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Chromium carbene complexes in the synthesis of molecules of biological interest

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Abstract - Several new synthetic approaches to functionalized chromium aminocarbene complexes have been developed, making a wide array of complexes, including those containing optically active auxiliaries, available. Photolysis of these optically active carbene complexes in the presence of imines produces optically active β-lactams in high chemical and optical yield. Procedures for removal of the optically active auxiliary to produce the optically active free amino β-lactams have been developed.

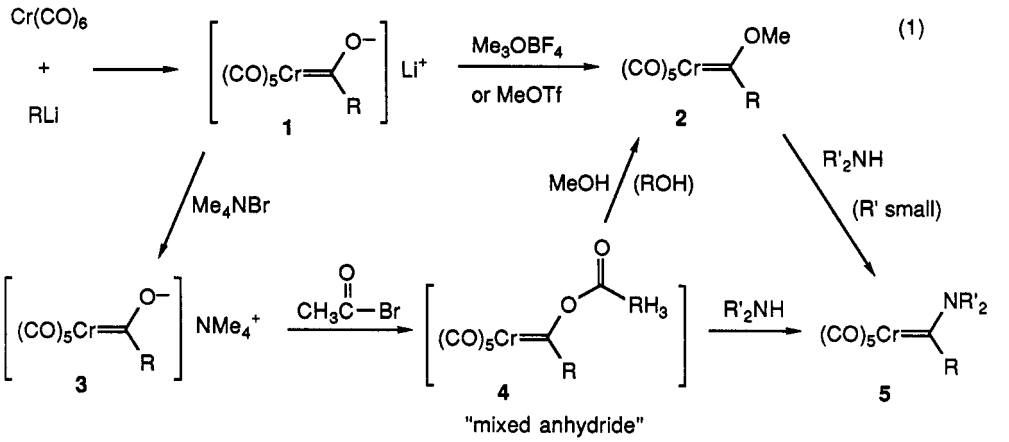
Photolysis of chromium carbene complexes was shown to produce species which react as if they were ketenes or metal-bound ketenes. Photolysis of aminocarbene complexes, synthesized from the reaction of amides with $Na_2Cr(CO)_5$ and trimethylsilyl chloride, in the presence of methanol produced α-amino esters in excellent yield, providing an efficient, unusual two step transformation of amides to α-amino acid derivatives. Optically active aminocarbene complexes produced optically active α-amino acids in excellent yield.

Procedures to efficiently α-alkylate simple chromium (methyl)(amino)-carbene complexes have been developed. Photolysis of these homologated carbene complexes in the presence of alcohols produced homoalanine derivatives in excellent yield, showing the (methyl)(amino) carbene complex to be an alanine homoenolate equivalent. Optically active aminocarbene complexes were similarly homologated and photolyzed to produce optically active homoalanine derivatives. Photolysis of aminocarbene complexes in the presence of α-amino esters produced dipeptides. Preliminary results in the application of this methodology will be presented.

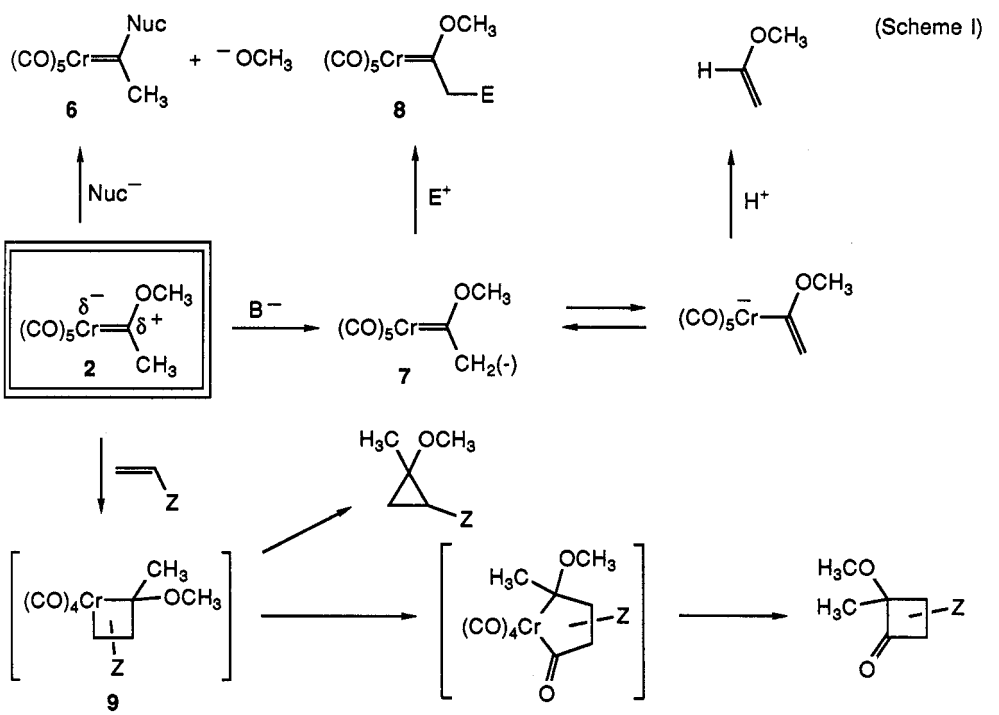
The synthesis, characterization, and organometallic reactions of heteroatom-stabilized Fischer carbene complexes of chromium, molybdenum and tungsten have been intensively investigated in the more than twenty years since their initial discovery.[1,2] In addition to reactions centered at the metal that produce new organometallic complexes, these carbenes have a very rich organic chemistry, and much recent effort has gone into the development of a variety of useful synthetic organic transformations utilizing the unique reactivity of these carbene complexes.[3]

