamide **37** (1.00 g, 4.06 mmol) in THF (10 mL) was added a solution of $LiAlH_4$ (9.13 mL, 18.3 mmol) and the mixture was heated at reflux for 72 h, then quenched at 0 °C with H_2O (0.69 mL), 40% KOH(aq) (0.69 mL) and further H_2O (2.07 mL), before drying with excess $MgSO_4$ and filtration through Celite. The product was obtained as a clear colourless oil (790 mg) after chromatographic purification (10% EtOAc/petrol). $[\alpha]_D^{20} = +0.3$ (*c* 1.6, $CHCl_3$). ν_{max} (thin film)/cm^{-1}: 3425 (br, N–H), 2958, 2930, 1644, 1504, 1443, 1055, 834, 741 and 697; δ_H (400 MHz, $CDCl_3$) 7.27–7.22 (4H, m, Ar*H*), 7.20–7.16 (2H, m, Ar*H*), 7.07 (1H, td, *J* 7.6, 1.4, N-Ar*H*-4), 6.63–6.58 (2H, m, Ar*H*), 4.76 (1H, t, *J* 4.4, ArN*H*), 3.74 (1H, d, *J* 12.8, PhCH_AH_B), 3.71 (1H, d, *J* 12.8, PhCH_AH_B), 3.20 (1H, dt, *J* 11.5, 4.4, ArNHCH_AH_B), 2.95 (1H, ddd, *J* 11.4, 6.6, 4.4, ArNHCH_AH_B), 2.65 (1H, td, *J* 6.6, 4.0, BnNHC*H*), 2.03–1.91 (1H, m, C*H*(CH_3)$_2$), 1.37 (9H, s, C(CH_3)$_3$), 0.97 (3H, d, *J* 6.8, CH_3) and 0.90 (3H, d, *J* 6.8, CH_3). δ_C (100 MHz, $CDCl_3$): 147.1, 140.5, 133.5, 128.5, 128.4, 127.2, 127.1, 126.2, 116.5, 111.5, 61.9, 51.1, 43.3, 34.4, 29.9, 29.3, 20.0 and 18.4; *m/z* 325.05 (79, M+H), 347.02 (M+Na); HRMS(ES+) $C_{22}H_{33}N_2$ requires 325.2644, found 325.2639 (−1.3 ppm).

5.6.18. (*S*)-1-Benzyl-3-(2-*tert*-butylphenyl)-5-isopropyl-4,5-dihydro-1*H*-imidazolium tetrafluoroborate 39



A mixture of diamine **38** (186 mg, 0.573 mmol), NH_4BF_4 (61.0 mg, 0.573 mmol), triethyl orthoformate (0.23 mL) and MeOH (1.6 mL) was heated at 80 °C for 16 h then concentrated in vacuo before dissolution in CH_2Cl_2 and filtration to remove excess NH_4BF_4. The product was obtained as a clear colourless oil (225 mg, 93%) after chromatographic purification (10% MeOH/CH_2Cl_2). $[\alpha]_D^{20} = -0.7$ (*c* 1.4, $CHCl_3$); ν_{max} (thin film)/cm^{-1}: 3389, 3069, 2957, 2924, 2850, 1635 (C=N), 1457, 1366, 1259, 1086, 1057, 1036, 753 and 703; δ_H (400 MHz, $CDCl_3$) 8.01 (1H, s, NC*H*N), 7.36 (1H, dd, *J* 8.1, 1.3, ArC*H*(6)), 7.27–7.21 (6H, m, ArC*H*), 7.17–7.13 (2H, m, ArC*H*), 4.87 (1H, ABq, *J* 14.6, PhCH_AH_B), 4.44 (1H, ABq, *J* 14.6, PhCH_AH_B), 4.32–4.26 (1H, m, Me_2CHC*H*), 4.11 (1H, app t, *J* 11.6, ArNCH_AH_B), 3.81 (1H, ABX, J_{BA} 11.6, J_{BX} 9.9, ArNCH_AH_B), 2.34–2.23 (1H, m, C*H*Me_2), 1.21 (9H, s, C(CH_3)$_3$), 0.93 (3H, d, *J* 6.8, CH_3), and 0.80 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$): 158.8, 147.0, 134.0, 132.2, 130.6, 130.0, 129.5, 129.3, 129.0, 128.8, 128.3, 65.0, 54.9, 50.2, 35.7, 32.0, 26.6, 18.0 and 14.4; *m/z* (ES+) 335.07 (100, M); HRMS(ES+) $C_{23}H_{31}N_2$ requires 335.2487, found 335.2479, (−2.4 ppm).

