Synthesis of $\beta $-lactams and $\alpha $-amino Acids by Photochemical Reactions of Chromium Carbene Complexes [and Discussion]

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Synthesis of β-lactams and α-amino acids by photochemical reactions of chromium carbene complexes

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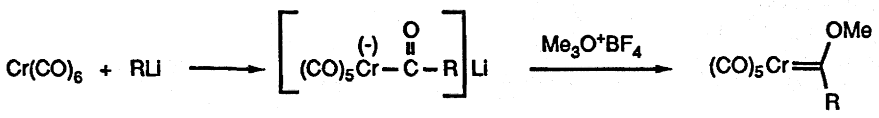
The photochemical reaction of chromium carbene complexes with imines has been developed into an efficient process for the synthesis of β-lactams. A new route to aminocarbene complexes, involving the reaction of $Na_2Cr(CO)_5$ with amides and trimethylsilyl chloride has been developed. By using this procedure, chiral, optically active aminocarbene complexes have been prepared, and their photochemical reactions with imines developed. Chiral, optically active β-lactams have been prepared with more than 90% diastereoselectivity by this procedure. Chiral, optically active aminocarbene complexes containing pendent alcohol groups have also been prepared. Photolysis of these produces aminolactones, which can be cleaved to natural and unnatural α-amino acids.

Introduction

Chromium carbene complexes, 1, have been known for 20 years, since their first intentional synthesis (Fischer & Aumann 1968) by the reaction of organolithium reagents with chromium hexacarbonyl, followed by alkylation with trimethyloxonium tetrafluoroborate (scheme 1).



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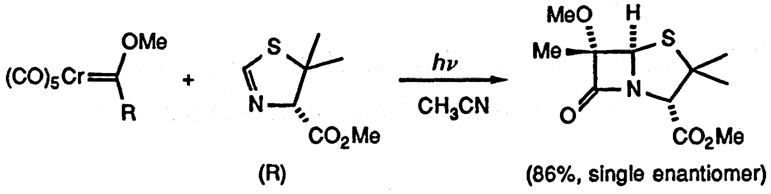
Scheme 1

These yellow, relatively air-stable crystalline solids have been extensively studied in the intervening years, but only very recently have they begun to be used for the efficient synthesis of complex organic compounds. The bulk of this research has focused on the thermal reactions of alkynes with chromium carbene complexes to produce napthoquinone derivatives (Dötz 1984). In contrast, research in our laboratories has centred on the development of synthetically useful transformations involving the *photolytic* reactions of chromium carbene complexes.

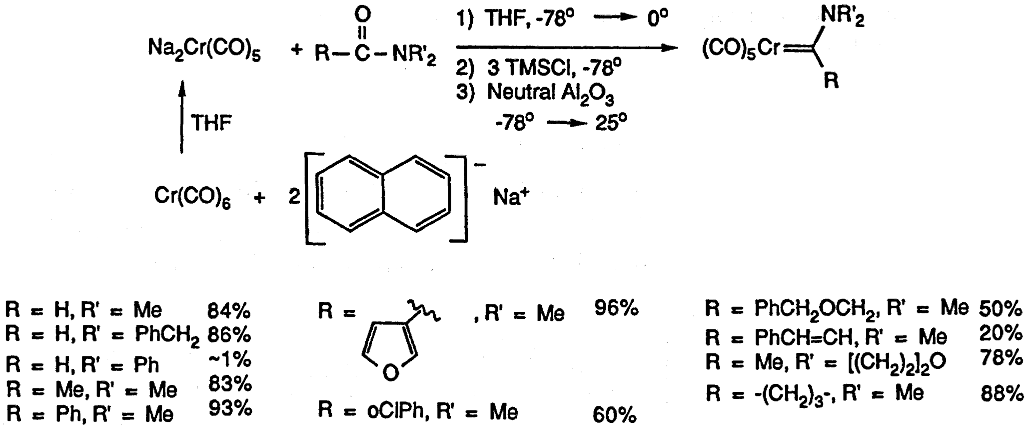
Results and discussion

Several years ago it was observed in the laboratories at Colorado State University that photolysis of chromium carbene complexes at wavelengths corresponding to the metal-to-ligand charge-transfer band (MLCT, 350–470 nm) in the presence of imines produced β-lactams in excellent yield, and with a high degree of stereoselectivity (Hegedus *et al.* 1984). An example of this process is seen in scheme 2, for which high yields and high enantioselectivities were



