Interaction of Dihydropyridines and Nucleophiles with Carbene Complexes of Chromium: Diastereo- and Enantioselective Synthesis of Polycyclic Butenolides

Henri Rudler,*[a] Andrée Parlier,[a] Victor Certal,[a] Gabriel Lastennet,[a] Max Audouin,[a] and Jacqueline Vaissermann[a]

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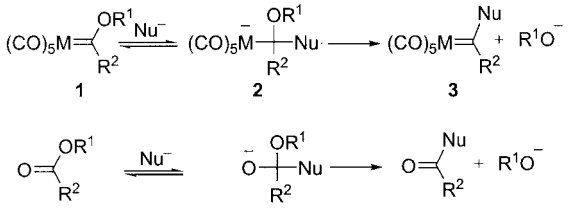
The interaction of *N*-methyldihydropyridine with carbene complexes of chromium promotes their spontaneous homologation upon addition of a hydride to the carbene carbon and an insertion of CO. This is followed in the case of complexes tethered to a triple bond by cascade insertions of the triple bond and of a CO ligand giving finally butenolides. The scope of the reaction has been established with its limitations, together with the stereochemical outcome, which is discussed. [5.5], [5.6], [5.7] bicyclic and tricyclic systems have been synthesised together with chiral butenolides starting from chiral carbene complexes. Most of the new structures have been assessed by X-ray crystallography. This transformation was first extended to dihydronicotinamides, to chiral dihydropyridines such as dihydronicotines which led to the butenolides in an enantioselective way, and to other sources of hydrides. Second, a series of nucleophiles such as alkoxides, alkyllithium and alkylmagnesium compounds led also to polycyclic, substituted butenolides. Moreover, the final lactone enolates could be trapped with oxygen and gave unsaturated lactonols. The key point in all of these reactions is the formation of tetrahedral intermediates upon interaction of the nucleophiles with the carbene carbon.

Introduction

Fischer alkoxycarbene complexes[1,2] owe their importance and success among the organic chemistry community to three reasons: they are easily prepared and obtained as fairly stable complexes,[3] and, in contrast to most other metal complexes, can suffer important modifications of the organic carbene moiety, going from the α-alkylation[4] to the metathesis of tethered olefinic groups.[5] They have thus been used as building blocks for the synthesis of a tremendous number of elaborate organic compounds.[6] Many of their reactions are similar to those of carbonyl compounds yet their reactivity is much higher.[7] This is especially striking in their behaviour towards nucleophiles and is directly linked to the presence of the metal with its carbonyl groups. One of the earliest transformations of alkoxy carbene complexes **1** was the substitution reaction of the alkoxy group by various nucleophiles — a reaction that leads to the new carbene complexes **3** (Scheme 1).



Scheme 1

However, most reported studies have been confined to the preparation of new carbene complexes, or a detailed study of the mechanism of these transformations, which were assumed to occur by a stepwise mechanism involving tetrahedral intermediates.[8] In contrast to the interaction products of esters with nucleophiles,[9] complexes such as **2** could be isolated and characterised in a few instances. However, these elusive addition products, which are in fact negatively charged, often highly functionalised alkylmetal compounds, have not been employed for further carbon−carbon bond formations.[10]

General Features

Access to complexes of the type $[(CO)_5MR]^-$ (M = Cr, Mo, W) has been achieved by Ruff,[11] Ellis[12] and Casey[13] starting either from $[M_2(CO)_{10}]^{2-}$ and alkyl halides or from $[M(CO)_5Br]^-$ and alkyllithium compounds. However, only a limited number of them (R = Me, Ph, CH_2Ph, CH_2CN) have been isolated, most of the other derivatives undergoing fast thermal decomposition. More recently, the interaction of $KHCr(CO)_5$ with methyl acrylate has been shown to lead to a (β-methoxycarbonyl)(pentacarbonyl)chromate.[14] Interestingly, a few such complexes have also been syn-

[a] Laboratoire de Chimie Organique, UMR CNRS 7611, Université P. M. Curie, T 44−45,
4 place Jussieu case 181, 75252 Paris Cedex 05, France
Fax: (internat.) +33-1-44275504
E-mail: rudler@ccr.jussieu.fr
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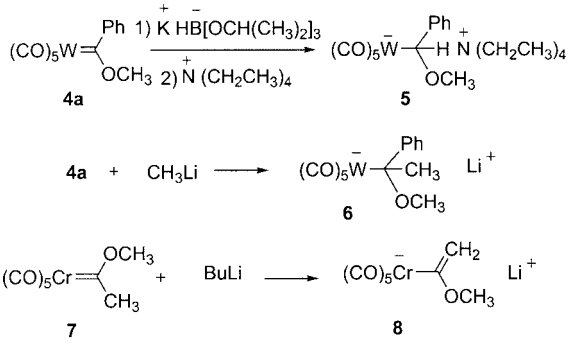
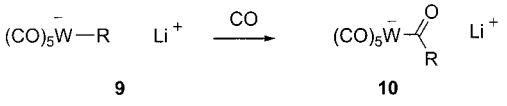
thesised from simple carbene complexes. The pioneering work in this area was carried out by Casey and co-workers who successfully characterised complexes **5**, **6**, and **8**, originating, for **5**, from the interaction of **4a** with a complex hydride,[15] for **6**, from the interaction of **4a** with methyllithium,[16] and for **8**, from the interaction of **7** with butyllithium.[17] In these complexes the negative charge is delocalised over the $[M(CO)_5]$ fragment[18] (Scheme 2).



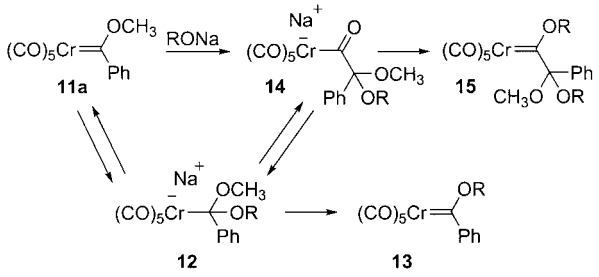
Scheme 2

Since alkylmetal compounds in general are known to undergo carbon monoxide insertions,[19] such transformations have also been attempted. Thus, Casey found that even low pressures of CO induce an almost quantitative formation of (acyl)metal complexes (**9** → **10**),[20] the rate of the insertion being highly dependent on the nature of the R group, with no reaction at all for R = Bn (Scheme 3). Such insertions were also induced by triphenylphosphane.



Scheme 3

That the ligands in these negatively charged alkyl- and acylmetal complexes are even more labile than in carbene complexes[13] has been firmly established by Cooper,[21] since scrambling of the carbonyl groups of the acyl ligand and the additional CO ligands of the metal was observed in the presence of labelled CO. However, the most important and early observation, as far as our investigations are concerned, came from the group of E. O. Fischer,[22a–22c] who demonstrated that the interaction of alkoxycarbene tungsten and chromium complexes with sodium alkoxides not only led to new carbene complexes upon exchange of the alkoxy groups (e.g. **11a** → **13**; Scheme 4) but also, although to only a small extent, to unexpected acylmetal complexes **14** as the result of a carbon monoxide insertion reaction (e.g. **11a** → **14** via **12**) and then to new carbene complexes **15**.[22d]

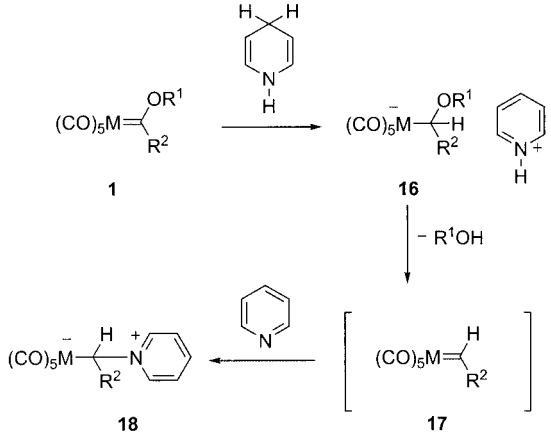


Scheme 4

This result is fundamental since it demonstrates that even in the absence of added external carbon monoxide an insertion can take place, at the expense of the starting material, giving coordinatively saturated complexes (**11a** → **15**). However, no general high yielding approach to such complexes starting from carbene complexes[23,24] existed until 1992 when we disclosed the first biomimetic reduction of alkoxycarbene complexes of tungsten and chromium with dihydropyridines.[25]

Biomimetic Reduction of Carbene Complexes with Dihydropyridines

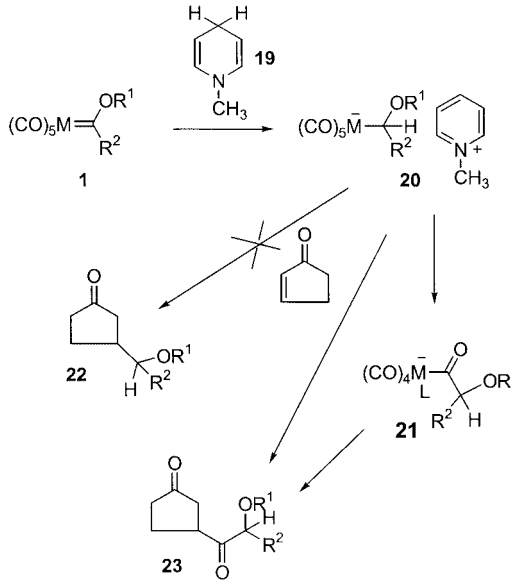
Two points guided our approach: the analogy which had been established between carbene complexes and carbonyl compounds[6,7] and the known biological and biomimetic reductions of carbonyl compounds by dihydronicotinamides.[26] We found indeed that simple dihydropyridines transferred a hydride to the carbene carbon almost quantitatively,[27] but that the intermediate alkylmetal compounds **16** underwent a spontaneous transformation into pyridinium ylide complexes **18** via unstable alkylidene complexes **17** (Scheme 5).



