in the new gradient experiment recorded with a single transient per FID have increased S/N relative to the corresponding peaks in the nongradient HSQC experiments (both enhanced and unenhanced) recorded with twice the number of transients. The decrease in sensitivity in the nongradient versions of the HSQC experiment is the result of presaturation applied for 1.2 s prior to the start of each scan. While the effects of presaturation on peak intensities vary, we find that for CBD presaturation attenuates the $^1H-^{15}N$ correlations on average by a factor of 1.7 relative to cross peak intensities in spectra acquired using schemes where saturation of the water resonance is avoided.

In summary, in this communication we have described a sensitivity enhanced pulsed field gradient $^1H-^{15}N$ HSQC experiment. Despite the increased number of pulses and delays over other HSQC pulse sequences, the gain in sensitivity can be significant for application to moderately sized proteins. The approach holds promise for application to a number of 3D NMR experiments such as the $^1H-^{15}N$ NOESY- and TOCSY-HSQC experiments as well as several of the triple resonance experiments.

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Supplementary Material Available: Figure illustrating a 2D contour plot of the pure absorption spectrum of CBD obtained using the sensitivity enhanced gradient sequence with one transient/FID (2 pages). Ordering information is given on any current masthead page.

C–H Insertions in the Reactions of Fischer Carbene Complexes with Ketene Acetals

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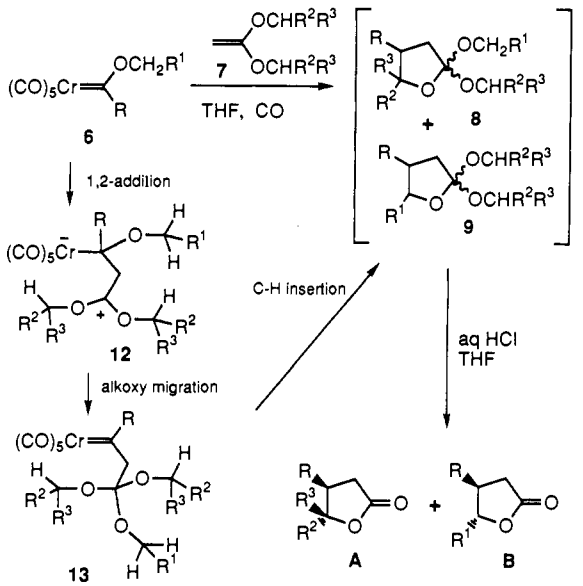
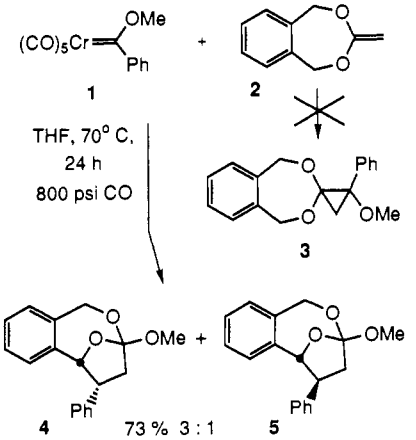
In the planning of synthetic strategies that involve oxidative addition of carbon to C–H bonds, the chemical tactician could best rely on the metal-catalyzed carbenoid reactions of diazo compounds.[1,2] While these processes are commonly observed in reactions involving metal carbenoids, they are rare for stoichiometric transition metal carbene complexes, with only a single known example for the group 6 Fischer carbene complexes[3] and with the recent studies by Helquist on a group 8 complex as the only example that has been examined for synthetic utility.[4] We report the first examples of the reactions of Fischer carbene complexes with ketene acetals, which were found to stereoselectively give trans-3,4-disubstituted butanolides via a C–H insertion reaction of an in situ generated nonheteroatom-stabilized chromium carbene complex.

