A Contribution to the Confusion Surrounding the Reaction of Ketenes with Imines To Produce β-Lactams. A Comparison of Stereoselectivity Dependence on the Method of Ketene Generation: Acid Chloride/Triethylamine vs Photolysis of Chromium–Carbene Complexes

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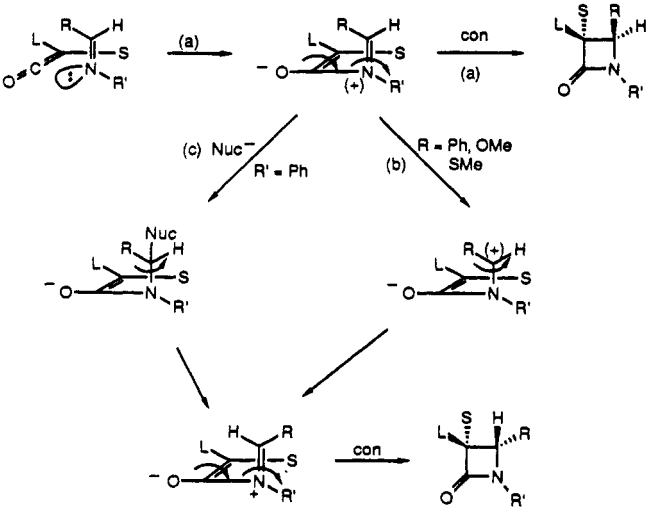
Abstract: The stereoselectivity of the reaction of imines of benzaldehyde and cinnamaldehyde with ketenes generated by the reaction of optically active oxazolidinone acid chlorides with triethylamine and complexed ketenes generated by photolysis of optically active oxazolidine- and oxazolidinone–chromium–carbene complexes in the presence and absence of added triethylamine was compared. The absolute stereochemistry was determined primarily by the structure of the chiral auxiliary. The relative (cis–trans) stereochemistry was determined primarily by the structure of the imine and the free or bound character of the ketene. Triethylamine addition to reactions of carbene complexes afforded results that closely paralleled that of acid chloride generated ketenes. A mechanistic scheme accounting for these results and the general trends observed in other ketene/imine cyclizations is provided.

Introduction

Although the reaction of ketenes with imines to produce β-lactams (the Staudinger reaction)[1] has been known for over 80 years, the mechanism(s) by which this reaction proceeds and the rationale for the stereoselectivity observed remain obscure. This uncertainty is, in part, due to the high reactivity of ketenes and the necessity to generate the less stable members in situ, usually from acid chlorides and tertiary amines.[2] This raises the possibility that species such as the acid chloride, the tertiary amine, the amine hydrochloride salt, *N*-acylammonium, or *N*-acyliminium species may play a role in the reaction. A recent low-temperature FTIR study of the reaction of acid chlorides with imines in the presence of base to form β-lactams was interpreted to show β-lactam formation occurring exclusively through a ketene intermediate.[3] Two chiral centers may be generated in this process, and both the relative and absolute stereochemistries of these two centers are often of critical concern in the use of this reaction in the synthesis of biologically active β-lactams.[4] However, the stereochemical outcome of the reaction is hard to predict and depends on the structure of the imine, on the ketene precursor, on the sequence of reagent addition, on the solvent, and on the nature of the base used to produce the ketene from the acid chloride. The current view of the reaction mechanism (Scheme I)[5] accounts for some of this variability.

Nucleophiles attack the LUMO of the ketene carbonyl group, which is coplanar to the ketene substituents.[6] Attack is thought to occur from the *less* hindered side of the ketene (path a, over the Small group) with the plane of the imine perpendicular to that of the ketene (although, because of symmetry, any dihedral angle is permitted), generating the zwitterionic intermediate. Rotation of the imine into the plane of the ketene in concert with a conrotatory ring closure produces the β-lactam in which the imine R group and the *large* group on the ketene are cis, the thermodynamically *less* stable β-lactam. This is, in fact, the stereochemistry observed with many imines. Note that conrotatory ring closure can *only* occur with the sense shown (clockwise), since closure in the other direction (counterclockwise) would necessitate the R and S groups to pass through each other. This is of no consequence with achiral systems but becomes important in chiral systems, since these closures are enantiomeric at the two newly formed stereogenic centers. Asymmetry can be induced in this process by controlling the orientation of the imine with respect to the plane of the ketene; attack with R over the top face of the ketene followed by conrotatory ring closure, as shown, will produce one enantiomer, while attack with R under the bottom face followed by conrotatory ring closure will produce the other enantiomer.

Scheme I



When the substituent R on the imine sp^2 carbon can stabilize positive charge (e.g., Ph, OMe, or SMe), the zwitterionic intermediate may undergo isomerization from the more stable trans imine geometry[7] to the cis form (path b) before (or during) cyclization, producing the thermodynamically more stable β-lactam having the R group and the large group trans to each other. This is, in fact, the stereoselectivity observed with imidates and thioimidates, and in some cases with benzaldehyde imines. If the

(1) Staudinger, H. *Justus Liebigs Ann. Chem.* **1907**, *356*, 51.
(2) For a review of ketene–imine cycloaddition to produce β-lactams, see: Holden, K. G. *Total Synthesis of Penicillins, Cephalosporins, and Their Nuclear Analogs.* In *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; Vol. 2, pp 114–131.
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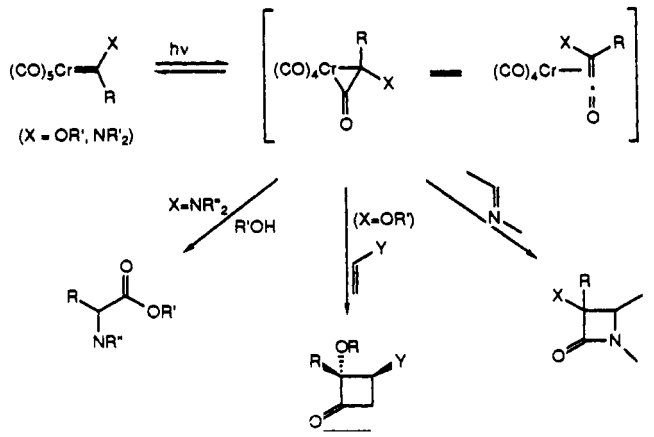
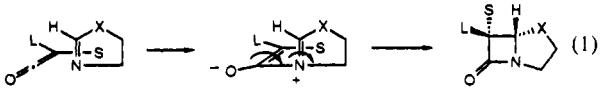
Scheme II

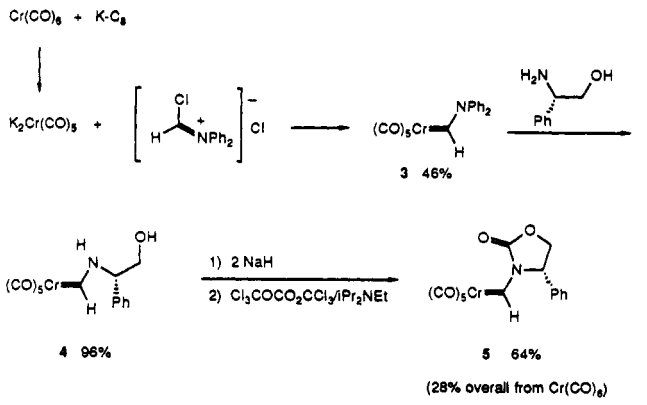


R′ group on nitrogen is large, this isomerization can be suppressed to some degree.[8] Isomerization of the zwitterionic intermediate can also occur by addition of nucleophiles to the zwitterion followed by rotation and elimination (path c).[9] The relative rates of each of these processes determine the stereochemical outcome of any particular ketene/imine reaction. Note that with cyclic imines such as thiazolines, oxazolines, etc., the imine substituents are held in the cis geometry by the ring and rearrangement cannot occur. Thus, cyclic imines generally give β-lactams having trans geometry (eq 1).

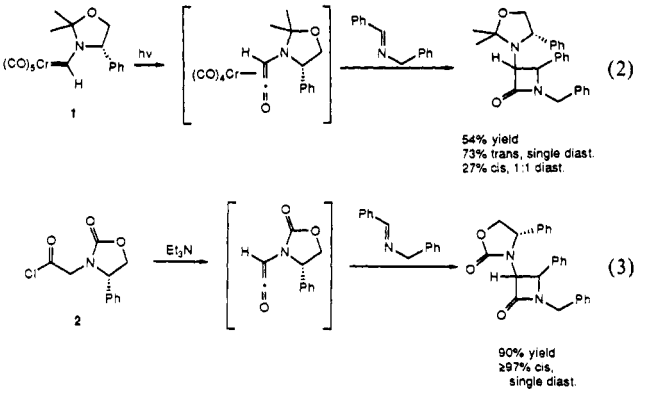


Recent research in these laboratories has shown that photolysis of heteroatom-stabilized "Fischer" chromium–carbene complexes[10] generates species that undergo reactions typical of ketenes,[11] although free ketenes could not be detected nor were products typical of free ketenes (ketene dimers, multiple incorporation of ketene) produced (Scheme II). Thus, photolysis of aminocarbene complexes in the presence of alcohols produced α-amino esters,[12] the product expected from reaction of an aminoketene with an alcohol. Photolysis of alkoxycarbene complexes in the presence of olefins produced cyclobutanones[13] with exactly the same stereoselectivity (the large groups cis) expected and observed in acid chloride/triethylamine/olefin reactions.[14,15] Aminocarbene complexes failed to react with olefins unless electron-withdrawing aryl groups were on the nitrogen to enhance the electrophilicity of the "ketene" carbonyl.[16] Similarly, only *N*-arylglycine derivatives produced cyclobutanones when exposed to olefins under "ketene-generating" conditions.[17] Photolysis of both alkoxy[18] and aminocarbene[19,20] complexes in the presence of imines produced β-lactams, with a high degree of stereoselectivity. In most cases, the stereoselectivity was exactly that expected for a typical ketene–imine cycloaddition—cyclic imines and imidates gave exclusively trans-substituted β-lactams, while acyclic imines gave mixtures of cis and trans β-lactams. Thus, the chromium appeared to exert little influence on the stereoselectivity, raising the possibility that free, not metal-bound, ketenes were indeed involved.

