N-Heterocyclic carbene catalysed β -lactam synthesis[†]

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N-Heterocyclic carbenes promote the formal [2+2] cycloaddition of ketenes with *N*-tosyl imines to give the corresponding β -lactams in good to excellent isolated yields; chiral NHCs give β -lactams in high e.e. after crystallisation.

Introduction

N-Heterocyclic carbenes (NHCs) readily promote a range of organocatalytic reactions.¹ The majority of these transformations are initiated by nucleophilic attack of the NHC upon an aldehyde or acylsilane to generate the corresponding acyl anion equivalent. Alternatively, the reaction of an NHC with α -functionalised aldehydes can generate homoenolates² for use in redox reactions,³ a reaction sequence that has been utilised to promote formal [4+2]⁴ and [3+3]⁵ cycloaddition processes. As part of a research programme directed towards developing alternative uses of NHCs as organocatalysts,⁶ their ability to promote the formal [2+2] cycloaddition of ketenes and imines for the synthesis of β -lactams was investigated (Fig. 1).



Fig. 1 Proposed NHC catalysed β -lactam formation.

The β -lactam skeleton is a widely recognised pharmacophore that has received extensive biological and synthetic investigation. A number of methodologies exist for the preparation of β -lactams,^{7,8} with asymmetric routes including the ring expansion of aziridines⁹ and chiral auxiliary methods,¹⁰ amongst others.¹¹ The Staudinger reaction¹² is perhaps the most widely recognised procedure for the synthesis of β -lactams,¹³ and Lectka *et al.*¹⁴ and Fu *et al.*¹⁵ have elegantly shown that chiral amines can catalyse this reaction asymmetrically. Although the addition of nucleophiles to ketenes has been utilised for a number of synthetic applications,¹⁶ only limited studies concerning the activation of a ketene with an NHC have been reported.¹⁷ We delineate herein that NHCs catalyse the formation of β -lactams from ketenes and imines and show that enantiomerically pure NHCs provide an important platform for a catalytic enantioselective variant of this reaction.

of Developing an NHC mediated β-lactam synthesis

At the onset of these studies, a reliable working procedure for β lactam formation from diphenylketene and N-tosyl imine 4 using triazolinylidene NHC 2 was sought. Deprotonation of azolium salt 1 (20 mol%) with KHMDS (19 mol%) in toluene was used to pre-generate NHC 2, with the order of addition of reactants critical to the successful generation of β -lactam 5. Addition of NHC 2 to an equimolar solution of diphenylketene and imine 4, or the inverse addition, gave 25% and 75% conversion to 5 respectively after 24 hours. Addition of imine 4 to NHC 2 followed by diphenylketene gave no conversion to 5 even after 5 days, consistent with reports of N-tosyl imine inhibition of catalyst turnover in NHC reactions through irreversible nucleophilic addition.¹⁸ However, addition of diphenylketene to NHC 2, followed by imine 4, gave >95% conversion to product, giving 5 in 59\% isolated yield, implying that NHC activation of the ketene is necessary to allow catalytic turnover in this reaction (Table 1, entry 1). To further test this hypothesis, addition of diphenylketene (0.2 eq) to NHC 2, followed by imine 4(1.0 eq) and then a further portion of diphenylketene (0.8 eq) gave 90% conversion to 5. Further reaction optimisation showed that the initial addition of 1.3 eq of ketene 3 to NHC 2 in this procedure allowed full consumption of imine 4, giving 5 in 84% isolated yield (entry 2). With a working protocol in hand, the effect of solvent upon the catalytic efficiency of this process was investigated. As a standard, using 19 mol% of NHC 2 in toluene gave 66% conversion to 5 after 1 hour, while the corresponding reactions in THF or Et₂O gave 83% and >95%conversion respectively. Progressively lowering the catalyst loading in Et₂O showed that 4.5 mol% of NHC 2 gave > 95% conversion to 5 within 1 hour, giving 5 in 93% isolated yield (entries 6-8). Lower catalyst loadings (<1 mol%) of NHC 2 can be used to generate moderate levels of conversion to β -lactam 5 but require extended reaction times (entry 9).