Scheme 5

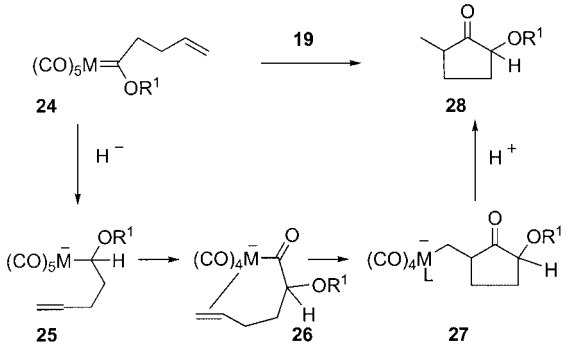
We discovered, however, that this reduction evolved in a quite different direction when *N*-methyldihydropyridine (**19**) was used instead: it led to the fairly stable complexes **20**.[28] This result prompted us to examine the behaviour of these ''ate'' complexes towards conjugated ketones. The

interaction of **20** with cyclopentenone did not, however, lead to **22**, the possible 1,4-addition product, but to **23** due to the formation of **21** and its addition to the double bond of the ketone[29] (Scheme 6).



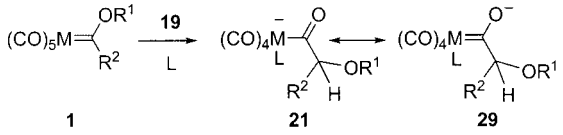
Scheme 6

Along the same lines, complex **24**, containing a tethered double bond, led to the substituted cyclopentanone **28** upon reduction with *N*-methyldihydropyridine, a reaction reminiscent of those observed for alkylcarbonylferrates[30] (Scheme 7).



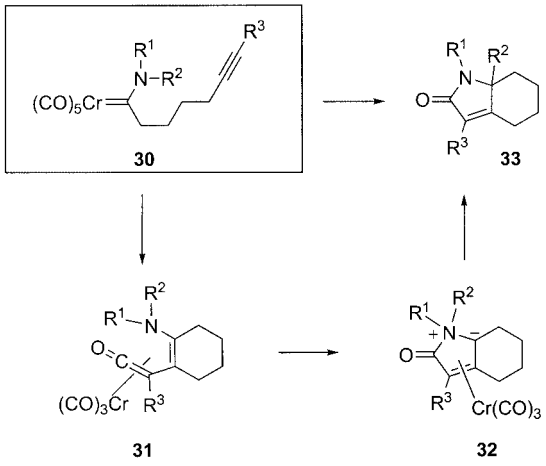
Scheme 7

To summarise, we had established that the alkoxycarbene complexes **1** of tungsten and chromium could be transformed in a single step into elaborate **21**, which can also be described as carbene complexes **29** bearing an exceptional electron-rich substituent. The transformation of **1** into **29** can thus be viewed as a *spontaneous homologation* of the carbene complex **1** induced by a hydride (Scheme 8).



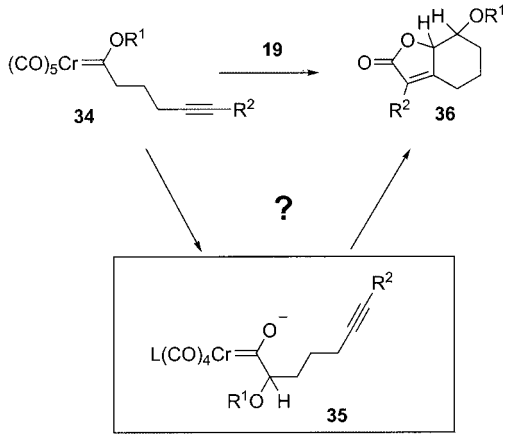
Scheme 8

Due to our experience in the thermal rearrangement of alkynyl(amino)carbene complexes of the type **30**, which led to the lactams **33** via the nitrogen ylide complexes **32** (Scheme 9),[31] we focused our attention on the behaviour of complexes of the type **34** towards *N*-methyldihydropyridine.



Scheme 9

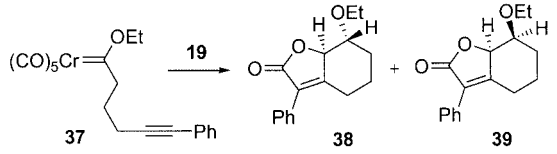
Such complexes might indeed lead to transients such as oxycarbene species **35**, similar to **30**, upon successive reduction of the carbene function and insertion of CO, and then undergo transformations akin to those of **30**; this was indeed the case (Scheme 10).



Scheme 10

Thus, complex **37**, when mixed with an excess of *N*-methyldihydropyridine (**19**, mixture of two isomers) led to a mixture of two isomeric butenolides **38** and **39** (73%; *de*

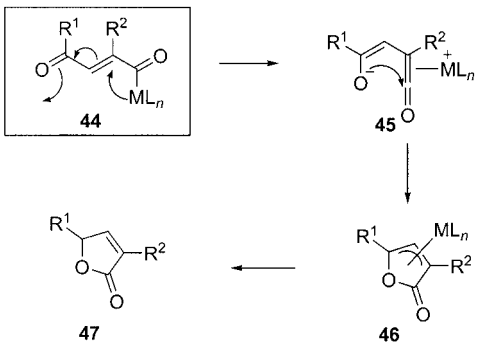
80%) (Scheme 11). The structure of the less abundant, crystalline compound **39** was firmly established by X-ray crystallography.[28]



Scheme 11

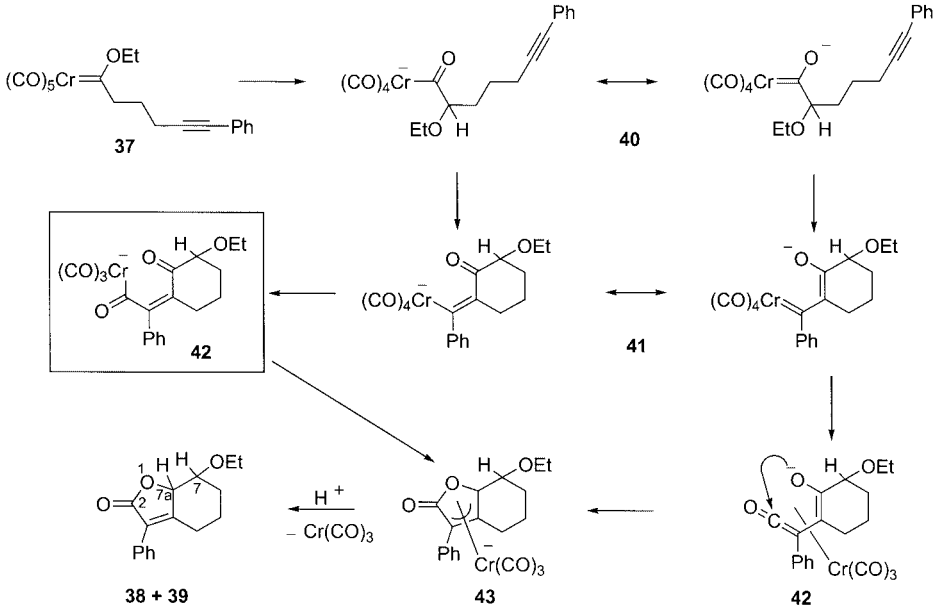
These compounds are the result of the reduction of the carbene function of **37** (C^7-H), the insertion of a first carbonyl group, (C^{7a}–O^1), the insertion of the triple bond (six-membered ring), and the insertion of a second carbonyl group (C^2–O). The key point of this transformation is the efficient transfer of a hydride to the carbene carbon. The steps leading to **42** (described as a ketene complex or a dicarbonyl metal complex) are classical routes in organometallic chemistry.[32] The formation of the subsequent lactone enolate **43**, which at first sight seems less obvious, can be explained as for the transformation of **31** into **32** (Scheme 9).