Scheme III



Photolysis of optically active aminocarbene complex **1** with a wide variety of imines produced optically active β-lactams in excellent chemical yield and with very high (≥97%) diastereoselectivity.[20] However, with the *N*-benzylimine of benzaldehyde, a mixture of both cis and trans β-lactams was obtained and the desired cis isomer was a ~1:1 mixture of diastereoisomers. Thus, control of both relative and absolute stereochemistry was low (eq 2). This stands in stark contrast to the reaction of a structurally



closely related optically active ketene generated from the acid halide (eq 3),[21] which underwent reaction with the same imine with very high cis selectivity and diastereoselectivity. The following experiments were carried out to probe if this difference in stereoselectivity was due to the small differences in the structures of the chiral auxiliary (oxazolidine vs oxazolidinone) or, instead, due to differences in behavior between free and metal-bound ketenes.

Results and Discussion

A major difficulty in directly comparing ketenes derived from acid chlorides with those species derived from the photolysis of chromium–carbene complexes is that the very features that stabilize carbene complexes and make them easy to prepare and handle (electron rich, donating heteroatoms on the carbene carbon) destabilize ketenes and are often incompatible with acid chlorides. For example, (aminocarbene)chromium complexes are among the most stable and easily prepared, while the corresponding α-amino acid chlorides are unstable and difficult to prepare. α-*N*-Acylamino acid chlorides (such as **2**) can be prepared, but the corresponding [(*N*-acylamino)carbene]chromium complexes are difficult to prepare and are relatively unstable.[22] This makes these

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(11) Hegedus, L. S.; deWeck, G.; D'Andrea, S. *J. Am. Chem. Soc.* **1988**, *110*, 2122.
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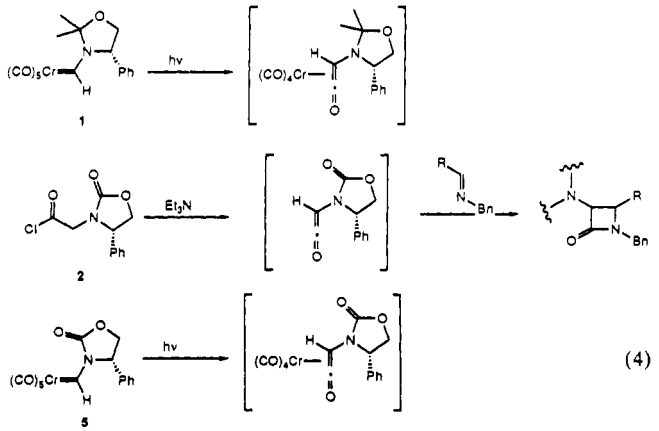
Table I

ketene precursor	imine subst R	additive	chem yield, %	isomer distribn			
				cis_a	cis_b	$trans_a$	$trans_b$
1	MeO (6)	CO	90			>97	
2		Et_3N	65			>97	
5		CO/Et_3N	43			>97	
		CO	56			>97	
1	Ph (7)	CO	54	16	11	73	
		CO/Et_3N	53	47	45	8	
2		Et_3N	90	97	3		
5		CO/Et_3N	67	>97			
		CO	85	34		38	28
1	PhCH=CH (8)	CO	82	10	16	70	4
		CO/Et_3N	75	16	18	57	9
		CO/DMAP	66	50	36	11	3
2		Et_3N	82	95	5		
5		CO/Et_3N	40	78	7	15	
		CO	37	36	18	46	
1	CH_3 (9)	CO	61	17		83	
		CO/Et_3N	56	46		54	
2		Et_3N	30			>97	
1		CO	95			>97	
2		Et_3N	<10			>97	
5		CO	10			>97	
	10						
1		CO	91			>97	
2		Et_3N	0				
	11						

two methods for ketene generation complementary instead of competitive, but also makes direct comparison difficult. However, recently developed methods[23] for synthesizing functionalized (aminocarbene)chromium complexes made it possible to synthesize the chromium–carbene complex corresponding to the optically active (oxazolidinone)ketene in eq 3, for use in comparative studies. The synthesis is outlined in Scheme III.

(Aminocarbene)chromium complexes are normally made from alkoxycarbene complexes by exchange.[24] However, chromium–alkoxycarbene complexes having a hydrogen on the carbene carbon have not yet been reported and may not be stable. The (diphenylamino)carbene complex **3** is readily prepared, albeit in modest yield, and undergoes facile exchange with a wide range of nucleophiles, including phenylglycinol, to give carbene complex **4**. Closure of the oxazolidinone ring using triphosgene as the acylating agent gave the desired (oxazolidinone)carbene complex **5**. With this material in hand, *direct* comparisons of reactivity toward imines between oxazolidinone acid chloride **2**, (oxazolidinone)carbene complex **5**, and (oxazolidine)carbene complex **1** could be made (eq 4).



(4)

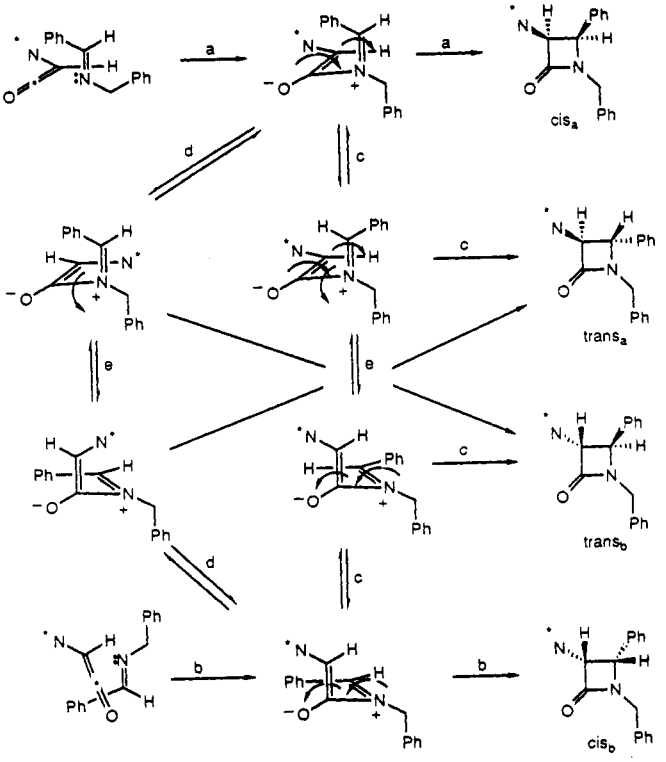
(23) (a) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814. (b) Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 6255.

(24) For a detailed discussion of aminolysis of alkoxycarbene complexes see: Kreissl, F. R. In *Transition Metal Carbene Complexes*; Seyferth, D., Ed.; Verlag Chemie: Deerfield Beach, FL, 1983.

The reactions with acid chloride **2** were all run under the standard conditions originally reported for this compound[21]—addition of 1.5 equiv of triethylamine to **2** at −78 °C in methylene chloride, followed by addition of the imine. The reactions with carbene complexes **1** and **5** were carried out under two different sets of conditions: (1) irradiation in methylene chloride solvent at ~30 °C under an atmosphere (60 psi) of carbon monoxide; (2) the same, but in the presence of 2 equiv of triethylamine, to correspond to the excess triethylamine used in the acid chloride **2** experiments. The relative (cis, trans) stereochemistry of the β-lactams was assigned by comparison to previously reported compounds for imines **7** and **8** and from ^1H NMR coupling constants of the β-lactam methine protons, with J_{cis} = 4–6 Hz and J_{trans} = 0–2 Hz. The results are presented in Table I.