Wilhelm and Sereda have recently shown that metal amides such as KHMDS can catalyse directly the [2+2] cycloaddition of ketenes and *N*-nosyl imines.¹⁹ To confirm that NHC **2** is the catalytic species in this reaction manifold, control experiments indicated that using KHMDS (5 mol%) alone gave <10% conversion to βlactam **5** after 24 hours in Et₂O. Further experiments showed that treatment of **3** and **4** with HMDS, or simply mixing **3** and **4** in Et₂O, returned only starting material. Using this information, a simplistic mechanistic rationale for this process can be proposed. Deprotonation of azolium salt **1** with KHMDS generates NHC

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^{*a*} All reaction conversions and product distributions were judged by ¹H NMR spectroscopic analysis of the crude reaction product. ^{*b*} Isolated yield of homogeneous product after chromatographic purification.

2, that adds to diphenylketene to generate azolium enolate 6. Enolate addition to *N*-tosyl imine 4 gives the β -amido carbonyl 7, which upon intramolecular cyclisation produces the β -lactam 5 and regenerates the NHC 2 (Fig. 2). While this mechanism remains our current hypothesis, Fu *et al.* have proposed an alternative mechanism when employing *N*-triflyl imines in this reaction manifold that involves initial nucleophilic activation of the imine.^{15b} Preliminary mechanistic studies cannot, as yet, unambiguously rule out this alternative pathway when employing NHC mediated catalysis, and further investigations to delineate conclusively the mechanism of this transformation are underway.



Fig. 2 Proposed mechanism of β -lactam synthesis using NHC 2.

Probing reaction scope

The generality of this catalytic process was next examined. Using diphenylketene, a range of *N*-tosyl substituted imines derived from aryl (entries 1 and 2), heteroaryl (entry 3), substituted aryl (entries 4 and 5) and α , β -unsaturated aldehydes (entry 6) are readily tolerated. High levels of conversion to the desired β -lactams were readily achieved with <10 mol% of NHC **2** within one hour,

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Table 2 Probing the generality of NHC catalysed β-lactam synthesis



^{*a*} Isolated yield of homogeneous product after chromatographic purification.

although with an electron rich 4-MeOC₆H₄ substituent (entry 4), 9 mol% of NHC **2** and a longer reaction time of 24 hours was required, giving **10** in 59% isolated yield (Table 2).

The ability of NHC **2** to catalyse the formation of β -lactams from unsymmetrical ketenes was next investigated. Addition of isobutylphenylketene **13** to NHC **2** (9 mol%) followed by addition of *N*-tosyl imine **4** gave full conversion after one hour to the desired β -lactam **14** as a 68 : 32 mixture of *syn* : *anti* diastereoisomers in 89% isolated yield (entry 1).²⁰ Lower catalyst loadings could be used to achieve reasonable levels of conversion in this reaction without altering the diastereoselectivity of this process (4.5 mol% of NHC **2**, 16 hours, 87% conversion). This protocol proved general as a range of imines are readily tolerated, proceeding to completion using 9 mol% of NHC **2** within one hour. The desired β -lactams **14–17** are readily isolated in good yield (72– 94%) as a mixture of diastereoisomers, with a preference for the *syn*-diastereoisomer observed in each case (Table 3).²¹

Catalytic asymmetric β-lactam synthesis employing NHCs

Subsequent investigations probed the ability of enantiomerically pure NHCs to catalyse an enantioselective version of this reaction. As C_2 -symmetry has proven a useful tool in asymmetric catalysis,²² a C_2 -symmetric tetrafluoroborate NHC precatalyst **19** was prepared from (1*R*,2*R*)-cyclohexane-1,2-diammonium mono-(+)-tartrate²³ via bis-reductive amination and subsequent cyclisation, giving **19** in good yield over three steps (Scheme 1).

