Arenetricarbonylchromium Complexes as Chiral Auxiliaries: Asymmetric Synthesis of β-Lactams

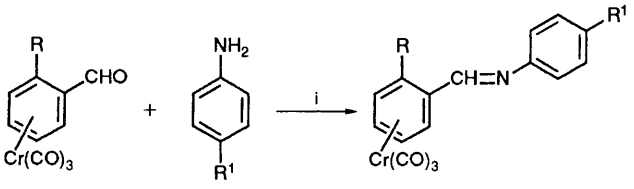
Clara Baldoli and Paola Del Buttero*

Dipartimento di Chimica Organica e Industriale dell'Università, Centro CNR, Via Venezian 21, 20133 Milano, Italy

A new enantioselective synthesis of β-lactams *via* condensation of optically pure *ortho*-substituted benzylideneaminetricarbonylchromium complexes with ester-enolates is reported; the enantiomeric excess is higher than 98%.

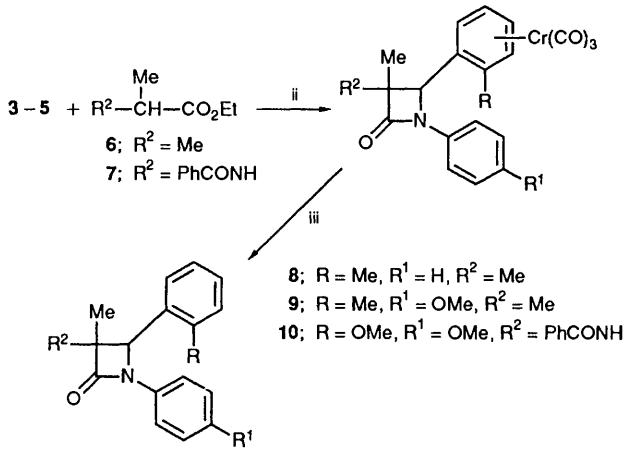
Monocyclic β-lactam antibiotics were first described in the mid-seventies, but initially they were treated as curiosities particularly because of their moderate antibacterial activity. Only after the discovery of monobactams by the teams of Takeda[1] and Squibb[2] in 1981 did a new increasing interest develop concerning the total synthesis of these compounds.

In recent years different methods have been reported for preparing novel more active derivatives or developing a more convenient synthesis for known ones. In addition, an important goal is the control of the relative and absolute stereochemistry of the two contiguous centres in the azetidinone ring. Although several kinds of organometallic reagents have been



1; R = Me, R^1 = H, OMe
2; R = OMe

3; R = Me, R^1 = H
4; R = Me, R^1 = OMe
5; R = OMe, R^1 = OMe

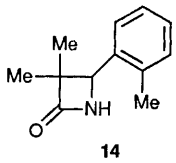


6; R^2 = Me
7; R^2 = PhCONH

8; R = Me, R^1 = H, R^2 = Me
9; R = Me, R^1 = OMe, R^2 = Me
10; R = OMe, R^1 = OMe, R^2 = PhCONH

11; R = Me, R^1 = H, R^2 = Me
12; R = Me, R^1 = OMe, R^2 = Me
13, R = OMe, R^1 = OMe, R^2 = PhCONH

Scheme 1 *Reagents and conditions*: i, Et_2O–EtOH, room temp.; ii, LDA, THF, −78 °C for 4–5 h, 25 °C for 8 h; iii, CH_2Cl_2 solution exposure to sunlight or mercury lamp



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widely used in the synthesis of monocyclic β-lactams,[3] the arenetricarbonylchromium complexes represent a new approach to this class of compounds.

In previous work we and other authors have reported the synthesis of some optically pure *ortho* and *meta* substituted benzaldehyde tricarbonylchromium complexes through the separation of their diastereoisomeric derivatives[4] or by kinetic resolution with baker's yeast,[5] as well as some useful applications in enantioselective syntheses.[6] In this paper we report the preliminary results on the use of chiral tricarbonylchromium complexed benzylideneamines in the stereoselective synthesis of azetidinones *via* imine–ester enolate condensation. Thus, condensation of (−)-(*R*)-*ortho*-methoxy-**1** or -*ortho*-methyl-**2**-benzaldehydetricarbonylchromium with an equivalent amount of aniline or 4-methoxyaniline in ethanol–diethyl ether solution (1 : 1) at room temperature produces in nearly quantitative yield (93–97%) the corresponding optically pure *trans* imines **3–5** (Scheme 1).†

Reaction of imines **3–5** with lithium enolates generated *in situ* from the corresponding ethyl isobutyrate **6** or from the ethyl ester of *N*-benzoyl alanine **7** in tetrahydrofuran (THF) solution at −78 °C with lithium diisopropylamide (LDA), provides after a standard work-up the target compounds **8–10**‡ in good yields (64–77%).

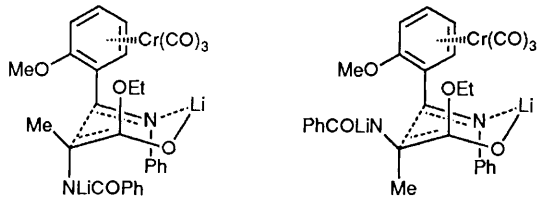

Fig. 1

Exposure of the solutions of complexes **8–10** in CH_2Cl_2 for 2–3 h to sunlight affords the uncomplexed β-lactams **11–13**§ in quantitative yield. Enantiomeric excesses, determined by ^1H NMR with (+)-Eu(hfc)$_3$ [tris(heptafluoropropyl-hydroxymethylene)-(−)-camphoratoeuropium(III)] are in all cases greater than 98%. In the case of **9**, treatment with an excess (5 equiv.) of cerium(IV) ammonium nitrate in water–acetonitrile solution directly affords the uncomplexed *N*-unsubstituted β-lactam derivative **14** ([α]$_D$ +159°, *c* 1.1 $CHCl_3$, yield 97%).

