Rhodium-catalysed hydroformylation of N-(2-propenyl)- β -lactams as a key step in the synthesis of functionalised N-[4-(2-oxoazetidin-1-yl)but-1-enyl]acetamides[†]

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Biologically relevant functionalised N-[4-(2-oxoazetidin-1-yl)but-1-enyl]acetamides have been prepared in a two-step approach starting from N-(2-propenyl)- β -lactams, involving initial rhodiumcatalysed hydroformylation followed by subjection of the obtained aldehydes to Staudinger reaction conditions after initial imination.

In the past decade, the catalytic hydroformylation of alkenes has acquired a prominent position in the field of homogeneous catalysis.¹ The general interest in metal-catalysed hydroformylation reactions is due to their high atom efficiency and the availability of active and selective catalysts. In addition, the transformation of alkenes into aldehydes creates a significant added value, as the latter functional group represents an enormous synthetic potential towards the preparation of a variety of relevant target compounds. Nevertheless, the catalytic hydroformylation of alkenes is mainly considered as a valuable industrial process, and applications in the small-scale synthesis of fine chemicals² are rather limited. However, in recent years, metal-catalysed hydroformylations have found their way towards useful applications in organic synthesis, for example for the construction of interesting oxa- and azaheterocycles.² These examples illustrate the fact that the integration of catalytic hydroformylations in the design of novel organic syntheses constitutes an emerging area with promising prospects in terms of efficiency and selectivity.

Within medicinal chemistry, the synthesis and transformation of β -lactams comprises an important field of research, as the class of β -lactam antibiotics is generally recognised as a cornerstone of human health care due to their unparalleled clinical efficacy and safety.⁴ Furthermore, β -lactams have proven to be excellent substrates for further elaboration, which has led to the introduction of the term " β -lactam synthon method" in 1997.^{5,6}

In the present report, the application of catalytic hydroformylation in the synthesis of functionalised β-lactams is disclosed, thus providing a useful example of the successful integration of homogeneous catalysis within β-lactam chemistry. In particular, the unprecedented rhodium-catalysed hydroformylation of N-(2-propenyl)- β -lactams is employed as a key step in the synthesis of functionalised N-[4-(2-oxoazetidin-1-vl)but-1-envllacetamides. The latter compounds are of interest in the framework of anticancer research, as the presence of an enamido moiety embedded in a larger molecular architecture constitutes a relevant pharmacophore in that respect. The interest in this type of compounds stems from the isolation of different natural products with pronounced antitumor activities, such as the marine lipopeptide Somocystinamide A^7 and the macrolides Apicularen A, isolated from the myxobacterial genus Chondromyces,8 and lobatamide C, isolated from southwestern Pacific tunicates.9 All of these natural compounds accommodate an enamide functionality as an essential part of their structure. Apart from a few reports on the hydroformylation of 4-vinyl-β-lactams,¹⁰ the catalytic hydroformylation of β-lactams remains an unexplored field of research to date.

Initially, a synthetic concept was devised based on the preparation of *N*-allyl- β -lactams, followed by metal-catalysed hydroformylation as a key step and finally subjection of the obtained aldehydes to classical Staudinger reaction conditions.

Thus, N-(2-propenyl)- and N-(2-methyl-2-propenyl)imines 2 were synthesised via condensation of benzaldehydes 1 with allylamine or 2-methylallylamine in CH2Cl2 in the presence of MgSO₄ (Scheme 1).¹¹ In case of N-(2-methyl-2-propenyl)imines 2 ($R^2 = Me$), the hydrochloride salt of 2-methylallylamine was used in the presence of Et₃N. Subsequently, the obtained N-(arylmethylidene)amines 2 were used as such for the Staudinger synthesis of β-lactams 3, affording cis-3-(alkoxy or phenoxy)-4-arylazetidin-2-ones¹² 3a-j in 81-90% yield upon treatment with methoxy-, phenoxy- or benzyloxyacetyl chloride in CH₂Cl₂ in the presence of Et₃N (Scheme 1, Table 1). The observed cis-selectivity is in accordance with the known cis-selectivity associated to the use of Bose-Evans ketenes¹³ and could be deduced from the ¹H NMR spectra of β -lactams 3, as the coupling constants between the protons at C3 and C4 varied between 4.4 and 4.7 Hz (CDCl₃).¹⁴