Scheme 1 Preparation of C_2 -symmetric imidazolinium salt 19.

Initial results showed that NHCs 21 and 22, prepared by deprotonation of 19 and the popular triazolium salt 20 (10 mol%) with KHMDS (9 mol%) respectively, promote readily the formal cycloaddition of diphenylketene and N-tosyl imine 4, giving complete conversion to β -lactam 5 in 58% and 64% e.e. respectively and in good isolated yields (Table 4, entries 1 and 2). Preferential crystallisation of the racemate from the 64% e.e. sample, and concentration of the mother liquor, gave access to β -lactam (R)-5 in >98% e.e. The absolute configuration of 5 was proven unambiguously by X-ray crystallographic analysis (Fig. 3).[‡] This procedure was subsequently applied to a number of N-tosyl imines, giving access to enantiomerically enriched β lactams (R)-8, (S)-9 and (R)-11 in 56-75% e.e. and in good isolated yields (79-96%).²⁴ In each case, crystallisation and re-isolation of the β -lactam from the mother liquor was used to enhance the e.e. of the β -lactam to >92% e.e. (entries 4, 5 and 8, Table 4).

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^{*a*} Isolated yield of homogeneous product after chromatographic purification. ^{*b*} e.e. of isolated β-lactam after chromatography as shown by HPLC analysis. ^{*c*} e.e. of β-lactam after crystallisation and re-isolation of the mother liquor as shown by HPLC analysis.

Andrews Mass Spectrometry facility or from the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS was carried out on a Micromass LCT spectrometer and low and high resolution CI MS was carried out on a Micromass GCT. At the EPSRC National Mass Spectrometry Service Centre, low and high resolution EI MS was carried out on a Micromass Quattro II spectrometer.

General procedure 1 for the synthesis of β -lactams (\pm)-5 and (\pm)-8

A 0.45 M solution of KHMDS in toluene (0.04 mL, 0.0174 mmol, 4.5 mol% or 0.08 mL, 0.0347 mmol, 9 mol%) was added to a

suspension of triazolium salt 1 (5.3 mg, 0.0193 mmol, 5 mol% or

10.5 mg, 0.0386 mmol, 10 mol%) in Et₂O (1.5 mL) under a nitrogen atmosphere and the mixture was stirred for 30 minutes at room

temperature. A solution of diphenylketene **3** (97.4 mg, 0.501 mmol, 1.3 equiv) in Et₂O (1.5 mL) was added, followed immediately by

the imine (0.386 mmol, 1.0 equiv) as a solid, then the reaction

mixture was stirred at room temperature before concentration in

Following general procedure 1, β -lactam (±)-5 was obtained using diphenylketene 3 (97.4 mg, 0.501 mmol, 1.3 equiv)

and N-benzylidene-4-methylbenzenesulfonamide 4 (100.0 mg,

0.386 mmol, 1.0 equiv). The reaction mixture was concentrated after stirring for 1 hour at room temperature and the residue was

purified by column chromatography (EtOAc-petroleum ether 20:

80 then CH_2Cl_2 -petroleum ether-EtOAc 50 : 45 : 5) to give β -

lactam (\pm)-5 (162.6 mg, 93% yield) as a white solid (mp = 184–

185 °C). IR (KBr disk) v_{max} 3063, 3037, 2928, 1776 (C=O), 1597,

1495, 1452, 1447, 1383, 1370, 1262, 1210, 1188, 1172, 1141, 1090,

1070, 1028; ¹H NMR δ 2.32 (3H, s), 5.70 (1H, s), 6.77–6.94 (7H,

m), 6.98 (2H, t, J = 7.6), 7.05 (1H, t, J = 7.2), 7.11-7.27 (5H, m),

7.31 (2H, d, J = 7.2), 7.65 (2H, d, J = 8.0); ¹³C NMR δ 21.8 (CH₃),

69.3 (CH), 72.9 (C), 127.0 (2 CH), 127.3 (CH), 127.7 (2 CH), 127.9

(3 CH), 128.0 (2 CH), 128.1 (2 CH), 128.4 (2 CH), 128.5 (CH),

129.0 (2 CH), 129.9 (2 CH), 134.0 (C), 135.4 (C), 135.9 (C), 139.0

 $[M + NH_4^+]$ C₂₈H₂₇N₂O₃S requires 471.1737, found, 471.1738;

Anal. Calcd. for C₂₈H₂₃NO₃S: C 74.15, H 5.11, N 3.09%, Found:

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to (±)-12

vacuo.

