Enantiospecific Formation of 3,6-Dihydro-1*H*-pyridin-2-ones: Low-Pressure Palladium-Catalysed Decarboxylative Carbonylation of 3-Tosyl-5-vinyloxazolidin-2-ones

Julian G. Knight,*[a] Iain M. Lawson,[a] Christopher N. Johnson[b]

[a] School of Natural Sciences, Chemistry, Bedson Building, University of Newcastle-Upon-Tyne, Newcastle-Upon-Tyne, NE1 7RU, UK
Fax +44(191)2227068; E-mail: J.G.Knight@ncl.ac.uk

[b] GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, UK

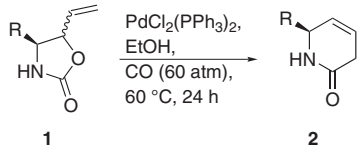
Received 16 September 2005

This paper is dedicated to Professor Steven Ley on the occasion of his 60th birthday.

Abstract: Palladium-catalysed decarboxylative carbonylation of 3-tosyl-5-vinyloxazolidin-2-ones **5** occurs at atmospheric pressure to give 1-tosyl-3,6-dihydro-1*H*-pyridin-2-ones **6**. The reaction proceeds with no loss of enantiopurity and detosylation with sodium naphthalenide gives the title compounds in good yields.

Key words: carbonylation, catalysis, palladium, cyclisation, lactams

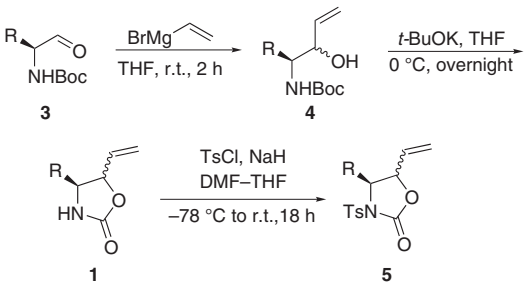
The use of transition metal mediated carbonylation reactions has been shown to be a useful method for the formation of a variety of functionalised heterocyclic compounds.[1] We have shown that 5-vinyloxazolidin-2-ones **1** undergo a stereospecific, palladium-catalysed decarboxylative carbonylation to give 3,6-dihydro-1*H*-pyridin-2-ones **2**[2] (Scheme 1). Lactams such as **2** have been shown to be useful intermediates in the synthesis of polyhydroxylated piperidines,[3] pumiliotoxins[4] and (*Z*)-ethylenic pseudodipeptides.[5] Reduction of the necessary carbon monoxide pressure from 60 atmospheres (Scheme 1) would increase the synthetic utility of this carbonylation reaction.



Scheme 1 High-pressure carbonylation of 5-vinyloxazolidin-2-ones.

Placing a strongly electron withdrawing group on the nitrogen of the oxazolidinone was expected to activate it towards decarboxylation which might facilitate the carbonylation reaction. We recently reported the palladium-catalysed cycloaddition of 3-tosyl-5,5-divinyloxazolidin-2-ones to electron deficient alkenes, which involves decarboxylation under mild conditions.[6] Since we have already shown[2a] that a *N*-Boc-5-vinyloxazolidin-2-one derivative does not undergo carbonylation to give a lactam, we turned our attention to carbonylation of the corresponding *N*-tosyl derivative.

Ibuka has reported that 3-tosyl-5-vinyloxazolidin-2-ones undergo palladium-catalysed decarboxylation to give *cis*-*N*-tosyl-2-vinylaziridines.[7] In addition, Tanner has shown that the palladium-catalysed carbonylation of *N*-tosyl-2-vinylaziridines occurs under one atmosphere of carbon monoxide to give β-lactams.[8] Considering these reports, it was envisaged that a low-pressure palladium-catalysed decarboxylative carbonylation of *N*-tosyl-5-vinyloxazolidin-2-ones might result in the formation of β-lactams via in situ formation of the corresponding aziridines. In this article, we report that the palladium-catalysed decarboxylative carbonylation of amino acid derived *N*-tosyl-5-vinyloxazolidin-2-ones does indeed proceed under one atmosphere of carbon monoxide but gives *N*-tosyl-3,6-dihydro-1*H*-pyridin-2-ones and not the expected β-lactams.