Scheme 2

observed. This process proved generally effective for the synthesis of a wide range of β-lactams. However, it was severely limited for use in the synthesis of biologically active β-lactams, because *these* compounds almost invariably have a hydrogen and an acylamido group α to the β-lactam carbonyl group, whereas typical Fischer carbene complexes, produced from the reaction of organolithium reagents with $Cr(CO)_6$, ultimately place an *alkyl* group in the α-position of the β-lactam. To overcome this problem, a new approach to chromium aminocarbenes was developed (scheme 3) (Imwinkelried & Hegedus 1988). It involves the

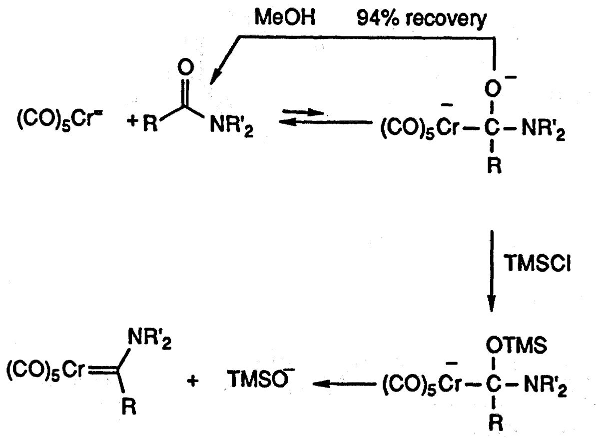


Scheme 3

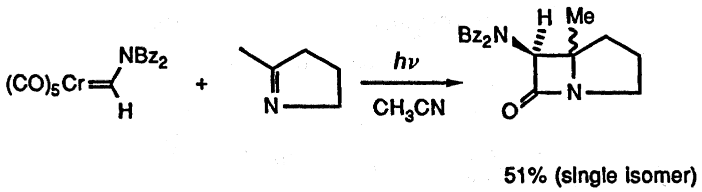
reaction of $Na_2Cr(CO)_5$, readily produced by the reduction of $Cr(CO)_6$ with sodium naphthalenide, with amides in the presence of trimethylsilyl chloride. The process is very general, and formamides, acetamides and benzamides are converted to the corresponding aminocarbene complexes in excellent yield. The process is thought to involve reversible addition of the dianion to the amide, followed by *O*-silylation and irreversible loss of $TMSO^-$ (scheme 4).

The most useful carbene complex for β-lactam syntheses is the (dibenzylamino)methylene complex. This complex proved generally reactive toward a wide variety of imines to give β-lactams in excellent yield (Borel *et al.* 1987) (schemes 5–10). Again, with rigid, chiral, cyclic imines, very high enantioselectivity was observed (scheme 11). Debenzylation by hydrogenolysis produced the free α-amino β-lactams.

The synthetic approach to aminocarbenes shown in scheme 3 has also been used to synthesize chiral, optically active carbene complexes efficiently (scheme 12). In preliminary studies, this chiral carbene complex efficiently induced asymmetry in the β-lactam forming



SCHEME 4



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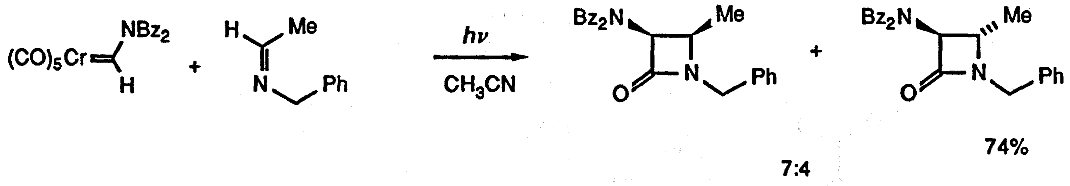

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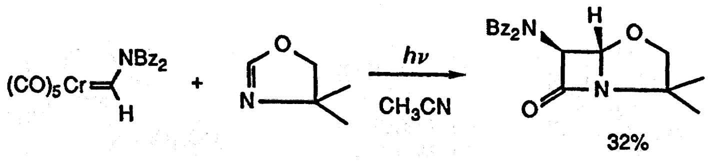

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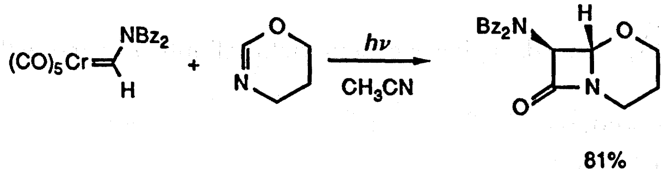

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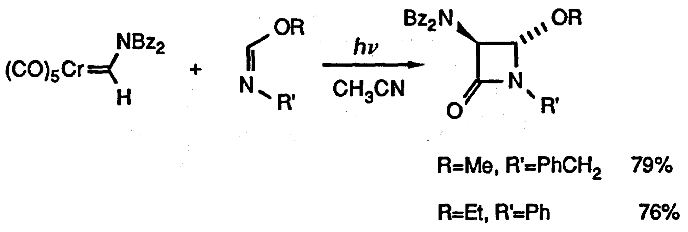

