(16 H, m, CH_2), 2.62 (6 H, s, CH_3), 3.33 (3 H, s, CH_3).

To a stirred solution of 20 mg of **45** in 3 mL of ethanol was added successively a solution of 8 mg (7 μL) of ethyl chloroformate in 1 mL of ethanol and 12 mg of anhydrous potassium carbonate. The reaction mixture was stirred at room temperature under nitrogen for 12 h, and the resulting inorganic precipitate was removed by filtration. The filtrate was concentrated, and the residue was extracted with chloroform. The extract was dried and concentrated. Recrystallization of the residual solid from benzene gave 12 mg (82%) of white needles: mp 259 °C dec; IR (KBr) ν_{max} 1627 cm^{-1} (C=O), 1280, 1085; UV (C_2H_5OH) λ_{max} 253 nm (ϵ 4660), 311 (5990), 332 (sh, 3030); ^1H NMR δ 7.46 (1 H, s, Ar H), 6.95 (1 H, s, Ar H), 4.11 (2 H, q, J = 7 Hz, CH_2CH_3), 3.96–2.86 (16 H, m, CH_2), 1.29 (3 H, t, J = 7 Hz, CH_2CH_3); mass spectrum, m/e 349 (M^+), 263, 262, 261, 247.

Anal. Molecular weight calcd for $C_{21}H_{23}N_3O_2$: 349.179. Found: 349.180 (high-resolution mass spectrum).

***N*-((Ethoxycarbonyl)imino)-5,12-diaza[2$_4$](1,2,4,5)cyclophanonium Ylide (49).** A solution of 17 mg of *O*-(mesitylsulfonyl)hydroxylamine in 3 mL of dichloromethane was added dropwise with stirring to 15 mg of 5,12-diaza[2$_4$](1,2,4,5)cyclophane (**2**) in 3 mL of dichloromethane with cooling. The reaction was then allowed to warm and was stirred at room temperature for 1 h. Addition of ether caused the separation of a precipitate, which was collected by filtration. Recrystallization of this precipitate from a mixture of acetonitrile and methanol gave 18 mg (66%) of **48** as white powdery crystals: mp 264 °C dec; IR (KBr) ν_{max} 3240 cm^{-1} (NH), 1210, 1191, 1098, 1027, 683; ^1H NMR (CD_3OD) δ 7.28 (1 H, s, Ar H), 6.86 (2 H, s, Ar H), 6.84 (1 H, s, Ar H), 3.90–2.90 (16 H, m, CH_2), 2.62 (6 H, s, CH_3), 2.22 (3 H, s, CH_3).

To a stirred solution of 14 mg of **48** in 2 mL of ethanol was added successively a solution of 6 mg of ethyl chloroformate in 1 mL of ethanol and 10 mg of anhydrous potassium carbonate. The reaction mixture was stirred at room temperature under nitrogen for 12 h before removing the inorganic precipitate by filtration. The precipitate was extracted with chloroform, and the combined chloroform extracts and filtrate was concentrated. Recrystallization of the residual solid from benzene gave 8 mg (80%) of white needles: mp 225 °C dec; IR (KBr) ν_{max} 1600 cm^{-1} (C=O), 1370, 1300, 1080; UV (C_2H_5OH) λ_{max} 255 nm (ϵ 3810), 315 (4950), 338 (sh, 2530); ^1H NMR δ 6.51 (1 H, s, Ar H), 6.46 (1 H, s, Ar H), 4.11 (2 H, q, J = 7 Hz, CH_2CH_3), 4.00–2.72 (16 H, m, CH_2), 1.28 (3 H, t, J = 7 Hz, CH_2CH_3); mass spectrum, m/e 349 (M^+), 263, 262, 261, 247.

Anal. Molecular weight calcd for $C_{21}H_{23}N_3O_2$: 349.179. Found: 349.179 (high-resolution mass spectrum).

Photorearrangement of 46 To Give 47. A stirred solution of 15 mg of **46** in 10 mL of benzene was irradiated with a 450-W Hanovia medium-pressure mercury lamp through a Pyrex filter under argon for 2.5 h until all the starting material was consumed. The consumption of starting material was monitored by thin-layer chromatography over silica gel. After concentration of the solution, the residual solid was purified by preparative, thin-layer chromatography over silica gel using 5% methanol in chloroform as eluant to give 14 mg (95%) of yellow crystals. Recrystallization from acetonitrile gave yellow prisms: mp 240 °C dec; IR (KBr) ν_{max} 2946 cm^{-1}, 2918, 1695 (C(=O)OEt), 1409, 1379, 1342, 1321, 1180, 1140; UV (C_2H_5OH) λ_{max} 267 nm (3770), 293 (sh, 2710); ^1H NMR δ 6.94 (1 H, s, Ar H), 4.54 (1 H, brs, CH=C) 4.23 (2 H, several overlapping quartets, J = 7 Hz, CH_2CH_3), 3.60–2.10 (16 H, m, CH_2), 1.30 (3 H, t, J = 7 Hz, CH_2CH_3); (toluene-d_8) δ 6.52 (1 H, s, Ar H), 4.29 (1 H, brs, CH=C), 4.04 (2 H, q, J = 7 Hz, CH_2CH_3), 3.10–2.00 (16 H, m, CH_2), 1.07 (3 H, t, J = 7 Hz, CH_2CH_3); (CD_3CN) δ 6.99 (1 H, s, Ar H), 4.40 (1 H, brs, CH=C), 4.08 (2 H, q, J = 7 Hz, CH_2CH_3), 3.40–2.10 (16 H, m, CH_2), 1.22 (3 H, t, J = 7 Hz, CH_2CH_3); mass spectrum, m/e 350, 349 (M^+), 277, 276, 263, 262, 261.

Anal. Molecular weight calcd for $C_{21}H_{23}N_3O_2$: 349.179. Found: 349.178 (high-resolution mass spectrum).

Photorearrangement of 49 To Give 50. A stirred solution of 11 mg of **49** in 10 mL of benzene was irradiated in the same manner as described for the preparation of **47**. Purification of the crude product by preparative thin-layer chromatography over silica gel using 10% methanol in chloroform as eluant gave 10 mg (92%) of yellow crystals: mp 155 °C dec; IR (KBr) ν_{max} 2979 cm^{-1}, 2895, 1694 (C=O), 1450, 1413, 1378, 1188, 1175, 1107, 1056; UV (C_2H_5OH) λ_{max} 263 nm (ϵ 3770), 298 (2930); ^1H NMR δ 7.18 (1 H, s, Ar H), 4.50 (1 H, brs, CH=C), 4.18 (2 H, several overlapping quartets, J = 7 Hz, CH_2CH_3), 3.60–2.10 (16 H, m, CH_2), 1.28 (3 H, t, J = 7 Hz, CH_3); (toluene-d_8) δ 6.52 (1 H, s, Ar H), 4.29 (1 H, brs, CH=C), 4.04 (2 H, q, J = 7 Hz, CH_2CH_3), 3.10–2.00 (16 H, m, CH_2), 1.07 (3 H, t, J = 7 Hz, CH_2CH_3); (CD_3CN) δ 7.32 (1 H, s, Ar H), 4.37 (1 H, brs, CH=C), 4.09 (2 H, q, 7 Hz, CH_2CH_3), 3.40–2.10 (16 H, m, CH_2), 1.22 (3 H, t, J = 7 Hz, CH_2CH_3); mass spectrum, m/e 350, 349, (M^+), 276, 262.

Anal. Molecular weight calcd for $C_{21}H_{23}N_3O_2$: 349.179. Found: 349.179 (high-resolution mass spectrum).

Acknowledgment. We thank the National Science Foundation for their support of this investigation under Grant CHE-8210282.

Registry No. 2, 77825-18-4; **3**, 77225-38-8; **5**, 1149-24-2; **6**, 77825-09-3; **7**, 77825-10-6; **8**, 77825-11-7; **9**, 77825-13-9; **10**, 77825-12-8; **11**, 89398-77-6; **12**, 77825-14-0; **13**, 77825-17-3; **14**, 77825-15-1; **16**, 89398-78-7; **17**, 89398-79-8; **18**, 89398-80-1; **19**, 89398-81-2; **23**, 89398-82-3; **24**, 89398-84-5; **25**, 89398-85-6; **26**, 89398-87-8; **27**, 89398-89-0; **28**, 89398-91-4; **29**, 89414-13-1; **30**, 89398-92-5; **31**, 89398-94-7; **32**, 89398-95-8; **33**, 89398-97-0; **34**, 6574-83-0; **36**, 89398-99-2; **37**, 89399-01-9; **38**, 89399-02-0; **39**, 89399-04-2; **45**, 89399-06-4; **46**, 89399-07-5; **47**, 89399-08-6; **48**, 89399-10-0; **49**, 89399-11-1; **50**, 89399-12-2; [6,7:13,14]dicyclobuta-5,12-diaza[2$_2$](1,3)cyclophanium iodide, 89399-13-3; *N*-methyl 4,12-diaz[2$_2$](1,3)cyclophanium iodide, 89399-14-4; silver trifluoromethanesulfonate, 2923-28-6; methyl *p*-toluenesulfonate, 80-48-8; 1,2-dibromoethane, 106-93-4; 1,3-dibromopropane, 109-64-8; *O*-(mesitylsulfonyl)hydroxylamine, 36016-40-7; ethyl chloroformate, 541-41-3.