As stated earlier, metal-catalysed hydroformylations comprise a powerful tool in organic synthesis. Up to now,

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Scheme 1

Table 1 Synthesis of β-lactams 3a-j

Entry	\mathbf{R}^1	\mathbb{R}^2	R^3	β -Lactam 3 (yield)
1	Н	Н	Ph	3a (89%)
2	Н	Η	Me	3b (90%)
3	Н	Η	Bn	3c (86%)
4	4-C1	Н	Ph	3d (81%)
5	2-Br	Η	Bn	3e (85%)
6	Н	Me	Ph	3f (86%)
7	Н	Me	Me	3g (86%)
8	Н	Me	Bn	3h (89%)
9	4-C1	Me	Ph	3i (85%)
10	2-Br	Me	Bn	3j (84%)

this transformation has not been applied to (2-oxoazetidin-1-yl)methyl-substituted alkenes, although this approach would constitute a convenient alternative for the conventional synthesis involving the preparation of 1-(4-hydroxybutyl)- β -lactams (*via* alcohol protection/deprotection)¹⁵ and a final oxidation step.

Consequently, N-(2-propenyl)- β -lactams 3 were evaluated as substrates for catalytic hydroformylation towards the corresponding aldehydes. At first, N-allyl-β-lactams 3a-e $(\mathbf{R}^2 = \mathbf{H})$ were subjected to standard hydroformylation conditions, *i.e.* treatment with syngas (20 bar CO/H_2 , 1/1) using (acetylacetonato)dicarbonylrhodium(1) [Rh(acac)(CO)₂] as a catalyst precursor (substrate/Rh = 500) and xantphos¹⁶ as a ligand (xantphos/Rh = 2) in toluene ($c_{\rm S}$ = 0.25 M) at 80 °C (preformation: 1 h, reaction: 16 h). Gratifyingly, complete conversion of β -lactams **3a–e** occurred under the given reaction conditions as monitored by GC analysis using n-decane as an internal standard, furnishing a mixture of linear and branched aldehydes 4a-e ($R^2 = H$) and 5a-e ($R^2 = H$) in good yields (Scheme 2, Table 2). Spectroscopic analysis (¹H NMR) of the reaction mixtures revealed the presence of linear N-(4-oxobutyl)azetidin-2-ones 4a-e as the major regioisomers (83-93%). In addition, a diastereomeric mixture of branched isomers 5a-e was formed as the minor regioisomers (7–17%, dr \approx 1/1). Attempts to improve the regioselectivity by increasing the xantphos/Rh ratio from 2 to 4 or 8 were not successful. The major isomers 4a-e were isolated in pure form through column chromatography on silica gel.

N-(2-methyl-2-propenyl)-β-lactams Subsequently, 3f_i $(R^2 = Me)$ were studied as substrates for rhodium-catalysed hydroformylation. Initial attempts using triphenylphosphine as a ligand applying a range of reaction conditions (20 bar CO/H_2 , substrate/Rh = 500, PPh_3/Rh = 20, 80–120 °C, 16-40 h) always led to partial conversion (12-71%). On the other hand, the use of tris(2,4-di-tert-butylphenyl)phosphite as a bulky π -acceptor ligand expectedly led to full conversion of β -lactams **3f**-i ($\mathbf{R}^2 = \mathbf{M}\mathbf{e}$) under the given reaction conditions (20 bar CO/H₂ (1/1), substrate/Rh = 1000, ligand/Rh = 10, toluene, $c_{\rm S} = 0.25$ M, preformation: 1 h, 100 °C, reaction: 16 h, 100 °C). As foreseen, only the corresponding linear aldehydes 4f-j ($R^2 = Me$) were obtained in good yields (Scheme 2, Table 2), as 1.1-disubstituted alkenes are known to afford linear aldehydes in high regioselectivity upon hydroformylation according to Keulemans' empirical rule.¹⁷

The relative *cis*-stereochemistry of the substituents attached to the β -lactam nucleus did not affect the diastereoselectivity during hydroformylation, as a 1/1 mixture of *syn* and *anti* isomers—concerning the position of the methyl group (R² = Me) with respect to the β -lactam substituents at C3 and C4—was obtained. Furthermore, it is worth mentioning that a Rh-catalysed isomerisation of the double bond in *N*-(2-methyl-2-propenyl)- β -lactams towards *N*-(2-methyl-1propenyl)- β -lactams took place as well under the given reaction conditions, albeit to a limited extent (<5%, ¹H NMR).