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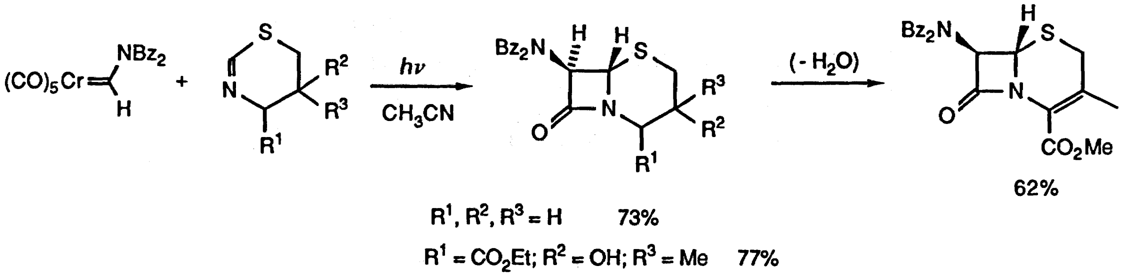

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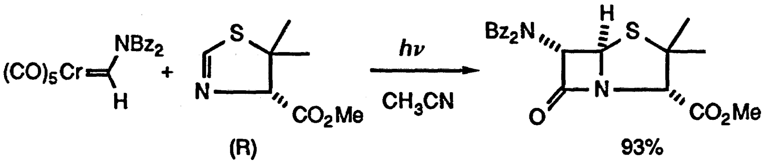

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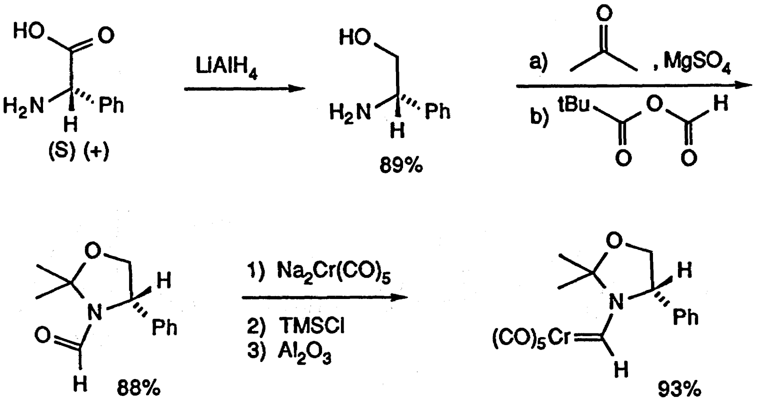
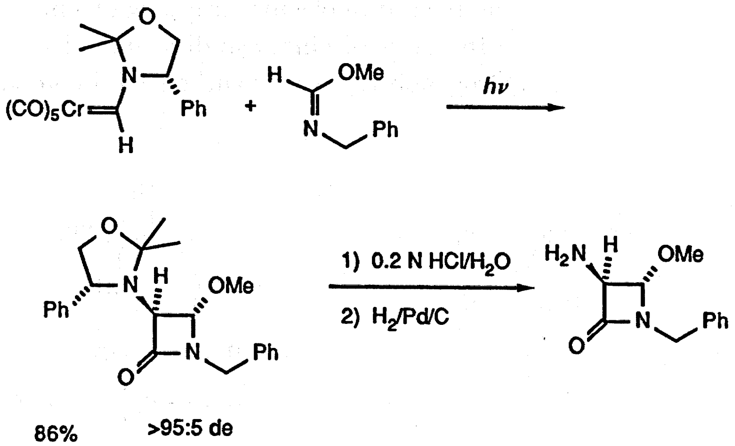


SCHEME 12

process, and was readily cleaved to give excellent yields of optically active β-lactams in a direct manner (scheme 13).

Recent mechanistic studies of the β-lactam forming process presented above have implicated a photolytically driven, reversible CO insertion to produce a metal-bound ketene complex (scheme 14) (Hegedus *et al.* 1988). Reaction of this ketene complex with an imine is thought to produce the β-lactam in a two-step process. Indeed, the stereochemistry observed in the