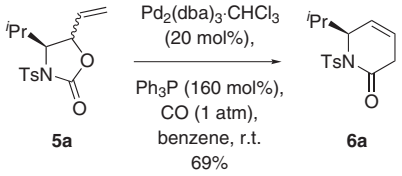
Scheme 2 Synthesis of 3-tosyl-5-vinyloxazolidin-2-ones.

5-Vinyloxazolidin-2-ones **1a–d** were prepared in two steps, as previously reported,[2a,3] from the corresponding α-amino aldehydes **3** (Scheme 2) which, in turn, were prepared either by Swern oxidation of *N*-Boc α-amino alcohols **3a–c** (R = *i*-Pr, Bn, Ph) or by DIBAL-H reduction of *N*-Boc α-amino methyl ester **3d** (R = $CH_2OTBDMS$). Addition of vinyl magnesium bromide to the aldehydes gave allylic alcohols **4** which were cyclised by treatment with potassium *tert*-butoxide to give oxazolidinones **1**. N-Tosylation by reaction with sodium hydride and *p*-toluenesulfonyl chloride gave 3-tosyl-5-vinyloxazolidin-2-ones **5** in good yields. N-Tosylation of **1d** (R = $CH_2OTBDMS$) was accompanied by removal of the

SYNTHESIS 2006, No. 2, pp 0227–0230
Advanced online publication: 21.12.2005
DOI: 10.1055/s-2005-924765; Art ID: C09505SS

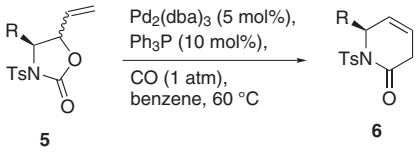
silicon-protecting group, giving *N*-tosyl vinyl oxazolidinone **5e** (R = CH_2OH). Reprotection of the alkoxy group, to give **5d**, was achieved by reaction with TBDMSCl and imidazole in DMF.

Attempted carbonylation of 3-tosyl-5-vinyloxazolidin-2-one **5a** (R = *i*-Pr) using the conditions reported for the carbonylative ring expansion of *N*-tosyl vinylaziridines[8] [$Pd_2(dba)_3{\cdot}CHCl_3$ (20 mol%), PPh_3 (160 mol%), CO (1 atm), benzene, r.t.] gave δ-lactam **6a** in 69% yield (Scheme 3), with no β-lactam evident.[9] Aggarwal reported a single example of the unexpected carbonylation of an *N*-sulfonyl-2-(β-trimethylsilylvinyl)aziridine to give a pyridin-2-one, but ascribed this result to the directing effect of the silyl group.[10]



Scheme 3 Carbonylation of 3-tosyl-5-vinyloxazolidin-2-ones.

Despite the absence of the β-lactam, formation of the δ-lactam **6a** under an initial pressure of one atmosphere of carbon monoxide was encouraging. Use of such a high palladium loading (40 mol%) makes the process very costly, and the high phosphine loading (160 mol%) hinders purification of the product. In our recent investigation of the decarboxylative cycloaddition of *N*-tosyl-5,5-divinyloxazolidin-2-ones,[6] we found that $Pd_2(dba)_3$ (5 mol%) could be used successfully with a phosphine/Pd ratio of 1:1 (i.e. 10 mol% of PPh_3). We were pleased to find that carbonylation of *N*-tosyl-5-vinyloxazolidin-2-ones **5a**–**d**, under these conditions, in benzene at 60 °C, gave δ-lactams **6a**–**d** in good yields (Scheme 4, Table 1, entries 1–4). Attempted carbonylation of **5e**, bearing a free hydroxyl group, was unsuccessful (Table 1, entry 5).