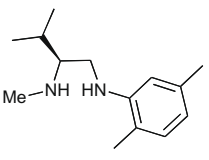
5.6.19. (*S*)-*tert*-Butyl 1-(2,5-dimethylphenylamino)-3-methyl-1-oxobutan-2-ylcarbamate 40



To a solution of L-valine (35.1 g, 300 mmol) in NaOH(aq) (12.0 g in 300 mL) was added *tert*-butanol (200 mL) followed by the slow addition of di-*tert*-butyl dicarbonate (75.2 g, 360 mmol), with vigorous stirring. The mixture was stirred for 48 h at ambient temperature then the reaction was quenched with 1 M $KHSO_4$(aq) to pH ~1. The mixture was saturated with NaCl, and then extracted with Et_2O (3 × 300 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude Boc-L-valine product as a colourless oil which partly solidified on standing (52.6 g, 81%). The product was used without further purification. $[\alpha]_D^{20} = -4.7$ (*c* 1.00, MeOH). The product was obtained as a mixture of rotamers. Data for the major rotamer: δ_H (400 MHz, $CDCl_3$) 7.94 (1H, br s, COO*H*), 5.06 (1H, d, *J* 8.9, N*H*CH), 4.28 (1H, dd, *J* 8.9, 4.5, NHC*H*), 2.27–2.19 (1H, m, C*H*Me_2), 1.02 (3H, d, *J* 6.8, CH_3) and 0.96 (3H, d, *J* 6.8, CH_3).

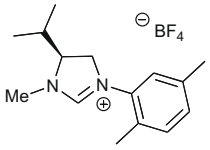
A solution of Boc-L-valine (6.74 g, 31.0 mmol) in CH_2Cl_2 (80 mL) was cooled to 0 °C, followed by addition of *N*-methylmorpholine (3.41 mL, 31.0 mmol) and dropwise addition of ethyl chloroformate (2.97 mL, 31.0 mmol) and then the mixture was stirred for 20 min. 2,5-Dimethylaniline (3.82 mL, 31.0 mmol) was added slowly, then warmed to ambient temperature over 16 h, then the reaction was quenched with H_2O (100 mL) and the mixture was extracted with CH_2Cl_2 (100 mL × 3). The organic fractions were combined and washed sequentially with 4% $NaHCO_3$(aq) (100 mL) and 1 M HCl(aq) (100 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was then triturated with ice-cold pentane to obtain the purified product as a very pale green solid (9.01 g, 91%). Mp 155–156 °C; $[\alpha]_D^{20} = -54.4$ (*c* 1.00, MeOH); ν_{max} (KBr)/cm^{-1}: 3316 (NH), 2973, 2963, 1691 (C=O), 1660 (C=O), 1579, 1524, 1491, 1457, 1379, 1368, 1298, 1283, 1247, 1171, 1048, 1024, 887, 814 and 684; δ_H (DMSO-d_6, 400 MHz) 9.22 (1H, s, amide N*H*), 7.14 (1H, s, Ar*H*-3), 7.07 (1H, d, *J* 8.0, carbamate N*H*), 6.90–6.88 (1H, m, Ar*H*-6), 6.85 (1H, d, *J* 8.5, Ar*H*-4), 3.93 (1H, t, *J* 8.0, BocNHC*H*), 2.23 (3H, s, 5-ArCH_3), 2.12 (3H, s, 2-ArCH_3), 2.06–1.95 (1H, m, C*H*Me_2), 1.39 (9H, s, C(CH_3)$_3$), 0.93 (3H, d, *J* 6.8, CH_3) and 0.90 (3H, d, *J* 6.8, CH_3); δ_C (DMSO-d_6, 100 MHz) 170.5, 156.1, 135.9, 135.5, 130.5, 130.3, 126.1, 125.8, 78.4, 60.4, 30.5, 28.4, 20.7, 19.6, 18.5 and 17.5; *m/z* (ES+) 321.2174 (100, M+H$^+$) 265.1549 (M−*t*-Bu, 69), 221.1649 (M-Boc, 17). HRMS(ES+) $C_{18}H_{29}O_3N_2^+$, requires 321.2173, found 321.2174 (+0.4 ppm).