To summarize, (oxazolidine)carbene complex **1** gave excellent chemical yields of *single* diastereoisomers of β-lactams in photochemical reactions with imidates, oxazines, thiazines, and cyclic and acyclic aliphatic imines, but moderate chemical yields of *mixtures* of diastereoisomers of β-lactams with imines of benzaldehyde and cinnamaldehyde. With these two imines, trans β-lactams were the major products formed, with high diastereoselectivity. Added triethylamine drastically suppressed the formation of trans β-lactams, but diastereoselectivity in the cis manifold remained very low. In contrast, oxazolidinone acid chloride **2** gave low to very low yields of single trans diastereoisomers of β-lactams with imidates, oxazines, and cyclic and acyclic aliphatic imines, but excellent chemical yields of *single* cis diastereoisomers of β-lactams with imines of benzaldehyde and cinnamaldehyde.[21] In the presence of triethylamine, (oxazolidinone)carbene complex **5** was very similar to **2** in its reactions with these same imines, giving cis β-lactams with excellent diastereoselectivity. In the absence of triethylamine, substantial amounts of trans β-lactams were formed. Only imidate **6** gave comparable results with all three ketene precursors. That the same *absolute* configuration was obtained with this substrate in all three cases was shown by conversion of the *oxazolidine* auxiliary, in the β-lactam derived from **1**, to the *oxazolidinone*, by hydrolysis followed by recyclization to the *oxazolidinone* with triphosgene to produce the *same* compound obtained from the reaction of **6** with **2** and with **5**. These differences in stereoselectivity among the three ketene precursors and particularly the changes in stereoselectivity upon addition of triethylamine are best considered in the context of Scheme IV, which details the possible stereo-

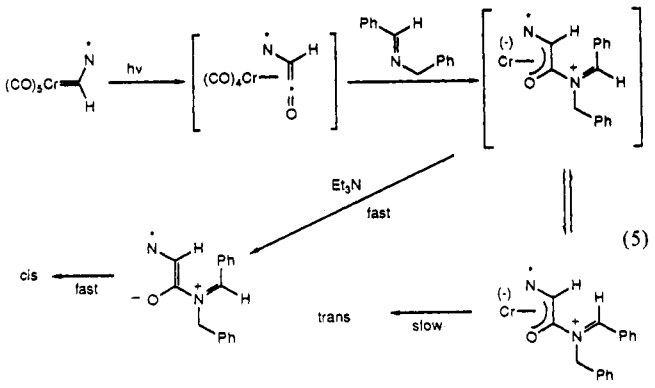
Scheme IV



chemical outcomes of ketene/imine reactions.

With optically active ketenes such as those from **1**, **2**, and **5**, attack by the imine from the less hindered side of the ketene can occur with two different perpendicular orientations: above, as in path a or, below, as in path b. For ketenes exhibiting high diastereoselectivity in the cis manifold, such as those derived from **2** or **5** in the presence of triethylamine, differentiation between these two approaches must be high and cyclization of the zwitterion must be faster than any of the possible isomerizations. If reaction conditions or structural features in the ketene or imine slow the cyclization step or accelerate isomerization or both, stereoselectivity may be drastically altered, even if initial selectivity between paths a and b is high. If Scheme IV is accurate, *any* formation of the thermodynamically more stable trans β-lactam from a trans imine can only result from isomerization of either the iminium portion (path c) or the enolate portion (path d) of the zwitterion prior to cyclization. Isomerization should be promoted by substituents that stabilize positive charge on the iminium carbon and/or by substituents that stabilize the enolate, slowing cyclization relative to isomerization. If cyclization does not proceed directly from the initially formed zwitterion, all four diastereoisomeric β-lactams are accessible from any single zwitterion by isomerization followed by rotation about the C–N single bond (path e).

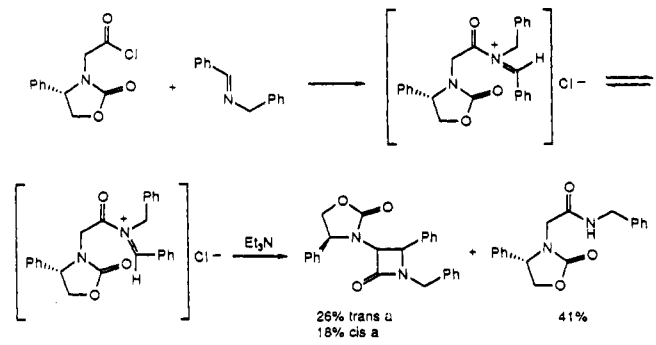
Formation of a single trans β-lactam as the major product and minor amounts of a 1:1 mixture of cis β-lactams from photolysis of carbene complex **1** with the trans benzaldehyde and cinnamaldehyde imines **7** and **8** is consistent with attack of the imine on the chromium-complexed ketene to give zwitterions in which the enolate portion is stabilized by coordination to chromium,[25] slowing cyclization. Isomerization of these zwitterions to the one that produces the single observed trans β-lactam followed by ring closure leads to the observed results. The small amount of cis β-lactam results from direct cyclization of the two zwitterions formed either by nonselective attack of the imine (path a ≅ path b) or by isomerization about the C–N single bond (path e). Addition of triethylamine destabilizes (in the case of **8** *p*-(dimethylamino)pyridine/(DMAP) is more efficient) the chromium enolate, perhaps through coordination to chromium, accelerating cyclization directly from the initially formed intermediates, giving a ~1:1 mixture of cis β-lactams and very little trans (eq 5).



(5)

Similar arguments hold for carbene complex **5** in its reactions with **7**, except this chromium-bound ketene, as does the free ketene, discriminates cleanly between paths a and b, giving a single cis β-lactam and an equilibrated 1:1 mixture of trans β-lactams in the absence of triethylamine and predominantly a single cis β-lactam in the presence of this additive. With cinnamaldehyde imine **8**, carbene complex **5** is less selective in the cis manifold (2:1) in the absence of triethylamine. Addition of triethylamine again almost completely supressed formation of trans product and greatly improved selectivity in its cis manifold (11:1).

Two additional experiments support this interpretation. Treatment of acid chloride **2** with the benzaldehyde imine **7** at 0 °C resulted in complete consumption of acid chloride (by infrared spectroscopy) in 1 h. Addition of triethylamine and stirring overnight resulted in a 60:40 mixture of $trans_a$ and cis_a (by comparison to material from Table I) β-lactams as well as substantial amounts of hydrolysis product (eq 6). In this case, isomerization of the *N*-acyliminium ion prior to cyclization as is postulated in eq 6 could occur.

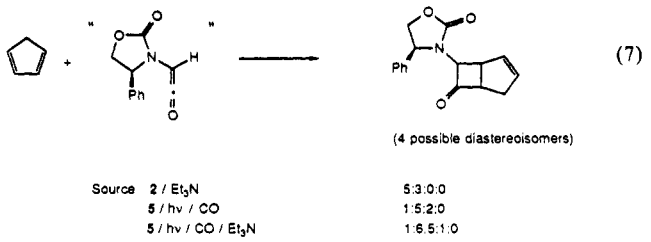


(6)

Generation of free ketene by photolysis of carbene complex **5** in the presence of triethylamine (an alternative explanation for the change in stereoselectivity) was discounted by comparison of the reaction of cyclopentadiene with acid chloride **2**, carbene complex **5**, and carbene complex **5** plus triethylamine, to give the cyclobutanone (eq 7). In contrast to the two-step mechanism proposed for β-lactam formation, ketene/olefin reactions are thought to proceed in a concerted manner without the possibility of isomerization, the stereoselectivity being determined solely by structural features in the ketene and olefin.[14] Thus, free ketene, regardless of its genesis, should always give the same distribution of diastereoisomers. The fact that carbene complex **5** gave the *same* distribution of diastereoisomeric cyclobutanones in the presence and absence of triethylamine and that distribution was

(25) Analogous tungsten and molybdenum carbon and η^3-bound enolates have been isolated. Burkhardt, E. R.; Doney, J. J.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 2022.

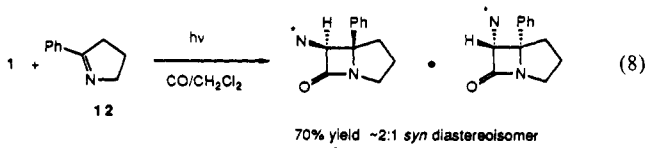
(26) The syn (phenyl vs N) stereochemistry for these β-lactams was assigned based on the relatively downfield position of the C–H α to the chiral amino group. Protons syn to a phenyl in the position appear at δ ~3.7–3.8, while those anti appear at δ 4.3–4.6. The CH signals for the β-lactams in eq 9 and 10 are at δ 4.29 and 4.56, respectively, indicating that they are anti to the phenyl group.



(7)

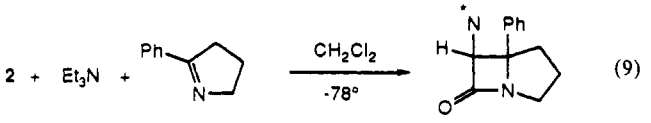
different from that obtained from acid chloride **2** argues against the intermediacy of free ketenes in the photochemical reactions of carbene complexes **1** and **5** in the presence of triethylamine.

To determine if the lack of diastereoselectivity of (oxazolidine)carbene complex **1** in its reactions with imines of aromatic aldehydes was related to the ability of the imine to undergo isomerization during the reaction process, cyclic imine **12**, which cannot isomerize, was treated with (oxazolidine)carbene complex **1** and oxazolidinone acid chloride **2** under the conditions described above (eqs 8 and 9). As expected from Scheme IV, only β-lactams



(8)

70% yield ~2:1 *syn* diastereoisomer



(9)

6% single, *syn* diastereoisomer

having the phenyl and amino groups syn[23] were obtained, confirming attack from the less hindered side of the ketene and no enolate isomerization at the zwitterionic stage. However, even with this cyclic substrate, the (oxazolidine)carbene complex **1** was relatively nondiscriminating, giving good yields of a ~2:1 mixture of the two syn diastereoisomers, while the oxazolidinone acid chloride was very selective, giving a single syn β-lactam, albeit in very poor yield.

