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Tricarbonyl(η^6arene)Chromium(0) Complexes as Chiral Auxiliaries. Homochiral β-Lactams Synthesis "via" [2+2] Cycloaddition Reaction.

Clara Baldoli, Paola Del Buttero*, Emanuela Licandro, Stefano Maiorana*, Antonio Papagni.

Dipartimento di Chimica Organica e Industriale dell'Universita'
Centro CNR - Via C. Golgi 19, I-20133 Milano, Italy.

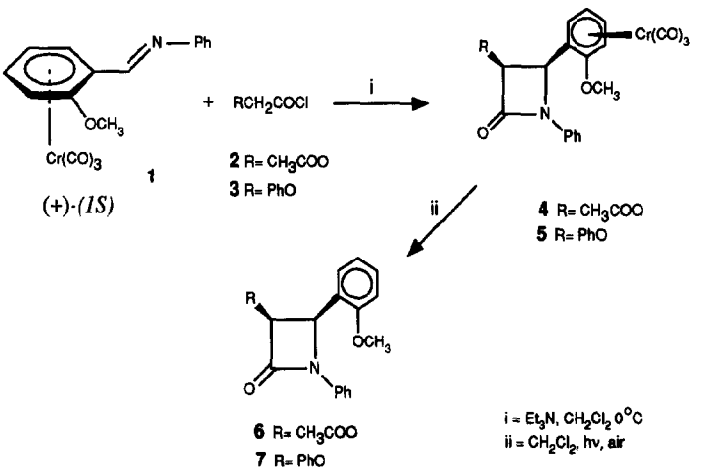
Abstract: A highly enantioselective synthesis of β-lactams "via" a [2+2] cycloaddition reaction of homochiral tricarbonyl [*N*-(2-methoxybenzylidene)aniline]chromium with ketenes is reported. Moreover the reaction of (+)-(*1S*)-tricarbonyl[4-methoxy-*N*-(2-methoxy cinnamylidene)aniline]chromium with acetoxy ketene gives the corresponding 4-styryl-β-lactam in good yield but with moderate stereoselection.

The use of tricarbonyl(η^6-arene)chromium (0) complexes in enantiomeric pure form as chiral synthons in asymmetric synthesis is well documented.[1-9] In a previous paper, we reported that the condensation of some lithium enolates of esters with optically pure tricarbonyl chromium complexes of *ortho* substituted benzaldimines affords β-lactams with nearly complete enantioselection.[10] Pursuing our research on the use of such complexes for the synthesis of compounds with potential biological activity, we were interested in achieving some other stereoselective approaches to β-lactams. The Staudinger reaction,[11] a [2+2] cycloaddition between ketenes and imines, was the first reported method for preparing racemic azetidinone rings; it has recently received renewed attention due to its stereochemical predictability and the possibility of incorporating chiral elements in either ketene or imine precursors.[12-14] We therefore thought that chiral chromium complexed arylimines could be promising synthons for stereoselective Staudinger reactions.

In this paper, we report the first example of [2+2] cycloaddition[15] between optically pure tricarbonyl chromium complexes of aryl imines with ketenes generated *"in situ"* from acid chlorides. The *(+)-(1S)*-tricarbonyl[*N*-(2-methoxybenzylidene)aniline]chromium **1** (0.3 mmol) was allowed to react with acetoxyacetyl chloride **2** (1 mmol) or phenoxy acetyl chloride **3** (1 mmol) in the presence of an excess (1.84 mmol) of freshly distilled Et_3N in dry dichloromethane (5 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. and then at room temperature for 2 h. Usual work-up of the mixture, followed by flash-cromatography, afforded compounds (-)-**4**[17] (m.p. 103 °C from diisopropyl ether, $[\alpha]_D$=-154, c=0.14 $CHCl_3$) or (-)-**5**[18] (m.p.184 °C from diisopropyl ether, $[\alpha]_D$=-191, c=0.26 $CHCl_3$,) as *cis* isomers in 92 and

98% yields respectively. Exposure of the solution of complexes **4** and **5** in CH_2Cl_2 for 4 h to air and sunlight gave the corresponding optically active β-lactams (-)-**6** (m.p. 85 °C from 2-propanol, $[\alpha]_D$=-66, c=0.4 $CHCl_3$) and (-)-**7** (m.p. 110 °C from petroleum ether $[\alpha]_D$=-74, c=0.123 $CHCl_3$) in about 95% yield. Enantiomeric excesses, determined by means of ^1H NMR using (+) $Eu(hfc)_3$, was more than 98% for both products (-)-**6** and (-)-**7** . (Scheme 1)