Reaction of Chromium Carbene Complexes with Imines. Synthesis of β-Lactams

Louis S. Hegedus,* Michael A. McGuire, Lisa M. Schultze, Chen Yijun, and Oren P. Anderson

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received July 25, 1983*

Abstract: Under thermal conditions imines react with pentacarbonyl[(methoxy)(alkyl)carbene]chromium(0) complexes at the α-carbon of the carbene complex, producing new carbene complexes. When photolyzed with visible light (sunlight) a clean cycloaddition occurs to give β-lactams in good yield. Acyclic N-alkylated imines were converted to monocyclic β-lactams. Cyclic imines such as dihydroisoquinolines, quinolines, and benzothiazines were converted to polycyclic β-lactams. Thiazolines were converted to penam derivatives. Methyl D-5,5-dimethyl-Δ^2-thiazoline-4-carboxylate was converted to the penicillin analogue stereospecifically, giving an optically active bicyclic β-lactam. Acyclic chiral imines underwent reaction with lower stereoselectivity, giving a maximum of 60% diastereomeric excess.

Heteroatom-stabilized carbene complexes of chromium are readily synthesized in a number of different ways.[1] Most commonly used is the reaction of chromium hexacarbonyl with organolithium reagents to produce the "ate" complex, alkylation of

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which using trialkyloxonium salts produces pentacarbonyl(alkoxyalkyl- or -arylcarbene)chromium complexes in excellent yield.[2] Since the alkoxy group is readily replaced by nitrogen,[3] sulfur,[4] and other heteroatom nucleophiles, a wide range of differently substituted alkyl–heteroatom carbene complexes is readily available. Alternatively, chromium carbyne complexes react with nucleophiles at the carbyne carbon to yield carbene complexes which are inaccessible by other routes.[5] This approach has most often been used to make chromium carbene complexes containing two (similar or dissimilar) heteroatoms.

Heteroatom-stabilized carbene complexes of chromium are reactive species, which, until recently, have found little use in organic synthesis. The alkoxy displacement reaction discussed above was used to make the chromium carbene complexes of α-amino esters and these complexes were used as an amino protecting group in the synthesis of polypeptides.[6] The protons attached to the α-carbon of the type $(CO)_5Cr{=}C(CH_2R)(OMe)$ are quite acidic, and are easily removed by bases.[7] The resulting anion is sufficiently nucleophilic to react with electrophiles such as epoxides,[8] bromoesters,[9] benzyl and allyl halides,[10] and some aldehydes[11] to give more highly functionalized carbene complexes. α,β-Unsaturated carbene complexes, $(CO)_5Cr{=}C(OMe)(CH{=}CHR)$ undergo Michael addition reactions with enolate anions, again elaborating the alkyl side chain of the carbene.[12] Carbene complexes undergo oxidative cleavage of the Cr=C group to produce the corresponding organic carbonyl compound.[13]

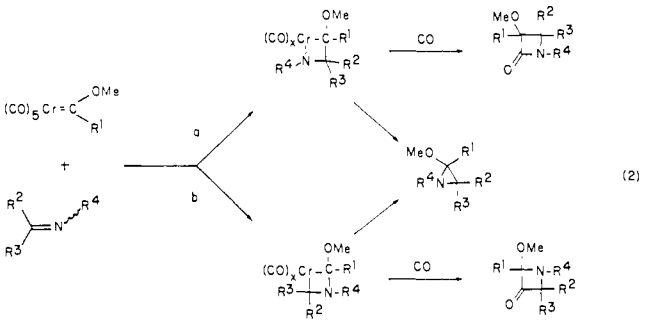
Heteroatom-stabilized chromium carbene complexes also react with a variety of unsaturated substrates. Enol ethers and α,β-unsaturated esters react to form cyclopropanes when heated (often under a carbon monoxide atmosphere) with these carbene complexes.[14] (Unactivated olefins do not react with these chromium complexes.) These reactions appear to involve cycloaddition of the olefin to the chromium carbene Cr=C group, to give a chromacyclobutane, followed by reductive elimination to form the cyclopropane, rather than reaction of a free carbene species (R_2C:). Particularly interesting, and synthetically useful as well, are the reactions of chromium carbene complexes with alkynes. Methoxyarylcarbene- and diarylcarbenechromium complexes react with alkynes to give substituted naphthol or naphthoquinone derivatives, incorporating the aryl group of the carbene complex, one carbon monoxide, and the alkyne, as well as the carbene carbon.[15] This chemistry has been used to synthesize vitamin K derivatives[16] and deoxyfrenolicin.[17] In contrast, pentacarbonyl[(methoxy)(methyl)carbene]chromium reacts with diphenylacetylene to give 4-methoxy-4-methyl-1,2-diphenylcyclobuten-1-one. A similar reaction occurs between the diphenyl carbene complex of chromium and bis(dimethylamino)acetylene.[18]

Herein we report the results of a detailed study of the reactions of imines with heteroatom-stabilized chromium carbene complexes.[19] In principle, imines may react with carbene complexes in *all* of the ways presented above, since they have both nucleophilic and electrophilic sites and are unsaturated. In practice the chemistry observed depends strongly on the reaction conditions.

Results and Discussion

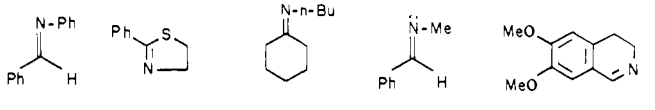
Benzophenone imine reacts with pentacarbonyl[methylmethoxycarbene] chromium (**1**) to produce the carbene complex in which the methoxy group is replaced by the imine group (eq 1).[20]

1



It was thought that N-alkylation of the imine might prevent this reaction pathway, and permit a cycloaddition reaction to ensue in its place. There are two possible modes of cycloaddition (paths a and b, eq 2). (Path b was considered most likely since it places the nucleophilic nitrogen on the electrophilic carbene carbon.) Should a metallacycle form, it could either reductively eliminate to give the aziridine, or it might insert carbon monoxide and then reductively eliminate, giving β-azetidinones (path b) or β-lactams (α-azetidinones, path a). The intrinsic interest of these heterocyclic systems prompted these studies.

Initial studies focussed on the thermal reactions of chromium carbene complexes with imines. Reaction of [methoxymethylcarbene]pentacarbonylchromium complex (**1**) with weakly basic imines **2** and **3** under a variety of conditions resulted in extensive



2 3 4 5 6

decomposition of the carbene complex, but no corresponding production of organic compounds containing both the imine and

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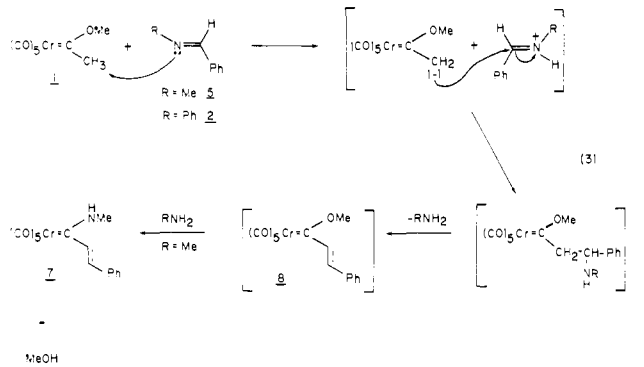
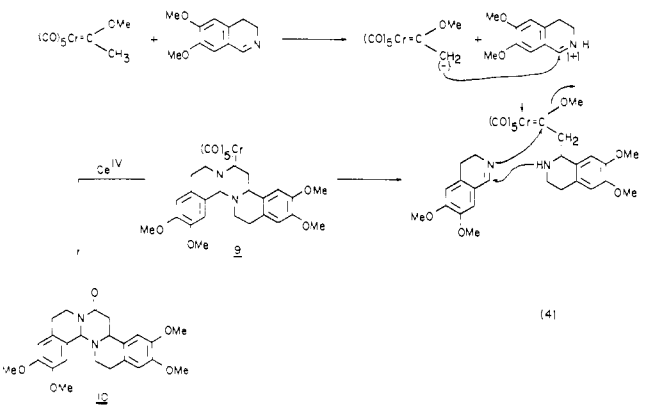
carbene fragments. With the more basic imine **4**, complex **1** was converted in low yield to the [methyl(*n*-butylamino)carbene]-pentacarbonylchromium complex, most likely by reaction with free *n*-butylamine liberated by the thermal dimerization of imine **4**. In contrast, heating a mixture of **1** and the *N*-methyl imine of benzaldehyde (**5**) at 50 °C in the absence of solvent produced a new carbene complex **7** which, upon oxidation, gave *N*-



methylcinnamide in 40% yield. This was thought to occur by abstraction of the acidic α-proton[7] of the carbene complex by the basic imine, followed by condensation of the resulting carbanion with the iminium salt. Loss of methylamine to generate the α,β-unsaturated carbene complex, followed by displacement of methanol by methylamine[6] generated the observed carbene complex **7** (eq 3).

To demonstrate the feasibility of this pathway, the hydrochloride salt of imine **2** was treated with the preformed lithium carbanion of carbene complex **1**. In this case, the α,β-unsaturated *methoxy* carbene complex **8** was obtained. Apparently aniline was not sufficiently nucleophilic to attack this carbene complex.

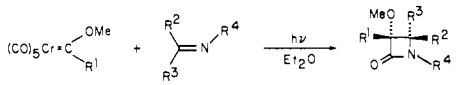
Dihydroisoquinoline **6** is an imine which cannot easily lose amine as in eq 3. Treatment of **6** with carbene complex **1** produced a new carbene complex (**9**) containing two molecules of the di-



hydroisoquinoline. This complex was readily cleaved, by oxidation, to lactam **10** (over 60% yield of **9** was obtained by using the hydrochloride salt of **6** and the preformed anion of the carbene). This reaction is thought to proceed as in eq 4.