In conjunction with the studies discussed above, these results suggest that the observed differences in stereoselectivity among ketene precursors **1**, **2**, and **5** are indeed primarily due to the relatively small differences in structure between the oxazolidine and oxazolidinone chiral auxiliaries, although coordination to chromium also influences the stereochemical outcome of reactions involving photolysis of chromium–carbene complexes. The absolute stereochemistry was determined primarily by the structure of the chiral auxiliary. The relative (cis, trans) stereochemistry was determined primarily by the structure of the imine and the free or bound character of the ketene. Triethylamine addition to reactions of carbene complexes afforded results that closely paralleled that of acid chloride generated ketenes.

Experimental Section

General Procedures. Photolysis reactions were carried out in Pyrex test tubes or Pyrex pressure tubes placed at a distance of 10 cm from a Conrad-Hanovia 7825 medium-pressure mercury lamp operating at 450 W, which was placed in a water-cooled immersion well. A Conrad-Hanovia 7830-C power supply was used. Reactions run under CO pressure were saturated with CO (three cycles to 80 psi of CO) and were photolyzed under atmospheric pressure or 80 psi of CO. Oxidation of reaction mixtures was carried out by saturating a 1:1 hexane/EtOAc solution of the crude product with air and oxidizing in a light box equipped with six 20-W Vitalite fluorescent lamps until most of the chromium residue had turned brown and precipitated (usually overnight).

Materials. Literature methods were used to prepare (*S*)-phenylglycinol,[27] the *N*-benzylimine of benzaldehyde,[18] the *N*-benzylimine of cinnamaldehyde,[18] the *N*-benzylimine of acetaldehyde,[18] methyl *N*-benzylformimidate,[28] 3,4-dihydro-5-phenyl-2*H*-pyrrole,[29] 5,6-dihydro-4*H*-1,3-oxazine,[30] 2,3,4,5-tetrahydropyridine trimer,[31] [(*S*)-4-phenyl-2-oxooxazolidin-3-yl]acetyl chloride (**2**),[21] and pentacarbonyl[((5*S*)-2,2-dimethyl-5-phenyl-1,3-azoxacyclopentyl)methylene]chromium.[23a]

Synthesis of Pentacarbonyl[(diphenylamino)methylene]chromium (3). To *N*,*N*-diphenylformamide (2.96 g, 15 mmol) in dry THF (45 mL) under argon was added oxalyl chloride (1.96 mL, 22.5 mmol) by syringe, and the mixture was heated at reflux for 5 h. The solvent was removed by rotary evaporation, and the crude mixture was left under vacuum overnight to remove unreacted oxalyl chloride. The potassium dianion ($K_2Cr(CO)_5$; 15 mmol) was prepared[23a] in a 100-mL airlessware flask in dry THF (50 mL). The dianion solution was cooled to −78 °C, and the orange Vilsmeier reagent was added by cannula as an airless solution in THF (15 mL). This solution was warmed to −20 °C over 4 h and was then stirred in a 25 °C bath for 0.5 h. The final deep red solution was filtered through Celite, was adsorbed onto silica gel, and was transferred onto a silica gel column. Elution with hexane gave an orange band followed by a red band. The orange band was collected and concentrated to yield 2.60 g (46%) of pentacarbonyl[(*N*,*N*-diphenylamino)-methylene]chromium(0) as a yellow crystalline solid. Spectroscopic data were identical with that previously reported.[32]

Synthesis of Carbene Complex 4. A flask was charged with pentacarbonyl[(*N*,*N*-diphenylamino)methylene]chromium(0) (1.66 g, 4.46 mmol) and (*S*)-phenylglycinol (0.733 g, 5.35 mmol) under argon, and 10 mL of dry DMF was added by syringe. The reaction was stirred at 25 °C for 12 h. The crude reaction mixture was taken up in ether (50 mL) and was washed with water (4 × 25 mL). The water layers were combined and were washed with hexane (5 × 20 mL) until the organic layer became almost clear. The ether and hexane layers were combined, dried with $MgSO_4$, filtered, and concentrated to yield a yellow solid. The yellow solid was dissolved in a minimum of CH_2Cl_2 and was loaded onto a silica gel column. Elution with 9:1 hexane/EtOAc removed the diphenylamine, and further elution with 3:1 hexane/EtOAc afforded compound **4** (1.452 g, 96%) as a yellow oil: R_f = 0.15, 3:1 hexane/EtOAc; ^{1}H NMR (300 MHz) δ 2.05 (br s, 1 H, OH), 4.04 (br s, 2 H, CH_2O), 4.66 (br s, 1 H, C*H*Ph), 7.25 (m, 2 H, Ph), 7.43 (m, 3 H, Ph), 9.56 (br s, 1 H, NH), 11.14 (d, J = 20.8 Hz, 1 H, Cr=C*H*); ^{13}C NMR (75 MHz) δ 64.92, 72.46 (*C*HPh, *C*H_2O), 126.87, 129.16, 129.50, 135.27 (Ph), 217.32 (M − CO cis), 223.44 (M − CO trans), 272.82 (Cr=*C*); IR (film) ν 3600–2800 (br, OH, NH), 2058 (s), 1979 (sh), 1908 (vs, CrCO) cm^{-1}; mass spectrum, m/e (% relative intensity) CI (NH_3) 342 (0.2%, M^+ + 1). Anal. Calcd for $C_{14}H_{11}NO_6Cr$: C, 49.28; H, 3.25; N, 4.10. Found: C, 49.44; H, 3.48; N, 4.08.

Synthesis of Carbene Complex 5. A 100-mL airlessware flask was fitted with a rubber septum, magnetic stir bar, and argon-filled balloon. The apparatus was charged with sodium hydride (0.072 g, 3.0 mmol) under argon, and carbene complex **4** (0.930 g, 2.73 mmol) was added by cannula as an airless solution in 50 mL of freshly distilled and degassed THF. Stirring was continued for 1 h at 25 °C. Meanwhile, a 200-mL airlessware flask was fitted with a rubber septum, magnetic stir bar, and an argon-filled balloon. This apparatus was charged with triphosgene (0.920 g, 3.10 mmol) under argon, and degassed THF (30 mL) was added by syringe. This solution was cooled to −78 °C, and diisopropylethylamine (1.62 mL, 9.29 mmol) was added dropwise by syringe. This was stirred in a 25 °C bath for 10 min, and the temperature was recooled to −78 °C. Under a gentle flow of argon, sodium hydride (0.072 g, 3.0 mmol) was added as a solid (carefully in a fume hood since free phosgene may be present at this point). The carbene solution was added by cannula over 5 min, the bath was removed, and stirring was continued for 1 h. This orange-red solution was filtered through a short plug of silica gel, and the solvent was removed by rotary evaporation. The crude reaction mixture was dissolved in a minimum of CH_2Cl_2 and was transferred onto a flash silica gel column. A red band was eluted with 9:1 hexane/EtOAc, which was concentrated in vacuo to yield complex **5** (0.643 g, 64%) as a red oil: R_f = 0.38, 3:1 hexane/EtOAc; ^{1}H NMR (300 MHz) δ 4.45 (dd, J = 8.78, 1.83 Hz, 1 H, ring CH), 4.94 (t, J = 8.36 Hz, 1 H, ring CH), 6.04 (d, J = 7.52 Hz, 1 H, ring CH), 7.26 (m, 2 H, Ph), 7.43 (m, 3 H, Ph), 13.08 (s, 1 H, Cr=C*H*); ^{13}C NMR (75 MHz) δ 61.81 (*C*Ph), 70.96 (*C*H_2O), 125.68, 129.57, 129.90, 138.06

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(Ph), 148.25 (C=O), 215.04 (M - CO cis), 224.70 (M - CO, trans), 294.83 (Cr=C), ^{13}C assignments were confirmed by a DEPT experiment; IR (film) ν 2066 (m), 1993 (sh), 1923 (vs, CrCO), 1803 (C=O) cm^{-1}; mass spectrum, *m/e* (% relative intensity) EI 367 (0.4%, M^+). Anal. Calcd for $C_{15}H_9NO_7Cr$: C, 49.06; H, 2.47; N, 3.81. Found: C, 49.25; H, 2.65; N, 4.00.

General Procedure for the Photolysis of Carbene Complex 1 with Imine 7 or 8 in the Presence or Absence of Additive. In a Pyrex test tube was placed a solution of carbene complex **1** (1.0 mmol) in freshly distilled CH_2Cl_2 (15 mL), and the imine (1.0 mmol) and appropriate additive (1.0 mmol) were added to this. After the test tube was sealed with a rubber septum, the vessel was evacuated and purged with CO three times. It was then irradiated under an atmosphere of CO for 17–20 h. The consumption of the carbene complex was monitored by analytical TLC. After the reaction, the mixture was transferred to a flask and was stirred at room temperature overnight open to the air for air oxidation of chromium byproduct. The end point of the oxidation was indicated by a clear solution. Insoluble materials were removed by filtration through Celite, and the filtrate was concentrated in vacuo to give a crude product, which was analyzed by ^1H NMR and HPLC to determine the isomer ratio. This crude product was then purified by flash chromatography to afford the pure β-lactam product whose isomer ratio was also determined by HPLC.