Product **10** derived from the ethyl ester of the *N*-benzoyl alanine **7** was obtained as a diastereoisomeric mixture in a 1 : 1 ratio. The *cis–trans* isomers **10** were separated by column chromatography on silica gel; each isomer afforded, after decomplexation, the corresponding β-lactam **13**.¶ To rationalize the low stereochemical control[7,8] we repeated the reaction, under identical experimental conditions, starting from the uncomplexed *N*-(2-methoxybenzylidene)-4-methoxyaniline. No appreciable difference in the *cis* : *trans* ratio (35 : 65) was found; the isomers were defined by NMR analysis.[8]

Based on these findings, we think that the Cr(CO)$_3$ group, which is probably *exo* in the Zimmermann-Traxler transition state (Fig. 1), only partially affects the stereoselectivity, whereas the *ortho* substituent on the complexed ring produces an unexpected competition between two transition states. In fact, in the presence of the OME substituent on the arene ring, the methyl group of the benzoylalaninate results in steric hindrance nearly comparable to the NHCOPh group, and this could determine the loss of discrimination of the imine towards the enol configuration.[7]

To validate this hypothesis we are currently testing imines with different *ortho* and *meta* substituents. In fact, some

† All the new compounds were characterized by elemental analysis, IR and ^1H NMR spectroscopy: (*R*)-(−)-**4**, [α]$_D$ −413° (c, 0.3, $CHCl_3$), m.p. 97 °C (from diisopropyl ether); (*R*)-(−)-**3**, [α]$_D$ −383°, m.p. 113 °C (from diisopropyl ether); (*R*)-(−)-**5**, [α]$_D$ −280°, m.p. 138 °C (from diisopropyl ether).

‡ Analytical and spectroscopic data of all products are in agreement with proposed structures. Compound **8**: ^1H NMR ($CDCl_3$) δ 7.6–7.1 (5H, m, arom.), 5.4–5.1 (4H, m, complexed arom.), 4.9 (1H, s), 2.2 (3H, s, Me), 1.6 (3H, s, Me), 1.0 (3H, s, Me); **9**: ^1H NMR ($CDCl_3$) δ 7.2 (4H, AB system), 5.4–5.1 (4H, m, complexed arom.), 4.9 (1H, s), 3.8 (3H, s, OMe), 2.2 (3H, s, Me), 1.6 (3H, s, Me), 1.0 (3H, s, Me); **10** *cis*: ^1H NMR ($CDCl_3$) δ 7.7–6.8 (9H, m, arom.), 6.3 (1H, s, NH), 5.7 (1H, s), 5.5–4.7 (4H, m, complexed arom.), 3.7 (3H, s, OMe), 3.6 (3H, s, OMe), 1.4 (3H, s, Me); [α]$_D$ +221° (*c* 0.3, $CHCl_3$); **10** *trans*; ^1H NMR ($CDCl_3$) δ 7.7–6.8 (9H, m, arom.), 6.1 (1H, s, NH), 5.7–4.7 (5H, m, complexed arom. +1H), 3.8 (6H, 2s, OMe), 1.8 (3H, s, Me); [α]$_D$ +157° (*c* 0.3, $CHCl_3$).

§ Compound **11**: m.p. 143 °C, ^1H NMR ($CDCl_3$) δ 7.4–7.0 (9H, m, arom.), 5.0 (1H, s), 2.4 (3H, s, Me), 1.6 (3H, s, Me), 0.8 (3H, s, Me). Compound **12**: m.p. 155 °C; ^1H NMR ($CDCl_3$) δ 7.3–6.8 (8H, m, arom.), 5.0 (1H, s), 3.8 (3H, s, OMe), 2.4 (3H, s, Me), 1.6 (3H, s, Me), 0.8 (3H, s, Me). Compound **13** *cis*: m.p. 140 °C, ^1H NMR ($CDCl_3$) δ 7.9–6.8 (13H, m, arom.), 6.4 (1H, s, NH), 5.9 (1H, s,), 3.75 (3H, s, OMe), 3.8 (3H, s, OMe), 1.4 (3H, s, Me); [α]$_D$ = +60° (*c* 1.1, $CHCl_3$). Compound **13** *trans*: m.p. 158 °C, ^1H NMR δ 7.4–6.7 (13H, m, arom.), 6.0 (1H, s, NH), 5.3 (1H, s), 3.9 (3H, s, OMe), 3.7 (3H, s, OMe), 1.9 (3H, s, Me); [α]$_D$ +93° (*c* 1.1, $CHCl_3$).

¶ Enantiomeric excess was determined separately for **13** *cis* and **13** *trans* by ^1H NMR spectroscopy on a Varian XL-300 spectrometer.

preliminary results seem to suggest that, in the absence of the *ortho* substituent on the arene ring of the complexed or uncomplexed *N*-benzylideneaniline, the diastereoselection greatly favours formation of the *trans* β-lactam. In conclusion, tricarbonylchromium complexed benzylideneamines can be considered as promising chiral synthons in β-lactam ring construction and their full synthetic potential in this field is under active investigation.

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