These results clearly show that, under thermal conditions, the chemistry of the α-carbon of the carbene complex dominates in reactions with imines. There was no evidence that a metallacyclic intermediate had ever formed or that any reaction had taken place at the chromium center of the *intact* carbene complex. In order for the desired cycloaddition to occur, the nitrogen (or carbon) of the imine must, at some point, coordinate to the chromium center, which, in the starting carbene complex, is coordinatively saturated. It was (naively) thought that creation of a vacant site on chromium would facilitate the desired cycloaddition reaction of imines. Carbene complexes are known to undergo facile photodissociation of a CO ligand upon irradiation.[21] Thus, ether solutions of chromium carbene complexes and imines were exposed to sunlight irradiation in Pyrex flasks under an atmosphere of argon for 2–4 h, during which time the reaction mixture changed from a clear yellow solution to a brown-red heterogeneous mixture. (In climates lacking significant sunlight, these reactions can be carried out by using six 20-W Vitalite (Duro-Lite Lamps Inc.) fluorescent tubes as a light source and irradiating for 10–20 h.) Exposure of these solutions to air with further irradiation (2 h) to remove chromium residues from solution followed by filtration produced the desired β-lactams in fair to excellent yield.

A variety of imines were reactive under these conditions. Acyclic imines produced monocyclic β-lactams (eq 5). The

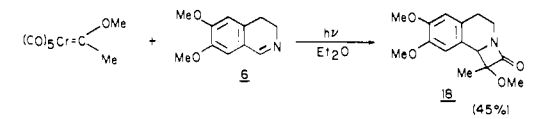


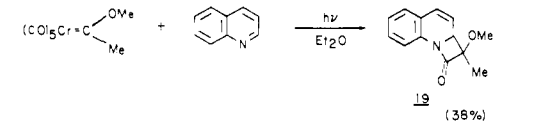
	R^1	R^2	R^3	R^4	yield, %
11	Me	H	Ph	Me	75
12	Me	H	Ph	Ph	52
13	Ph	H	Ph	Me	72
14	Me	Ph	Ph	Me	36
15	Ph	H	Ph	Ph	20
16	Me	H	Ph	p-MeOPh	60
16a	Me	H	Ph	H	90
17	Me	H	PhCH=CH	$PhCH_2$	45

reaction was stereospecific, producing only one diastereomer of the product. With imines of aromatic carbonyl compounds, the *O*-methyl and adjacent phenyl groups were syn to each other in all cases. (It had been previously shown that the methoxy singlet in the NMR spectrum appears at $\sim\delta$ 3.0 for *syn*-3-methoxy-4-phenyl-β-lactams and at $\sim\delta$ 3.6 for the anti isomer.)[22] *N*-Phenyl imines were less reactive than *N*-methyl imines, and methoxyphenylcarbene complexes were less reactive than methoxymethylcarbene complexes. The *N*-benzyl imine of cinnamaldehyde reacted exclusively in a 1,2-fashion with no 1,4-addition product being detected.

β-Lactams lacking an N-substituent could not be directly made by this route since the corresponding imine exchanged with the methoxy group rather than undergoing the cyclization reaction (eq 1). However, an *N*-*p*-methoxyphenyl imine was converted to the β-lactam (**16**) in fair yield. The *N*-*p*-methoxyphenyl group was subsequently cleaved from the β-lactam product by using cerium IV,[23] to give the N-unsubstituted β-lactam (**16a**) in high yield.

Cyclic imines also underwent facile conversion to the corresponding β-lactams. Again, in all cases, a single diastereomer was produced, and adjacent phenyl and methoxy groups were always syn. Dihydroisoquinoline **6**, which dimerized under thermal conditions, was converted to the β-lactam in fair yield under photolytic conditions (eq 6). Quinoline itself was converted in





good yield to the β-lactam (eq 7). This adduct was somewhat unstable to silica gel, and the modest isolated yield reflects losses during purification.

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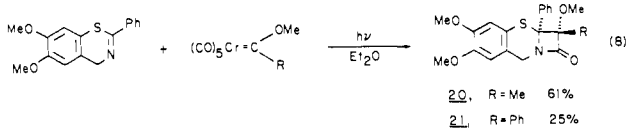
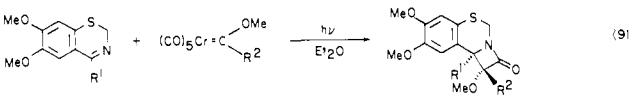
A number of 4*H*- and 2*H*-1,3-benzothiazines underwent conversion to β-lactams in fair yield (eq 8 and 9).[24,25] Thiazolines



(8)

20, R = Me 61%

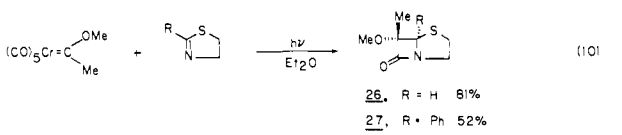
21, R = Ph 25%



(9)

	R¹	R²	yield, %
22	Ph	Me	51
23	Ve	Me	38
24	H	Me	37
25	Ph	Ph	27

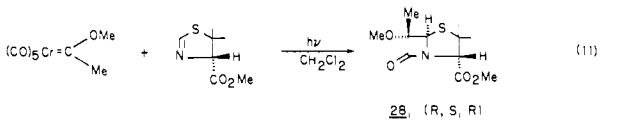
were even more reactive (eq 10) giving fair to good yields of the



(10)

26, R = H 81%

27, R = Ph 52%

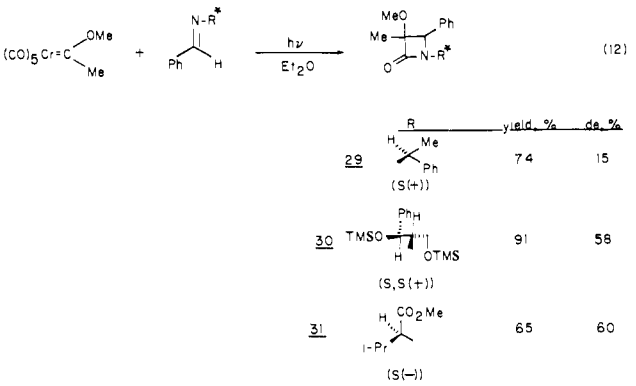


(11)

28, (R, S, R)

penam ring system. The stereochemistry of **27** was confirmed by a single-crystal X-ray diffraction study. Particularly interesting is the reaction of the optically active D-thiazoline ester ($[\alpha]^{25}_D$ +51.9°) (from degradation of Penicillin G methyl ester[26]) with the methoxymethylcarbene complex (eq 11). A single, sharp-melting product **28** (mp 59 °C), was obtained in 42% isolated yield. Examination of the crude product, before purification, showed only a single β-lactam product to be present, and high-field NMR (360 MHz) spectroscopy failed to detect the presence of any diastereoisomers. The purified material had a rotation of $[\alpha]^{25}_D$ +218.1° (*c* 1, $CHCl_3$). Thus, the β-lactam-forming reaction appears to have proceeded stereospecifically to give 100% diastereomeric excess. Provided that partial epimerization of the starting thiazoline did not occur during reaction, the product **28** should be optically pure. The absolute stereochemistry of **28** was determined by single-crystal X-ray diffraction to be as shown, *R,S,R*. (Epimerization of product **28** did not occur during reaction or isolation since that would produce diastereoisomers, which were not detected.)

In contrast, the use of acyclic imines of chiral amines as substrates resulted in only modest asymmetric induction (eq 12). Although the chemical yields were high in all cases, the diastereomeric excess, as measured by 360-MHz NMR spectroscopy, was disappointingly low using *S*-(+)-α-phenethylamine (15%). It improved somewhat (58%) when the considerably more bulky (2*S*,3*S*)-*N*-[1,3-bis(trimethylsiloxy)-3-phenylpropan-2-yl]-benzylideneimine was used as substrate. (Note the high chemical yield for this very bulky imine.) Roughly the same diastereomeric excess was obtained by using L-valine methyl ester as the chiral



(12)

	R	yield, %	de, %
29	Me, Ph (S(+))	74	15
30	PhH, TMSO, H, OTMS (S,S(+))	91	58
31	CO_2Me, H, i-Pr (S(−))	65	60

center. Efforts to induce asymmetry in this process, including the use of chiral ligands on chromium and chiral ester groups in place of the carbene methoxy group are in progress, as are studies using other heteroatom- (N,S) stabilized carbenes and other imine substrates (oxazolines, thiazines).

Mechanistic Considerations. Since no experiments directed toward mechanistic information have been carried out, the discussion presented below should be viewed as speculation and should form the basis for designing rational mechanistic studies rather than the basis for understanding the results reported above. The most notable feature of the β-lactam-forming reaction is that it is a photolytic process that takes place with visible light (sunlight through Pyrex or Vitalite). Under thermal conditions, the chemistry of the α-carbon results rather than chemistry to form the β-lactam. Chromium–carbene complexes are known to readily photodissociate a carbon monoxide,[21] and initially it was thought that this was the sole role of photolysis in the β-lactam-forming reaction. However, carbon monoxide dissociation from chromium carbene complexes is also rapid under thermal conditions (for $(CO)_5Cr{=}C(Ph)(OMe)$, rate = 1.8×10^{-4} at 44 °C, $t_{1/2}$ = 1 h[28]), yet β-lactams do not form under thermal conditions. Thus photolysis must be playing some other role in this reaction. The visible spectrum of pentacarbonyl[methoxymethylcarbene]chromium has one absorption (λ_{max} 377 nm, ϵ 4500) in the range of irradiation studied. By comparison with the analogous tungsten complex,[21] this absorption is due to the spin-allowed Cr → carbene π* metal to ligand charge transfer band, corresponding to the transfer of an electron from the HOMO to the LUMO of the complex. From molecular orbital calculations, "the LUMO is energetically isolated and spatially located on the carbene–carbon atom."[29a] Thus this excited state should have significant electron density on the carbene carbon. Further, ab initio calculations[30] on [hydroxyhydridocarbene]pentacarbonylchromium indicate significant negative charge on the carbene carbon even in the ground state.