Reaction Product from 1 with Imine 7. Isomer ratios of β-lactam products before and after chromatography were as follows: With triethylamine, cis_a:cis_b:$trans_a$ = 47:45:8 before chromatography and cis_a:cis_b:$trans_a$ = 43:49:8 after chromatography. With no additive, cis_a:cis_b:$trans_a$ = 16:11:73 before and cis_a:cis_b:$trans_a$ = 5:13:82 after.

$Cis_{a,b}$ isomers (isolated in 53% yield as a mixture of cis_a:cis_b:$trans_a$ = 43:49:8.): ^1H NMR (270 MHz) δ 0.78 (s, 3 H, CH_3, cis_b), 1.31 (s, 3 H, CH_3, cis_b), 1.50 (s, 3 H, CH_3, cis_a), 1.53 (s, 3 H, CH_3, cis_a), 3.49 (dd, *J* = 5.8, 7.9 Hz, 1 H, CH_2O, syn to Ph cis_a), 3.56 (dd, *J* = 6.1, 8.7 Hz, 1 H, CH_2O, syn to Ph, cis_b), 3.62 (d, *J* = 14.7 Hz, 1 H, CHPh, cis_b), 3.66 (d, *J* = 14.7 Hz, 1 H, CHPh, cis_a), 3.77 (t, *J* = 7.5 Hz, 1 H, CH_2O, anti to Ph, cis_a), 3.84 (t, *J* = 5.8 Hz, 1 H, CHPh(CH_2), cis_a), 4.16 (dd, *J* = 7.7, 8.7 Hz, CH_2O, anti to Ph, cis_b), 4.25 (d, *J* = 4.5 Hz, 1 H, CHC=O), cis_a), 4.37 (d, *J* = 4.5 Hz, 1 H, CHC=O, cis_b), 4.52 (d, *J* = 4.5 Hz, 1 H, CHCHC=O), cis_a), 4.55 (d, *J* = 4.5 Hz, 1 H, CHCH-C=O, cis_b), 4.65 (m, 1 H, CHPh(CH_2), cis_b), 4.67 (d, *J* = 14.7 Hz, 1 H, CHPh, cis_b), 4.75 (d, *J* = 14.7 Hz, 1 H, CHPh, cis_a), 7.0–7.4 (m, 30 H, C_6H_5); IR (film) ν 1749 (C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79. Found: C, 78.44; H, 7.00; N, 6.86.

$Trans_a$ isomer (isolated in 54% yield as a mixture of cis_a:cis_b:$trans_a$ = 5:13:82): ^1H NMR (270 MHz) δ 1.29 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 3.62 (d, *J* = 14.7 Hz, 1 H, CHPh), 3.70 (m, 1 H, CH_2O, syn to Ph), 3.73 (d, *J* = 2.4 Hz, 1 H, CHC=O), 3.96 (d, *J* = 2.4 Hz, 1 H, CHCHC=O), 4.30 (m, 2 H, CH_2O, anti to Ph, CHPh(CH_2)), 4.69 (d, *J* = 14.7 Hz, 1 H, CHPh), 6.9–7.3 (m, 15 H, C_6H_5); IR (film) ν 1748 (C=O) cm^{-1}.

Reaction Product from 1 with Imine 8. Isomer ratios of β-lactam products before and after chromatography were as follows: With no additive, cis_a:cis_b:$trans_a$:$trans_b$ = 10:16:70:4 (before) and cis_a:cis_b:$trans_a$:$trans_b$ = 11:15:70:4 (after, 82% yield). With triethylamine, cis_a:cis_b:$trans_a$:$trans_b$ = 16:18:57:9 (before) and cis_a:cis_b:$trans_a$:$trans_b$ = 14:17:62:7 (after, 75% yield). With DMAP, cis_a:cis_b:$trans_a$:$trans_b$ = 50:36:11:3 (before) and cis_a:cis_b:$trans_a$:$trans_b$ = 52:42:4:2 (after, 66% yield). This reaction product was further chromatographed to give cis_a-major and cis_b-major products.

Cis_b isomer (isolated in 15% yield as a mixture of cis_a:cis_b:$trans_a$:$trans_b$ = 20:78:<1:2): ^1H NMR (270 MHz) δ 1.30 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 3.79 (dd, *J* = 4.4, 8.5 Hz, 1 H, CH_2O, syn to Ph), 3.96 (dd, *J* = 4.6, 9.3 Hz, 1 H, CHCHC=O), 3.99 (d, *J* = 15.0 Hz, 1 H, CHPh), 4.33 (t, *J* = 7.7 Hz, 1 H, CH_2O, anti to Ph), 4.36 (d, *J* = 15.0 Hz, 1 H, CHPh), 4.47 (d, *J* = 4.6 Hz, 1 H, CHC=O), 4.80 (dd, *J* = 4.4, 7.8 Hz, 1 H, CHPh(CH_2)), 5.47 (dd, *J* = 9.3, 15.9 Hz, 1 H, CHCH=), 6.29 (d, *J* = 15.9 Hz, 1 H, PhHC=), 7.0–7.5 (m, 15 H, C_6H_5); IR (film) ν 1747 (C=O) cm^{-1}.

Cis_a isomer (isolated in 20% yield as a mixture of cis_a:cis_b:$trans_a$:$trans_b$ = 83:9:3:5): ^1H NMR (270 MHz) δ 1.48 (s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 3.71 (dd, *J* = 6.5, 8.1 Hz, 1 H, CH_2O, syn to Ph), 3.91 (dd, *J* = 4.6, 8.3 Hz, 1 H, CHCHC=O), 3.97 (d, *J* = 14.9 Hz, 1 H, CHPh), 4.12 (t, *J* = 7.7 Hz, 1 H, CH_2O, anti to Ph), 4.26 (t, *J* = 6.8 Hz, 1 H, CHPh(CH_2)), 4.43 (d, *J* = 4.6 Hz, 1 H, CHC=O), 4.44 (d, *J* = 14.9 Hz, 1 H, CHPh), 5.96 (dd, *J* = 8.3, 16.0 Hz, 1 H, CHCH=), 6.17 (d, *J* = 16.0 Hz, 1 H, PhHC=), 7.0–7.4 (m, 15 H, C_6H_5); IR (film) ν 1748 (C=O) cm^{-1}.

$Trans_a$ isomer (isolated in 82% yield as a mixture of cis_a:cis_b:$trans_a$:$trans_b$ = 11:15:70:4): ^1H NMR (270 MHz) δ 1.42 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 3.39 (dd, *J* = 2.4, 8.7 Hz, 1 H, CHCHC=O), 3.71 (dd, *J* = 4.2, 7.1 Hz, 1 H, CH_2O, syn to Ph), 3.90 (d, *J* = 14.9 Hz, 1 H, CHPh), 4.00 (d, *J* = 2.4 Hz, 1 H, CHC=O), 4.32 (m, 2 H, CH_2O, anti to Ph, CHPh(CH_2)), 4.46 (d, *J* = 14.9 Hz, 1 H, CHPh), 5.88 (dd, *J* = 8.7, 15.8 Hz, 1 H, CHCH=), 6.17 (d, *J* = 15.8 Hz, 1 H, PhHC=), 7.0–7.4 (m, 15 H, C_6H_5); IR (film) ν 1746 (C=O) cm^{-1}. Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.90; N, 6.39. Found: C, 79.14; H, 7.09; N, 6.47.

Photolysis of Carbene Complex 1 with Imine 9 in the Presence or Absence of Triethylamine. These reactions were carried out as described in the reaction with imine **7** or **8**. Isomer ratios of β-lactam product before and after chromatography were as follows: With no additive, cis_a:$trans_a$ = 17:83 (before) and cis_a:$trans_a$ = 33:67 (after, 61% yield). With triethylamine, cis_a:$trans_a$ = 46:54 (before) and cis_a:$trans_a$ = 50:50 (after, 50% yield). These products were identical in every respect with those reported previously.[20]

Photolysis of Carbene Complex 1 with Imine 12. Carbene complex **1** (100 mg, 0.26 mmol) and imine **12** (45 mg, 0.31 mmol) in 6 mL of CH_2Cl_2 were photolyzed under CO pressure.[18] The reaction gave 66.1 mg (0.18 mmol, 70%) of a clear oil as a 2:1 mixture of two syn diastereomers (N* and Ph syn). The two diastereomers were partially separated by flash chromatography on silica gel (7:1 benzene/EtOAc).