The introduction of an aldehyde functionality within β -lactams **4** creates a variety of synthetic opportunities for further elaboration such as alcohol synthesis, α -halogenation or α -alkylation, formation of imines and subsequent α -functionalisation or reduction. In light of the known reactivity of imines towards ketenes under Staudinger reaction conditions, our initial plan comprised imination of aldehydes **4**, followed by [2+2]-cycloaddition with different Bose–Evans ketenes to form novel bis- β -lactams. Whereas the condensation of aldehydes **4** with a variety of primary amines proceeded smoothly under standard imination conditions, subsequent reaction with methoxy-, phenoxy- or benzyloxyacetyl chloride in benzene in the presence of Et₃N did not afford the contemplated bis-azetidin-2-ones. Nonetheless, full and selective substrate conversion occurred, furnishing novel products in



Table 2	Catalytic hydroformylation	of N-(2-propenyl)azetidin-2-ones 3a-j
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Entry	Substrate	R ¹	R ²	R ³	Ligand ^a	Conditions ^b	4 5 (vield ratio $4/5$) ^{<i>c</i>,<i>d</i>}
	Subblicte				Ziguila	conditions	i, e (jield, idde ije)
1	3a	Η	Н	Ph	Xantphos	А	4a, 5a (79%, 89/11)
2	3b	Н	Н	Me	Xantphos	А	4b , 5b (89%, 88/12)
3	3c	Н	Н	Bn	Xantphos	А	4c, 5c (86%, 93/7)
4	3d	4-Cl	Н	Ph	Xantphos	А	4d, 5d (97%, 89/11)
5	3e	2-Br	Н	Bn	Xantphos	А	4e, 5e (81%, 83/17)
6	3f	Н	Me	Ph	$P(OR)_3$	В	4f, 5f $(82\%, >99/1)$
7	3g	Н	Me	Me	$P(OR)_3$	В	4g, 5g (95%, >99/1)
8	3h	Н	Me	Bn	$P(OR)_3$	В	4h , 5h $(92\%, >99/1)$
9	3i	4-C1	Me	Ph	$P(OR)_3$	В	4i, 5i $(89\%, >99/1)$
10	3ј	2-Br	Me	Bn	$P(OR)_3$	В	4j , 5j (77%, >99/1)

^{*a*} Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; $P(OR)_3 = tris(2,4-di-tert-butylphenyl)phosphite. ^{$ *b* $} A: 20 bar CO/H₂ (1/1), substrate/Rh = 500, xantphos/Rh = 2, <math>c_S = 0.25$ M, preformation: 1 h, 80 °C, reaction: 16 h, 80 °C; B: 20 bar CO/H₂ (1/1), substrate/Rh = 1000, $P(OR)_3/Rh = 10, c_S = 0.25$ M, preformation: 1 h, 100 °C, reaction: 16 h, 100 °C. ^{*c*} Yield of the mixtures of β-lactams 4 and 5. ^{*d*} Ratio determined by ¹H NMR analysis.



Scheme	3
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Table 3 Synthesis of 1-(4-iminobutyl)- β -lactams 6a–f and N-[4-(2-oxoazetidin-1-yl)-but-1-enyl]acetamides 7a–f

Entry	\mathbf{R}^1	\mathbb{R}^2	\mathbb{R}^3	\mathbb{R}^4	\mathbb{R}^5	Imine 6 (yield)	Enamide 7 (yield)
1	Н	Н	Ph	Bn	Me	6a (97%)	7a (59%)
2	Н	Н	Bn	<i>i</i> Pr	Ph	6b (92%)	7b (68%)
3	4-Cl	Н	Ph	nPr	Bn	6c (95%)	7c (63%)
4	Н	Me	Bn	cHex	Ph	6d (96%)	7d (35%)
5	Н	Me	Me	Bn	Ph	6e (93%)	7e (33%)
6	4-Cl	Me	Ph	iPr	Bn	6f (98%)	7f (31%)
^a Yield	ls afte	r col	umn	chrom	atogi	aphy on silica g	el.