Interaction of the negatively charged oxygen with the central carbon of the ketene might lead to the lactone enolate **43** (Scheme 12, **42** → **43**). Alternatively, the oxygen in **41** might interact with a coordinated carbonyl group and give, after reductive elimination of the metal, the same enolate complex **43** and finally lead, upon protonation, to the observed lactones. Rearrangements of dicarbonyl-metal complexes of the general structure **44**, similar to **42**, had already been observed and described in many instances for Fe, Rh, Pd, Ni, Co, Mn, Mo and W complexes.[32] They lead to unsaturated lactones **47** or lactone complexes **46** (Scheme 13).[32d,33] This rearrangement can also be related to the organic Halban–White rearrangement of cross-conjugated ketenes, which also leads to butenolides.[34]



Scheme 13

The behaviour of complexes of the type **30** and **35** is therefore the same. However, whereas the former leads to lactams at rather elevated temperatures (refluxing toluene), the transformation of the latter into butenolides takes place spontaneously at low temperature (−10 °C to room temperature). An interesting structural feature of these new lactones is the location of the carbonyl groups originating from the starting (hexacarbonyl)chromium: they are contiguous and respectively linked by a carbon–carbon, a carbon–oxygen and an oxygen–carbon bond.[35,36] Thus, alkylcarbonyl complexes obtained from easy to synthesise carbene complexes allow the elaboration of polycyclic lactones in a single step without the need for external CO. This contrasts sharply with earlier assumptions.[12] Butenolides of this type, bearing extra functional groups, are well-known among natural products and exhibit, for some of them, important biological properties.[32]



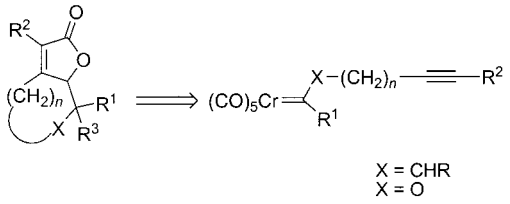
Scheme 12

The purpose of this paper is linked to our general interest in the synthesis of such compounds in a diastereo- and enantioselective way,[38] which led us to examine carefully the possibility and limits of this new approach by structurally modifying the starting carbene complexes and the dihydropyridines and to show how this chemistry could be extended to nucleophiles different from hydrides.

Results and Discussion

Synthesis of the Carbene Complexes

A retrosynthetic picture indicates which modifications can easily be carried out: a major structural feature is the location of the triple bond-containing fragment. It can either be bound directly to the carbon or to the oxygen atoms of the carbene ligand (X = CHR or X = O). Other modifications concern the nature of the substituents of the carbene carbon (R^1), of the triple bond (R^2), and of the alkyl chain bearing the triple bond and finally of the oxygen atom (Scheme 14).

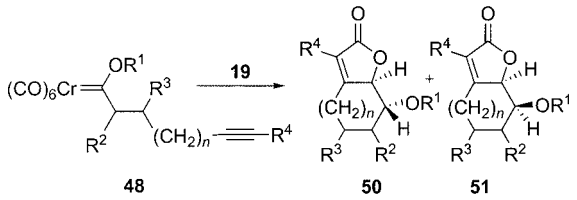


Scheme 14

Two main methods have been used for the synthesis of the different complexes.[3,39] The direct Fischer method involving the interaction of a suitable alkyllithium derivative with (hexacarbonyl)chromium led to complexes **37** and **48a**,**b**. Complex **37** was then modified by α-alkylation[4,40] to give **48c**,**d**. For complexes bearing alkoxy groups different from ethoxy and methoxy, the reaction of a suitable alcohol with a carbonylchromium acylate salt gave complexes **49a**−**l**. Finally, combination of the two methods led to two alkynyl(alkoxy)carbene complexes **48e**,**f** bearing different alkoxy groups. The preparation of the various complexes together with their physical data can be found in the Exp. Sect.

N-Methyldihydropyridine-Induced Transformations of Complexes 48a−f into the Butenolides 50a−f and 51a−f − Scope of the Reaction and Influence of the Nature of the Substituents on the Carbene Complexes

All of the reactions were performed according to the procedure used for the transformation of complex **37** into the butenolides **38** and **39** (Scheme 15). Table 1 confirms that the transformation is of a general scope, which led in each case to a mixture of isomers, the *trans* isomers being the major products.

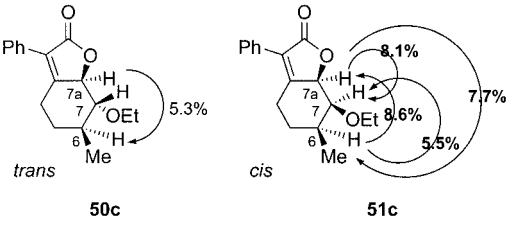


Scheme 15

Table 1. Reduction of complexes **48a**−**f** with *N*-methyldihydropyridine **19**

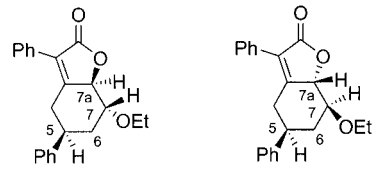
Entry	Complex	OR^1	R^2	R^3	R^4	n	Yield [%]	*de* [%]	Products
1	**37**	OEt	H	H	Ph	1	63	80	**38**, **39**
2	**48e**	OCH_2cPr	H	H	Ph	1	62	60	**50e**, **51e**
3	**48f**	OBn	H	H	Ph	1	32	60	**50f**, **51f**
4	**48d**	OEt	Bn	H	Ph	1	65	40	**50d**, **51d**
5	**48c**	OEt	Me	H	Ph	1	70	22	**50c**, **51c**
6	**48a**	OEt	H	Ph	Ph	1	42	33	**50a**, **51a**
7	**48b**	OEt	H	H	Et	0	58	0	**50b**, **51b**

The following comments can, however, be addressed. First, the nature of the substituent on the oxygen of the carbene complex does not modify the stereochemical outcome of the reaction: only a drop in the yield of the reaction is observed in going from ethyl to benzyl (Entries 1−3). Whereas the introduction of substituents on the alkyl chain had no influence on the yield of the reaction (Entries 4−6), a change in the *trans*/*cis* ratios appeared however. This was especially important in the case of an α-substituent (Entries 4 and 5 vs. Entry 1). Indeed, complex **48d** led to a mixture of butenolides **50d** and **51d** in which the major isomer has a *cis* geometry. However, complex **48c** led again to a mixture of two isomers **50c** and **51c** in about a 1:1 ratio, the *trans* isomer ($J_{H7,H7a}$ = 8.2 Hz) being slightly more abundant than the *cis* isomer ($J_{H7,H7a}$ = 3.4 Hz). In the *trans* compound **50c**, the ethoxy and the methyl groups are equatorial and the protons H^{7a}, H^7, and H^6 are axial. An NOE enhancement (5.3%) is indeed observed for H^{7a} and H^6 upon irradiation of H^7. In the *cis* isomer, the ethoxy group is axial whereas the methyl group is equatorial. Again, NOE enhancements are observed as indicated in Scheme 16.

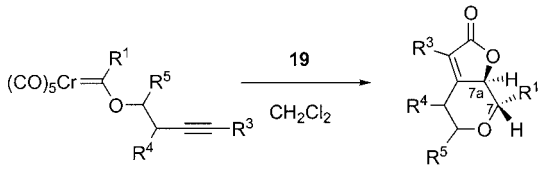


Scheme 16

Introduction of a phenyl group β to the carbene carbon (Entry 6, complex **48a**) led to a similar result, the most abundant compound being also the *trans* isomer **50a**, (J = 8.1 Hz). The configurations of the various substituents were also assessed by NOE experiments (Scheme 17).



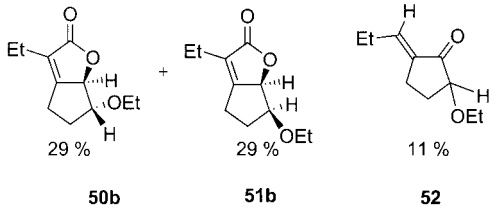
Scheme 17



Scheme 19

Modification of the Length of the Alkyl Chain

Up to now we have described the synthesis of [5.6]-fused systems. A [5.5]-fused bicyclic lactone could also be synthesised from the appropriate carbene complex **48b**, which led to a 1:1 mixture of two isomeric lactones **50b** and **51b** in a 58% overall yield. Besides these two expected compounds, the (ethoxy)propylidenecyclopentanone **52** was obtained in 11% yield (Scheme 18). The formation of such a ketone, lacking an inserted CO group with respect to the butenolides **50b** and **51b**, had already been observed in the case of the reduction of similar tungsten carbene complexes.[28,35]



Scheme 18

Interaction of Complexes 49a−l with *N*-Methyldihydropyridines: Diastereospecific Formation of Butenolides 53a−l

Since access to ω-acetylenic alcohols is very easy, a large variety of complexes such as **49a−l** (Table 2) could be synthesised. Their reaction with the dihydropyridine **19** led to the butenolides **53a−l** (Scheme 19).