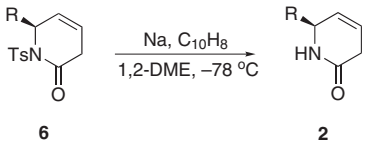
Scheme 4 Atmospheric pressure carbonylation of 3-tosyl-5-vinyloxazolidin-2-ones.

Holmes has reported the detosylation of *N*-tosyl ε-lactams in good yield using sodium naphthalenide.[11] This method was therefore applied to the detosylation of δ-lactams **6a**–**d**. A solution of sodium naphthalenide in DME was added to each *N*-tosyl δ-lactam **6a**–**d**, producing detosylated δ-lactams **2a**–**d** in good yield (75–87%, Scheme 5 and Table 2).

Table 1 Palladium-Catalysed Decarboxylative Carbonylation of 3-Tosyl-5-vinyloxazolidin-2-ones[a]

Entry	Oxazolidinone	R	Yield of lactam **6** (%)[b]
1	**5a**	*i*-Pr	74
2	**5b**	Bn	75
3	**5c**	Ph	77
4	**5d**	$CH_2OTBDMS$	71
5	**5e**	CH_2OH	0[c]

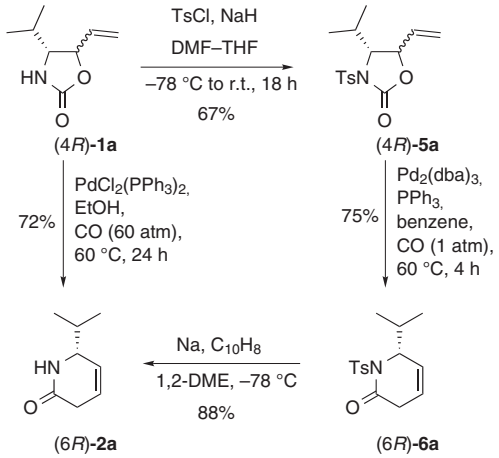
[a] Conditions: $Pd_2(dba)_3$ (5 mol%), PPh_3 (10 mol%), CO (1 atm), benzene, 60 °C, 4 h.
[b] Isolated yield.
[c] No starting material was observed in the NMR spectrum of the crude.



Scheme 5 Detosylation of *N*-tosyl-3,6-dihydropyridin-2-ones.

Table 2 Detosylation of *N*-Tosyl-3,6-dihydropyridin-2-ones **6**

Lactam **6**	R	Yield of **2** (%)
6a	*i*-Pr	84
6b	Bn	87
6c	Ph	75
6d	$CH_2OTBDMS$	81



Scheme 6 Formation of *ent*-**2a** by both low- and high-pressure carbonylation routes.

The high-pressure carbonylation of 5-vinyloxazolidin-2-ones **1** to give δ-lactams **2** (Scheme 1) has been shown to occur without loss of enantiomeric purity.[2a] In order to demonstrate that this was also true in the *N*-tosyl series, oxazolidinone (4*R*)-**1a** was synthesised from D-valine.

High pressure carbonylation [$PdCl_2(PPh_3)_2$, CO (60 atm), EtOH, 60 °C, 24 h] of (4*R*)-**1a** gave the corresponding lactam (6*R*)-**2a** in good yield (72%). N-Tosylation of (4*R*)-**1a**, followed by low-pressure carbonylation, and subsequent detosylation using sodium naphthalenide also gave *N*-H lactam (6*R*)-**2a** (44% over three steps) (Scheme 6).

Analysis of (6*R*)-**2a**, formed both by the high- and low-pressure carbonylation routes, by chiral gas chromatography[12] and comparison with (6*S*)-**2a**, showed that each lactam was formed as a single enantiomer.