Scheme I



The reaction of carbene complex **1** and the ketene acetal **2** was originally performed in an effort to develop a new approach to the synthesis of cyclopropanone acetals. Although cyclopropanes can be obtained from the reactions of group 6 carbene complexes with a variety of olefins including enol ethers, the corresponding reactions with ketene acetals have never been investigated.[5,6] Surprisingly, the reaction of **1** and **2** in THF under CO did not produce any of the cyclopropanone acetal **3**, but instead produced the two isomeric tricyclic orthoesters **4** and **5** in a total of 73% yield. The stereochemistry of the major isomer **4** was determined to be that shown by an X-ray crystal structure, and the details can be found in the supplementary material.



The same class of compounds was obtained from the reactions of acyclic ketene acetals as indicated in Scheme I and Table I. In this case the orthoesters **8** and **9** were not stable to silica gel and were converted to the butyrolactones **A** and **B** by treatment of the crude reaction mixture with aqueous acid during workup.

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Table I. Butyrolactones from C–H Insertions in the Reactions of Complex **6** with Ketene Acetals **7**[a]

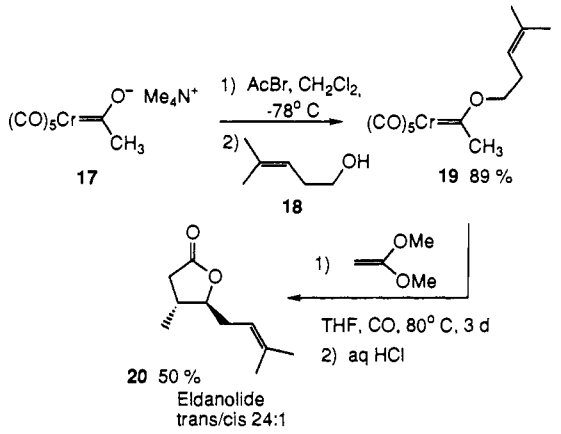
entry	carbene complex	R	R¹	ketene acetal	R²	R³	% yield[b] A lactone	% yield[b] B lactone	C–H partition	insertion selectivity
1	**6a**	Ph	H	**7a**	H	H	68 **10a**			
2	**6a**	Ph	H	**7b**	Me	H	76 **10b**	<1 **10a**	methyl/methylene	1/100
3	**6a**	Ph	H	**7c**	Me	Me	66 **10c**	<1 **10a**	methyl/methine	1/100
4	**6b**	Ph	Me	**7c**	Me	Me	12 **10c**	69 **10b**	methine/methylene	1/6
5	**6b**	Ph	Me	**7a**	H	H		90 **10b**		
6	**6c**	Ph	Ph	**7b**	Me	H	10 **10b**[c]	65 **10d**[d]	benzyl/methylene	12/1
7	**6d**	Ph	*p*-OMePh	**7b**	Me	H	3 **10b**	75 **10e**	benzyl/methylene	50/1
8	**6e**	Ph[e]	*p*-NO_2Ph	**7b**	Me	H	33 **10b**	14 **10f**	benzyl/methylene	0.85
9	**6f**	Ph	$CH{=}CH_2$	**7b**	Me	H	15 **10b**	67 **10g**	allyl/methylene	9/1
10	**6g**	Ph	CH_2Ph	**7a**	H	H	7 **10a**	64 **10h**	methyl/methylene	1/28
11	**6h**	Ph	CH_2OBn	**7a**	H	H	4 **10a**	64 **10i**	methyl/methylene	1/27
12	**6i**	Ph	X[f]	**7a**	H	H		89 **10j**[g]	x =	
13	**6j**	Me	H	**7b**	Me	H	80 **10k**[h]			
14	**6k**	Me	*n*-Pr	**7b**	Me	H	52 **10k**	17 **10l**[i]		
15	**6l**	Me	*n*-C_4H_9	**7a**	H	H		59 **10m**[j]		
16	**6m**	*n*-Bu	H	**7b**	Me	H	64 **10n**			
17	**6n**	$(CH_2)_3$Ph	Me	**7b**	Me	H	58 **10o**[k]			