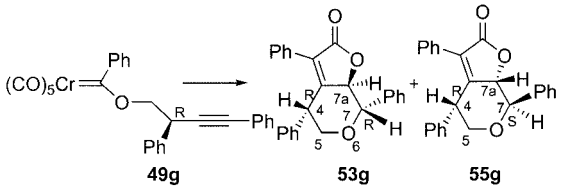
One of the most striking results is the stereochemical outcome of these reactions: as can be seen in Table 2, all but one transformation took place in a diastereospecific way, with the yields of the lactones ranging from 30 to 74%. The structures of these new butenolides were assessed both by ^{1}H NMR spectroscopy — the 8.8 Hz coupling constant indicating a *trans* relationship between H^7 and H^{7a} — and by X-ray crystallography. Neither the introduction of different substituents on the carbene carbon, nor the modification of the substituents on the triple bond had any influence on the isomers' distribution. The only exception which has to be noticed arose in the case of complex **49c**, which led, besides the *trans* isomer **53c** (57% yield), to a small percentage of the *cis* isomer **54c** (7%).

An interesting modification of the carbene complexes was achieved by the introduction of substituents on the alkyl chain. This allowed the synthesis of enantiomerically pure substituted butenolides (Entry 7), of polysubstituted butenolides (Entries 8−10), and ultimately, of tricyclic butenolides (Entries 11 and 12, Table 2). In the first example (Entry 7, complex **49g**), a phenyl group is present α to the triple bond. This chiral complex was obtained upon interaction of the corresponding chiral alcohol derived from optically pure styrene oxide and lithium phenylacetylide[41] with the appropriate chromium complex. Upon reaction of complex **49g** with *N*-methyldihydropyridine (**19**), two isomeric butenolides were isolated in 58% yield. The main isomer (49%), isolated as a solid [m.p. 97 °C, $[\alpha]_D^{20} = +171$] shows the typical doublet at $\delta = 4.96$ ppm for the proton at the ring junction. The coupling constant with the adjacent proton (9.0 Hz), is in agreement with a *trans* configuration as in **53g**. This was confirmed by an X-ray crystallographic analysis.

Table 2. Reduction of complexes **49a−l** with *N*-methyldihydropyridine (**19**)

Entry	Complex	R^1	R^3	R^4	R^5	Yield [%]	*de* [%]	Products
1	**49a**	Ph	Ph	H	H	46	100	**53a**
2	**49b**	Me	Ph	H	H	47	100	**53b**
3	**49c**	*c*Pr	Ph	H	H	64	80	**53c**, **54c**
4	**49d**	Ph	H	H	H	63	100	**53d**
5	**49e**	Me	H	H	H	38	100	**53e**
6	**49f**	*c*Pr	H	H	H	48	100	**53f**
7	**49g**	Ph	Ph	Ph*	H	58	100	**53g**, **55g**
8	**49h**	Ph	Ph	Me	Me	53	100	**53h**
9	**49i**	Me	Ph	Me	Me	30	100	**53i**
10	**49j**	*c*Pr	Ph	Me	Me	39	100	**53j**
11	**49k**	Ph	Ph	$-CH_2-(CH_2)_2-CH_2-$		74	100	**53k**
12	**49l**	*c*Pr	Ph	$-CH_2-(CH_2)_2-CH_2-$		53	100	**53l**

The second isomer, **55g**, isolated as a solid [m.p. 174 °C, $[\alpha]_D^{20} = +91$] corresponded also, according to its ^{1}H NMR spectrum, to a *trans* isomer ($J_{H7,H7a} = 9.4$ Hz). Since the butenolides **53g** and **55g** are isomers, then H^4 and H^{7a} must be in a *cis* relationship. Moreover, since the absolute configuration of carbon C-4 is known (*R*), then the absolute configurations of the stereogenic centres of the second butenolide **55g** are as indicated in Scheme 20.



Scheme 20

Starting from complexes **49h−j** containing a disubstituted alkyl chain, a single *trans* butenolide was isolated each time (Entries 8−10). Thus, butenolides containing four stereogenic centres could be synthesised very efficiently. As an example, the reduction of complex **49h** led to the crystalline butenolide **53h**. Its structure was confirmed both by NMR and by X-ray crystallography.

Easy access to an acetylenic alcohol derived from cyclohexene oxide[41] prompted us to synthesise complexes of the type **49k,l** (Entries 11 and 12). They led again to single isomers upon reduction with dihydropyridine. Thus, in the case of complex **49k**, the butenolide **53k** was isolated as a solid (m.p. 184 °C). Its structure was again determined by X-ray crystallography, the molecular projection appearing in Figure 1. This confirmed the *trans* configuration of H^{3a} and H^4, and of H^{5a} and H^{9a}, and the *cis* relationship between H^{3a} and H^{9a}, and between H^4 and H^{5a}. Surprisingly, only one enantiomer of **53k** appears in the lattice, a spontaneous separation of the two enantiomers of **53k** having taken place upon recrystallisation (Scheme 21).[42]

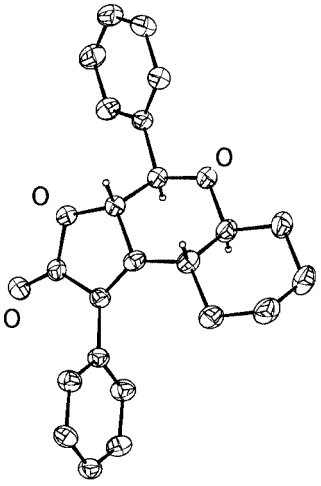
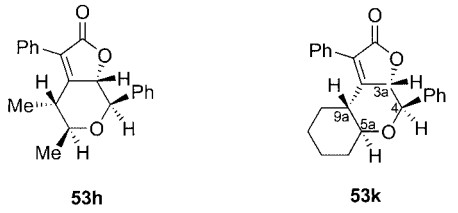
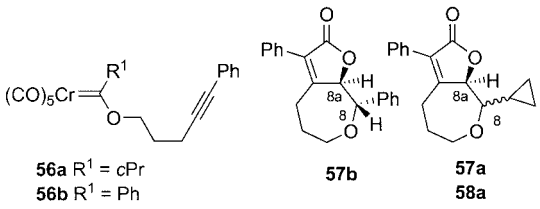


Figure 1. X-ray structure of the butenolide **53k** (CAMERON view), atoms drawn at 50% probability



Scheme 21

Finally, attempts were made to prepare [7.5] bicyclic lactones although the formation of a seven-membered ring system seemed to be less obvious.[43] For that purpose, the two complexes **56a** and **56b** were submitted to the reduction reaction and led, surprisingly, to the expected butenolides (Scheme 22). However, whereas **56a** gave **57a** and **58a** in a satisfactory 52% yield (*de* = 37%), only a low 8% yield of **57b** was observed from **56b**. The two isomers originating from **56a** were separated by chromatography. A *trans* configuration of H^8 and H^{8a} (J = 8.6 Hz) could be assigned to the main isomer **57a** (m.p. 73 °C) and finally confirmed by X-ray crystallography (molecular projection shown in Figure 2).



Scheme 22

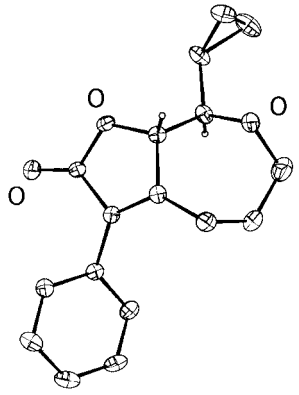


Figure 2. X-ray structure of the butenolide **57a** (CAMERON view), atoms drawn at 50% probability

Influence of the Nature of the Solvent

A point which might be of importance in a reaction involving coordinatively unsaturated species, and during which a triple bond must enter in the coordination sphere of the metal, is the nature of the solvent. We found that most solvents, with the exclusion of alcohols, were suitable for the synthesis of the butenolides. Whereas no straightfor-

ward difference was observed in going from dichloromethane (the most usual solvent) to acetonitrile, via DMF and THF, in the case of phenyl-substituted carbene complexes, a significant variation of the *de*'s appeared in the case of methyl-substituted carbene complex **49e**.

Table 3. Influence of the solvent in the reduction of complexes **49d** and **49e**

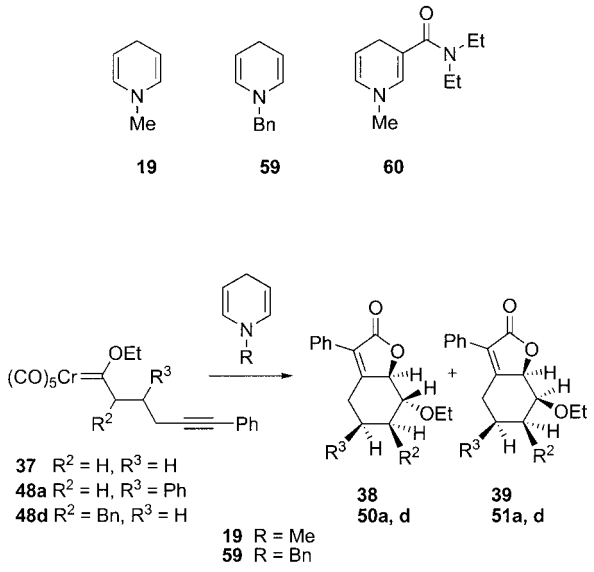
Entry	Complex	Solvent	Yield [%]	*de* [%]	Products
1	**49d**	CH_2Cl_2	63	100	**53d**
2	**49e**	CH_2Cl_2	38	100	**53e**
3	**49e**	THF	30	60	**53e**
4	**49d**	MeCN	56	100	**53d**
5	**49e**	MeCN	56	82	**53e**
6	**49d**	DMF	42	100	**53d**
7	**49d**	MeOH	0	–	–

Behaviour of Dihydropyridines Different from *N*-Methyldihydropyridine

The dihydropyridines involved in both biological and biomimetic reductions are far more complex than *N*-methyldihydropyridines. We thus considered the possibility of using first simple dihydronicotinamides closer to the structure of the prosthetic group of NADH, and then chiral dihydropyridines, to see whether they would also reduce carbene complexes, possibly in an enantioselective way.