In conclusion, we have demonstrated that palladium-catalysed decarboxylative carbonylation of *N*-tosyl-5-vinyloxazolidin-2-ones **5** occurs under atmospheric pressure of carbon monoxide to give the corresponding *N*-tosyl-3,6-dihydropiperidin-2-ones **6** which may be detosylated under mild conditions. The carbonylation/detosylation sequence occurs without loss of enantiomeric purity.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Brüker WM 300 and JEOL LA 500 machines at ambient temperature. GC was performed on a Packard 427GC using a β-dextrin 120 column (20 m × 0.25 mm) and recorded on a Hitachi D2500 chromato integrator. IR spectra were obtained on an ATI Mattson Genesis REV I FTIR spectrometer. MS were recorded on a Micromass autospec M and Kratos MS80 RF spectrometers. Elemental analyses were performed on a Carlo Erba 1106 instrument. Petroleum ether (PE) used had a bp range 40–60 °**C**.

N-Tosyl-5-vinyloxazolidin-2-ones 5; General Procedure

To a stirred suspension of NaH (2 equiv) in a mixture of THF (1 mL·mmol^{-1} oxazolidinone) and DMF (2.5 mL·mmol^{-1} oxazolidinone) at 0 °C were added successively 5-vinyloxazolidin-2-one **1** (1 equiv) in THF (0.5 mL·mmol^{-1} oxazolidinone) and *p*-TsCl (1.3 equiv). Stirring was continued for 18 h at r.t., then the reaction was quenched by the addition of a sat. solution of NH_4Cl (1 mL·mmol^{-1} oxazolidinone) at –78 °C with vigorous stirring. The mixture was extracted with Et_2O (2 × 30 mL), and the extract was washed successively with HCl (2 M, 30 mL), $NaHCO_3$ (30 mL), H_2O (30 mL), dried ($MgSO_4$) and the solvents removed under reduced pressure. Purification by column chromatography on silica gel (PE–EtOAc, 10:1) afforded the *N*-tosyl-protected oxazolidinone **5**.

(4*S*,5*RS*)-4-Isopropyl-3-[(4-methylbenzene)sulfonyl]-5-vinyloxazolidin-2-one (5a)

(4*S*,5*RS*)-4-Isopropyl-5-vinyloxazolidin-2-one (**1a**; 2.408 g, 16 mmol) gave *N*-tosyl vinyl oxazolidinone **5a** as white needles (4.144 g, 86%, 1.5:1 ratio of diastereoisomers).

IR (film): 2965, 1773, 1646, 1595, 1370 cm^{-1}.

Major Diastereoisomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.4 Hz, 2 H, $MeC_6H_4SO_2$), 7.27 (d, *J* = 8.4 Hz, 2 H, $MeC_6H_4SO_2$), 5.60–5.71 (ddd, *J* = 5.8, 10.4, 16.6 Hz, 1 H, *H*C=CH_2), 5.14–5.23 (m, 2 H, HC=CH_2), 4.58–4.61 (m, 1 H, CHN), 4.01–4.03 (m, 1 H, CHO), 2.47 [s, 4 H, CH_3ArSO$_2$, $(CH_3)_2$C*H*], 0.90 (d, *J* = 6.9 Hz, 3 H, $(CH_3)_2$CH), 0.76 [d, *J* = 6.9 Hz, 3 H, $(CH_3)_2$CH].