Syn_a (major product; contained 16% of syn_b): ^1H NMR (300 MHz) δ 1.30 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.80 (m, 2 H, CH_2), 2.03 (m, 1 H, CH_2), 2.18 (m, 1 H, CH_2), 2.90 (m, 1 H, CH_2), 3.4–3.7 (m, 2 H, CH_2 and CH_2O syn to Ph), 4.14 (t, *J* = 8.1 Hz, 1 H, CH_2O anti to Ph), 4.26 (s, 1 H, CHC=O), 4.47 (dd, *J* = 6.0, 7.6 Hz, 1 H, NCHCH$_2$O), 6.7–7.5 (m, 10 H, Ph); ^{13}C NMR (75 MHz) δ 22.34 (CH_3), 28.01 (CH_3), 28.65 (CH_2), 38.31, 45.24, 62.80, 72.34, 72.70, 74.26, 96.21 (CMe_2), 126.49, 126.56, 126.81, 127.65, 127.76, 127.93, 138.95, 141.77 (Ph), 174.61 (C=O); IR ($CDCl_3$) ν 1754 (s, C=O) cm^{-1}; mass spectrum, *m/e* (% relative intensity) CI (NH_3) 362 (1, M^+).

Syn_b (minor product, 1:1 mixture of syn_a and syn_b; peaks distinguishable from those of syn_a): ^1H NMR (300 MHz) δ 1.50 (s, 3 H, CH_3), 3.72 (t, *J* = 6.2 Hz, 1 H, CH_2O), 4.29 (s, 1 H, CHC=O); ^{13}C NMR (75 MHz) δ 15.24, 26.25, 27.74, 38.60, 44.97, 61.73, 65.80, 71.69, 74.41, 95.19, 140.59, 140.77, 176.45.

Photolysis of Carbene Complex 1 with Imines 6, 10, and 11. These reactions were reported previously.[20]

General Procedure for the Preparation of 2-Azetidinones from 2. These compounds were prepared following a general procedure as cited in the literature.[21] Triethylamine (1.5 equiv) was added to a −78 °C solution of the acid chloride **2** (100 mg, 0.41 mmol) in CH_2Cl_2 (0.35 M). The reaction was stirred for 15 min under an argon atmosphere, and then a 0.65 M solution of the imine (1.1 equiv) in toluene was added via syringe. The reaction was immediately warmed to 0 °C and stirred for an additional 2 h. The solution was filtered through a short pad of silica gel and washed through with ethyl acetate. The reaction mixture was concentrated, and an ^1H NMR spectrum was obtained of the crude reaction mixture. The products were then isolated by flash chromatography.

General Procedure for the Photolytic Reactions of Carbene Complex 5. The chromium–carbene complex (handled briefly in air) was placed into a pressure tube equipped with a septum under argon. The imine (1.2 equiv) was dissolved in dry degassed dichloromethane (0.06 M), and triethylamine (if called for) was injected by syringe into the imine solution. This solution was added by cannula to the pressure tube, the mixture was agitated until homogeneous, and the septum was replaced by a pressure head. The solution was irradiated under 80 psi of CO pressure at room temperature for 30 min. The color changed from deep red to yellow-brown. The solvent was evaporated, and the crude material was oxidized as described in the General Procedures. This was then filtered through silica gel (washing with EtOAc) and was concentrated. Diastereomeric ratios were determined by ^1H NMR spectroscopy or analytical normal-phase HPLC. The products were then purified by radial chromatography using a hexane/EtOAc gradient.

Reaction of Imine 6. (a) With Acid Chloride 2. The reaction of acid chloride **2** and imine **6** gave a complex mixture of products by TLC and ^1H NMR. The products were separated by chromatography (1:1 hexane/EtOAc). The only identifiable product obtained was 90 mg (0.26 mmol, 64%) of a single trans diastereoisomer ($trans_a$) as a colorless oil.

(b) With Carbene Complex 5. The general procedure was used to produce 0.080 g (0.23 mmol, 56%) of β-lactam from 0.150 g (0.41 mmol) of chromium–carbene **5** (0.073 g, 0.49 mmol), of imidate **6**, and no triethylamine as a single observable trans diastereomer ($trans_a$). Exactly the same was done with the addition of 0.11 mL (0.82 mmol) of triethylamine to produce 0.062 g (0.18 mmol, 43%) of β-lactam as a single observable trans diastereomer ($trans_a$).

$Trans_a$: ^1H NMR (300 MHz) δ 3.19 (s, 3 H, OCH_3), 3.99 (d, *J* = 15.1 Hz, 1 H, CH_2Ph), 4.11 (d, *J* = 1.0 Hz, 1 H, lactam ring CH), 4.18 (dd, *J* = 6.4, 8.8 Hz, 1 H, CH_2O, syn to Ph), 4.41 (d, *J* = 15.1 Hz, 1 H, CH_2Ph), 4.67 (t, *J* = 8.9 Hz, 1 H, CH_2O, anti to Ph), 4.70 (d, *J* = 1.0 Hz, lactam ring CH), 4.97 (dd, *J* = 6.5, 9.0 Hz, 1 H, NCHCH$_2$O),

6.98 (m, 2 H, Ph), 7.28 (m, 8 H, Ph); ^{13}C (75 MHz) δ 44.1 (OCH_3), 55.2, 58.7, 65.6, 70.6, 86.7, 127.2, 127.7, 128.2, 128.7, 129.4, 134.4, 138.1, 157.2 (C=O), 162.1 (C=O); IR (film) ν 1760 (s, C=O) cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 67.85; H, 5.76; N, 7.67.

Reaction of Imine 7. (a) With Acid Chloride 2. The reaction of acid chloride **2** and imine **7** provided 157 mg (0.39 mmol, 96%) of a white solid. The ^1H NMR of the crude reaction mixture showed a single cis diastereoisomer (cis_a) and some remaining imine. The product was recrystallized from ethyl acetate.

(b) With Acid Chloride 2 Employing Reverse Addition of the Imine and Triethylamine. A solution of imine **7** (97.6 mg, 0.49 mmol in 2 mL of CH_2Cl_2) was added by syringe to a 0 °C solution of acid chloride **2** (108 mg, 0.45 mmol in 1 mL of CH_2Cl_2). The solution was stirred under an argon atmosphere for 1 h. Triethylamine (94 μL, 0.67 mmol) was added via syringe, and the solution was stirred for 20 h. The products were isolated by flash chromatography (1:1 hexane/EtOAc) to provide 26% (37 mg, 0.09 mmol) of $trans_a$, 18% (25 mg, 0.06 mmol) of cis_a, and 41% (45 mg, 0.145 mmol) of the hydrolyzed product.

(c) With Carbene Complex 5. The general procedure was used to produce 0.139 g (0.35 mmol, 85%) of β-lactam from 0.150 g (0.41 mmol) of chromium–carbene **5**, 0.096 g (0.49 mmol) of imine **7**, and no triethylamine as a mixture of three separable diastereomers in the ratio cis_a:$trans_a$:$trans_b$ = 34:38:28. Exactly the same was done with the addition of 0.11 mL (0.82 mmol) of triethylamine to produce 0.110 g (0.28 mmol, 67%) of β-lactam, with only the cis_a isomer detectable.

Cis_a: R_f = 0.33, 1:1 hexane/EtOAc; mp 226–228 °C (lit.[21] mp 228–230 °C); ^1H NMR (300 MHz) δ 3.91 (dd, J = 7.4, 8.5 Hz, 1 H, CH_2O, syn to Ph), 3.96 (d, J = 14.7 Hz, 1 H, CH_2Ph), 4.18 (t, J = 8.7 Hz, 1 H, CH_2O anti to Ph), 4.30 (t, J = 8.8 Hz, 1 H, NC*H*CH_2O), 4.44 (d, J = 4.9 Hz, 1 H, lactam ring CH), 4.54 (d, J = 4.8 Hz, 1 H, lactam ring CH), 4.95 (d, J = 14.8 Hz, 1 H, CH_2Ph), 7.0–7.4 (m, 15 H, Ph); ^{13}C NMR (75 MHz) δ 45.16, 59.58, 60.56, 63.50, 70.15, 127.43, 127.68, 127.84, 128.56, 128.77, 129.23, 129.37, 133.14, 134.81, 136.49 (Ph), 156.86 (C=O), 163.27 (C=O); IR ($CDCl_3$) ν 1750 (s, C=O) cm^{-1}. Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.36, H, 5.56; N, 7.02. Found: C, 75.10; H, 5.51; N, 6.90.

$Trans_a$: R_f = 0.39, 1:1 hexane/EtOAc, SiO_2; ^1H NMR (300 MHz) δ 3.65 (d, J = 14.9 Hz, 1 H, CH_2Ph), 3.91 (d, J = 2.3 Hz, 1 H, lactam ring CH), 4.14 (dd, J = 6.3, 8.8 Hz, 1 H, CH_2O, syn to Ph), 4.64 (t, J = 8.9 Hz, 1 H, CH_2O, anti to Ph), 4.66 (d, J = 14.9 Hz, 1 H, CH_2Ph), 4.79 (d, J = 2.3 Hz, 1 H, lactam ring CH), 4.90 (dd, J = 6.3, 9.0 Hz, 1 H, NC*H*CH_2O), 6.9, 7.0, 7.25 (m, 15 H, Ph); ^{13}C NMR (75 MHz) δ 44.3, 58.8, 59.9, 68.4, 70.5, 126.4, 126.9, 127.3, 127.6, 128.5, 128.8, 128.9, 129.2, 129.3, 134.4, 135.2, 138.2, 157.2 (C=O), 164.6 (C=O); mass spectrum, m/e (% relative intensity) EI 398 (0.5, M^+), 265 (100, M – BnNCO$^+$).