[a] All reactions were run in THF at 0.08–0.10 M in **6** with 2–3 equiv of **7** under 400–800 psi of CO in a Paar reactor. For **6a–i** the reactions were run at 50 °C for 24 h and for **6j–n** at 75 °C for 48–72 h. Unless otherwise specified, only the *trans*-lactones were observed within the detection limits by ^{1}H NMR (≥95:5). [b] Isolated yields on silica gel. [c] trans:cis = 6.2:1.0. [d] trans:cis = 29:1. [e] The reaction of this unstable complex also produced *p*-nitrobenzyl alcohol (34%) and *p*-nitrobenzyl benzoate (6%). [f] X = *trans*-2-phenylcyclopropyl. [g] 1:1 mixture of diastereomers. [h] trans:cis = 15:1. [i] trans:cis = 16:1. [j] trans:cis = 17:1. [k] trans:cis = 28:1; also a 21% yield of 1-ethoxy-2-(2-phenylethyl)-1-buten-3-one is produced.

A reasonable mechanism that accounts for these overall transformations is outlined in Scheme I and involves nucleophilic addition to form the zwitterion **12** and then alkoxy transfer to give the nonheteroatom carbene complex **13**. Certain cyclopropanation reactions are also thought to proceed via zwitterions,[6b,7,8] and in one case we were able to provide evidence for an initial zwitterionic formation followed by alkoxy transfer.[7] The formation of the orthoesters **8** and **9** could be accounted for by the insertion of the carbene carbon into a C–H bond α to an oxygen atom in intermediate **13**.

That the alkoxy group of the carbene complex is migrating can be demonstrated in the reaction of the ethoxy complex **6b** with dimethylketene acetal **7a** (Table I, entry 5), where *trans*-3-methyl-4-phenylbutanolide **10b** is the exclusive product in 90% yield resulting from C–H insertion into the ethoxyl group of **13** (R^1 = CH_3) and not into either of the methoxyl groups (R^2, R^3 = H). By this method the relative rates for insertions into different types of C–H bonds could be established by pairwise competitions between different alkoxy groups that were introduced either through the carbene complex or through the ketene acetal. The order of insertion is allyl/benzyl > methylene > methine > methyl. With the exception of the methyl, this order is completely reversed with respect to the order of C–H insertion observed in the rhodium-catalyzed reactions of α-diazo carbonyl compounds.[9] The observed order of insertion here correlates with the carbon–hydrogen bond strengths, with the exception of methine hydrogens whose decreased reactivity relative to methylene hydrogens may be due to steric factors. As has been observed for carbenoid reactions[2,9] and iron carbene complexes,[4] there is a preference for the formation of five-membered rings over six-membered rings even in cases where equivalent or more reactive C–H bonds are provided (entries 10 and 11). It is unlikely that a radical is generated in the C–H insertion step since the *trans*-2-phenylcyclopropyl carbinol derived carbene complex **6i** leads to butyrolactone **10j** in high yield with no evidence for cyclopropyl ring opening (entry 12). The C–H insertion reactions are highly stereoselective for the formation of the trans isomers of the butyrolactones with a minimum of 94% selectivity for every entry in Table I and in most cases higher.

The facility for this reaction to produce trans-3,4-disubstituted butanolides is illustrated in the synthesis of Quercus lactone **10m**[10] (entry 15) found in oak wood and aged spirits and eldanolide **20**, the sex pheromone of the male of the species *Eldana saccharina* which feed on sugar cane and maize.[11] The synthesis of eldanolide can be achieved in two steps from the easily preparable and commercially available salt **17**[12] with a 96% selectivity for the natural trans stereochemistry. Further studies on the mechanism and synthetic methodology associated with these novel transformations will be reported in due course.



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Supplementary Material Available: Listings of spectral data for all new compounds and X-ray data for **4** including fractional coordinates, isotropic and anisotropic thermal parameters, bond distances, and bond angles (14 pages). Ordering information is given on any current masthead page.

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