Scheme 1

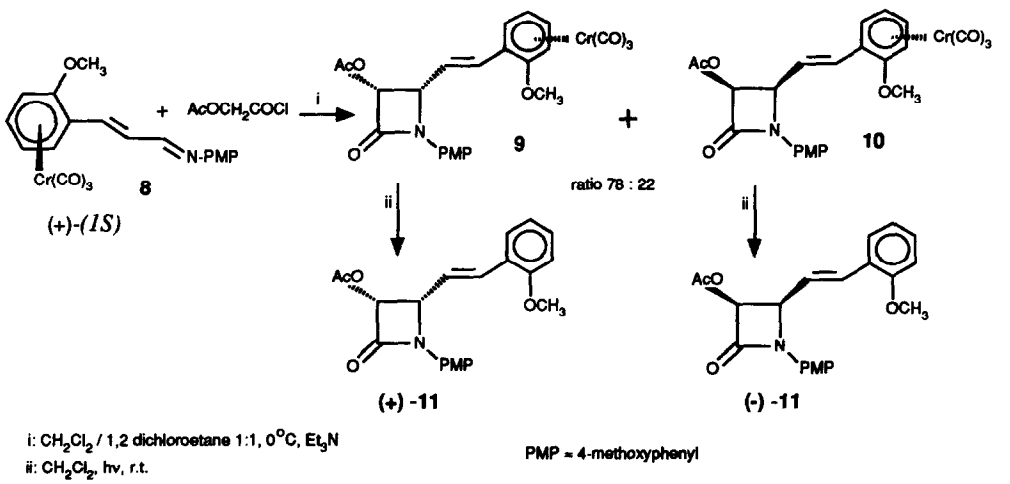


The complete *cis* diastereoselection found in this reaction is in line with what has been reported by other authors for analogous reactions.[12-14] The absolute configuration of β-lactam (-)-**6** was assigned as *(3S,4R)* after comparison of its CD spectrum[19] with that of the 3-acetoxy-1-(4-methoxyphenyl)-4-phenylazetidin-2-one of known configuration.[20] This configuration is rationalized by the attack of the ketene species on the *si*-face of the (+)-(*1S*)-imine[1] in an *anti* disposition of the imine double bond with respect to the methoxy group on the arene ring. The latter should be the preferred conformation of the imine moiety in analogy to the accepted model for complexed benzaldehydes and styrenes.[1,16]

In order to investigate the potential of this enantioselective reaction and obtain β-lactams with a more useful substituent at the 4-position of the azetidinone ring, the (+)-(*1S*)-tricarbonyl [4-methoxy-*N*-(2-methoxycinnamylidene) aniline] chromium **8**[21] was allowed to react with **2** under similar experimental conditions. The complexed 3-acetoxy-1-(4-methoxyphenyl)-4-(2-methoxystyryl)azetidin2-one was obtained in 90% yield as a diastereoisomeric 78:22 mixture of *cis* isomers **9** and **10**. (Scheme 2) No change in stereoselection was found even when the reaction was run at -20 °C although, at this temperature, a longer reaction time was needed and a small amount of uncomplexed product was obtained.

It is worth noting that a major diastereoisomer **9**[22] (70% yield, m.p. 185 °C from diisopropyl ether, $[\alpha]_D$=+524, c=0.16 $CHCl_3$) and a minor diastereoisomer **10** (17% yield, m.p. 179-80 °C from diisopropyl ether, $[\alpha]_D$=+224, c=0.43 $CDCl_3$) could be obtained by the flash-chromatographic separation (eluent: ethyl ether/ petroleum ether 1:1) of the reaction mixture. Decomplexation by means of air and sunlight of **9** and

Scheme 2



10 gave β-lactams (+)-**11** ($[\alpha]_D$=+13, c=0.2 $CHCl_3$) and (-)-**11** ($[\alpha]_D$=-15, c=0.21 $CHCl_3$) in nearly quantitative yields. The optical purity of both (+)-**11** and (-)-**11**, checked by ^1H NMR with $Eu(hfc)_3$ was greater than 98%. An absolute configuration (*3R,4S*) was assigned to (+)-**11**,[23] again as a result of correlations with a series of CD spectra.[24]

The present study shows that optically pure tricarbonyl chromium imine complexes are promising chiral synthons also in a [2+2] cycloaddition reaction for the enantioselective synthesis of *cis* azetidin-2-one. Further investigations will be directed towards analysing the behaviour of these compounds in some other types of cycloaddition reaction.