In light of the above discussion, a reasonable mechanism for the β-lactam-forming reaction is shown in eq 13. Photoexcitation of the carbene complex produces an excited state in which the carbene carbon has significant nucleophilic character. Attack of the carbene carbon on the electrophilic imine carbon and attack of chromium by nitrogen form a metallacyclic intermediate. Carbon monoxide insertion followed by reductive elimination generates the β-lactam and a CO deficient chromium fragment. The "cycloaddition" step may be stepwise, involving C–C bond formation followed by Cr–N bond formation. Alternatively, the nitrogen may already be coordinated to the metal through its lone pair, as a ligand in place of one of the carbon monoxides, making the initial C–C bond-forming step intramolecular. Some association of the imine with the carbene complex is likely, since

(24) We thank Dr. Lajos, Fodor, Department of Laboratory Medicine, County Hospital, Gyulapo, Hungary, for suggesting these benzothiazines as substrates and providing samples for study.

(25) For syntheses and reactions of related β-lactams see: Fodor, L.; Szabo, J.; Bermath, G.; Parkani, L.; Sohar, P. *Tetrahedron Lett.* **1981**, *22*, 5077. Fodor, L.; Szabo, J.; Sohar, P. *Tetrahedron* **1981**, *37*, 963.

(26) Bell, M. R.; Carlson, J. A.; Oesterlin, R. *J. Org. Chem.* **1972**, *37*, 2733.

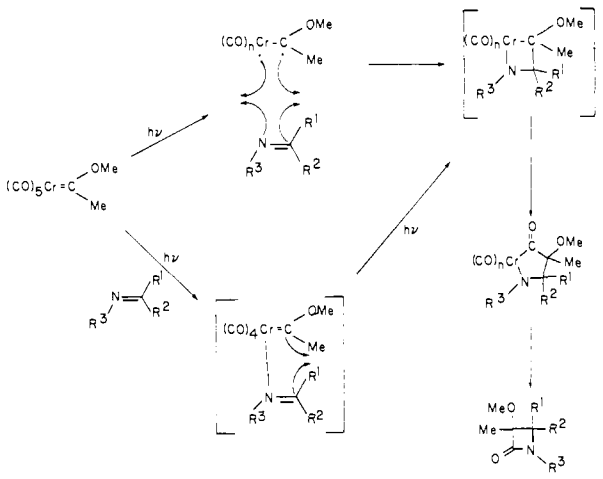
(27) Chiral imines were converted to β-lactams using ketene acetals and titanium(IV) chloride: (a) Ojima, I.; Inaba, S.; Yoshida, K. *Tetrahedron Lett.* **1977**, 3643. (b) Ojima, I.; Inaba, S. *Ibid.* **1980**, *21*, 2077.

(28) Casey, C. P.; Cesa, M. C. *Organometallics* **1982**, *1*, 87.

(29) (a) Block, T. F.; Fenske, R. F.; Casey, C. P. *J. Am. Chem. Soc.* **1976**, *98*, 441. (b) Block, T. F.; Fenske, J. R. *J. Organomet. Chem.* **1977**, *139*, 235.

(30) Nakatsuji, H.; Ushio, J.; Han, S.; Yonezawa, T. *J. Am. Chem. Soc.* **1983**, *105*, 426.

(13)



photoexcited states of organometallic complexes are likely to have life times too short to permit an intermolecular reaction to ensue. Support for this mechanism, as well as an explanation of the stereospecificity of this reaction must await further experimental work.

Experimental Section

General Procedures. All melting points were obtained with a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on either a Beckmann 4200 or a Beckmann Acculab spectrophotometer. All 60-MHz ^1H NMR spectra were recorded on either a Varian Model EM360 or a Varian Model T-60 spectrometer using Me_4Si as an internal standard and are reported in δ. All ^{13}C NMR spectra were recorded on a JEOL JNM FX-100 Fourier Transform spectrometer. High-field NMR spectra were recorded on a Nicolet NT360 spectrometer. Mass spectra were recorded on a V.G. Micromass 16F spectrometer. Exact mass spectra were obtained at Midwest Center for Mass Spectroscopy, University of Nebraska, Lincoln, NE.

All chromatographic isolations were accomplished by either medium-pressure liquid chromatography (MPLC), using a Michel-Miller column (37 mm × 350 mm) packed with Merck Silica Gel-60 (230–400 mesh), or by radial-layerchromatography, using a Chromatotron Model 7924 with Kiesel gel 60 PF silica gel. Products isolated by MPLC were detected with an ISCO Model UA-5 absorbance–fluorescence monitor at wavelength 254 nm.

Analyses were performed by either Midwest Microanalytical Labs, Indianapolis, IN, or by M-H-W Laboratories, Phoenix, AZ.

Materials. All solvents were freshly distilled and stored under an argon atmosphere. Immediately before use they were degassed and saturated with argon. Tetrahydrofuran (THF) (Fischer, Spectra Grade) was predried over Na wire, heated at reflux over Na wire with benzophenone, and distilled at atmospheric pressure under a N_2 atmosphere. Diethyl ether (Fischer, Reagent Grade) was predried over $MgSO_4$, heated at reflux over Na with benzophenone, and distilled at atmospheric pressure under a N_2 atmosphere. Petroleum ether (Skelly solve F, petroleum naphtha) was heated at reflux over CaH_2 and distilled at atmospheric pressure under a N_2 atmosphere. Methyllithium was purchased from Aldrich as a 1.4 M solution in Et_2O. Phenyllithium was purchased from Alfa as a 2.0 M solution in (3:1) benzene/ether. Butyllithium was purchased from Alfa as a 1.44 M solution in hexane. Trimethyloxonium tetrafluoroborate was obtained from Alfa and was used without further purification. Chromium hexacarbonyl was purchased from Strem Chemicals and was finely ground in a mortar and pestle before use. [Methylmethoxycarbene]pentacarbonylchromium(0) and [phenylmethoxycarbene]pentacarbonylchromium(0) were synthesized by literature procedures.[31,32] Acyclic aldimines were prepared by the following procedure.

Into a round bottom flask fitted with stir bar and dropping funnel was placed benzaldehyde (1 equiv). Methylene chloride (1.5 mL/mmol) was added and stirring commenced. The reaction mixture was cooled to 0 °C in an ice bath. After stirring for 15 min at 0 °C the amine (H_2N–R, R = alkyl, aryl; 1 equiv) was added dropwise over 15 min, and the reaction mixture was stirred for 0.5 h. Anhydrous $MgSO_4$ (2–3 equiv) was added all at once, and the reaction mixture was allowed to come to room temperature and to stir for an additional 2 h. After this time the reaction mixture was filtered, the solvent removed in vacuo, and the oily residue purified by vacuum distillation or by recrystallization (EtOH/H_2O).

Thermal Reaction of [Methylmethoxycarbene]pentacarbonylchromium(0) (1) with *N*-Methylbenzylideneimine (5). Preparation of 7. [Methylmethoxycarbene]pentacarbonylchromium(0) (**1**) (125 mg, 0.5 mmol) was placed in a 50-mL Airlessware flask. The flask was charged with a pea-shaped stir bar and fitted with a rubber serum cap. The flask was evacuated and filled with argon (3 cycles). *N*-Methylbenzylideneimine (60 mg, 0.5 mmol) was injected and stirring was commenced. The reaction was heated at 50 °C for 2 h, then cooled to 25 °C. The red oil was taken up in $CHCl_3$ (1 mL), diluted with hexane (10 mL), and filtered to produce a yellow-orange solution. The solvent was removed in vacuo to give a red oil. Purification by MPLC (Al_2O_3, 1:1 CH_2Cl_2–Hexane) gave [(methylamino)-β-styrenyl)carbene]pentacarbonylchromium(0) (**7**) a yellow, oily solid (59 mg, 35%) homogeneous by TLC and NMR: NMR ($CDCl_3$) δ 3.18 (s, 1.5, N–CH_3), 3.30 (s, 1.5, NCH_3), 6.95 (d, J = 12 Hz, 1, Ph–CH=C*H*), 7.22 (d, J = 12 Hz, 1, Ph–C*H*), 7.38 (m, 5, Ph); IR (Nujol) 3400, 3290, 2945, 2920, 2845, 2045, 1955, 1910, 1640, 1615, 1565, 1540, 1510, 1490, 1455, 1375, 1175, 1155, 1085, 1070, 960, 755, 720, 675, 660 cm^{-1}; MS, m/e 309 (P – CO), 281 (P – 2CO), 253 (P – 3CO), 225 (P – 4CO), 197 (P – 5CO), 144 (P – $(CO)_5CrH$), 131 (Ph–CH=CHCHO), 77 (C_6H_5), 52 (Cr).

This compound was oxidized by $(NH_4)_2Ce(NO_3)_6/H_2O$, CH_3CN to yield *N*-methylcinnamide which was identical in all respects (IR, NMR, mp 111 °C [reported[33] 111 °C]) with authentic material.[33]

Thermal Reaction of [Methylmethoxycarbene]pentacarbonylchromium(0) (1) with 6,7-Dimethoxy-3,4-dihydroisoquinoline (6).[34] Preparation of 9 and 10. [Methylmethoxycarbene]pentacarbonylchromium(0) (125 mg, 0.5 mmol) was placed in a 50-mL Airlessware flask which contained a pea-shaped stir bar and was sealed with a rubber serum cap. The flask was evacuated and filled with argon (3 cycles) then fitted with an argon-filled balloon. 6,7-Dimethoxy-3,4-dihydroisoquinoline (**6**) (86 mg, 0.5 mmol) was added and the mixture heated at 50 °C with stirring. After 6 h the red-black oil was taken up in $CHCl_3$ (1 mL), diluted with hexane (10 mL), filtered, and the solvent removed in vacuo to give a yellow oil. MPLC purification (Al_2O_3, neutral, 1:1 $CHCl_3$–hexane) gave a yellow solid which was shown spectroscopically and by chemical means to be substituted diisoquinolino[2,1-*a*:2′,1′-*c*]-pyrimidinediyl **9** (64 mg, 40%): NMR (360 MHz) ($CDCl_3$) δ 2.31–3.23 (m, 7, CH_2's), 3.68 (d, J = 9 Hz, 2, Cr=C–CH_2), 3.84 (s, 3, OMe), 3.88 (s, 3, OMe), 3.94 (s, 3, OMe), 3.96 (s, 3, OMe), 4.39 (t, J = 9 Hz, 1, Cr=C–CH_2–C*H*), 5.19 (dt, J = 3.6 Hz, J = 13.7 Hz, 1, CH), 5.87 (s, 1, N–CH–N), 6.55 (s, 1, ArH), 6.63 (s, 1, ArH), 6.70 (s, 1, ArH), 6.97 (s, 1, ArH); IR 2990, 2920, 2820, 2050, 1989, 1910, 1635, 1605, 1510, 1455, 1355, 1257, 1243, 1223, 1160, 1123, 1030, 855, 780, 750, 675, 665 cm^{-1}; MS, m/e 408 (P – $((CO)_5Cr)$), 217 ($C_{13}H_{16}NO_3$), 191 ($C_{11}H_{13}NO_2$ (A)), 176 (A – Me), 52 (Cr), 28 (CO). This compound was relatively unstable and an acceptable elemental analysis could not be obtained.