$Trans_b$: R_f = 0.19, 1:1 hexane/EtOAc; ^1H NMR (300 MHz) δ 3.76 (d, J = 15.1 Hz, 1 H, CH_2Ph), 4.05 (d, J = 2.6 Hz, 1 H, lactam ring CH), 4.21 (dd, J = 6.0, 8.7 Hz, 1 H, CH_2O, syn to Ph), 4.67 (d, J = 2.4 Hz, 1 H, lactam ring CH), 4.69 (t, J = 8.7 Hz, 1 H, CH_2O, anti to Ph), 4.83 (m, 2 H, NC*H*CH_2O and CH_2Ph), 6.9, 7.05–7.40 (m, 15 H, Ph); ^{13}C NMR (75 MHz) δ 44.5, 60.0, 61.4, 68.3, 70.4, 126.3, 126.8, 127.6, 128.5, 128.7, 129.2, 134.4, 135.3, 137.5, 156.6 (C=O), 165.1 (C=O); mass spectrum, m/e (% relative intensity) EI 398 (0.3, M^+), 265 (95.6, M – BnNCO$^+$).

Hydrolyzed product: mp 144–145 °C; ^1H NMR (300 MHz) 3.34 (d, J = 16.4 Hz, 1 H, NCH_2C=O), 4.07 (d, J = 16.4 Hz, 1 H, NCH_2C=O), 4.15 (dd, J = 7.3, 8.7 Hz, CH_2O, syn to Ph), 4.37 (m, 2 H, $PhCH_2NH$), 4.67 (t, J = 8.8 Hz, 1 H, CH_2O anti to Ph), 5.04 (dd, J = 7.3, 8.8 Hz, 1 H, NC*H*CH_2O), 6.57 (bs, 1 H, NH), 7.1–7.5 (m, 10 H, Ph); ^{13}C NMR (75 MHz) δ 43.34, 45.21, 60.50, 70.13, 127.21, 127.37, 127.62, 128.57, 129.23, 129.30, 136.84, 137.82, 158.78 (C=O), 167.40 (C=O); IR ($CDCl_3$) ν 1746 and 1670 (s, C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85. Found: C, 69.57; H, 5.86.

Reaction of Imine 8. (a) With Acid Chloride 2.[21] The reaction of acid chloride **2** and imine **8** gave 156 mg (0.37 mmol, 90%) of cis_a as a white solid. The ^1H NMR of the crude reaction mixture showed only two cis diastereomers in a ratio of 95:5. The major product was recrystallized from ethyl acetate.

(b) With Carbene Complex 5. The general procedure was used to produce 0.057 g (0.13 mmol, 37%) of β-lactam from 0.135 g (0.37 mmol) of chromium–carbene **5**, 0.098 g (0.44 mmol) of imine **8**, and no triethylamine as a mixture of three separable diastereomers in the ratio cis_a:cis_b:$trans_a$ = 36:18:46. Exactly the same was done with 0.10 mL (0.74 mmol) of triethylamine to produce 0.062 g (0.15 mmol, 40%) of β-lactam in the ratio cis_a:cis_b:$trans_a$ = 78:7:15. Diastereomeric excesses were measured by HPLC using 46:54 hexane/EtOAc (SiO_2).

Cis_a: mp 183–185 °C (lit.[21] mp 186–187 °C); ^1H NMR (300 MHz) δ 4.18 (m, 3 H), 4.58 (m, 3 H), 4.88 (dd, J = 7.3, 8.9 Hz, 1 H, NC*H*CH_2O), 5.89 (dd, J = 8.9, 15.9 Hz, 1 H, CHC*H*=), 6.48 (d, J = 15.9 Hz, 1 H, PhCH=), 7.1–7.5 (m, 15 H, Ph); ^{13}C NMR (75 MHz) δ 44.92, 59.97, 60.88, 62.85, 70.72, 123.28, 126.78, 127.70, 127.76, 128.42, 128.56, 128.68, 129.36, 129.42, 135.11, 135.63, 136.84, 137.11, 157.73 (C=O), 163.29 (C=O); IR ($CDCl_3$) ν 1757 (s, C=O) cm^{-1}. Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.39, H, 5.70; N, 6.60. Found: C, 76.12; H, 5.61; N, 6.52.

Cis_b: R_f = 0.08, 1:1 hexane/EtOAc; ^1H NMR (300 MHz) δ 3.96 (dd, J = 5.0, 8.7 Hz, 1 H, C*H*CH=), 4.12 (d, J = 14.8 Hz, 1 H, CH_2Ph), 4.14 (t, J = 8.1 Hz, 1 H, CH_2O, syn to Ph), 4.41 (d, J = 5.0 Hz, 1 H, C*H*C=O), 4.64 (t, J = 8.9 Hz, 1 H, CH_2O, anti to Ph), 4.66 (d, J = 14.9 Hz, 1 H, CH_2Ph), 4.85 (t, J = 8.1 Hz, 1 H, NC*H*CH_2O), 6.25 (d, J = 16.0 Hz, 1 H, PhC*H*=), 6.38 (dd, J = 8.7, 15.9 Hz, 1 H, CHC*H*=), 7.2–7.4 (m, 15 H, Ph); ^{13}C NMR (75 MHz) δ 44.8, 61.4, 62.5, 63.9, 70.2, 123.8, 126.8, 127.6, 127.7, 128.4, 128.5, 128.7, 129.0, 129.4, 135.3, 135.8, 137.2, 137.4, 157.1 (C=O), 163.8 (C=O); IR (film) ν 1754 (s, C=O) cm^{-1}; mass spectrum, m/e (% relative intensity) EI 424 (2.2, M^+).

$Trans_a$: R_f = 0.26, 1:1 hexane/EtOAc; ^1H NMR (300 MHz) δ 3.59 (dd, J = 2.1, 8.7 Hz, 1 H, C*H*CH=), 3.94 (d, J = 15.0 Hz, 1 H, CH_2Ph), 4.19 (dd, J = 6.6, 8.8 Hz, CH_2O, syn to Ph), 4.46 (d, J = 15.0 Hz, 1 H, CH_2Ph), 4.68 (t, J = 9.0 Hz, CH_2O, anti to Ph), 4.77 (d, J = 2.0 Hz, 1 H, CHC=O), 4.96 (dd, J = 6.6, 9.0 Hz, NC*H*CH_2O), 5.90 (dd, J = 8.7, 15.8 Hz, 1 H, CHC*H*=), 6.25 (d, J = 15.8 Hz, 1 H, PhC*H*=), 7.0, 7.2–7.4 (m, 15 H, Ph); ^{13}C NMR (75 MHz) δ 44.6, 59.1, 59.9, 66.2, 70.6, 124.3, 126.6, 127.0, 127.2, 127.7, 128.4, 128.5, 128.6, 128.7, 129.4, 134.9, 135.4, 135.5, 138.2, 157.3 (C=O), 164.0 (C=O); IR (film) ν 1756 (s, C=O) cm^{-1}; mass spectrum, m/e (% relative intensity), EI 424 (0.5, M^+).

Reaction of Imine 9 with Acid Chloride 2. The reaction of acid chloride **2** and imine **9** gave a complex mixture of products. Separation by flash chromatography provided 40 mg (0.12 mmol, 30%) of a clear oil ($trans_a$) as the only identifiable product.

$Trans_a$: ^1H NMR (300 MHz) δ 1.11 (d, J = 6.2 Hz, 3 H, CH_3), 3.02 (dq, J = 2.1, 6.2 Hz, 1 H, C*H*CH_3), 3.91 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.18 (dd, J = 6.4, 8.8 Hz, 1 H, CH_2O, syn to Ph), 4.36 (d, J = 15.2 Hz, 1 H, CH_2Ph), 4.58 (d, J = 2.1 Hz, 1 H, CHC=O), 4.67 (t, J = 8.9 Hz, 1 H, CH_2O anti to Ph), 5.03 (dd, J = 6.4, 9.1 Hz, 1 H, NC*H*CH_2O), 6.87 (m, 2 H, Ph), 7.2–7.4 (m, 8 H, Ph); ^{13}C NMR (75 MHz) δ 16.81 (CH_3), 44.04, 54.64, 58.81, 66.08, 70.73, 127.26, 127.66, 128.09, 128.70, 129.27, 129.32, 134.73, 138.56, 157.66 (C=O), 163.51 (C=O); IR (film) ν 1755 (s, C=O) cm^{-1}; mass spectrum, m/e (% relative intensity) EI 336 (1.1, M^+).

Reaction of Imine 10. (a) With Acid Chloride 2. The reaction gave a complex mixture of products. Separation by flash chromatography provided a less than 10% yield of $trans_a$.

(b) With Carbene Complex 5. The general procedure was used to produce 0.012 g (0.042 mmol, 10%) of β-lactam from 0.150 g (0.41 mmol) of chromium–carbene **5**, 0.042 g (0.49 mmol) of imidate **10**, and no triethylamine as a single observable trans diastereomer ($trans_a$).