Minor Diastereoisomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 2 H, $MeC_6H_4SO_2$), 7.27 (d, *J* = 8.4 Hz, 2 H, $MeC_6H_4SO_2$), 5.81–5.92 (m, 1 H, *H*C=CH_2), 5.34–5.46 (m, 2 H, HC=CH_2), 4.91–4.96 (m, 1 H, CHN), 4.37–4.40 (m, 1 H, CHO), 2.47 (s, 3 H, CH_3ArSO$_2$), 2.11 [m, 1 H, $(CH_3)_2$C*H*], 0.90 (d, *J* = 6.9 Hz, 3 H, $(CH_3)_2$CH), 0.76 [d, *J* = 6.9 Hz, 3 H, $(CH_3)_2$CH].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4, 152.1, 145.7, 145.6, 136.3, 135.8, 134.8, 129.9, 129.4, 129.3, 128.9, 128.8, 121.5, 118.4, 81.4, 75.5, 67.6, 66.6, 31.1, 30.1, 21.8, 19.5, 19.3, 17.9, 17.5, 15.2

MS: *m*/*z* (%) = 310 (M^+ + H, 0.1), 226 (19), 202 (22), 155 (100), 91 (70), 65 (13).

HRMS: *m*/*z* calcd for $C_{15}H_{19}NO_4S$: 309.103480; found: 309.103480.

(4*S*,5*RS*)-4-(*tert*-Butyldimethylsilanyloxymethyl)-3-[(4-methylbenzene)sulfonyl]-5-vinyloxazolidin-2-one (5d)

TBDMSCl (92 mg, 1.35 mmol) was added at 0 °C to a stirred solution of (4*S*,5*RS*)-4-hydroxymethyl-3-[(4-methylbenzene)sulfonyl]-5-vinyloxazolidin-2-one (**5e**; 200 mg, 0.67 mmol) in DMF (1 mL). Imidazole (112 mg, 0.74 mmol) was then added to the solution and the reaction was stirred at r.t. for 6 h. The mixture was then poured into PE–EtOAc (1:1, 500 mL) and washed with H_2O (3 × 100 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. Purification of the crude product by column chromatography on silica gel (PE–EtOAc, 10:1) afforded *O*-TBDMS, *N*-tosyl-protected vinyl oxazolidinone **5d** as a cream coloured solid (254 mg, 92%, 2:1 ratio of diastereoisomers).

IR (film): 2956, 1786, 1647, 1597, 1371, 1046 cm^{-1}.

Major Diasteroisomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (m, 2 H, $MeC_6H_4SO_2$), 7.27 (d, *J* = 8 Hz, 2 H, $MeC_6H_4SO_2$), 5.64 (ddd, *J* = 6.5, 10.5, 17 Hz, 1 H, *H*C=CH_2), 5.16–5.41 (m, 2 H, HC=CH_2), 4.88 (m, 1 H, CHN), 4.02 (m, 1 H, CHO), 3.72 (m, 2 H, CH_2OSi), 2.37 (s, 3 H, CH_3ArSO$_2$), 0.94 [s, 9 H, $(CH_3C)_3$Si], –0.04 [s, 6 H, $(CH_3)_2$Si].

Minor Diastereoisomer

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (m, 2 H, $MeC_6H_4SO_2$), 7.27 (d, *J* = 8 Hz, 2 H, $MeC_6H_4SO_2$), 5.95–6.05 (m, 1 H, *H*C=CH_2), 5.16–5.41 (m, 2 H, HC=CH_2), 4.92 (m, 1 H, CHN), 4.02 (m, 3 H, CH_2OSi, C*H*O), 2.37 (s, 3 H, CH_3ArSO$_2$), 0.94 [s, 9 H, $(CH_3C)_3$Si], –0.04 [s, 6 H, $(CH_3)_2$Si].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2, 145.9, 145.7, 136.0, 135.4, 133.9, 130.4, 130.3, 128.7, 128.6, 123.0, 119.1, 79.9, 71.8, 63.5, 63.0, 62.0, 60.4, 26.0, 25.8, 22.0, 21.4, 18.3, 18.0.

MS: *m*/*z* (%) = 411 (M^+, 0.3), 396 (1.7), 354 (100), 280 (27), 229 (65), 149 (46), 91 (83), 73 (49), 43 (48).