Compound **9** (500 mg) was placed in a 100-mL Erlenmeyer flask and dissolved in a mixture of hexane–chloroform (10:1, 50 mL) giving an orange solution. The solution was exposed to the light of a 500-W tungsten filament floodlamp. After 12 h the brown, heterogeneous mixture was filtered and the solvent was removed in vacuo. The resulting yellow oil was recrystallized from ethyl acetate to give **10** (219 mg, 62%) as a white crystalline solid: mp 246 °C dec; NMR (360 MHz) ($CDCl_3$) δ 2.51–2.97 (m, 9, CH_2), 3.85 (s, 3, OMe), 3.87 (s, 3, OMe), 3.90 (s, 3, OMe), 3.91 (s, 3, OMe), 4.49 (dd, J = 7.38 Hz, J = 10.8 Hz, 1, N–C*H*ArR), 4.91 (m, 1, CH), 5.80 (s, 1, N–CH–N), 6.55 (s, 1, Ar H), 6.62 (s, 2, Ar H), 7.03 (s, 1, Ar H); IR (neat) 2980, 2940, 2910, 2820, 1645, 1505, 1450, 1425, 1400, 1375, 1350, 1320, 1250, 1220, 1140, 1120, 1020, 975, 900, 845, 770, 715 cm^{-1}; mass spectrum, m/e 424 (parent ion), 233 (P – $C_{11}H_{13}NO_2$), 191, ($C_{11}H_{13}NO_2$). Anal. Calcd $C_{24}H_{28}N_2O_5$ (C, H, N).

Thermal Reaction of the Carbanion of [Methylmethoxycarbene]pentacarbonylchromium(0) (1) with 6,7-Dimethoxy-3,4-dihydroisoquinoline Hydrochloride. Synthesis of 9. [Methylmethoxycarbene]pentacarbonylchromium(0) (**1**) (63 mg, 0.25 mmol) was placed in a 50-mL Airlessware flask equipped with a pea-shaped stir bar and rubber serum cap. The flask was evacuated and filled with argon (3 cycles), THF (4 mL) was added, and stirring was commenced. The solution was cooled to −78 °C and stirred for 10 min. *n*-Butyllithium (0.25 mmol) was added and the solution became very light yellow. The solution was allowed to

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(33) Prasad, K.; Venkatratnam, R. *Indian J. Chem.* **1975**, *13*, 94. *Beilstein* 9, 587.
(34) Whaley, W. M.; Meadow, M. *J. Chem. Soc.* **1953**, 1067.

come to 0 °C (45 min) and was kept at 0 °C for 15 min. At this point the solution was light yellow-green. It was cooled to −78 °C and stirred for 15 min. Then 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride was added as a solid, and the flask was flushed with argon and resealed. The mixture was inhomogeneous and orange. After stirring at −78 °C for 10 min the solution was allowed to come to −30 °C (30 min), and triethylamine (25 mg, 0.25 mmol) was added. The solution became deep red. The temperature was allowed to come to 0 °C (15 min), kept at 0 °C for 1 h, and then was raised to room temperature. After 3 h at room temperature the solution was light green and heterogeneous. Petroleum ether (20 mL) and diethyl ether (20 mL) were added to the reaction mixture and the green solution was filtered to give a clear yellow solution. The solvent was removed in vacuo to give **9** (85 mg, 63%) as a light yellow solid.

Thermal Reaction of the Carbanion of [Methylmethoxycarbene]pentacarbonylchromium(0) (1) with *N*-Phenylbenzylideneimine·HCl (2). [Methoxymethylcarbene]pentacarbonylchromium(0) (**1**) (63 mg, 0.25 mmol) was allowed to react with *n*-butyllithium (0.25 mmol) and *N*-phenylbenzylideneimine·HCl (54 mg, 0.25 mmol) in the same manner as the previous reaction. Standard isolation produced a red oil which was purified by MPLC (neutral Al_2O_3, 1-1 Hexane/ether) to give **8** (54 mg, 60%) as a red solid. This was identical (IR, NMR, 73–75 °C) with the compound reported by Casey.[35]

Complex **8** was oxidized by $(NH_4)_2Ce(NO_3)_6/H_2O$, CH_3CN to give methyl cinnamate (24 mg, 60% overall) which was identical with authentic material.

General Procedure for the Synthesis of β-Lactams through the Photolytic Reaction of Imines with Chromium Carbenes. $(CO)_5Cr{=}C(X)(Y)$ (X = OMe; Y = Me, Ph) (1 equiv) was weighed into a Pyrex 100-mL Erlenmeyer flask which was then sealed with a rubber serum cap. The reaction vessel was evacuated and filled with argon (3 cycles). (If the imine was a solid it was introduced into the reaction vessel before the vessel was sealed.) Distilled petroleum ether or diethyl ether (40–100 mL/mmol) was added by means of a cannula. When the imine was a liquid it was introduced (1 equiv) by syringe. The reaction vessel was then either placed in a sunny spot outdoors at ambient temperature or irradiated with four 20-W Vitalite fluorescent tubes. After *x* h the solution became heterogeneous, cloudy, and often changed and darkened in color. The end point was determined to be when no more color changes in the reaction solution could be observed. Isolation consisted of filtration and removal of solvent in vacuo to yield a colored oil. The oil in several cases was nearly pure β-lactam but in most cases the oil contained small amounts of starting imine plus chromium byproducts. These byproducts were eliminated by dissolving the oil in a nonprotic solvent. The solution was then exposed to air in sunlight. After 1 h a great deal of precipitate formed and the solution was clear and colorless. Filtration and removal of solvent in vacuo yielded the desired β-lactam along with starting material. Purification was accomplished by recrystallization or by chromatography.

Synthesis of 1,3-Dimethyl-3-methoxy-4-phenyl-β-azetidinone (11). Carbene complex **1** (5.0 mmol, 1.25 g) and *N*-methylbenzylideneimine (5.0 mmol, 595 mg) were combined in the usual manner in a 500-mL Erlenmeyer flask, in petroleum ether (200 mL). The flask was placed in direct sunlight at 24 °C. After 3 h the mixture was brown and heterogeneous. Standard isolation and purification by recrystallization from 50 °C (not boiling!) absolute ethanol gave **11** (760 mg, 75%) as a white solid: mp 74–75 °C; NMR (60 MHz) ($CDCl_3$) δ 1.60 (s, 3, CH_3), 2.80 (s, 3, NCH_3), 3.00 (s, 3, OCH_3), 4.30 (s, 1, CH), 7.25 (s, 5, Ar H); IR 1750 (C=O) cm^{-1}. Anal. $C_{12}H_{15}NO_2$ (C, H, N).

Synthesis of 1,4-Diphenyl-3-methyl-3-methoxy-β-azetidinone (12). Carbene complex **1** (125 mg, 0.5 mmol) and *N*-phenylbenzylideneimine (90 mg, 0.5 mmol) were combined in an Erlenmeyer flask in petroleum ether (20 mL). The flask was placed in sunlight at 20 °C. After 6 h the mixture was brown and heterogeneous. Filtration, oxidation, and standard isolation yielded an oily solid. Purification by recrystallization from hexane/CH_2Cl_2 gave **12** (70 mg, 52%) as a white solid: mp 155–156 °C; NMR (60 MHz) ($CDCl_3$) δ 1.70 (s, 3, CH_3), 3.10 (s, 3, OCH_3), 4.90 (s, 1, CH), 7.3 (m, 10, Ar H); IR(neat) 1755 (C=O) cm^{-1}; mass spectrum, *m/e* 267 (parent), 181, 148 (*p*-Ph-CNO), 77 (C_6H_5) 28 (CO). Anal. $C_{17}H_{17}NO_2$ (C, H, N).

Synthesis of 1-Methyl-3-methoxy-3,4-diphenyl-β-azetidinone (13). [Phenylmethoxycarbene]pentacarbonylchromium(0) (156 mg, 0.5 mmol) was combined with *N*-methylbenzylideneimine (60 mg, 0.5 mmol) in an Erlenmeyer flask in petroleum ether (20 mL). The solution was deep red. The flask was put in direct sunlight at 20 °C. The solution turned extremely dark within an hour. The solution was filtered, the filtrate washed with petroleum ether, and the now clear solution was placed in a flask which was sealed, degassed, and placed in the sunlight. This sequence was repeated several times in 16 h. Standard isolation and recrystallization from pentane yielded **13** (96 mg, 72%) as a white crystalline solid: mp 91–92 °C; NMR (60 MHz) ($CDCl_3$) δ 2.82 (s, 3, NCH_3), 3.18 (s, 3, OCH_3), 4.62 (s, 1, CH), 7.21 (m, 10, Ar H); IR (neat) 1765 (C=O) cm^{-1}. Anal. $C_{17}H_{17}NO_2$ (C, H, N).