Fig. 3 Molecular representation of the X-ray crystal structure of (R)-5.

In conclusion, we have shown that NHCs can catalyse effectively the formal [2+2] cycloaddition of ketenes and imines to generate β -lactams, and that chiral NHCs show promising levels of enantioselectivity in this reaction manifold. Current investigations are focused upon expanding the reactions of chiral NHCs to a variety of catalytic enantioselective processes.

Experimental

General experimental

All reactions involving moisture sensitive reagents were performed under an atmosphere of nitrogen via standard vacuum line techniques and with freshly dried solvents. All glassware was flame dried and allowed to cool under vacuum. Toluene, tetrahydrofuran (THF), diethyl ether (Et₂O) and dichloromethane were obtained dry from a solvent purification system (MBraun, SPS-800). Potassium hexamethyldisilazide (KHMDS) was supplied as a 0.5 M solution in toluene (Aldrich), titrated before use,²⁵ and used as a 0.45 M solution. Petrol is defined as petroleum ether 40-60 °C. All solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Room temperature refers to 20-25 °C. Reflux conditions were obtained using an oil bath equipped with a contact thermometer. In vacuo refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC₂ vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller. Analytical thin layer chromatography was performed on aluminium sheets coated with 60 F₂₅₄ silica. TLC visualisation was carried out with ultraviolet light (254 nm). Column chromatography was performed on Kieselgel 60 silica in the solvent system stated. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were acquired on a Bruker Avance II 400 (400 MHz 1H, 100 MHz ¹³C) spectrometer and in CDCl₃ unless stated otherwise. Coupling constants (J) are reported in Hz. Infrared spectra (v_{max}) were recorded on a Perkin-Elmer Spectrum GX FT-IR Spectrometer using KBr discs as stated. Only the characteristic peaks are quoted. Microanalyses were carried out on a Carlo Erba CHNS analyser. Melting points were recorded on an Electrothermal apparatus and are uncorrected. Mass spectrometric (m/z) data were acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI), either at the University of St

(C), 145.4 (C), 166.9 (C); CIMS (NH₃) m/z 471 (M + NH₄⁺, 4), 257 (67), 256 (Ph₂C=CH⁺-Ph, 29), 212 (Ph₂C=C=O + NH₄⁺, 27), 106 (O=C-N-SO₂, 100), 91 (C₆H₅⁺-CH₃, 77); HRMS (CI, NH₃)

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C 73.84, H 4.97, N 3.12%.