Reaction of chromium hexacarbonyl with organolithium reagents generates lithium acylate complexes (**1**) which can either be directly O-alkylated by hard alkylating agents such as Meerwein's salts or triflates, or isolated as their stable tetraalkylammonium salts (**3**) (eqn 1). O-Acylation by acid halides produces a relatively unstable complex (**4**)

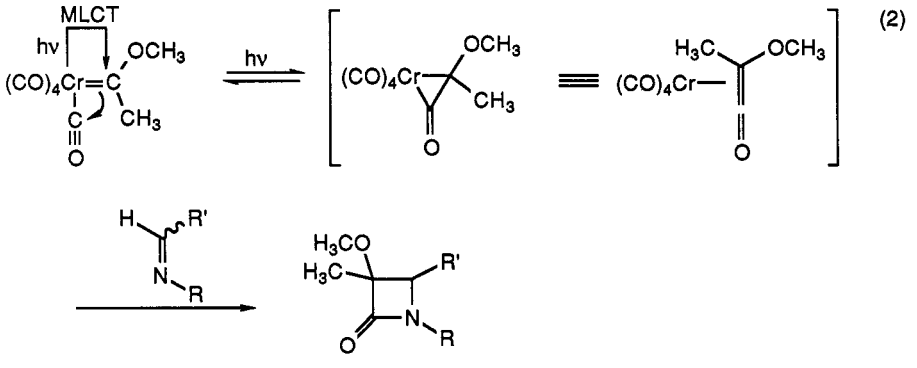
having mixed anhydride-like reactivity towards alcohols and amines, producing alkoxy- (2) or aminocarbene complexes (5), usually in excellent yield. These yellow-to-orange-to-red complexes are relatively stable and easy to handle in air, making them ideally suited to organic synthetic applications. (They are, however, relatively unstable to oxidation in solution.)



(Alkyl)(alkoxy)carbene complexes such as 2 undergo a number of interesting thermal reactions involving the carbene ligand (Scheme 1).[1,2] The carbene-chromium bond appears to be polarized such that the carbene carbon is electrophilic, and a variety of O, N, C, S, and P nucleophiles readily displace the alkoxy group to give a new carbene complex 6. (This step is quite sensitive to steric hindrance in the nucleophile.) The α-hydrogens are quite acidic and are readily removed by a variety of bases to give a stabilized carbanion 7, which can react with reactive electrophiles at carbon to give homologated carbene complex 8 or, with protons, at chromium to give enol ethers. With both electron-rich and electron poor olefins, cyclopropanes form,[3,4] presumably via metallocyclobutane complexes such as 9. Occasionally, CO insertion can occur to give cyclobutanones. Aryl- and (vinyl)(alkoxy)carbene complexes undergo an exceptionally useful cyclization reaction with alkynes to produce naphthoquinones, indanones, benzoquinones and other interesting organic compounds.[5]