Synthesis of 1,3-Dimethyl-3-methoxy-4,4-diphenyl-β-azetidinone (14). Carbene complex **1** (250 mg, 1 mmol) was allowed to react in the usual manner with (*N*-methylbenzophenonylimine) (195 mg, 1 mmol) in petroleum ether (40 mL) in a 100-mL Pyrex Erlenmeyer flask in direct sunlight at 13 °C. After 12 h the mixture was dark and heterogeneous. Standard isolation, oxidation, and recrystallization (20:1 hexane/CH_2Cl_2) gave **14** (91 mg, 36%) as a white crystalline solid: mp 133–134 °C; NMR (60 MHz) ($CDCl_3$) δ 1.19 (s, 3, CH_3), 2.91 (s, 3, NCH_3), 3.10 (s, 3, OCH_3), 7.33 (m, 10, Ar); IR (Nujol) 1758 (C=O) cm^{-1}. Anal. $C_{18}H_{19}NO_2$ (C, H, N).

Synthesis of 1,3,4-Triphenyl-3-methoxy-β-azetidinone (15). [Phenylmethoxycarbene]pentacarbonylchromium(0) (156 mg, 0.5 mmol) was combined, in the usual manner, with *N*-phenylbenzylideneimine (90 mg, 0.5 mmol) in petroleum ether (10 mL), in a 100-mL Pyrex Erlenmeyer flask. The reaction was placed in direct sunlight at 27 °C. After 12 h the reaction mixture was heterogeneous and red. Standard oxidative isolation and recrystallization (hexane) yielded **15** (25%, 32 mg) as a white crystalline solid: mp 162–164 °C; NMR (60 MHz) ($CDCl_3$) δ 3.26 (s, 3, OCH_3), 5.14 (s, 1, CH), 7.40 (m, 15, Ar); IR (Nujol) 1750 (C=O) cm^{-1}. Anal. $C_{22}H_{19}NO_2$ (C, H, N).

Synthesis of 1-(4-Methoxyphenyl)-3-methyl-3-methoxy-4-phenyl-β-azetidinone (16). Carbene complex **1** (250 mg, 1 mmol) was combined, in the usual manner, with *N*-(4-methoxyphenyl)benzylideneimine, in petroleum ether (40 mL), in a 100-mL Pyrex Erlenmeyer flask. The flask was irradiated in a Rayonet Photochemical Reactor at 3000 Å. The solution was filtered and placed in a clean flask every 8 h. After 48 h the solution was clear and colorless. Standard nonoxidative isolation and recrystallization (hexane) yielded **16** (178 mg, 60%) as a white crystalline solid: mp 117–119 °C; NMR (CCl_4) δ 1.65 (s, 3, CH_3), 3.10 (s, 3, OCH_3), 3.65 (s, 3, ArOMe), 4.65 (s, 1, CH), 6.60 (m, 1, ArH), 7.10 (m, 7, Ar H); IR (Nujol) 1750 (C=O) cm^{-1}. Anal. $C_{18}H_{19}NO_3$ (C, H, N).

Synthesis of 3-Methyl-3-methoxy-4-phenyl-β-azetidinone (16a) by Oxidation of 16.[23] Ceric ammonium nitrate (480 mg, 0.875 mmol) in 10 mL of H_2O was added to a stirred solution of **16** (52 mg, 0.175 mmol) in CH_3CN (10 mL) over 15 min at 0 °C. After 30 min, water (50 mL) was added, and the resulting aqueous solution was extracted with 2 × 50 mL of ethyl acetate. The organic phase was washed with 3 × 40 mL of 5% aqueous Na_2CO_3 and dried over anhydrous Na_2SO_4. Filtration and solvent removal in vacuo gave **16a** (32 mg, 95%) as a yellow oil, greater than 95% pure by ^1H NMR and homogeneous by analytical thin-layer chromatography: NMR (60 MHz) ($CDCl_3$) δ 1.67 (s, 3, CH_3), 3.05 (s, 3, OMe), 4.45 (s, 1, Ar-CH-N), 6.93 (m, 1, NH), 7.25 (s, 5, Ar); IR (neat) 1755 (C=O) cm^{-1}; exact mass calcd for $C_{11}H_{13}NO_2$, 191.0947; found, 191.0950; mass spectrum, *m/e* 191 (parent), 176 (P − Me), 148 (P − (O=C=NH)), 133 (P − (O=C=NH) + Me), 106 (Ph-C=NH_2), 77 (C_6H_5), 58 (CH_3O-C-CH_3), 43 (CH_3C=O), 28 (CO).

Synthesis of 1-Benzyl-3-methyl-3-methoxy-4-(β-styryl)-β-azetidinone (17). Carbene complex **1** (250 mg, 1.0 mmol) and the *N*-benzylimine of cinnamaldehyde (221 mg, 1.0 mmol) in petroleum ether (50 mL) were irradiated for 6 h with four 20-W Vitalite fluorescent tubes. The resulting brown heterogeneous mixture was filtered, transferred to a Fischer-Porter pressure bottle, pressurized to 90 psi with carbon monoxide, and further irradiated for 24 h. Oxidative isolation and purification with the Chromatotron (40% EtOAc/hexane) followed by recrystallization from hexane/CH_2Cl_2 (95:5) gave a white solid (139 mg, 45%): mp 83–84 °C; ^1H NMR (360 MHz) ($CDCl_3$) δ 1.52 (s, 3, CH_3), 3.45 (s, 3, OCH_3), 3.82 (d, 1, J = 9 Hz, C^4-H), 4.02 (d, 1, J = 15 Hz, CH_2Ph), 4.69 (d, 1, J = 15 Hz, CH_2Ph), 6.18 (dd, 1, J_A = 9 Hz, J_B = 16 Hz, ArCH=CHPh), 6.49 (d, 1, J = 16 Hz, =CHPh), 7.30 (m, 10, Ar); IR ($CDCl_3$) 1755 (C=O) cm^{-1}. Anal. $C_{20}H_{21}NO_2$ (C, H, N).

Synthesis of 18. Carbene complex **1** (125 mg, 0.5 mmol) and 6,7-dimethoxy-3,4-dihydroisoquinoline (85 mg, 0.5 mmol) were combined in an Erlenmeyer flask in diethyl ether (20 mL) in the usual fashion. The flask was placed in the sunlight at 25 °C. After 6 h the solution was deep red and heterogeneous. Standard isolation and oxidation gave an oily solid which was purified by MPLC (florasil, 2:1 hexane/EtOAc) to give **18** (60 mg, 45%) as a white crystalline solid: mp 106–107 °C (this compound slowly decomposes at 25°C); NMR (360 MHz) ($CDCl_3$) δ 1.05 (s, 3, CH_3), 2.84–3.16 (m, 3, CH_2-CH_2), 3.60 (s, 3, OCH_3), 3.85 (s, 6, Ar-OCH_3), 4.08 (m, 1, CH_2CH_2), 4.70 (s, 1, Ar-CH-N), 6.56 (s, 1, Ar H), 6.62 (s, 1, Ar H); IR (Nujol) 1760 (C=O) cm^{-1}; exact mass calcd for $C_{15}H_{19}NO_4$, *m/e* 277.1309; found, *m/e* 277.1317; mass spectrum, *m/e* 277 (parent), 262 (P − 15, 192 ($C_{11}H_{14}NO_2$), 43 (CH_3C=O), 28 (CO).

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Synthesis of 19. Carbene complex **1** (500 mg, 2.0 mmol) and quinoline (325 mg, 2.5 mmol) in petroleum ether (70 mL) were irradiated with four 20-W Vitalite fluorescent tubes for 48 h. Oxidative isolation followed by purification on the Chromatotron (Si_2O) and recrystallization at −78 °C from ether/hexane gave 162 mg (38%) of a solid **19**: mp 59–62 °C. This product decomposes slowly on standing, and acceptable elemental analysis was not obtained. ^1H NMR (360 MHz) ($CDCl_3$) δ 1.56 (s, 3, CH_3), 3.56 (s, 3, OCH_3), 4.79 (dd, 1, CH), 5.93 (dd, 1, J_{cis} = 10 Hz, $J_{allylic}$ = 1.7 Hz, CH=C*H*—CH), 6.48 (dd, 1, J_{cis} = 10 Hz, J = 2.1 Hz, C*H*=CH—CH), 7.08 (m, 2), 7.21–7.28 (m, 1), 7.32 (d, 1, Ar H); IR ($CDCl_3$) 1765 (C=O) cm^{-1}; mass spectrum (NH_3 chemical ionization), m/e 216 (P + 1).

Synthesis of 20. Carbene complex **1** (250 mg, 1.0 mmol) and 6,7-dimethoxy-2-phenyl-4*H*-1,3-benzothiazine (285 mg, 1.0 mmol) were weighed into a 125-mL Pyrex Erlenmeyer flask. The flask was sealed with a rubber serum cap, was evacuated, and was filled with argon (4 cycles) by means of a needle. Dry diethyl ether (60 mL) was transferred by cannula into the flask. The flask was irradiated with either direct sunlight or the Vitalites for 24 h at 25 °C, during which time the mixture turned brown and heterogeneous. The mixture was allowed to air oxidize in ether/hexane in sunlight. After filtration and concentration on a rotary evaporator, the crude product was purified by Chromatotron (2 mm silica gel, 40% ethyl acetate/hexane). Recrystallization from ethanol afforded 226 mg (61%) of **20** as white crystals: mp 187–188 °C; NMR (360 MHz) ($CDCl_3$) δ 1.57 (s, 3, CH_3), 2.92 (s, 3, OCH_3), 3.83 (s, 3, $ArOCH_3$), 3.87 (s, 3, $ArOCH_3$), 4.19 (d, J = 16 Hz, 1, CH_2), 4.87 (d, J = 16 Hz, 1, CH_2), 6.72 (s, 1, ArCH), 6.76 (s, 1, ArCH), 7.32–7.38 (m, 5, Ph); IR ($CDCl_3$) 1765 (C=O) cm^{-1}. Anal. $C_{20}H_{21}NO_4S$ (C, H, N).