good yields. Detailed spectroscopic analysis finally revealed the molecular structure of the latter products to be enamides 7, which can be explained considering the formation of intermediate iminium species 8, followed by α -deprotonation with respect to the iminium moiety (Scheme 3, Table 3). It is known that *N*-(alkylmethylidene)amines are less reactive towards [2+2]-cycloaddition reactions as compared to *N*-(arylmethylidene)amines, sometimes resulting in the formation of enamides instead of azetidin-2-ones.¹⁸ The *E*-stereochemistry assigned to the carbon–carbon double bond in enamides 7 is supported by the observed vicinal coupling constants between both olefinic protons (J = 13.8 Hz, ¹H NMR, CDCl₃). It should be noted that in case of enamides 7d–f (R² = Me) only one diastereoisomer could be isolated in pure form after column chromatography on silica gel, hence the lower yields. As described in the introduction, β -lactams 7 bearing an enamido moiety are of interest within the framework of anticancer research. Given the medicinal importance of functionalised azetidin-2-ones, the combination of the β -lactam entity with an enamido moiety might create new opportunities for the development of novel lead compounds.

In conclusion, biologically relevant functionalised N-[4-(2-oxoazetidin-1-yl)-but-1-enyl]acetamides have been prepared starting from N-(2-propenyl)- β -lactams in a two-step approach, involving (i) the unprecedented catalytic hydroformylation of the olefinic moiety in the latter β -lactams and (ii) treatment of the obtained aldehydes with alkoxyacetyl chlorides under Staudinger reaction conditions after initial imination.

Experimental

Hydroformylation of N-(2-propenyl)-β-lactams 3a-j

General procedure for the hydroformylation of *N*-(2-propenyl)- β -lactams **3a–e**: in a typical experiment, a stainless steel standard autoclave was dried under vacuum at 100 °C overnight and filled with argon. Afterwards, the autoclave was flushed 20 times with argon to remove oxygen traces and was charged with a solution of Rh(acac)(CO)₂ (0.03 mmol) and xantphos (0.06 mmol) in degassed toluene (10 mL) under argon. The atmosphere was further exchanged with a 1 : 1 mixture of CO/H₂ and the reactor was heated to 80 °C and

pressurised with CO/H₂ to 20 bar. The catalyst was preformed at 20 bar (CO/H₂) and 80 °C for 1 h at 2000 rpm (mechanical stirring). Subsequently, the substrate **3** (7.5 mmol), dissolved in degassed toluene (20 mL), was added from a dropping funnel, followed by hydroformylation at 20 bar (CO/H₂) and 80 °C for 16 h at 2000 rpm. The reaction was stopped by cooling the reactor to room temperature and venting. The catalyst was removed by filtration through neutral alumina, the solvent was evaporated and the crude reaction mixture was purified by means of column chromatography on silica gel (hexane/EtOAc 1/1).

The hydroformylation of *N*-(2-methyl-2-propenyl)- β -lactams **3f**-**j** was performed applying similar reaction conditions using Rh(acac)(CO)₂ (substrate/Rh = 1000) and tris(2,4-ditert-butylphenyl)phosphite as a ligand (ligand/Rh = 10) in degassed toluene ($c_{\rm S} = 0.25$ M). The catalyst was preformed at 20 bar (CO/H₂) and 100 °C for 1 h at 2000 rpm, and hydroformylation took place at 20 bar (CO/H₂) and 100 °C for 16 h at 2000 rpm.