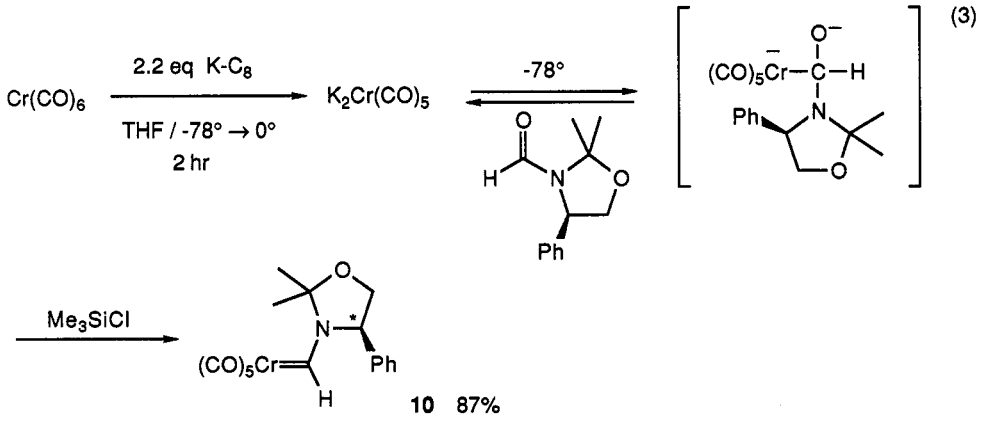
Chromium carbene complexes also have interesting photochemical properties. The visible absorption responsible for the color of these complexes has been ascribed to a metal-to-ligand-charge-transfer band.[6] We[7] have found photolysis of chromium carbene complexes in the region of this absorption (340-450 nm, hν Pyrex) appears to photolytically drive a reversible CO-insertion into the chromium-carbene carbon double bond, generating a species which reacts as if it were a metal-bound ketene.[8] Photolysis in the presence of imines produces β-lactams in excellent yield and with high stereoselectivity (eqn 2).



(2)

single diastereoisomer

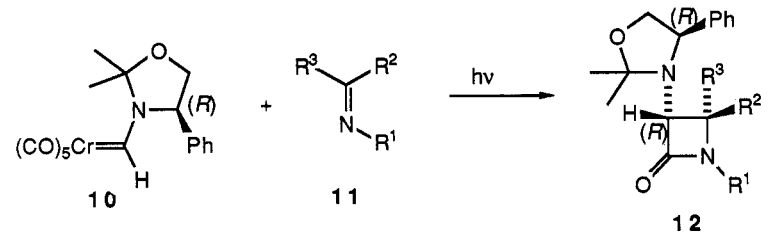
β-Lactams constitute an important class of antibiotics, and new synthetic approaches are valuable. However, most biologically active β-lactams share two common features: (1) they are optically active; (2) the carbon adjacent to the β-lactam carbonyl has an acylamino group and a hydrogen on it, not a methyl group and a methoxy group as do those in eqn 2. To use chromium carbene chemistry to make biologically active β-lactams, it was necessary to devise a route to optically active aminocarbene complexes having a hydrogen on the carbene carbon, a class of carbenes not available by the conventional approach shown in eqn 1. Our solution to this problem is shown in eqn 3.



(3)

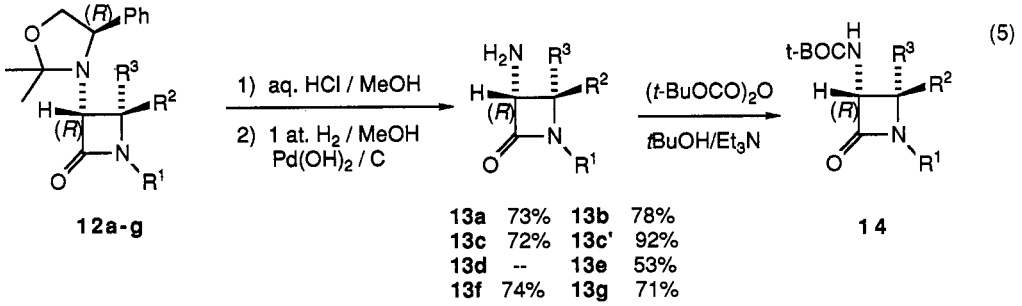
10 87%

Potassium-graphite[9] proved a convenient and efficient reagent for the reduction of chromium hexacarbonyl. Treatment of the resulting dianion with the optically active formamide (from R-phenylglycinol) followed by trimethylsilyl chloride produced the desired optically active carbene **10** in excellent yield.[10] (This was a general reaction and permitted the synthesis of a wide range of amino carbene complexes from amides.) This optically active carbene underwent efficient photoreaction with a range of imines to produce optically active β-lactams **12** in good yield and with high stereoselectivity (eqn 4).[11] Removal of the chiral auxiliary produced the desired amino β-lactams **13** (eqn 5) in good yield. The absolute stereochemistry at the newly-formed chiral center was identical to that of the chiral auxiliary used. The reaction was not restricted to simple substrates. Racemic oxazine **15** converted cleanly to cepham **16** in excellent yield and with high diastereoselectivity (1:1 because of racemic starting material) (eqn 6).