Synthesis of 21. By the same procedure as described for **20**, [phenylmethoxycarbene]pentacarbonylchromium(0) (312 mg, 1.0 mmol) and 6,7-dimethoxy-2-phenyl-4*H*-1,3-benzothiazine (285 mg, 1.0 mmol) were irradiated in an ether solution (80 mL) under argon. After 30 h, the solution was allowed to oxidize. Standard isolation and purification by Chromatotron (2 mm silica gel plate, 25% ethyl acetate/hexane) afforded 180 mg (25%) of the β-lactam **21**: mp 151–152 °C; ^1H NMR (360 MHz) ($CDCl_3$) δ 3.21 (s, 3, OCH_3), 3.68 (s, 3, $ArOCH_3$), 3.82 (s, 3, $ArOCH_3$), 4.35 (s, J = 16 Hz, 1, CH_2), 5.00 (d, J = 16 Hz, 1, CH_2), 6.32 (s, 1, ArCH), 6.62 (s, 1, ArCH), 7.25–7.55 (m, 10, Ph); IR ($CDCl_3$) 1770 (C=O) cm^{-1}. Anal. $C_{25}H_{23}NO_4S$ (C, H, N).

Synthesis of 22. By the same procedure as described for **20**, carbene complex **1** (250 mg, 1.0 mmol) and 6,7-dimethoxy-4-phenyl-2*H*-1,3-benzothiazine (285 mg, 1.0 mmol) were irradiated in an ether solution (60 mL) under argon. After 48 h, the solution was allowed to oxidize. Standard isolation and recrystallization from ethyl acetate/hexane afforded 190 mg (51%) of the β-lactam **22**: mp 142–143 °C; NMR (360 MHz) ($CDCl_3$) δ 1.25 (s, 3, CH_3), 3.07 (s, 3, OCH_3), 3.81 (s, 3, $ArOCH_3$), 3.85 (s, 3, $ArOCH_3$), 4.48 (d, J = 12 Hz, 1, CH_2), 5.01 (d, J = 12 Hz, 1, CH_2), 6.63 (s, 1, ArCH), 6.88 (s, 1, ArCH), 7.32–7.51 (m, 5, Ph); IR ($CDCl_3$) 1780 (C=O) cm^{-1}. Anal. $C_{20}H_{21}NO_4S$ (C, H, N).

Synthesis of 23. By the same procedure as described for **20**, carbene complex **1** (125 mg, 0.5 mmol) and 6,7-dimethoxy-4-methyl-2*H*-1,3-benzothiazine (112 mg, 0.5 mmol) were irradiated in an ether solution (50 mL) under argon. After 30 h, the solution was allowed to oxidize. Standard isolation and purification by Chromatotron (2 mm silica gel plate, 40% ethyl acetate/hexane) afforded 59 mg (38%) of the β-lactam **23**: mp 146–147 °C; NMR (360 MHz) ($CDCl_3$) δ 1.05 (s, 3, CH_3), 1.59 (s, 3, N-C-CH_3), 3.59 (s, 3, OCH_3), 3.85 (s, 3, $ArOCH_3$), 3.86 (s, 3, $ArOCH_3$), 4.31 (d, J = 13 Hz, 1, CH_2), 4.80 (d, J = 13 Hz, 1, CH_2), 6.59 (s, 2, ArCH); IR ($CDCl_3$) 1765 (C=O) cm^{-1}. Anal. $C_{15}H_{19}NO_4S$ (C, H, N).

Synthesis of 24. To a solution of the carbene complex **1** (250 mg, 1.0 mmol) in 20 mL of dry CH_2Cl_2 was added 6,7-dimethoxy-2*H*-1,3-benzothiazine (210 mg, 1 mmol) in 20 mL of dry CH_2Cl_2. The solution was irradiated under argon for 48 h during which time the solution turned dark red. The solvent was removed by rotary evaporation. The residue was washed with hexane, and the solid was redissolved in CH_2Cl_2. Both the hexane and CH_2Cl_2 solutions were allowed to oxidize with sunlight. Standard isolation and purification by Chromatotron (2 mm silica gel, 40% EtOAc/hexane) afforded 111 mg (37%) of **24**: mp 161–162 °C; NMR (360 MHz) ($CDCl_3$) δ 1.04 (s, 3, CH_3), 3.57 (s, 3, OCH_3), 3.86 (s, 3, $ArOCH_3$), 3.87 (s, 3, $ArOCH_3$), 4.22 (d, J = 13 Hz, 1, CH_2), 4.80 (s, 1, CH), 4.84 (d, J = 13 Hz, 1, CH_2), 6.56 (s, 1, ArCH), 6.65 (s, 1, ArCH); IR ($CDCl_3$) 1765 (C=O) cm^{-1}. Anal. $C_{14}H_{17}NO_4S$ (C, H, N).

Synthesis of 25. By the same procedure as described for **20**, the phenylcarbene complex (312 mg, 1.0 mmol) and 6,7-dimethoxy-4-phenyl-2*H*-1,3-benzothiazine (285 mg, 1.0 mmol) were irradiated in an ether solution (80 mL) under argon. After 30 h, the solution was allowed to oxidize. Standard isolation and recrystallization from EtOAc/hexane afforded 118 mg (27%) of the β-lactam **25**: mp 186–187 °C; NMR (360 MHz) ($CDCl_3$) δ 3.35 (s, 3, OCH_3), 3.52 (s, 3, $ArOCH_3$), 3.76 (s, 3, $ArOCH_3$), 4.82 (d, J = 12 Hz, CH_2I), 5.15 (d, J = 12 Hz, 1, CH_2), 6.07 (s, 1, ArCH), 6.50 (s, 1, ArCH), 7.30–7.50 (m, 9, Ar), 7.96 (d, 1, Ar); IR ($CDCl_3$) 1755 (C=O) cm^{-1}. Anal. $C_{25}H_{23}NO_4S$ (C, H, N.)

Synthesis of 26. Carbene complex **1** (125 mg, 0.5 mmol) was combined in the usual manner with 2-thiazoline[36] (46 mg, 0.5 mmol) in diethyl ether (20 mL), in a Pyrex 100-mL Erlenmeyer flask. The reaction mixture was placed in direct sunlight at 25 °C. After 4 h the mixture was light orange and heterogeneous. Standard isolation with oxidation afforded **26** (69 mg, 81%) as a crystalline solid: mp 29 °C; NMR (360 MHz) ($CDCl_3$) δ 1.38 (s, 3, CH_3), 2.75, 2.82, 3.05, 4.18 (m, 1 each, CH_2–CH_2), 3.48 (s, 3, OMe), 5.06 (s, 1, CH); IR (neat) 1755 (C=O) cm^{-1}. Anal. $C_7H_{11}NO_2S$ (C, H, N).

Synthesis of 27. Carbene complex **1** (125 mg, 0.5 mmol) was combined with 2-phenyl-2-thiazoline[36] (85 mg, 0.5 mmol) in diethyl ether (20 mL) in a 100-mL Pyrex Erlenmeyer flask. The flask was placed in direct sunlight at 25 °C. After 4 h the mixture was brownish red and heterogeneous. Standard isolation with oxidation and purification by recrystallization (hexane) gave **27** (59 mg, 52%) as a highly crystalline white solid: mp 105–106 °C; NMR (360 MHz) ($CDCl_3$) δ 1.63 (s, 3, CH_3), 3.00 (s, 3, OCH_3), 3.15 (m, 2, CH_2–CH_2), 3.20 (m, 1, CH_2CH_2), 4.31 (m, 1, CH_2CH_2), 7.30 (m, 5, Ar H); IR (Nujol) 1770 (C=O) cm^{-1}. Anal. $C_{13}H_{15}NO_2S$ (C, H, N).

Synthesis of 28. A solution of methyl D-5,5-dimethyl-Δ2-thiazoline-4-carboxylate ($[\alpha]^{25}_D$ +51.9°)[26] (0.17 g, 1.00 mmol) in CH_2Cl_2 (50 mL) was introduced into an Erlenmeyer flask containing complex **1** (0.25 g, 1.00 mmol) under argon at room temperature. The yellow solution was irradiated under sunlight or fluorescent tubes. After 1 h of irradiation the solution became orange, and after 2 days it became black. The black solution was evaporated in vacuo to give a greenish residue to which 100 mL of petroleum ether was added. The mixture was filtered and the yellow filtrate was oxidized in air with irradiation until it became colorless. After filtration, the filtrate was evaporated in vacuo. Purification by recrystallization from hexane gave white crystals: mp 59 °C (0.11 g, 42%); $[\alpha]^{25}_D$ +218.1° (c 1, $CHCl_3$); NMR ($CDCl_3$) 1.46 (s, 3, CH_3), 1.52 (s, 3, CH_3), 1.57 (s, 3, CH_3), 3.50 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 4.44 (s, 1, CH), 5.42 (s, 1, CH); IR (CCl_4) 1780 (s, C=O), 1755 (s, C=O), 1460 (m, OCH_3), 1440 (m, OCH_3). Anal. $C_{11}H_{17}NO_4S$ (C, H, N).