cis-1-(4-Oxobutyl)-3-phenoxy-4-phenylazetidin-2-one 4a. Light-brown crystals. Mp 79.5 °C. $R_{\rm f} = 0.16$ (hexane/EtOAc 1/1). ¹H NMR (300 MHz, CDCl₃): δ 1.65–1.88 (2H, m); 2.47 (2H, t × d, J = 6.9, 3.9 Hz); 2.96 (1H, d × d × d, J = 14.2, 6.8, 6.7 Hz); 3.43 (1H, d × d × d, J = 14.2, 7.2, 7.2 Hz); 4.88 (1H, d, J = 4.4 Hz); 5.34 (1H, d, J = 4.4 Hz); 6.63–6.65, 6.77–6.82 and 7.01–7.25 (10H, 3 × m); 9.69 (1H, s). ¹³C NMR (75 MHz, ref = CDCl₃): δ 20.0; 40.1; 41.5; 62.4; 81.9; 115.6; 122.1; 128.4; 128.7; 128.9; 129.3; 133.0; 156.9; 166.4; 201.2. IR (ATR, cm⁻¹): $\nu_{\rm NC=O} = 1750$; $\nu_{\rm HC=O} = 1716$; $\nu_{\rm max} = 1492$, 1240, 1089, 750, 688. MS (70 eV): m/z (%) 310 (M⁺ + 1, 100). Anal. Calcd. for C₁₉H₁₉NO₃: C 73.77, H 6.19, N 4.53. Found C 73.58, H 6.37, N 4.32.

Synthesis of N-(4-iminobutyl)-β-lactams 6a-f

General procedure: to a solution of aldehyde 4 (2.5 mmol) in dry CH₂Cl₂ (15 mL) was added anhydrous MgSO₄ (5 mmol, 2 equiv.) and the appropriate primary amine (2.5 mmol, 1 equiv.), and the resulting suspension was stirred for one hour at room temperature. Afterwards, MgSO₄ was removed through filtration and the solvent was evaporated under vacuum, affording the corresponding imine **6** in high purity (>95% based on ¹H NMR). Imines **6** were used as such in the next step due to their hydrolytic instability.

cis-1-(4-Benzyliminobutyl)-3-phenoxy-4-phenylazetidin-2-one 6a. Yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 1.78–1.89 (2H, m); 2.33 (2H, t × d, J = 7.6, 4.2 Hz); 3.01 (1H, d × d × d, J = 14.0, 6.9, 6.9 Hz); 3.56 (1H, d × d × d, J = 14.0, 7.3, 7.3 Hz); 4.54 (2H, s); 4.92 (1H, d, J = 4.4 Hz); 5.37 (1H, d, J = 4.4 Hz); 6.68–6.71, 6.83–6.88 and 7.08–7.31 (15H, 3 × m); 7.78 (1H, t, J = 4.2 Hz). ¹³C NMR (75 MHz, ref = CDCl₃): δ 23.7; 33.2; 40.2; 62.2; 65.0; 81.8; 115.6; 122.0; 126.8; 127.2; 128.0; 128.3; 128.6; 128.7; 129.3; 133.3; 139.4; 157.0; 164.2; 166.0. IR (ATR, cm⁻¹): $\nu_{C=0}$ = 1753; $\nu_{C=N}$ = 1666; ν_{max} = 2922, 1494, 1234, 751, 734, 698. MS (70 eV): m/z(%) 399 (M⁺ + 1, 100).

Synthesis of N-[4-(2-oxoazetidin-1-yl)but-1-enyl]acetamides 7a-f

General procedure: to a solution of imine 6 (2 mmol) and triethylamine (6 mmol, 3 equiv.) in benzene (10 mL) was added dropwise a solution of alkoxyacetyl chloride (2.6 mmol, 1.3 equiv.) in benzene (5 mL) under reflux. After complete addition, the reaction mixture was stirred for 15 h at room temperature. Subsequently, benzene was evaporated under reduced pressure and the reaction mixture was re-dissolved in dichloromethane (10 mL) and washed with water (10 mL). After extracting the aqueous phase with dichloromethane $(2 \times 10 \text{ mL})$, the combined organic fractions were dried (MgSO₄). Filtration of the drying agent and removal of the solvent afforded crude N-[4-(2-oxoazetidin-1-yl)but-1-enyl]acetamide 7, which was purified by column chromatography on silica gel (hexane/EtOAc 1/1). Due to hindered rotation across the amido moiety, a major and minor isomer was observed upon spectroscopic analysis.