5.6.20. (*S*)-N^1-(2,5-Dimethylphenyl)-N^2,3-dimethylbutane-1,2-diamine 41



To a solution of Boc-protected amide **40** (958 mg, 3.00 mmol) in THF (10 mL) was cautiously added $LiAlH_4$ (9.00 mL of a 2 M solution in THF, 18.0 mmol), then the mixture was heated at reflux for 24 h. The mixture was then cooled (0 °C) and H_2O (0.68 mL) was added cautiously (with vigorous effervescence), followed by 40% KOH(aq) (0.68 mL) and H_2O (2.04 mL). To the mixture was added an excess of $MgSO_4$ and stirred for 1 h, then the mixture was filtered through Celite, washing with THF (30 mL). The solution was concentrated in vacuo to afford the desired diamine (630 mg, 95%) as a pink/purple oil. Product was used without further purification. $[\alpha]_D^{20} = +5.0$ (*c* 1.73, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3370 (NH), 3015, 2958, 2927, 2871, 2796, 1715, 1615, 1582, 1520, 1455, 1387, 1368, 1313, 1298, 1155, 1137, 1100, 1035, 1001, 840, 792 and 716; δ_H (400 MHz, $CDCl_3$) 6.94 (1H, d, *J* 7.4, Ar*H*-3), 6.48 (1H, s, Ar*H*-4), 6.44 (1H, s, Ar*H*-6), 4.15 (1H, br s, ArN*H*), 3.22 (1H, dt, *J* 11.8, 4.2, ArNHCH_AH_B), 2.96 (1H, ddd, *J* 11.8, 7.5, 4.2, ArNHCH_AH_B), 2.51 (1H, ddd, *J* 7.5, 6.4, 4.2, MeNHC*H*), 2.41 (3H, s, NCH_3), 2.31 (3H, s, 5-ArCH_3), 2.12 (3H, s, 2-ArCH_3), 1.96 (1H, dt, *J* 13.2, 6.8, C*H*Me$_2$), 1.02 (3H, d, *J* 6.8, CHCH_3) and 0.96 (3H, d, *J* 6.8, CHCH_3); δ_C (100 MHz, $CDCl_3$) 146.9, 136.8, 130.0, 119.5, 117.3, 110.9, 64.2, 43.3, 33.9, 29.0, 21.4, 19.6, 18.5 and 17.2; *m/z* (ES+) $C_{14}H_{25}N_2$ requires 221.2012, found 221.2017 (+2.1 ppm).

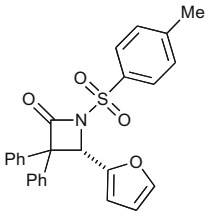
5.6.21. (*S*)-1-(2,5-Dimethylphenyl)-4-isopropyl-3-methyl-4,5-dihydro-1*H*-imidazol-3-ium tetrafluoroborate