Following general procedure 1, β -lactam (±)-8 was obtained using diphenylketene 3 (97.4 mg, 0.501 mmol, 1.3 equiv) and *N*-(2-naphthylidene)-4-methylbenzenesulfonamide (119.3 mg, 0.386 mmol, 1.0 equiv). The reaction mixture was concentrated after stirring for 1 hour at room temperature and the residue was purified by column chromatography (EtOAc–petroleum ether 20 : 80 then CH₂Cl₂–petroleum ether–EtOAc 50 : 45 : 5) to give β lactam (±)-8 (177.9 mg, 92% yield) as a white solid (mp = 182– 183 °C). IR (KBr disk) ν_{max} 3054, 1792 (C=O), 1595, 1496, 1449, 1374, 1361, 1167, 1128, 1121, 1088; ¹H NMR δ 2.39 (3H, s), 5.94 Downloaded on 06 July 2012 Published on 12 February 2008 on http://pubs.rsc.org | doi:10.1039/B800857B (1H, s), 6.81 (1H, dd, J = 8.4, 1.2), 6.83–7.03 (5H, m), 7.18 (2H, d, J = 8.0), 7.22–7.39 (4H, m), 7.39–7.51 (5H, m), 7.56 (1H, s), 7.63 (1H, dd, J = 5.6, 3.2), 7.69 (3H, d, J = 8.0); ¹³C NMR δ 27.7 (CH₃), 69.7 (CH), 72.8 (C), 124.8 (CH), 126.3 (CH), 126.5 (CH), 127.0 (2 CH), 127.3 (CH), 127.7 (4 CH), 128.0 (4 CH), 128.1 (CH), 128.2 (2 CH), 129.0 (2 CH), 129.8 (2 CH), 131.5 (C), 132.7 (C), 133.1 (C), 135.5 (C), 135.7 (C), 139.2 (C), 145.4 (C), 166.8 (C); CIMS m/z 504 (M + H⁺, 18), 308 (M – Ph₂C=C=O, 13), 307 (100), 306 (40), 198 (O=C–N=SO₂–tol, 38), 194 (Ph₂C=C=O, 18), 155 (SO₂–tol, 16), 141 (C₁₁H₉, 5); HRMS (CI) [M + H⁺] C₃₂H₂₆NO₃S requires 504.1633, found 504.1631.

General procedure 2 for the synthesis of β -lactams (±)-14 to (±)-18

A 0.45 M solution of KHMDS in toluene (0.08 mL, 0.0347 mmol, 9 mol%) was added to a suspension of triazolium salt 1 (10.5 mg, 0.0386 mmol, 10 mol%) in Et₂O (1.5 mL) under a nitrogen atmosphere and the mixture was stirred for 30 minutes at room temperature. A solution of isobutylphenylketene 13 (87.3 mg, 0.501 mmol, 1.3 equiv) in Et₂O (1.5 mL) was added, followed by the imine (0.386 mmol, 1.0 equiv) as a solid, then the reaction mixture was stirred at room temperature before concentration *in vacuo*. The initial diastereoselectivity was measured by ¹H NMR on the crude product and can be improved (after purification by column chromatography) by trituration of the product in Et₂O and filtration. This procedure allowed the characterisation of the major *syn* diastereoisomer.

Preparation of syn-3,4-diphenyl-3-isobutyl-1-tosylazetidin-2-one (±)-14¹⁵

Following general procedure 2, β -lactam (±)-14 was obtained using isobutylphenylketene 13 (87.3 mg, 0.501 mmol, 1.3 equiv) and N-benzylidene-4-methylbenzenesulfonamide 4 (100.0 mg, 0.386 mmol, 1.0 equiv). The reaction mixture was concentrated after stirring for 1 hour at room temperature (d.r. = 68 : 32 syn : anti) and the residue was purified by column chromatography (EtOAc-petroleum ether 10 : 90 then CH₂Cl₂-petroleum ether-EtOAc 50 : 45 : 5) to give β-lactam (\pm)-14 (148.7 mg, 89% yield). Trituration in Et₂O gave a white solid (mp = 156-158 °C, d.r. = 89:11 syn: anti). IR (KBr disk) v_{max} 3064, 3034, 2958, 2927, 2868, 2360, 1770 (C=O), 1597, 1496, 1447, 1364, 1241, 1188, 1170, 1145, 1090; ¹H NMR *syn*: δ 0.69 (3H, d, J = 6.8), 0.87 (3H, d, J = 6.4), 1.48-1.61 (1H, m), 1.92 (1H, dd, J = 14.6, 6.0), 2.04 (1H, dd, J =14.0, 6.4), 2.43 (3H, s), 5.00 (1H, s), 6.77 (2H, d, J = 7.6), 6.85– 6.92 (2H, m), 6.95–7.05 (5H, m), 7.10 (1H, t, J = 7.4), 7.15–7.30 (2H, m), 7.71 (2H, d, J = 8.4); anti (visible peaks): $\delta 0.37 (3H, d, J)$ J = 6.4), 2.43 (3H, s), 5.05 (1H, s), 7.80 (2H, d, J = 8.4); ¹³C NMR syn: δ 21.7 (CH₃), 23.7 (CH₃), 23.8 (CH₃), 24.9 (CH), 47.5 (CH₂), 69.3 (C), 69.8 (CH), 127.0 (CH), 127.4 (2 CH), 127.6 (2 CH), 127.9 (2 CH), 127.95 (2 CH), 128.0 (2 CH), 128.4 (CH), 129.7 (2 CH), 134.2 (C), 134.9 (C), 135.7 (C), 145.2 (C), 168.1 (C); anti (visible peaks): δ 23.0, 24.0, 24.5, 42.1, 69.9, 126.1, 127.4, 127.8, 128.6, 128.8, 128.9, 129.8, 168.5.