N-Benzyl-2-methoxy-N-[4-(cis-2-oxo-3-phenoxy-4-phenylazetidin-1-yl)but-1-enyl]acetamide 7a. Light-yellow oil. $R_{\rm f}$ = 0.14 (hexane/EtOAc 1/1). ¹H NMR (300 MHz, CDCl₃): δ 2.11–2.34 (4H, m, major + minor); 2.94 (2H, $d \times d \times d$, J = 14.3, 6.9, 6.9 Hz, major + minor); 3.41 (3H, s, minor); 3.49 (3H, s, major); 3.39-3.54 (2H, m, major + minor); 4.13 (2H, s, major); 4.13 (2H, s, major);*minor*); 4.31 (2H, s, *major*); 4.63 (1H, d, J = 4.4 Hz, *major*); 4.72 (2H, s, minor); 4.80-4.97 (5H, m, major + minor); 5.26 and 5.31 (2 \times 1H, 2 \times d, J = 4.4 Hz, major + minor); 6.60–6.73, 6.85–6.90 and 7.10–7.36 (32H, 3 \times m, major + *minor*). ¹³C NMR (75 MHz, ref = CDCl₃): δ 28.7; 40.4; 40.8; 46.7; 47.9; 59.4; 62.3; 62.8; 71.5; 71.8; 81.9; 109.0; 109.5; 115.6; 122.1; 125.6; 127.0; 127.3; 127.7; 127.9; 128.3; 128.6; 128.8; 129.3; 133.1; 136.9; 156.9; 166.1; 168.1. IR (NaCl, cm^{-1}): $\nu_{C=0} = 1752; \nu_{C=C} = 1681; \nu_{max} = 2932, 1651, 1406,$ 1233, 1194, 752, 736, 699. MS (70 eV): m/z (%) 471 (M⁺ + 1, 100). Anal. Calcd. for C₂₉H₃₀N₂O₄: C 74.02, H 6.43, N 5.95. Found C 73.83, H 6.61, N 5.68.

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References

- 1 P. W. N. M. van Leeuwen and C. Claver, *Rhodium Catalyzed Hydroformylation*, Kluwer Academic Publishers, Dordrecht, 2000; P. W. N. M. van Leeuwen, *Homogeneous Catalysis: Understanding the Art*, Kluwer Academic Publishers, Dordrecht, 2004.
- 2 For a recent review on the palladium-catalysed synthesis of fine chemicals, see: C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, 351, 3027.
- 3 For a few recent examples, see: (a) E. Cini, G. Giorgi, M. Rodriquez and M. Taddei, Synlett, 2009, 1562; (b) P. S. Bäuerlein, I. Arenas Gonzalez, J. J. M. Weemers, M. Lutz, A. L. Spek, D. Vogt and C. Müller, Chem. Commun., 2009, 4944; (c) E. Airiau, N. Girard, A. Mann, J. Salvadori and M. Taddei, Org. Lett., 2009, 11, 5314; (d) P. Dübon, A. Farwick and G. Helmchen, Synlett, 2009, 1413; (e) T. Spangenberg, B. Breit and A. Mann, Org. Lett., 2009, 11, 261.
- 4 (a) Chemistry and Biology of β-Lactam Antibiotics, ed. R. B. Morin and M. Gorman, Academic Press, New York, 1982, vol. 1–3;

(b) G. I. Georg and V. T. Ravikumar, in *The Organic Chemistry of* β -*Lactams*, ed. G. I. Georg, VCH, New York, 1993, ch. 6, p. 295; (c) C. Palomo, J. M. Aizpurua, I. Ganboa and M. Oiarbide, *Eur. J. Org. Chem.*, 1999, 3223; (d) C. Palomo, J. M. Aizpurua, I. Ganboa and M. Oiarbide, *Curr. Med. Chem.*, 2004, **11**, 1837; (e) N. De Kimpe, in *Comprehensive Heterocyclic Chemistry II*, ed. A. Padwa, Elsevier, Oxford, 1996, vol. 1B, p. 507; (f) G. S. Singh, M. D'hooghe and N. De Kimpe, in *Comprehensive Heterocyclic Chemistry III*, ed. A. Katritzky, C. Ramsden, E. Scriven and R. Taylor, Elsevier, Oxford, 2008, vol. 2, p. 1.