Reduction of Carbene Complexes with *N*-Benzyldihydropyridine (59) and *N*,*N*-Diethyl-*N*-methyl-1,4-dihydronicotinamide (60)

N-benzyldihydropyridine (**59**) and *N*-methyl-*N*,*N*-diethyl-1,4-dihydronicotinamide (**60**) were prepared according to a literature procedure.[44]



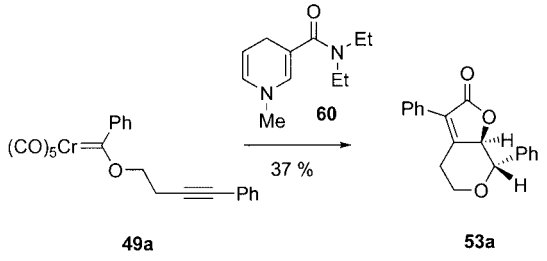
Scheme 23

Table 4. Reduction of complexes **37**, **48a** and **48d** with the dihydropyridines **19** and **59**

Entry	Complex	Dihydropyridine	Products	*de* [%]	Yield [%]
1	**37**	**19**	**38**, **39**	80	63
2	**37**	**59**	**38**, **39**	60	43
3	**48a**	**19**	**50a**, **51a**	34	42
4	**48a**	**59**	**50a**, **51a**	0	42
5	**48d**	**19**	**50d**, **51d**	40	65
6	**48d**	**59**	**50d**, **51d**	12	45

When complex **37** was treated with the dihydropyridine **59** at room temperature, a mixture of the expected butenolides **38** and **39** was obtained: only a slight decrease in the overall yield was observed (43 vs. 63% in the case of **19**; Scheme 23, Table 4). However, the diastereoselectivity was lower (*de*, 60% vs. 80%). A similar trend was observed in the case of substituted carbene complexes **48a**,**d**.

We then turned to the dihydronicotinamide **60**. To our delight it also induced the formation of the butenolides: **53a** was obtained in 37% yield from complex **49a** as a single isomer (Scheme 24).

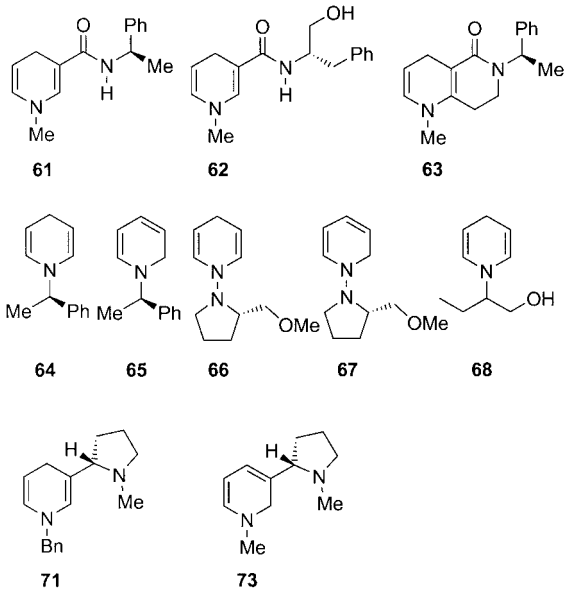


Scheme 24

Enantioselective Reduction of Alkoxycarbene Complexes: Formation of Chiral Butenolides

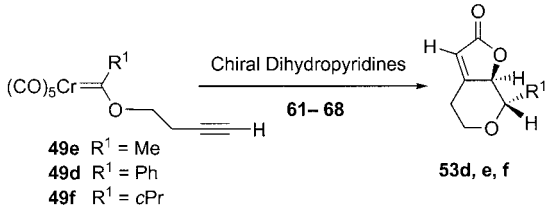
The biomimetic reduction of carbonyl compounds by dihydronicotinamides has been the subject of intense investigations both from a mechanistic and preparative point of view;[45] *ee's* of almost 100% were finally achieved by the use of elaborate chiral dihydronicotinamides.[46–48] The enantioselective synthesis of butenolides from carbene complexes and chiral dihydropyridines thus appeared feasible since in both cases the first step is the transfer of a hydride to an sp^2 carbon.

Three series of chiral dihydropyridines were tested: dihydronicotinamides **61**–**63** bearing the stereogenic centre on the nitrogen of the amide function,[46a–46i,49] dihydropyridines **64**–**68** bearing the stereogenic centre on the nitrogen of the pyridine,[50a–50e] and dihydropyridines **71** and **73** having a stereogenic centre on a substituent of the pyridine ring.



Behaviour of Chiral Dihydronicotinamides 61−68: Enantioselective Synthesis of Butenolides 53d,e upon Reduction of Carbene Complexes 49d,f

Among the complexes that were submitted to the reduction with the three dihydronicotinamides **61**, **62** and **63**, we chose **49d**,**e** for sake of simplicity since *N*-methyldihydropyridine (**19**) reduced them stereoselectively to a single butenolide (Scheme 25).



Scheme 25

Their interaction with the dihydronicotinamides **61**, **62** and **63** led to the expected butenolides as single isomers, in the case of **61** and **62** (Entry 1, Table 5), and as a mixture of isomers in the case of complex **49e** and the dihydronicotinamide **63** (Entry 3). The enantiomeric excesses determined by chiral GC were low, yet significant (*ee* = 20%) in the case of complex **49d** (Entry 2, R^1 = Ph) and the dihydronicotinamide **61**.

Changing the solvent had an important impact on the *ee*'s although the yields and the *de*'s remained almost unchanged, dichloromethane appearing as the most suitable solvent (*ee* = 20% vs. 1% in acetonitrile)

In the case of **64** and **65** (Entries 4, 5, 6), the reduction-insertions took place again with high diastereoselectivities (100%) but with low enantioselectivities, ranging from 0 to 27%. Similar results (*de*'s, 100%, *ee*'s, 8−18%) were observed with dihydropyridines **66**, **67** and **68** (Entries 7 and 8) bearing one or two extra heteroatoms in their structure. Moreover, the *ee*'s were again solvent dependent, the best results being observed in the case of the less-polar solvents (*ee* = 26% for pentane and 3% for acetonitrile). However, neither the yields nor the *de*'s and *ee*'s of the reactions were dependent on the dihydropyridine/complex ratio.

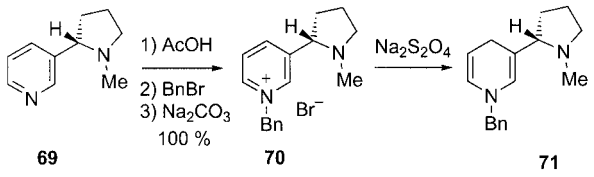
Stereogenic Center on a Substituent of the Pyridine Ring: Synthesis of Dihydronicotines 71 and 73 and their Interaction with Carbene Complexes

The most reliable and general reductants of alkoxycarbene complexes of chromium and tungsten appeared to be the simplest derivatives of pyridine — dihydropyridine and *N*-methyldihydropyridine.[28,35] We reasoned that chiral dihydropyridines bearing a stereogenic centre on a substituent of the pyridine nucleus might also be good candidates for these reactions. Among the substituted pyridines, nicotine **69**, a cheap, abundant yet toxic substituted pyridine which has attracted much attention due to its pharmacological properties, but not as a chiral ligand (or precursor), emerged as the most promising.[51] Indeed, we demonstrated that nicotine could be reduced, like pyridine, to a mixture of the three possible dihydronicotines. Moreover, this mixture reduced carbene complexes **4a**,**b** to give the expected nicotinium ylide complexes in high yield.[28] Although the synthesis of *N*-methyl-1,2-dihydronicotine from the known *N*-

Table 5. Reduction of complexes **49d**−**f** with chiral dihydropyridines **61**−**68**

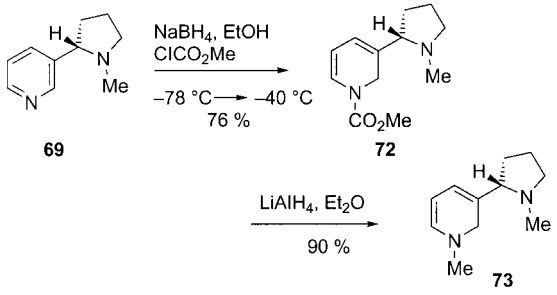
Entry	Complex	Yield [%]	*de* [%]	*ee* [%]	Products	Yield [%]	*de* [%]	*ee* [%]
		with **61**				with **62**		
1	**49e**	55	100	1	**53e**	–	–	–
2	**49d**	30	100	20	**53d**	13	100	2
		with **63**						
3	**49e**	15	49	11	–	–	–	–
		with **64**				with **65**		
4	**49e**	62	100	1.2	**53e**	67	100	11.5
5	**49d**	60	100	4.3	**53d**	72	100	27
6	**49f**	58	100	1.8	**53f**	60	100	1
		with **66**				with **67**		
7	**49d**	25	100	11	**53d**	68	100	18
		with **68**						
8	**49e**	50	100	8	**53e**	–	–	–

methylnicotinium iodide[52] failed, the reduction of the known[53] *N*-benzylnicotinium bromide (**70**) with sodium dithionite led to *N*-benzyl-1,4-dihydronicotine (**71**, Scheme 26).