A mixture of diamine **41** (200 mg, 0.908 mmol), triethyl orthoformate (0.37 mL, 2.27 mmol), MeOH (2.5 mL) and NH_4BF_4 (96 mg, 0.916 mmol) was heated at 100 °C for 6 h, then concentrated in vacuo. The mixture was triturated with Et_2O (×3) and EtOAc (×1). The mixture was redissolved in CH_2Cl_2 and loaded onto a short silica plug (~2 cm depth). The product was eluted with CH_2Cl_2 then ramped to 2.5% MeOH/CH_2Cl_2 to afford the product as a green/brown oil (140 mg, 48%). $[\alpha]_D^{20} = +38.7$ (*c* 0.5, $CHCl_3$); ν_{max} (thin film)/cm^{-1}: 3636, 3089, 2969, 2880, 1715 (C=N), 1652, 1619, 1576, 1515, 1509, 1464, 1428, 1397, 1377, 1315, 1270, 1215, 1161, 1134, 1058, 910, 823, 765, 719 and 675; δ_H (400 MHz, $CDCl_3$) 8.12 (1H, s, NC*H*N), 7.13 (1H, s, Ar*H*-6), 7.10 (2H, d, *J* 3.3, Ar*H*), 4.50–4.44 (1H, m, CHMe$_2$C*H*), 4.33 (1H, app t, *J* 11.7, NCH_AH_B), 3.80 (1H, dd, *J* 11.1, 7.8, NCH$_A$H$_B$), 3.26 (3H, s, N^+CH_3), 2.33–2.26 (4H, m, N^+C*H* and ArCH_3), 2.26 (3H, s, ArCH_3) and 0.97 (6H, app t, *J* 6.5, CH(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 157.8, 137.9, 134.6, 131.7, 130.6, 130.5, 126.5, 67.0, 52.0, 33.1, 27.0, 20.7, 17.8, 17.4 and 14.2; *m/z* HRMS(ES+) $C_{15}H_{23}N_2^+$ requires 231.1856, found 231.1856 (+0.1 ppm).

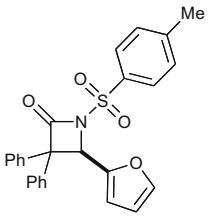
5.7. Synthesis of β-lactam 22 by NHC precatalysts 32 and 42

General procedure: A 0.50 M solution of KHMDS in toluene (9 mol %) was added to a suspension of chiral imidazolinium salt (10 mol %) in Et_2O (1.5 mL) under a nitrogen atmosphere and the mixture was stirred for 30 min at room temperature. A solution of ketene (1.3 equiv) in Et_2O (1.5 mL) was added, followed by the imine (1.0 equiv) as a solid, and the reaction mixture was stirred at room temperature for 16 h before concentration in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and washed with 0.1 M HCl(aq) (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were dried ($MgSO_4$) and concentrated in vacuo to yield the crude product as an orange oil.



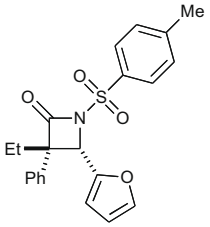
5.7.1. Scheme 8 entry 1: (*S*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*S*)-22

The β-lactam (*S*)-**22** was obtained using diphenylketene (82.5 mg, 0.31 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (81.5 mg, 0.33 mmol) with chiral imidazolinium salt **32** (14.0 mg, 0.033 mmol) and a 0.50 M solution of KHMDS in toluene (0.06 mL, 0.029 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (Et_2O/petrol 20:80) to give β-lactam (*S*)-**22** as a pale yellow solid (3.00 mg, 21%) with spectroscopic data in accordance with the literature[5] and as described above. HPLC analysis: 23% ee.



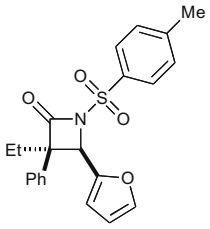
5.7.2. Scheme 8 entry 4: (*R*)-3,3-diphenyl-4-(2-furanyl)-1-tosylazetidin-2-one (*R*)-22

The β-lactam (*R*)-**22** was obtained using diphenylketene (50.7 mg, 0.261 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (50.1 mg, 0.201 mmol) with chiral imidazolinium salt **42** (4.7 mg, 0.020 mmol) and a 0.50 M solution of KHMDS in toluene (0.04 mL, 0.018 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (Et_2O/petrol 10:90 then Et_2O/petrol 30:70) to give β-lactam (*R*)-**22** as a pale yellow solid (33.0 mg, 37%) with spectroscopic data in accordance with the literature[5] and as described above. HPLC analysis: 31% ee.