HRMS: *m*/*z* calcd for $C_{19}H_{29}NO_5SSi$: 411.152611; found: 411.153574.

N-Tosyl-3,6-dihydropyridin-2-ones 6; General Procedure

A solution of *N*-tosyl-5-vinyloxazolidin-2-one **5** in benzene (9 mL·mmol^{-1} oxazolidinone) was placed in a glass flask fitted with a Young's tap under a N_2 atmosphere. $Pd_2(dba)_3$ (5 mol%) and PPh_3 (10 mol%) were weighed into a glass sample vial and dissolved in benzene (1 mL·mmol^{-1} oxazolidinone). The catalyst solution was injected into the flask and the flask was flushed with CO, sealed and the reaction was heated at 60 °C and stirred for 4 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed under reduced pressure. Lactam **6** was purified by flash column chromatography on silica (CH_2Cl_2).

(6*S*)-3,6-Dihydro-6-isopropyl-1-[(4-methylbenzene)sulfonyl]pyridin-2-one (6a)

(4*S*,5*RS*)-4-Isopropyl-3-[(4-methylbenzene)sulfonyl]-5-vinyloxazolidin-2-one (**5a**; 200 mg, 0.646 mmol) afforded lactam **6a** as a white solid (140 mg, 74%).

Mp 112–114 °C; $[a]_D^{21}$ +138.1 (*c* 1.5, $CHCl_3$).

IR (KBr): 2964, 1695, 1596, 1350 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.4 Hz, 2 H, $MeC_6H_4SO_2$), 7.21 (d, *J* = 8.4 Hz, 2 H, $MeC_6H_4SO_2$), 5.83 (ddd, *J* = 3.1, 5.5, 10.1 Hz, 1 H, *H*C=CHCH$_2$), 5.77 (ddd, *J* = 2.1, 4.6, 10.1 Hz, 1 H, HC=C*H*CH$_2$), 4.68 (m, 1 H, CHN), 2.94 (ddt, *J* = 22.3, 2.1, 3.1 Hz, 1 H, C*H*HC=O), 2.83 (ddd, *J* = 22.3, 4.6, 1.5 Hz, 1 H, CH*H*C=O), 2.45 [d sept, *J* = 4.6, 6.9 Hz, 1 H, $(CH_3)_2CH$], 2.34 (s, 3 H, CH_3ArSO_2), 0.97 [d, *J* = 7 Hz, 3 H, $(CH_3)_2CH$], 0.75 [d, *J* = 6.7 Hz, 3 H, $(CH_3)_2CH$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 144.6, 136.5, 129.1, 129.0, 123.4, 123.1, 63.2, 35.0, 34.6, 21.6, 19.1, 15.1.

MS: *m*/*z* (%) = 293 (M^+, 0.2), 250 (72), 186 (51), 156 (6), 91 (100), 65 (21), 41 (15).

HRMS: *m*/*z* calcd for $C_{15}H_{19}NO_3S$: 293.108565; found: 293.109802.

Detosylation of Lactams 6; General Procedure

Naphthalene (394 mg, 3.07 mmol) and freshly cut Na (79 mg, 3.44 mmol) were suspended in DME (10 mL) and the mixture was sonicated until the solution began to turn dark green. The mixture was then removed from the sonicator, cooled to 0 °C and stirred for a further 2 h.

A stirred solution of *N*-tosyl-3,6-dihydropyridin-2-one **6** in DME (1 mL) was cooled to –65 °C and the previously prepared sodium naphthelenide solution was added dropwise until the solution remained dark green. The mixture was stirred at –65 °C for a further 30 min and then quenched by the slow addition of a sat. solution of NH_4Cl. The reaction was allowed to warm to r.t. over 30 min and was then poured into H_2O (20 mL). The mixture was then extracted with CH_2Cl_2 (4 × 20 mL), the combined organic layers were dried ($MgSO_4$) and the solvents were removed under reduced pressure. Purification by flash column chromatography on silica (PE–EtOAc, 1:1) gave δ-lactam **2**.