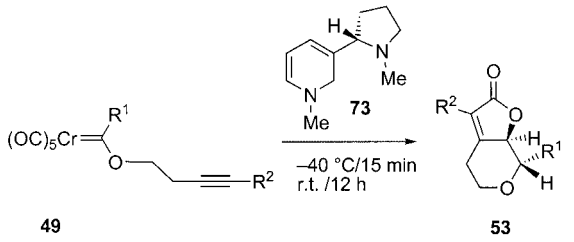
Scheme 26

N-Methyl-1,2-dihydronicotine (**73**) was, however, obtained by the method developed by Fowler for the synthesis of *N*-methyl-1,2-dihydropyridine.[54] Thus, sodium borohydride reduction of nicotine (**69**) in ethanol (instead of methanol) in the presence of methyl chloroformate, at low temperature, led to the protected dihydronicotine **72**, which was reduced with $LiAlH_4$ to afford pure **73** in 90% yield (Scheme 27).



Scheme 27

The interaction of *N*-benzyl-1,4-dihydronicotine (**71**) with complex **49e** led to a disappointing result: although a 51% yield of the expected butenolide **53e** was observed, the enantioselectivity was insignificant (*ee*, 4%).[55] Much better results were, however, observed in the case of *N*-methyl-1,2-dihydronicotine (**73**). Its interaction with complex **49e** gave the butenolide **53e** as a single isomer in 20% yield with a very encouraging *ee* of 55%. Although the chemical yields with the other complexes were in general higher, the enantiomeric excesses were unfortunately much lower, ranging from 12.5 to 37% (Scheme 28, Table 6).



Scheme 28

In all the cases examined the *de*'s were again 100%, with the *ee's* being dependent on the nature of the substituents on the carbene carbon; the cyclopropyl group appearing as the less enantiodifferentiating group. It is, however, noticeable that the nature of the substituents on the triple bond has no effect. Two other parameters were examined in the case of complex **49e** in order to try to improve the yields and the *ee*'s: the nature of the solvent and the dihydronicotine/carbene complex ratio in dichloromethane. However, neither of these parameters had any influence on the outcome of the reaction.

Behaviour of Carbene Complexes towards Other Nucleophiles: A General Access to Substituted Butenolides

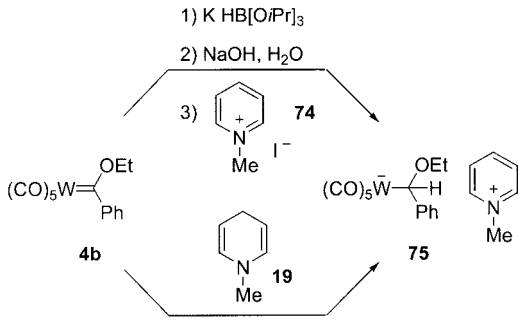
The reaction of nucleophiles, for example alkoxides or amines, with alkoxycarbene complexes, giving new carbene complexes upon exchange of the alkoxy group, strongly implicated the existence of a symmetric tetrahedral intermediate[56] similar to those known for organic carbonyl compounds (Scheme 1). Therefore such intermediates for Nu = H^-, OR^-, Me^- or Ph^- might also be trapped intramolecularly by alkynes and lead to substituted butenolides. The following results confirmed this assumption.[57]

Reaction of Complex 49a with $KHB(OiPr)_3$: Formation of Butenolide 53a

Casey has described the formation of the tungsten complex **5** upon interaction of $KHB(OiPr)_3$ with complex **4a** after cation exchange[15] (Scheme 2). We demonstrated that the reaction of **4b** with $KHB(OiPr)_3$ followed by cation exchange with *N*-methylpyridinium iodide (**74**) led to complex **75**, identical in all respect to the complex obtained upon reduction of **4b** with *N*-methyldihydropyridine **19** (Scheme 29).

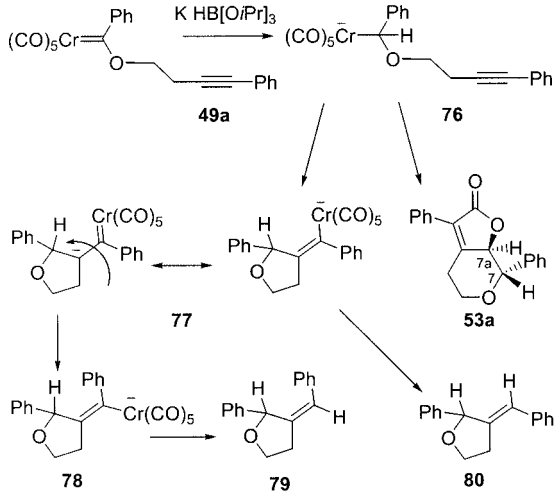
Table 6. Reduction of complexes **49a**−**f** with the dihydronicotine **73**

Entry	Complex	R^1	R^2	Product	Yield [%]	*de* [%]	*ee* [%]	$[\alpha]_D^{20}$ ($CHCl_3$)
1	**49e**	Me	H	**53e**	20	100	55	35.9, *c* = 2.3
2	**49b**	Me	Ph	**53b**	10	100	37	−30.4, *c* = 2.0
3	**49d**	Ph	H	**53d**	63	100	33	44.3, *c* = 2.3
4	**49a**	Ph	Ph	**53a**	38	100	30	54.0, *c* = 2.0
5	**49f**	*c*Pr	H	**53f**	32	100	14	9.3, *c* = 2.1
6	**49c**	*c*Pr	Ph	**53c**	43	100	12.5	5.5, *c* = 2.1



Scheme 29

Similarly, reaction of $KHB(OiPr)_3$ with complex **4b** followed by the addition of cyclopentenone led to the 1,4-addition product **23** (Scheme 6). This result was a good indication that the cascade insertions might also be induced by hydrides not originating from dihydropyridines. Indeed, when **49a** was reduced with $KHB(OiPr)_3$, the expected butenolide **53a** was isolated in a 21% yield together with a 32% mixture of two isomeric (benzylidene)phenyltetrahydrofurans **79** and **80** (Scheme 30).



Scheme 30

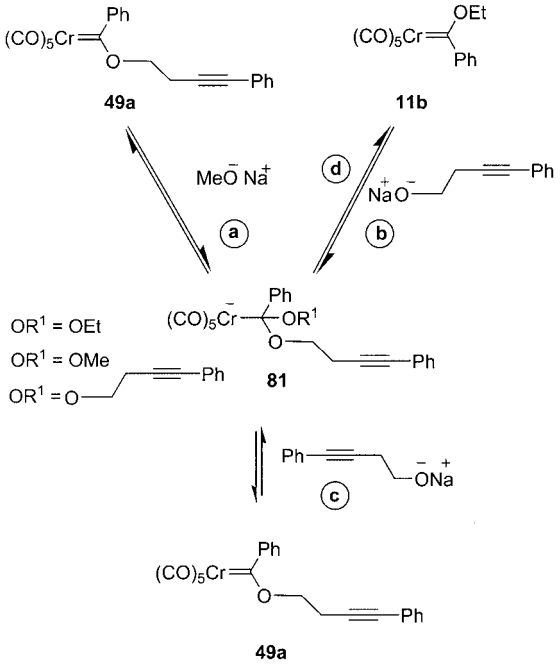
The formation of the latter can be explained by a hydride transfer to the carbene carbon, followed by a direct insertion of the triple bond into the chromate **76** to give **79** and **80** via **77** and **78**.