10 11 12 (4)

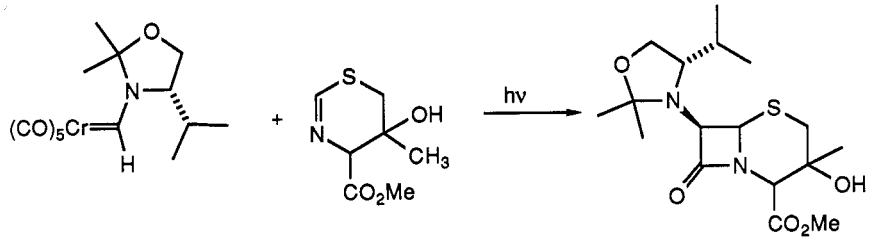
11	R^1	R^2	R^3	12	R^1	R^2	R^3	Yield %	d.e., %
a	Bn	H	H	a	Bn	H	H	74	70
b	Bn	Me	Me	b	Bn	Me	Me	79	70
c	Bn	Me, H		c	Bn	Me	H (trans)	41	≥97
				c'	Bn	H	Me (cis)	20	≥97
d	-$(CH_2)_3$-		H	d	-$(CH_2)_3$-		H	75	≥97
e	-$(CH_2)_4$-		H	e	-$(CH_2)_4$-		H	91	≥97
f	Bn	OMe	H	f	Bn	OMe	H	91	≥97
g	-$(CH_2)_3O$		H	g	-$(CH_2)_3O$		H	95	≥97



12a-g (5)

13a 73% 13b 78%
13c 72% 13c' 92%
13d -- 13e 53%
13f 74% 13g 71%

14



15 16 (79%) (6)

The realization that photolysis of carbene complexes generated species with ketene-like reactivity led to the development of a novel synthesis of α-amino acid esters from amides (Scheme 2). Photolysis of aminocarbene complexes (prepared either from amides as above, or by acylation/exchange processes) in alcohols produced α-amino acid esters in excellent yield. When the reaction was carried out under a modest (60 psi) pressure of carbon monoxide,[12] the starting $Cr(CO)_6$ precipitated from solution and could be recovered and reused. This was a very general reaction and a wide range of amides and lactams were readily converted to the corresponding α-amino acid esters (Table 1). Once again, biologically active α-amino acids are almost invariably optically active as well, and a vehicle for induction of optical activity is required to make this synthetic approach practical. Again, aminocarbenes having an optically active oxazolidine were effective precursors to optically active α-amino acid esters. The dimethyl oxazolidine-carbene **19c**, derived from phenyl glycinol and acetone, was most efficient, giving very high diastereoisomeric excesses (eqn 7).