(6*S*)-3,6-Dihydro-6-isopropyl-1*H*-pyridin-2-one (2a)[2a]

(6*S*)-3,6-Dihydro-6-isopropyl-1-[(4-methylbenzene)sulfonyl]pyridin-2-one (**6a**; 35 mg, 0.12 mmol) afforded δ-lactam **2a** as a white solid (14 mg, 84%).

^1H NMR (300 MHz, $CDCl_3$): δ = 6.40 (br s, 1 H, NH), 5.78–5.72 (m, 1 H, C*H*=CH), 5.61–5.56 (m, 1 H, CH=C*H*), 2.85 (m, 2 H, CH_2CO), 3.87 (br s, 1 H, CHN), 1.76 [d sept, *J* = 4.0, 6.7 Hz, 1 H, $(CH_3)_2CH$], 0.87 [d, *J* = 6.7 Hz, 3 H, $(CH_3)_2CH$], 0.84 [d, *J* = 6.6 Hz, 3 H, $(CH_3)_2CH$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 123.9, 123.2, 59.7, 34.2, 31.9, 17.9, 17.3.

Acknowledgment

We thank the EPSRC and GlaxoSmithKline for funding.

References

(1) (a) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem. Int. Ed.* **2002**, *41*, 2781. (b) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414. (c) Ley, S. V.; Cox, L. R.; Meek, G. *Chem. Rev.* **1996**, *96*, 423.

(2) (a) Knight, J. G.; Ainge, S. W.; Harm, A. M.; Harwood, S. J.; Maughan, H. I.; Armour, D. R.; Hollinshead, D. M.; Jaxa-Chamiec, A. A. *J. Am. Chem. Soc.* **2000**, *122*, 2944. (b) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 6659.

(3) Knight, J. G.; Tchabanenko, K. *Tetrahedron* **2003**, *59*, 281.

(4) O'Mahoney, G.; Nieuwenhuyzen, M.; Armstrong, P.; Stevenson, P. J. *J. Org. Chem.* **2004**, *69*, 3968.

(5) (a) Garro-Hélion, F.; Guibé, F. *J. Chem. Soc., Chem. Commun.* **1996**, 641. (b) Sauriat-Dorizon, H.; Guibé, F. *Tetrahedron Lett.* **1998**, *39*, 6711. (c) Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Tetrahedron* **2002**, *58*, 7275.

(6) Knight, J. G.; Tchabanenko, K.; Stoker, P. A.; Harwood, S. J. *Tetrahedron Lett.* **2005**, *46*, 6261.

(7) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **1997**, *62*, 999.

(8) Tanner, D.; Somfai, P. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2415.

(9) The ^1H NMR spectrum of the crude product mixture showed no evidence of β-lactam formation (in particular, no signals in the range 3.5–4 ppm for the azetidinone 3- and 4-protons); see also ref. 8.

(10) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 1433.

(11) Evans, P. A.; Holmes, A. B.; Russell, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3397.

(12) Gas chromatography analysis [138 °C, β-dextrin 120 column (20 m × 0.25 mm)] of (6*R*)-3,6-dihydro-6-isopropyl-1*H*-pyridin-2-one (6*R*)-**2a**, formed by the direct carbonylation of (4*R*)-**1a**, showed a single peak (t_R 36.963 min). Likewise, analysis of (6*R*)-**2a** formed by deprotection of the *N*-tosylpiperidinone (4*R*)-**6a** also showed only one peak (t_R 36.703 min), as did the analysis of the (*S*)-*N*-H lactam (6*S*)-**2a** (t_R 37.856 min). Analysis of a 1:4 mixture of the enantiomers, (6*R*)-**2a**/(6*S*)-**2a** showed two peaks in a 1:4 ratio (37.747 min; 38.590 min).