Preparation of *syn*-3-isobutyl-4-(2-naphthyl)-3-phenyl-1-tosylazetidin-2-one (\pm) -15

Following general procedure 2, β -lactam (±)-15 was obtained using isobutylphenylketene 13 (87.3 mg, 0.501 mmol,

1.3 equiv) and N-(2-naphthylidene)-4-methylbenzenesulfonamide (119.3 mg, 0.386 mmol, 1.0 equiv). The reaction mixture was concentrated after stirring for 1 hour at room temperature (d.r. =63 : 37 syn : anti) and the residue was purified by column chromatography (EtOAc-petroleum ether 10 : 90 then CH₂Cl₂petroleum ether-EtOAc 50 : 45 : 5) to give β -lactam (±)-15 (165.8 mg, 89% yield). Trituration in Et_2O gave a white solid (mp = $146-148 \,^{\circ}C, d.r. = 90: 10 \, syn: anti)$. IR (KBr disk) $v_{max} 3060, 2956, 2956, 3060, 3060, 2956, 3060, 30$ 2927, 2870, 2358, 1784 (C=O), 1597, 1496, 1467, 1448, 1368, 1187, 1172, 1088; ¹H NMR *syn*: δ 0.72 (3H, d, *J* = 6.8), 0.91 (3H, d, *J* = 6.8), 1.51–1.65 (1H, m), 2.00 (1H, dd, J = 14.4, 6.0), 2.11 (1H, dd, J = 14.0, 6.4, 2.38 (3H, s), 5.18 (1H, s), 6.62 (1H, dd, J = 8.4, 1.2), 6.88-7.00 (5H, m), 7.16 (2H, d, J = 8.0), 7.32 (1H, d, J = 8.8), 7.38–7.48 (3H, m), 7.60 (1H, dd, *J* = 6.0, 3.2), 7.60–7.69 (3H, m); *anti* (visible peaks): δ 0.33 (3H, d, J = 6.4), 2.45 (3H, s), 5.21 (1H, s); ¹³C NMR syn: δ 21.7 (CH₃), 23.7 (CH₃), 23.8 (CH₃), 24.9 (CH), 47.8 (CH₂), 69.2 (C), 70.0 (CH), 124.9 (CH), 126.2 (CH), 126.4 (CH), 127.0 (CH), 127.4 (2 CH), 127.5 (CH), 127.6 (2 CH), 127.9 (CH), 128.0 (2 CH), 128.2 (CH), 129.7 (2 CH), 131.7 (C), 132.6 (C), 133.1 (C), 134.8 (C), 135.6 (C), 145.1 (C), 168.0 (C); CIMS m/z 484 (M + H⁺, 100), 287 (MH⁺-O=C=N-SO₂tol, 37), 198 (O=C=N-SO₂-tol, 40), 174 (Ph(i-Bu)C=C=O, 75), 154 (SO₂tol, 29); HRMS (ESI⁺) [M + Na⁺] C₃₀H₂₉NNaO₃S requires 506.1766, found, 506.1768.