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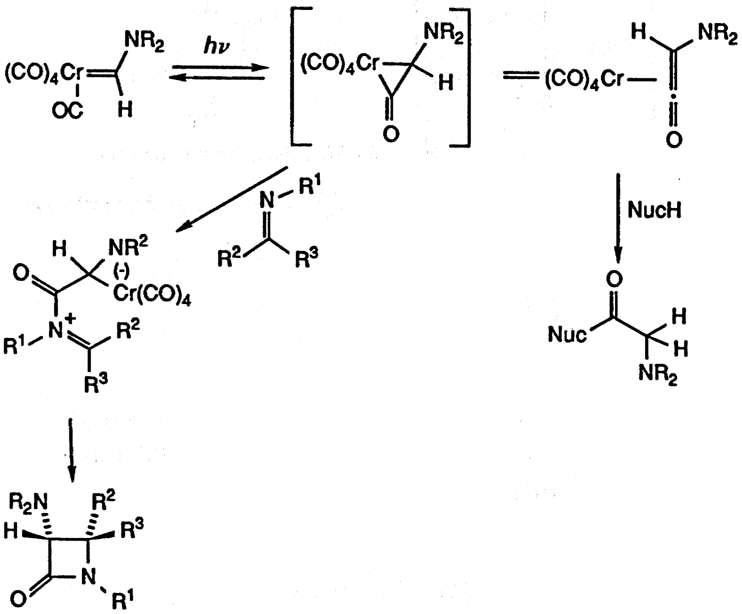

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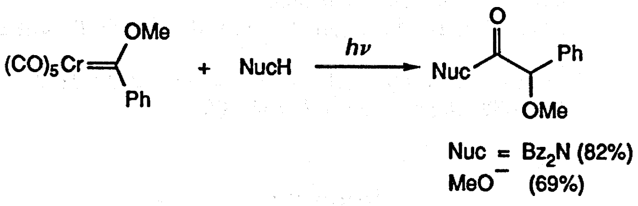
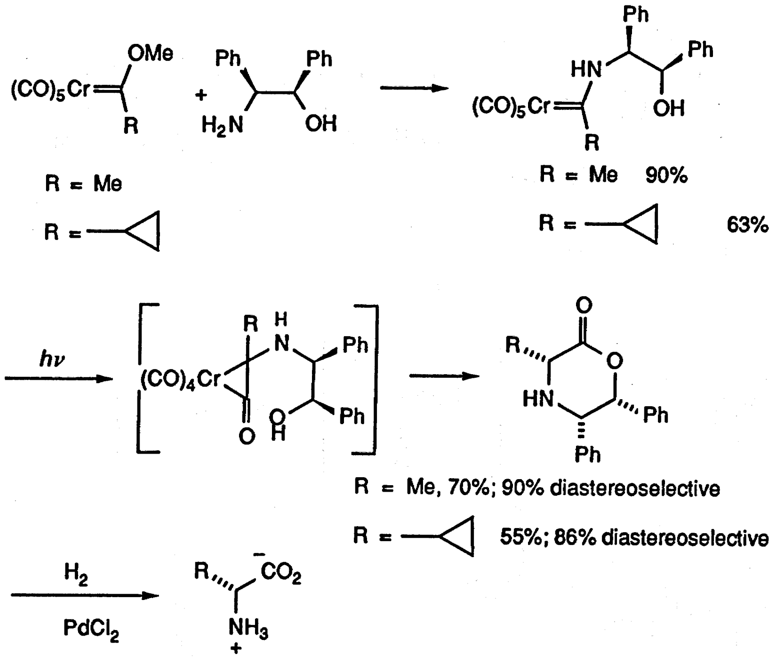


SCHEME 15

chromium carbene–imine reaction exactly parallels that of the corresponding imine–free ketene reaction, although yields are considerably higher in the chromium-carbene process. If metal-bound ketenes are indeed intermediate in this chemistry, they should be capable of being trapped by nucleophiles other than imines. This is indeed the case (scheme 15). These observations led to the development of an efficient synthesis of chiral, optically active natural and unnatural α-amino acids, utilizing the intramolecular trapping of a photogenerated ketene complex by a chiral alcohol (scheme 16). In preliminary studies, aminolactones, convertible to aminoacids by hydrolysis and hydrogenolysis, were synthesized in good yield and with excellent diastereoselectivity.



Scheme 16

The research discussed above was most ably carried out by Dr Yoshitaka Satoh, Dr Christian Borel, Dr Guy deWeck, Dr Rene Imwinkelried, and Mr Stan D'Andrea, and was generously supported by the National Institutes of Health, U.S.A.

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Discussion

J. E. BALDWIN, F.R.S. (*Dyson Perrins Laboratory, University of Oxford, U.K.*). Because the reaction of ketenes with imines is known and assumed to proceed via a dipolar adduct, and because the stereochemical outcome is very similar to the chromium chemistry, is it not possible that the photochemical reaction of the chromium carbene complex actually generates a small concentration of free ketene and that the reaction proceeds via this species?

L. S. HEGEDUS. The present evidence does not exclude this possibility.