- 5 I. Ojima and F. Delaloge, Chem. Soc. Rev., 1997, 26, 377.
- 6 (a) I. Ojima, Acc. Chem. Res., 1995, 28, 383; (b) J. F. Fisher, S. O. Meroueh and S. Mobashery, Chem. Rev., 2005, 105, 395; (c) B. Alcaide and P. Almendros, Synlett, 2002, 381; (d) G. S. Singh, Tetrahedron, 2003, 59, 7631; (e) B. Alcaide, P. Almendros and C. Aragoncillo, Chem. Rev., 2007, 107, 4437; (f) N. Fu and T. T. Tidwell, Tetrahedron, 2008, 64, 10465; (g) M. T. Aranda, P. Perez-Faginas and R. Gonzalez-Muniz, Curr. Org. Synth., 2009, 6, 325; (h) A. R. A. S. Deshmukh, B. M. Bhawal, D. Krishnaswamy, V. V. Govande, B. A. Shinkre and A. Jayanthi, Curr. Med. Chem., 2004, 11, 1889; (i) I. Ojima and F. Delaloge, Chem. Soc. Rev., 1997, 26, 377; (j) S. France, A. Weatherwax, A. E. Taggi and T. Lectka, Acc. Chem. Res., 2004, 37, 592.
- 7 L. M. Nogle and W. H. Gerwick, Org. Lett., 2002, 4, 1095.
- 8 B. Kunze, R. Jansen, F. Sasse, G. Hofle and H. Reichenbach, J. Antibiot., 1998, 51, 1075.
- 9 T. C. McKee, D. L. Galinis, L. K. Pannell, J. H. II Cardellina, J. Laasko, C. M. Ireland, L. Murray, R. J. Capon and M. R. Boyd, J. Org. Chem., 1998, 63, 7805.

- 10 (a) K. Nozaki, W. Li, T. Horiuch, H. Takaya, T. Saito, A. Yoshida, K. Matsumura, Y. Kato, T. Imai, T. Miura and H. Kumobayashi, J. Org. Chem., 1996, 61, 7658; (b) H. S. Park, E. Alberico and H. Alper, J. Am. Chem. Soc., 1999, 121, 11697; (c) E. Cesarotti and I. Rimoldi, Tetrahedron: Asymmetry, 2004, 15, 3841.
- (a) P. Sulmon, N. De Kimpe, R. Verhé, L. De Buyck and N. Schamp, Synthesis, 1986, 192; (b) P. Sulmon, N. De Kimpe, N. Schamp, B. Tinant and J.-P. Declercq, *Tetrahedron*, 1988, 44, 3653.
- (a) M. D'hooghe, S. Dekeukeleire and N. De Kimpe, Org. Biomol. Chem., 2008, 6, 1190; (b) M. D'hooghe, S. Dekeukeleire, K. Mollet, C. Lategan, P. J. Smith, K. Chibale and N. De Kimpe, J. Med. Chem., 2009, 52, 4058.
- 13 (a) G. I. Georg and V. T. Ravikumar, in *The Organic Chemistry of* β-*Lactams*, ed. G. I. Georg, Verlag Chemie, New York, 1993, pp. 295–368 and references therein; (b) X. Huang and J. X. Xu, *Heteroat. Chem.*, 2003, 14, 564; (c) L. Jiao, Y. Liang and J. Xu, *J. Am. Chem. Soc.*, 2006, 128, 6060.
- 14 (a) K. D. Barrow and T. M. Spotswood, *Tetrahedron Lett.*, 1965, 6, 3325; (b) J. Decazes, J. L. Luche and H. B. Kagan, *Tetrahedron Lett.*, 1970, 11, 3365.
- 15 S. Dekeukeleire, M. D'hooghe and N. De Kimpe, J. Org. Chem., 2009, 74, 1644.
- 16 P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek and P. Dierkes, *Chem. Rev.*, 2000, **100**, 2741.
- 17 (a) A. I. M. Keulemans, A. Kwantes and T. van Bavel, *Recl. Trav. Chim. Pays-Bas*, 1948, **67**, 298; (b) M. L. Clarke and G. J. Roff, *Chem.-Eur. J.*, 2006, **12**, 7978; (c) M. L. Clarke and G. J. Roff, *Green Chem.*, 2007, **9**, 792.
- 18 M. D'hooghe, Y. Dejaegher and N. De Kimpe, *Tetrahedron*, 2008, 64, 4575.