General procedure 3 for the enantioselective synthesis of β -lactams (*R*)-5, (*R*)-8, (*S*)-9 and (*R*)-11

A 0.45 M solution of KHMDS in toluene (0.08 mL, 0.0347 mmol, 9 mol%) was added to a suspension of chiral imidazolinium salt **19** (15.2 mg, 0.0386 mmol, 10 mol%) or chiral triazolium salt **20** (14.5 mg, 0.0386 mmol, 10 mol%) in Et₂O (1.5 mL) under a nitrogen atmosphere and the mixture was stirred for 30 minutes at room temperature. A solution of diphenylketene **3** (97.4 mg, 0.501 mmol, 1.3 equiv) in Et₂O (1.5 mL) was added, followed immediately by the imine (0.386 mmol, 1.0 equiv) as a solid, then the reaction mixture was stirred at room temperature before concentration *in vacuo*.

Preparation of (R)-3,3,4-triphenyl-1-tosylazetidin-2-one 5

Following general procedure 3, the β -lactam (R)-5 was obtained using diphenylketene 3 (97.4 mg, 0.501 mmol, 1.3 equiv) and Nbenzylidene-4-methylbenzenesulfonamide 4 (100 mg, 0.386 mmol, 1.0 equiv). The reaction mixture was concentrated after stirring for 1 hour (using the NHC from 19) or 3 hours (using the NHC from 20) at room temperature and the residue was purified by column chromatography (EtOAc-petroleum ether 10 : 90 then CH₂Cl₂petroleum ether-EtOAc 50 : 45 : 5) to give β -lactam (R)-5 as a yellow solid (158.0 mg, 90% yield, from chiral imidazolinium salt 19 and 167.2 mg, 96% yield from chiral triazolium salt 20). HPLC analysis: 64% e.e. (Daicel CHIRALCEL OD-H column, eluent: hexane-i-PrOH 90 : 10, flow: 1 mL min⁻¹, wavelengh: 254 nm, retention times: 9.4 min (major, R) and 16.5 min (minor, S)). $[a]_{D}^{20}$ +17.7 (c 1.00, CHCl₃, 64% e.e.). The initial e.e. can be improved by crystallisation (CH₂Cl₂-hexane) and re-isolation of the β-lactam from the mother liquor, giving (*R*)-5 in 98% e.e. (mp = 152-154 °C, 98% e.e.). $[a]_{D}^{20}$ +22.0 (c 0.63, CHCl₃, 98% e.e.).

Preparation of (*R*)-3,3-diphenyl-4-(2-naphthyl)-1-tosylazetidin-2-one 8

Following general procedure 3, β -lactam (R)-8 was obtained using diphenvlketene 3 (97.4 mg, 0.501 mmol, 1.3 equiv) and N-(2-naphthylidene)-4-methylbenzenesulfonamide (119.3 mg, 0.386 mmol, 1.0 equiv). The reaction mixture was concentrated after stirring for 1 hour (using the NHC from 19) or 3 hours (using the NHC from 20) at room temperature and the residue was purified by column chromatography (EtOAc-petroleum ether 10 : 90 then CH_2Cl_2 -petroleum ether-EtOAc 50 : 45 : 5) to give β -lactam (R)-8 as a pale yellow solid (184.1 mg, 95% yield, from chiral imidazolinium salt 19 and 178.5 mg, 92% yield from chiral triazolium salt 20). HPLC analysis: 75% e.e. (Daicel CHIRALCEL OD-H column, eluent: hexane-i-PrOH 90 : 10, flow: 1 mL min⁻¹, wavelengh: 254 nm, retention times: 10.0 min (major, R) and 20.5 min (minor, S)). $[a]_{D}^{20}$ -5.0 (c 1.00, CHCl₃, 75% e.e.). The initial e.e. can be improved by crystallisation (CH2Cl2-hexane) and re-isolation of the β -lactam from the mother liquor, giving (*R*)-8 in >99% e.e. (mp = 136–138 °C, >99% e.e.). $[a]_{\rm D}^{20}$ -5.9 (*c* 0.69, CHCl₃, >99% e.e.).

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