Remarks on the Behaviour of Other Inorganic Hydrides

Following this result, we carried out a series of reactions between **49e** and different inorganic hydrides. Whereas $LiAlH_4$, $LiAlH(tBuO)_3$ and 9-BBN did not lead to **53e**, both $NaBH_4$ and the complex 9-BBN/nicotine gave substantial amounts of this compound (13 and 22%, respectively).[23f,58,59]

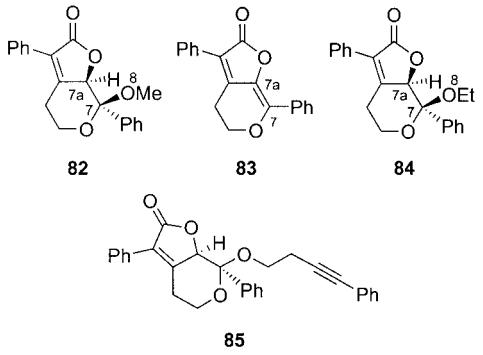
Reaction of Alkoxides with Carbene Complexes: Introduction of Alkoxy Groups into the Butenolides

As already mentioned in the introduction, the interaction of alcohols with alkoxycarbene complexes of chromium in the presence of sodium alkoxide was the first direct indication of the possible exchange of alkoxy groups in carbene complexes via a tetrahedral intermediate.[3a−3c] Moreover, this reaction brought to the fore an important ''side reaction'' — the easy insertion of CO into this tetrahedral intermediate and thus its possible use to synthesise butenolides bearing an alkoxy group on the former carbene carbon instead of a hydride. We therefore carried out three types of reactions which were supposed to give the same tetrahedral complex **81** bearing two alkoxy groups as the intermediate. Such a complex might form upon interaction of **49a** with MeONa (route a), upon interaction of **11b** with sodium phenylbutynolate (route b), or upon interaction of **49a** with sodium phenylbutynolate (route c). This latter would rule out the formation of a non-productive carbene complex (route d) (Scheme 31).



Scheme 31

The addition of a 30% solution of MeONa in MeOH to a THF solution of **49a**, at 0 °C, followed by stirring at room temperature for 15 h led indeed to two butenolides, **82** (22%) and **83** (8%), (Scheme 32) which were fully characterised by NMR spectroscopy and, for **83**, by X-ray crystallography.



Scheme 32

The NMR spectra of **82** display the expected signals for such a butenolide, with the methoxy group giving a signal at δ = 2.96 ppm in the ^{1}H NMR spectrum, and, in the ^{13}C NMR spectrum, signals at δ = 172.5 ppm (CO) and at δ = 101 ppm, characteristic of C-7, the former carbene carbon now bearing two oxygen atoms. Moreover, the hydrogen H^{7a}, at the ring junction, appears now as a singlet. The second product **83** could be the result of the elimination of methanol from **82** but probably originates directly from the intermediate lactone chromium enolate (vide infra).

Similarly, complex **11b** gave the ethoxy-substituted butenolide **84** in 25% yield in the presence of sodium butynolate, according to route b (Scheme 31). Most characteristic are the signals in the NMR spectra at δ = 172.6 ppm, and the multiplets at δ = 3.28−3.06 ppm for the two diastereotopic hydrogens of the ethoxy group. Its structure was confirmed by an X-ray struture analysis (Figure 3). The second product of the reaction was again the conjugated butenolide **83** (25%).

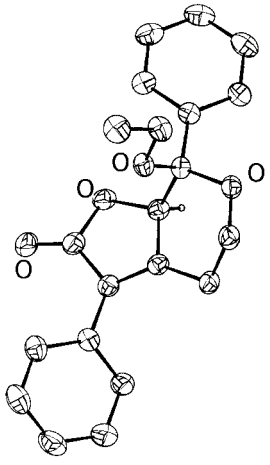
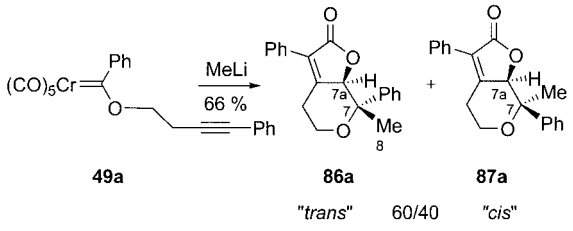


Figure 3. X-ray structure of the butenolide **84** (CAMERON view), atoms are drawn at 50% probability

Finally, sodium phenylbutynolate reacted with complex **49a**, according to *route c*, to give two products, the expected butenolide **85** with two incorporated phenylbutynol units, and the elimination product **83**, in 9 and 29% yield, respectively. The NMR spectra of **85** confirmed the presence of the unsaturated lactone, but also of three phenyl groups, a carbon−carbon triple bond with signals at δ = 86.9 and 81.6 ppm, and a signal at δ = 100.1 ppm for the carbon bearing the two oxygen atoms originating from butynol, the angular proton displaying a singlet at δ = 4.7 ppm.

Reaction of Complexes 49a and 49h with Alkyllithium and Magnesium Derivatives: Formation of Alkyl-Substituted Butenolides

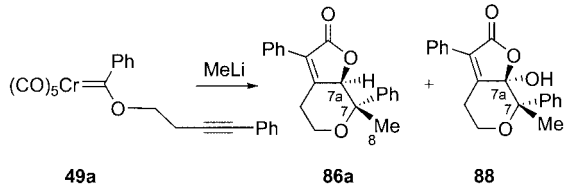
Casey, Fischer, and our group have studied the interaction of aryl- and alkyllithium derivatives with phenyl-substituted alkoxycarbene complexes en route to non-heteroatom-stabilized carbene (alkylidene) complexes[15c,16,59] via tetrahedral intermediates **2** (Scheme 1, Nu^{-} = Ph, Me). Attempts were thus made to carry out similar addition reactions on the more elaborate carbene complexes **49a** and **49h** in order to trap the triple bond-containing alkylmetallates intramolecularly. However, the interaction of complex **49a** with PhLi, at −40 °C, followed by stirring at room temperature, did not lead to the expected butenolide. When the same reaction was carried out with MeLi, the red colour of the starting complex faded rapidly. After 15 h at room temperature, two new products were isolated in 66% yield (Scheme 33).



Scheme 33

According to their elemental analysis, and mass and NMR spectra, these compounds were indeed the expected butenolides **86a** and **87a**, formed as a 40:60 *cis*/*trans* mixture of isomers. Both the angular protons and the methyl groups appear as singlets at δ = 4.96 and 5.08 ppm and at δ = 1.40 and 1.81 ppm, respectively. The structure, and thus the stereochemistry of the major isomer **86a** — a *trans* orientation of the methyl group with respect to the angular hydrogen — were confirmed by an X-ray analysis.

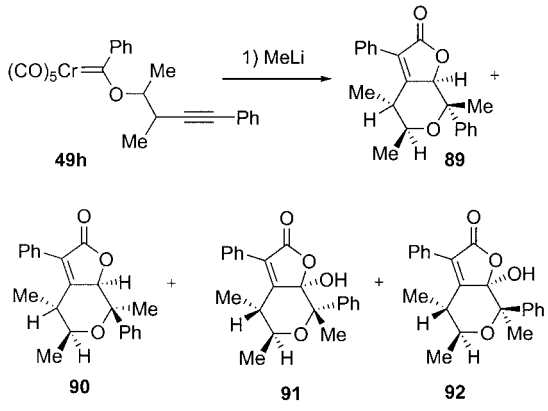
Attempts to improve the yield of this transformation led, however, to erratic results: besides the butenolides **86a**, variable amounts of a second product **88** were obtained (Scheme 34).



Scheme 34

According to its spectroscopic data, this product was also a butenolide [δ(CO) = 170 ppm] containing a methyl group [singlet, $\delta(CH_3)$ = 1.6 ppm]. Moreover, the signal corresponding to C-7a moved from δ = 85.2 to 102.1 ppm, confirming the introduction of an extra oxygen atom on this carbon. That the oxygen belongs to an alcohol is consistent with the presence of a broad singlet at δ = 3.2 ppm. All the data were thus consistent with the formation of a lactonol due to the presence of oxygen. The structure of this new type of product was finally assessed by an X-ray diffraction study which confirmed the presence of a tertiary alcohol at the ring junction, *cis* with respect to the phenyl group. Thus the efficiency and the reproducibility of the reaction relied on how carefully oxygen was removed from the reaction medium. This was confirmed in the following way: when the reaction was carried out as above, then the temperature of the solution raised to 0 °C, and oxygen added, **88** was obtained as a single product in 14.5% yield (Scheme 34).

Similar results were observed in the case of complex **49h** which led, depending on the reaction conditions, to up to four products, the two expected butenolides **89** and **90**, and two unsaturated lactonols **91** and **92** (Scheme 35).



Scheme 35

Their spectroscopic data are in full agreement with the proposed structures and confirmed by an X-ray structure of **91** (Figure 4).