$Trans_a$: R_f = 0.11, 1:1 hexane/EtOAc; ^1H NMR (300 MHz) δ 1.40 (m, 1 H, CH_2), 1.74 (m, 1 H, CH_2), 2.82 (dt, J = 4.6, 12.7 Hz, 1 H, CH_2), 3.43 (dt, J = 1.9, 12.3 Hz, 1 H, CH_2), 3.79 (dd, J = 6.0, 13.5 Hz, 1 H, CH_2), 3.99 (m, 1 H, CH_2), 4.23 (dd, J = 7.1, 8.8 Hz, 1 H, CH_2O, syn to Ph), 4.35 (s, 1 H, lactam ring CH), 4.68 (s, 1 H, lactam ring CH), 4.69 (t, J = 8.9 Hz, 1 H, CH_2O, anti to Ph), 4.92 (dd, J = 7.0, 9.0 Hz, 1 H, NC*H*CH_2O), 7.4 (m, 5 H, Ph); ^{13}C NMR (75 MHz) δ 23.5, 37.8, 59.5, 65.2, 67.5, 70.4, 82.5, 127.5, 129.3, 129.6, 137.8, 157.1 (C=O), 161.8 (C=O); mass spectrum, m/e (% relative intensity), EI 288 (17.1, M^+), 203 (12.9, M – N=CO$(CH_2)_3^+$).

Reaction of Cyclopentadiene. (a) With Acid Chloride 2. A solution of acid chloride **2** (100 mg, 0.41 mmol in 1 mL of CH_2Cl_2) was added over a period of 2 h (syringe pump) to an argon-purged solution of Et_3N (85 μL, 0.61 mmol), cyclopentadiene (56 μL, 0.82 mmol), and CH_2Cl_2 (1 mL). The solution was stirred an additional 4 h and was then concentrated onto Celite and purified by chromatography (2:1 hexane/EtOAc) to give 55 mg of cyclobutanone as roughly a 5:3:0:0 mixture of the inseparable diastereomers by ^{13}C NMR ((C=O) 209.4, 206.3 ppm). The ^1H spectrum was very difficulty to interpret.

(b) With Carbene Complex 5. The general procedure, with 4 equiv of cyclopentadiene rather than an imine, was used to produce 0.084 g (0.31 mmol, 76%) of cyclobutanone as roughly a 1:5:2:0 mixture of three inseparable diastereomers ((C=O) 209.4, 206.3, 205.5 ppm) from 0.150 g (0.41 mmol) of chromium–carbene complex **5** and 0.13 mL (1.6 mmol) of cyclopentadiene in CH_2Cl_2 (8 mL). Exactly the same was done with 0.11 mL (0.82 mmol) of triethylamine to produce 0.027 g, (0.10 mmol, 25%) of cyclobutanone as a 1:6:5:1:0 mixture of three inseparable diastereomers.

Major isomer from carbene reaction: R_f = 0.36, 1:1 hexane/EtOAc, SiO_2; ^1H NMR (300 MHz) δ 2.32 (ddd, J = 1.9, 9.3, 17.1 Hz, 1 H, H_2CC=), 2.53 (d, J = 17.1 Hz, 1 H, H_2CC=), 3.55 (m, 1 H, C*H*-

(CHN)), 3.75 (m, 1 H, C*H*(CH_2)(C=O)), 4.22 (dd, J = 5.2, 8.7 Hz, 1 H, CH_2O, syn to Ph), 4.67 (t, J = 8.8 Hz, 1 H, CH_2O, anti to Ph), 4.82 (dd, J = 2.2, 5.7 Hz, 1 H), 5.16 (dd, J = 1.6, 8.9 Hz, 1 H), 5.28 (d, J = 4.1 Hz, 1 H), C*H*(C=O)(N), *H*C=C*H*), 4.98 (dd, J = 5.1, 8.9 Hz, 1 H, CHPh), 7.2-7.5 (m, 5 H, Ph); ^{13}C NMR (75 MHz) δ 34.3, 45.8, 56.1, 57.6, 70.0, 71.3, 127.6, 128.1, 128.9, 129.0, 134.2, 139.8, 158.1, 206.4; IR (film) ν 1789 (C=O), 1747 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.39; H, 5.69; N, 5.35.

Reaction of Imine 12 with Acid Chloride 2. The reaction of acid chloride **2** (200 mg, 0.82 mmol) with cyclic imine **12** provided a complex mixture of products. The only isolable product obtained by column chromatography was 5.6% (17 mg, 0.05 mmol) of one syn diastereomer (N* and Ph syn) as a white solid: ^{1}H NMR (300 MHz) δ 1.90 (m, 2 H, CH_2), 2.07 (m, 1 H, CH_2), 2.19 (m, 1 H, CH_2), 3.01 (m, 1 H, CH_2), 3.67 (m, 1 H, CH_2), 3.96 (dd, J = 7.2, 8.8 Hz, 1 H, CH_2O, syn to Ph), 4.39 (t, J = 8.9 Hz, 1 H, CH_2O anti to Ph), 4.62 (s, 1 H, CHC=O), 4.81 (dd, J = 7.3, 9.1 Hz, 1 H, NC*H*CH_2O), 6.87 (m, 2 H, Ph), 7.0-7.5 (m, 8 H, Ph); ^{13}C NMR (75 MHz) δ 28.50, 38.02, 45.98, 59.42, 67.83, 70.66, 72.21, 126.34, 127.30, 127.64, 128.49, 128.66, 129.06, 136.86, 138.21, 157.74, 170.16 (C=O); IR ($CDCl_3$) ν 1754 (s, C=O) cm^{-1}; mass spectrum, m/e (% relative intensity) CI (NH_3) 348 (3.3, M$^+$).

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Studies on the Intramolecular Competitive Addition of Carbon Radicals to Aldehydo and Alkenyl Groups[1]

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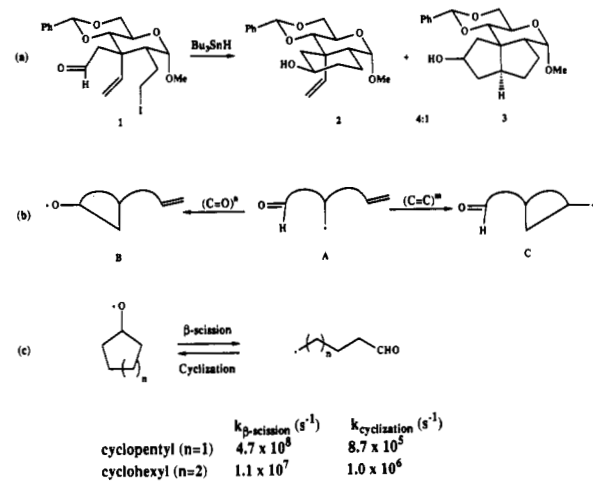
Abstract: Cyclizations of ω-formylalkyl radicals can provide an efficient route to the corresponding cycloalkanols. However, if an ω-vinyl group is present, an alternative mode of cyclization exists, and there is competition between cycloalkanol and methyl cycloalkane formation (i.e. $(C=O)^n$ versus $(C=C)^m$). Cyclohexanol formation, $(C=O)^6$, usually overwhelms any alternative process, but cyclopentanol and methylcyclopentane processes ($(C=O)^5$ and $(C=C)^5$) can be competitive. The latter process involves the well-studied 5-hexenyl radical ring closure, and hence by choice of a suitable substrate, where both modes of cyclization are optional, we have obtained rate data for cyclopentanol $(C=O)^5$ formation in a direct-competition experiment. The value $k_{C=O} \geq 9.6 \times 10^5$ s^{-1} is consistent with that obtained by Beckwith and Hay. The study has also helped to define some of the requirements for optimizing the formation of cycloalkanols. Concentration of H* source, usually through Bu_3SnH, must be maintained at a high level so that reduction of the cycloalkoxy radical intermediate overwhelms its decomposition by β-scission, which regenerates the acyclic precursor. However, at very high concentrations of Bu_3SnH, addition of the tin radical to the aldehydo group can also become a competitive process. The latter also occurs if radical generation is inefficient. Thus alkyl iodides that react extremely rapidly with Bu_3Sn* are the preferred precursors.

Introduction

The observation, in 1986, that compound **1** reacted with tri-*n*-butyltin hydride to give compounds **2** and **3** in a 4:1 ratio suggested that intramolecular radical-aldehyde addition (A → B; $(C=O)^n$) was a viable synthetic pathway, which could compete favorably with 5-hexenyl ring closure (A → C; $(C=C)^5$) (Scheme I).[3] Although intramolecular radical-aldehyde additions had been advanced to account for rearrangements[4] and for epimerization of hydroxyl groups in various systems,[5] the observations illustrated in Scheme Ia prompted us to evaluate the competitive pathways A → B versus A → C independently,[6] and since then radical-aldehyde cyclizations have been examined as viable synthetic operations in our laboratory[7] and elsewhere.[8] Mechanistically,

Scheme I



	$k_{\beta\text{-scission}}$ (s^{-1})	$k_{\text{cyclization}}$ (s^{-1})
cyclopentyl (n=1)	4.7×10^8	8.7×10^5
cyclohexyl (n=2)	1.1×10^7	1.0×10^6

seminal observations concerning the competing pathways in Scheme Ib have been offered by Curran,[9] and kinetic data for the reversible β-scission of cyclopentoxy and cyclohexoxy radicals (Scheme Ic) have been obtained by Beckwith and Hay.[10] We

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