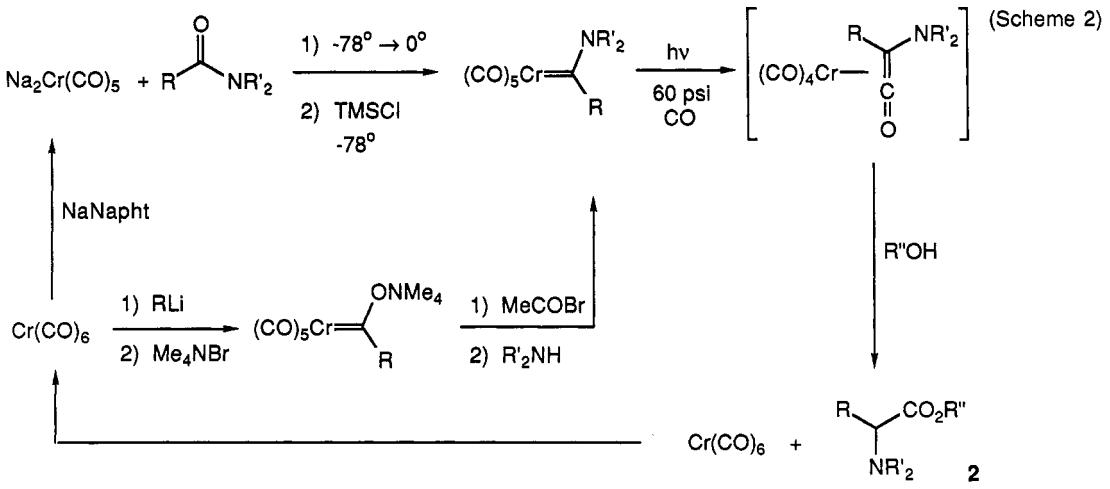
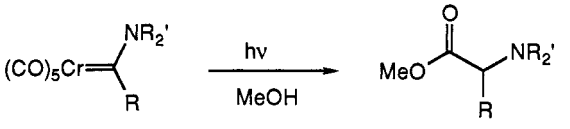
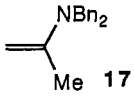
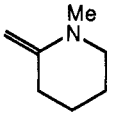
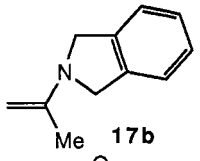
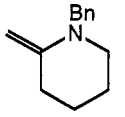
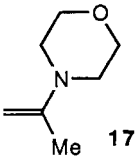
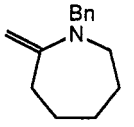
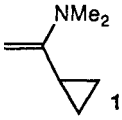
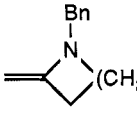
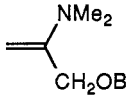
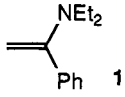
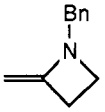
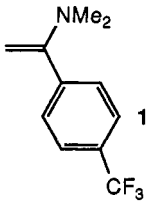
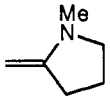
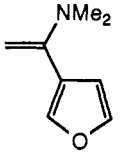
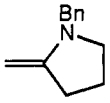
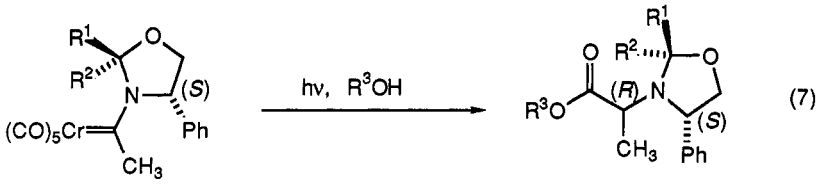


Table 1. Photolytic Conversion of Chromium Aminocarbene Complexes to α-Amino Esters.



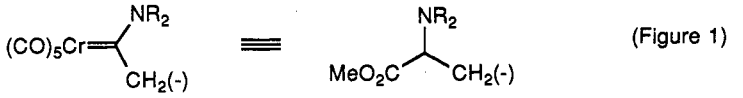
Complex **17**	Yield, %	Product, Yield %	Complex **17**	Yield, %	Product, Yield %
 **17a**	44	**18a** 87[b]	 **17i**	97	**18i** 90
 **17b**	57	**18b** 84	 **17j**	32	**18j** 90
 **17c**	78	**18c** 98	 **17k**	29	**18k** 58
 **17d**	43	**18d** 85	 **17l**	36	**18l** 96
 **17e**	50	**18e** 82	 **17m**	91	**18m** 98
 **17f**	35	**18f** 45	 **17n**	63[c]	**18n** 88
 **17g**	98	–	 **17o**	96	**18o** 76
 **17h**	49	–			



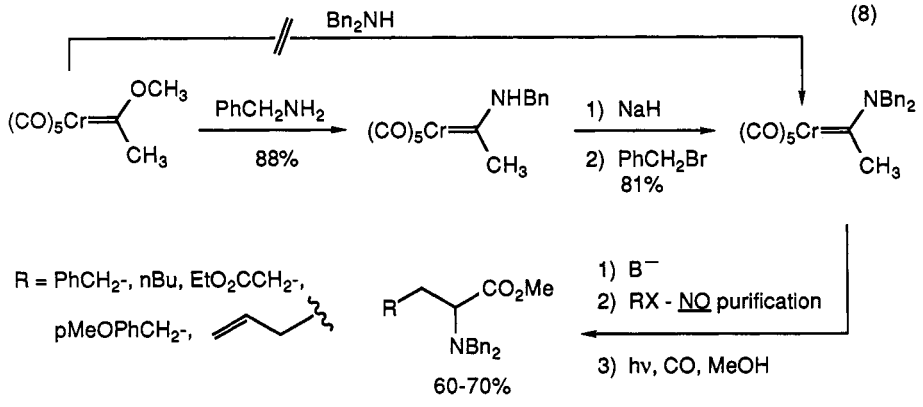
19a $R = R^2 = H$
19b $R^1 = iPr$; $R^2 = H$
19c $R^1 = R^2 = Me$