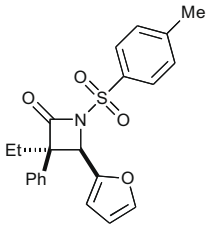
5.7.3. Scheme 8 entry 5: (3*S*,4*S*)-3-ethyl-4-(furan-2-yl)-3-phenyl-1-tosylazetidin-2-one (3*S*,4*S*)-25

The β-lactam (3*S*,4*S*)-**25** was prepared using ethylphenylketene (71.8 mg, 0.49 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (94.3 mg, 0.38 mmol) with chiral imidazolinium salt **32** (16.2 mg, 0.038 mmol) and a 0.50 M solution of KHMDS in toluene (0.07 mL, 0.034 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 5:95 then EtOAc/petrol 10:90) to give β-lactam (3*S*,4*S*)-**25** as a pale yellow solid (126 mg, 84%) and as a diastereomeric mixture (dr *syn*:*anti* 70:30) with spectroscopic data in accordance with the literature[4] and as described above. HPLC analysis: 30% ee.



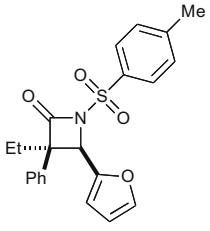
5.7.4. Scheme 8 entry 6: (3*R*,4*R*)-3-ethyl-4-(furan-2-yl)-3-phenyl-1-tosylazetidin-2-one (3*R*,4*R*)-25

The β-lactam (3*R*,4*R*)-**25** was prepared using ethylphenylketene (45.2 mg, 0.309 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (59.4 mg, 0.238 mmol) with chiral imidazolinium salt **35** (11.2 mg, 0.0238 mmol) and a 0.50 M solution of KHMDS in toluene (0.04 mL, 0.0214 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 5:95 then EtOAc/petrol 10:90) to give β-lactam (3*R*,4*R*)-**25** as a pale yellow solid (31.9 mg, 34%) and as a diastereomeric mixture (dr *syn*:*anti* 65:35) with spectroscopic data in accordance with the literature[4] and as described above. HPLC analysis: 4% ee.



5.7.5. Scheme 8 entry 7: (3*R*,4*R*)-3-ethyl-4-(furan-2-yl)-3-phenyl-1-tosylazetidin-2-one (3*R*,4*R*)-25

The β-lactam (3*R*,4*R*)-**25** was prepared using ethylphenylketene (38.2 mg, 0.261 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (50.1 mg, 0.201 mmol) with chiral imidazolinium salt **42** (6.7 mg, 0.020 mmol) and a 0.50 M solution of KHMDS in toluene (0.04 mL, 0.018 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 10:90 then EtOAc/petrol 30:70) to give β-lactam (3*R*,4*R*)-**25** as a pale yellow solid (41.0 mg, 46%) and as a diastereomeric mixture (dr *syn*:*anti* 70:30) with spectroscopic data in accordance with the literature[4] and as described above. HPLC analysis: 0% ee.



5.7.6. Scheme 8 entry 8: (3*R*,4*R*)-3-ethyl-4-(furan-2-yl)-3-phenyl-1-tosylazetidin-2-one (3*R*,4*R*)-25

The β-lactam (3*R*,4*R*)-**25** was prepared using ethylphenylketene (38.2 mg, 0.261 mmol) and *N*-(2-furfurylidene)-4-methylbenzenesulfonamide (50.1 mg, 0.201 mmol) with chiral imidazolinium salt **39** (4.7 mg, 0.020 mmol) and a 0.50 M solution of KHMDS in toluene (0.04 mL, 0.018 mmol) following the above-mentioned general procedure. The crude product was purified by silica chromatography (EtOAc/petrol 10:90 then EtOAc/petrol 30:70) to give β-lactam (3*R*,4*R*)-**25** as a pale yellow solid (67.8 mg, 76%) and as a diastereomeric mixture (dr *syn*:*anti* 68:32) with spectroscopic data in accordance with the literature[4] and as described above. HPLC analysis: 3% ee.

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