Synthesis of 29. Carbene complex **1** (125 mg, 0.5 mmol) was combined, in the usual manner, with (*S*)-*N*-(α-phenethyl)benzylideneimine (105 mg, 0.5 mmol) in petroleum ether (20 mL) in a Pyrex 100-mL Erlenmeyer flask. The reaction mixture was placed in direct sunlight at 29 °C. After 8 h the mixture was heterogeneous and green. Standard isolation, without oxidation, and Chromatotron purification (2 mm, 2:1 hexane/ethyl acetate) yielded **29** (74%, 108 mg) as a semi solid oil. NMR spectra indicated that the sample contained both the *S,R,S* and the *R,S,S* isomers but was free of detectable amounts of side products. The diastereomeric excess was 15%. Because of the low value, further purification was not carried out. NMR (360 MHz) ($CDCl_3$) δ 1.30 (d, J = 7.75 Hz, 1.28 (Ar-CH-C*H*$_3$), 1.85 (d, J = 7.75 Hz), 1.72 (Ar-C-H-CH_3), 1.41 (s, 1.28, CH_3), 1.56 (s, 1.72, CH_3), 2.95 (s, 1.28, OMe), 2.973 (s, 1.72, OMe), 3.97 (s, 0.426, CH), 4.08 (s, 0.573, CH), 4.23 (q, J = 7.75 Hz, 0.57, ArC*H*-CH_3), 5.04 (q, J = 7.75 Hz, 0.42, ArC*H*-CH_3), 7.20 (m, 10, Ar); IR (neat) 3055, 3025, 2970, 2925, 2830, 1750, 1490, 1450, 1370, 1340, 1310, 1270, 1210, 1105, 1040, 1025, 755, 695 cm^{-1}; mass spectrum, m/e 295 (parent), 209 (P − OC=C(OMe(Me)), 148 (P − OC=N-α-phenethyl), 105 ($PhCHCH_3$), 91 ($PhCH_2$), 77 (C_6H_5), 58 (CH_3–OC–CH_3), 28 (CO); exact mass calcd for $C_{19}H_{21}NO_2$, 295.1573; found, 295.1569.

Synthesis of 30. Carbene complex **1** (125 mg, 0.5 mmol) was combined in the usual manner, with *N*-[(2*S*,3*S*)-1,3-bis(trimethylsiloxy)-3-phenylpropan-2-yl]benzylidineimine[37] (204 mg, 0.5 mmol) in petroleum ether, in a 100-mL Pyrex Erlenmeyer flask. The reaction flask was placed in direct sunlight at 25 °C. After 8 h the mixture was yellow and heterogeneous. Standard oxidative isolation gave **30** (220 mg, 91%) as a clear oil. Compound **30** was found by NMR to be a mixture of two isomers in the ratio of 78.9 to 21.1 and was free of detectable amounts of side products. The diastereomeric excess was 57.8%, and further purification was not attempted. NMR (360 MHz) ($CDCl_3$) δ 0.1 (m, 18, $Si(Me)_3$), 1.26 (s, 2.37, CH_3), 1.61 (s, 0.63, CH_3), 3.01 (s, 2.37, OCH_3), 3.08 (s, 0.63, OCH_3), 3.40 (m, 1.58, O–C*H*$_2$–CH), 3.56 (m, 0.42, O–C*H*$_2$–CH), 4.08 (m, 0.79, N–C*H*–CH_2), 4.18 (m, 0.21, NC*H*–CH_2), 4.20 (s, 0.21, N–C*H*–Ph), 4.62 (s, 0.79, N–C*H*–Ph), 5.10 (d, J = 5.4 Hz, 0.21, Si–O–C*H*–Ph), 5.19 (d, J = 5.4 Hz, 0.79, Si–OC*H*–Ph), 7.35 (m, 10, Ph); IR (neat) 3060, 3025, 2950, 2900, 2830, 1750, 1595, 1575, 1490, 1445, 1390, 1360, 1240, 1200, 1100, 1080, 1060, 1040, 1015,

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860, 830, 740, 680, 635 cm^{-1}; exact mass calcd, m/e 485.2419; found, m/e 485.2441; mass spectrum, m/e 485 (parent), 470 (P – Me), 397, 276 (P – (2(OSi=)-(OMe))), 179 (Ph-CH-OSi=, 148 ((MeO)$_2$—C=CPhH), 131 (Ph—CH=CHC=O), 28 (CO).

Synthesis of 31. To a solution of complex **1** (375 mg, 1.5 mmol) in petroleum ether (50 mL) in a Pyrex Erlenmeyer flask under argon at 25 °C was added 328 mg (1.5 mmol) of the *N*-(L-valine methyl ester)-benzylideneimine. The flask was irradiated with either direct sunlight or the 20-W Vitalites. After 30 h, TLC showed unreacted imine still present. An additional 100 mg of the carbene was added, and the solution was irradiated for 48 h. Oxidation, filtration, and concentration gave 285 mg (62%) of a yellow oil. High-field NMR spectra indicated that the sample contained both the *S,R,S* and the *R,S,S* isomers and was free of detectable amounts of side products. The diastereomeric excess was 60%. Further characterization was not attempted. IR (neat) 1740–1730 cm^{-1} (strong, broad).

Minor isomer: NMR (360 MHz) 0.94 (d, J = 6.8 Hz, 3 H, CH_3), 1.13 (d, J = 6.8 Hz, 3 H, CH_3), 1.64 (s, 3 H, CH_3), 2.57 (m, 1 H, CH), 3.04 (s, 3 H, OCH_3), 3.46 (s, 3 H, CO_2CH_3), 3.72 (d, J = 8.6 Hz, 1 H, CH), 4.39 (s, 1 H, PhCH), 7.34–7.45 (m, 5 H, Ar).

Major isomer: NMR 0.78 (d, J = 6.8 Hz, 3 H, CH_3), 0.91 (d, J = 6.8 Hz, 3 H, CH_3), 1.63 (s, 3 H, CH_3), 2.03 (m, 1 H, CH), 3.05 (s, 3 H, OCH_3), 3.73 (s, 3 H, CO_2CH_3), 4.04 (d, J = 7.2 Hz, 1 H, CH), 4.65 (s, 1 H, PhCH), 7.34–7.45 (m, 5 H, Ar).

X-ray Structure Determinations.[38] For compound **27** ($C_{13}H_{15}NO_2S$) at −130 °C, a = 6.887 (2) Å, b = 13.042 (6) Å, c = 13.257 (8) Å; $P2_12_12_1$, ρ_c = 1.39 g cm^{-3} (Z = 4, formula weight = 249.32). The intensities of 1257 reflections ($h, k, l \geq 0$) were measured by $\theta - 2\theta$ scans on the Nicolet $R3m/E$ diffractometer (Mo K_α radiation, graphite monochromator). Intensities of 974 unique, observed reflections ($I > 2_\sigma(I)$) were used in refinement of the structure. The structure was solved (by Patterson interpretation and successive Fourier map analyses) and refined by using the SHELXTL programs supplied with the $R3m/E$ computing system. Anomalous scattering of Mo K_α radiation was not of sufficient magnitude to unambiguously fix the absolute configuration of the enantiomer contained in the data collection crystal. The final structural model included anisotropic thermal parameters for non-hydrogen atoms, together with placement of hydrogen atoms in idealized positions. This model refined to convergence with R = 0.039 R_w = 0.039, and GOF = 1.60.

For compound **28** ($C_{11}H_{17}NO_4S$) at 20 (1) °C, a = 6.357 (2) Å, b = 9.815 (4) Å, c = 20.987 (6) Å; $P2_12_12_1$, ρ_c = 1.32 g cm^{-3} (Z = 4, formula weight = 259.32). The intensities of 1417 reflections ($h, k, l \geq 0$) were measured by θ–2θ scans on the Nicolet $R3m/E$ diffractometer (Mo K_α radiation, graphite monochromator). Intensities of 1297 unique, observed ($I > 2\sigma(I)$) reflections were used in refinement of the structure. The structure was solved (by direct methods) and refined using the SHELXTL programs supplied with the $R3m/E$ computing system. The final structural model, which was consistent with the known absolute configuration at C3, included anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions. This model refined to convergence with R = 0.042, R_w = 0.047, and GOF = 1.38.

(38) Structural work performed by Professor Oren Anderson, Colorado State University. Full details of these structural studies will be published elsewhere.

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Preparative Production of Optically Active Esters and Alcohols Using Esterase-Catalyzed Stereospecific Transesterification in Organic Media

Bernard Cambou and Alexander M. Klibanov*

Contribution from the Laboratory of Applied Biochemistry, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.
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Abstract: A novel enzymatic approach to the production of optically active alcohols and esters from racemates is developed. It involves the use of esterase catalyzed transesterifications carried out in biphasic aqueous–organic mixtures. Water-insoluble substrates constitute the organic phase, while the enzyme is located in the aqueous phase. Since the fraction of the latter phase can be made very low, such an arrangement solves the problem of both the competition of an alcohol (the nucleophile) with water in the enzymatic reaction and poor solubility of most organic esters and alcohols in water. By use of porous supports (Sepharose or Chromosorb) filled with aqueous solutions of hog liver carboxyl esterase as a stereoselective catalyst and methyl propionate as a matrix ester, the following optically active alcohols and their propionic esters were produced on a preparative scale: 3-methoxy-1-butanol, 3-methyl-1-pentanol, 3,7-dimethyl-1-octanol, and β-citronellol. To overcome a rather narrow substrate specificity of hog liver carboxyl esterase, a nonspecific lipase from yeast (*Candida cylindracea*) also was employed as a stereoselective transesterification catalyst. Using an aqueous solution of this enzyme confined to the pores of Chromosorb and tributyrin as a matrix ester, we have prepared gram amounts of the following optically active alcohols and their butyric esters: 2-butanol, *sec*-phenethyl alcohol, 2-octanol, 1-chloro-2-propanol and 2,3-dichloro-1-propanol (subsequently nonenzymatically converted to optically active propylene oxide and epichlorohydrin, respectively), 6-methyl-5-hepten-2-ol, and 1,2-butanediol.

Most hydrolases can catalyze not only their "natural" reaction of hydrolysis but also that of transesterification.[2] For example, carboxylesterase[3] is capable of accepting nucleophiles other than water, such as various alcohols.[4] The ability of hog liver carboxylesterase to asymmetrically hydrolyze chiral and prochiral esters has been widely used for the preparative syntheses of op-

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