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17. Analytical data are in agreement with the proposed structure; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.7-7.3(m, 5H, arom.); 6.2(d, 1H, J=5.17 Hz); 5.67(d, 1H, J=5.17 Hz); 5.56(dd, 1H, arom.$Cr(CO)_3$, J=6.6, Hz); 5.54(d, 1H, arom.$Cr(CO)_3$, J=6.6 Hz); 4.99(d, 1H, arom.$Cr(CO)_3$, J=6.6 Hz); 4.85(dd, 1H, arom.$Cr(CO)_3$, J=6.6 Hz); 3.75(s, 3H, -OCH_3); 1.99(s, 3H, $COCH_3$).
18. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5-7.7(m, 10H, arom); 5.7(d, 1H, J= 5.0 Hz); 5.61(d, 1H, J=5.0 Hz); 5.6(d, 1H, arom.$Cr(CO)_3$, J=6.5 Hz); 5.5(dd, 1H, arom.$Cr(CO)_3$, J=6.5 Hz); 4.9(d, 1H, arom.$Cr(CO)_3$, J=6.5 Hz); 4.8(dd, 1H, arom.$Cr(CO)_3$, J=6.5 Hz); 3.6(s, 3H, -OCH_3).
19. We found the same Cotton effect in the CD curves measured on a series of (+) 4-aryl-3-acetoxy azetidin-2-ones of type **6** bearing different substituents on both phenyl rings, thus allowing correct correlation with a product of known absolute configuration[20]. The experimental details will be reported in the full paper. ^{1}H NMR of **6** ($CDCl_3$, 300 MHz) δ 6.8-7.4(m, 9H, arom.); 6.09(d, 1H, J=5.1 Hz); 5.79(d, 1H, J=5.1Hz); 3.85(s, 3H, OCH_3); 1.73(s, 3H, $COCH_3$).
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22. Analytical data are in agreement with the proposed structure: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4-6.8(m, 5H, arom.+ =CH); 6.1(dd, 1H, CH=, J=16.2 Hz, 8.3 Hz); 5.9(d, 1H, J=5.0 Hz); 5.8(d, 1H, arom.$Cr(CO)_3$, J=6.5 Hz); 5.6(dd, 1H, arom.$Cr(CO)_3$, J=6.5 Hz); 5.1(d, 1H, arom.$Cr(CO)_3$, J=6.5 Hz); 4.92(dd, 1H, arom.$Cr(CO)_3$, J=6.5 Hz); 4.89(dd, 1H, J=5.0, J=8.3 Hz); 3.8(s, 3H, -OCH_3); 3.78(s, 3H, -OCH_3); 2.2(s, 3H, $COCH_3$).
23. Borer, B. C.; Balogh, D. W. *Tetrahedron Lett.* **1991,** *32,* 1039-1040. This paper reports the absolute configuration *3S,4R* for the (-)3-hydroxy-1-(4-methoxyphenyl)-4-styryl azetidin-2-one. We have checked that the acetylation of this compound gave the corresponding (-) 3-acetoxy β-lactam (*3S,4R*). ^{1}H NMR of **11** ($CDCl_3$, 300 MHz) δ 7.43-7.22(m, 4H, arom.); 7.12(d, 1H, J=16.12 Hz); 6.96-6.82(m, 4H, arom.); 6.20(dd, 1H, J_1=8.5 Hz, J_2=16.12 Hz); 5.92(d, 1H; J=4.91 Hz); 4.93(dd, 1H, J_1=4.91 Hz, J_2=8.5 Hz); 3.85(s, 3H, OCH_3); 3.75(s, 3H, OCH_3); 2.10(s, 3H, $COCH_3$)
24. Again, we ascertained that the sign of the Cotton effect in the CD spectra of a series of 3-acetoxy-4-styryl β-lactams was independent of the substitution on the arene ring. Details of the CD correlations will be described in the full paper.

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