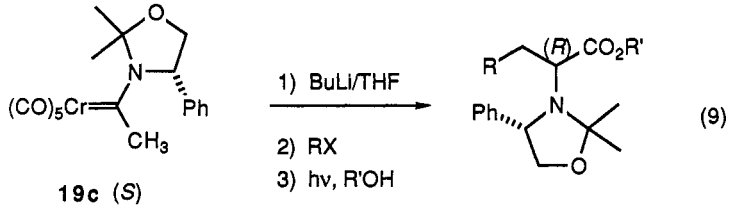
20a $R^3 = Me$ 86% (70% de)
20b $R^3 = Me$ 96% (70% de)
20b' $R^3 = tBu$ 81% (42% de)
20c $R^3 = Me$ 96% (≥93% de)
20c' $R^3 = tBu$ 77% (≥93% de)

The α-hydrogens on aminocarbene complexes are sufficiently acidic to be removed by strong base, and the resulting carbanions undergo reaction with electrophiles to result in homologation of the α-carbon. This chemistry, coupled with the photolytic carbonylation chemistry reported above, makes (methyl)(amino)carbene complexes synthetic analogs of the homoenolate of alanine (Fig 1). Using this methodology, ready access to a range of unusually substituted homoalanine derivatives was achieved (eqn 8). Optically active carbene complex **19c** could also be homologated and produced optically active homoalanine derivatives in fair yield and with excellent diastereoselectivity (eqn 9).



(Figure 1)

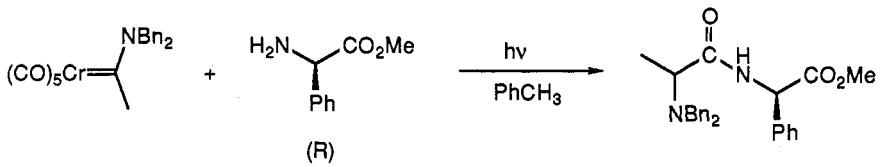




19c (*S*)

21a R = $PhCH_2$, R^1 = tBu, 42% yield
≥ 93% de
21b R = $tBuO_2CCH_2$, R^1 = Me
52% yield, ≥ 93% de

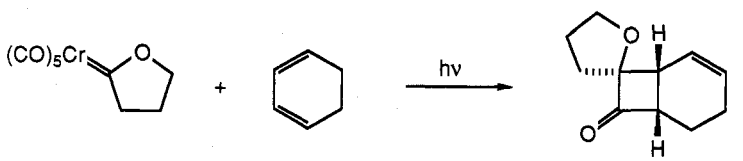
Preliminary studies utilizing photolytic reactions of chromium carbene complexes to produce other classes of biologically active compounds have also been initiated. Photolysis of aminocarbenes in the presence of α-amino acid esters produced dipeptides in excellent chemical yield but, with achiral carbenes and optically active amino acid esters, with poor diastereoselectivity (eqn 10). Studies to control and increase asymmetric induction in this very mild peptide-forming process are in progress. Finally, photolysis of alkoxycarbene complexes in the presence of olefins produces cyclobutanones in excellent yield.[14,15] Both inter- and intramolecular versions of this reaction are efficient, and the stereo- and regioselectivity parallels that observed in routine ketene-olefin cycloaddition reactions (eqns 11-13). Efforts to exploit this chemistry for the synthesis of biologically active compounds continues.



(10)

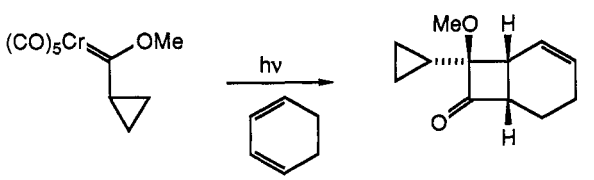
91% yield

70:30 RR/SR



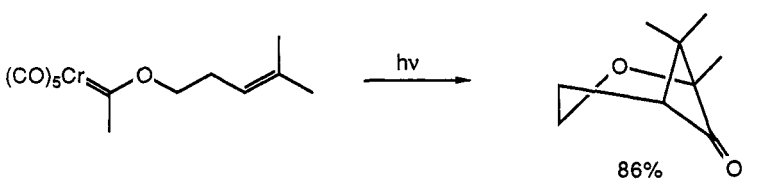
(11)

55%



(13)

48%



(12)

86%

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