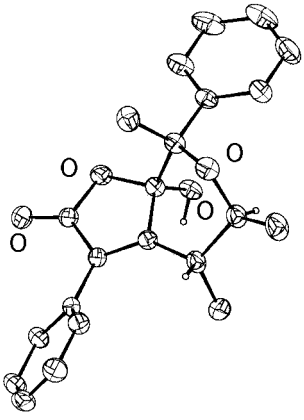
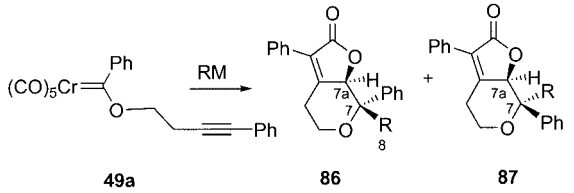


Figure 4. X-ray structure of the butenolide **91** (CAMERON view), atoms are drawn at 50% probability

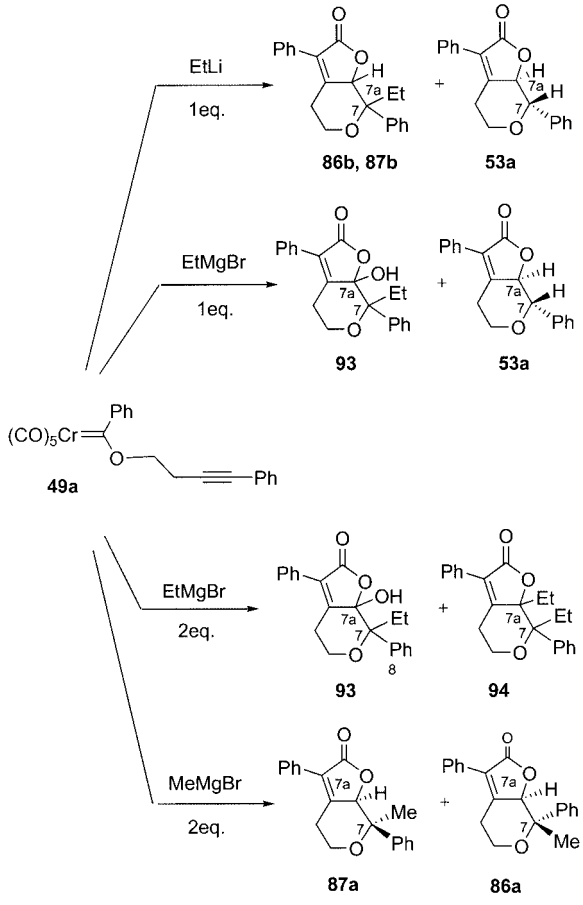
These results urged us to extend the reaction first to several organolithium and organomagnesium derivatives (Scheme 36): butyllithium, (trimethylsilyl)methyllithium, ethyllithium and methylmagnesium bromide led to the expected substituted butenolides (Table 7).



Scheme 36

Table 7. Reaction of complex **49a** with various alkyllithium and magnesium derivatives

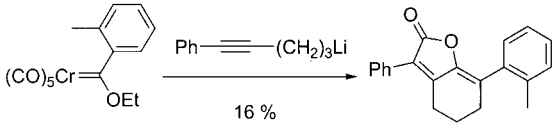
Entry	Nucleophile	Yield [%]	Products	*de* [%]
1	MeLi	66	**86a**, **87a**	20
2	EtLi	25	**86b**, **87b**	> 90
3	BuLi	43	**86c**, **87c**	> 90
4	Me_3SiCH_2Li	34	**86d**, **87d**	> 90
5	MeMgBr	30	**86a**, **87a**	46



Scheme 37

Peculiar results (not indicated in Table 7) were, however, observed in the case of ethyllithium and ethylmagnesium bromide. Whereas ethyllithium, on its own, gave the expected butenolides **86b** and **87b**, both reagents led to **53a**, the butenolide obtained previously upon reduction of the carbene function of **49a**. Moreover, when two equivalents of ethylmagnesium bromide were used, the course of the reaction was again different: besides small amounts (4%) of the lactonol **93**, a second unexpected butenolide **94** was also detected. Its physical data are in agreement with the introduction of two ethyl groups, one, as expected, on C-7, and the second one at the ring junction (Scheme 37). The origin of this product has not yet been established.

Finally, a triple bond could also be introduced into the carbene complexes by means of an alkynyllithium derivative; phenylbutynyllithium reacted with complex **95** to give a modest yield of the butenolide **96** (16%), one of the expected products of this reaction (Scheme 38).

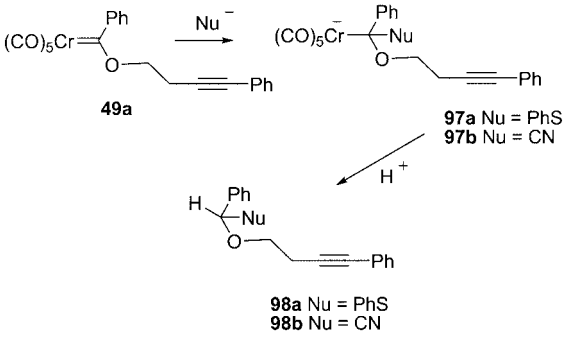


95 **96**

Scheme 38

Peculiar Behaviour of Sodium Phenylthiolate and Tetramethylammonium Cyanide

Thiols react with alkoxycarbene complexes to give alkyl- and arylthiocarbene complexes via tetrahedral intermediates.[4] These fleeting intermediates might thus also be trapped as such or as the CO insertion products by a suitable triple bond. We therefore reacted complex **49a** with sodium phenylthiolate at −40 °C, in THF, then, after heating to room temperature, at reflux of the solvent for 12 h. Work up, followed by silica gel chromatography, gave, however, **98a** in 46% yield; this product results from the addition of the thiolate to **49a** followed by the protonation of the resulting chromate **97a**. Neither of the expected insertions — CO and/or the triple bond — took place. A similar behaviour was observed with cyanide anions (Scheme 39).



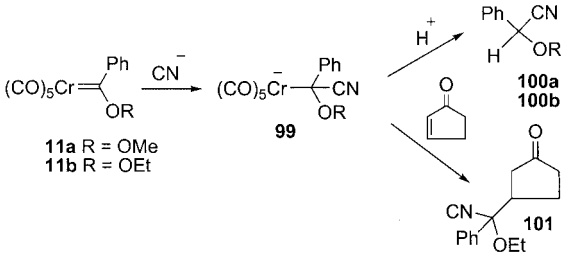
49a

97a Nu = PhS
97b Nu = CN

98a Nu = PhS
98b Nu = CN

Scheme 39

Calcium cyanide has been shown by Fischer to lead to the nitrile complex **100a** (2.5%)[60] via complex **99**, upon interaction with complex **11a**. We confirmed this result by using the more soluble tetramethylammonium cyanide: complex **11b** led indeed to ethoxy(phenyl)acetonitrile in 19% yield (Scheme 40).



11a R = OMe
11b R = OEt

99

100a
100b

101

Scheme 40

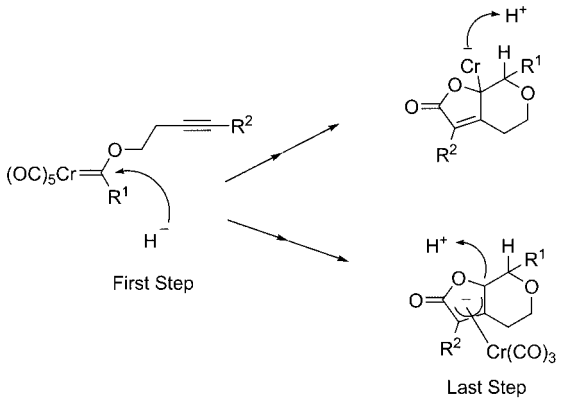
When the reaction was carried out in the presence of cyclopentenone, the 1,4-addition product **101** was obtained in 47% yield as a mixture of two isomers (Scheme 40). Finally complex **49a**, under the same conditions, led also to an addition/protonation product **98b** (Nu = CN) in 23% yield (Scheme 39).

Remarks on the Stereochemical Outcome of the Insertion Reactions

Achiral Dihydropyridines and Nucleophiles

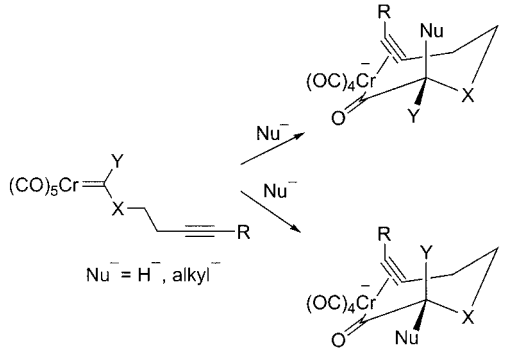
One of the remarkable points of these transformations, other than the large variety of butenolides which can be synthesised, is their stereochemical aspects. Indeed, high diastereoselectivities are very often observed, especially when the alkynyl group was directly bound to the oxygen atom of the carbene function. How can this result be explained? A first general remark: due to the presence of a five-membered unsaturated lactone, the hydrogen atom at the ring junction, adjacent to the stereogenic centres, is always axial, whereas the adjacent substituent of the former carbene carbon can either be axial or equatorial.

In the postulated mechanism, two fundamental steps must be considered. In the first one, the carbene function is reduced by the hydride originating from a dihydropyridine or undergoes the addition of a nucleophile. In the most simple cases, the two faces of the carbene function are enantiotopic since no stereogenic centre is included in the substituents of the carbene function (Scheme 41).[61] The last step is the protonation of an η^5-bonded lactone, one limiting form of the chromium enolate. Here, the two faces of the enolate are diastereotopic, thus two isomers can form.



Scheme 41

Let's first consider the case of the more simple carbene complexes in which no substituent is present on the alkyl chain. The transfer of a hydride to the carbene carbon will lead to an alkylchromate as a single isomer. This is followed by the insertion of a CO ligand with the critical step, as far as the stereochemistry is concerned, probably being a concerted coordination of the triple bond. In the transition state, the pre-formed cycle B of the butenolide most probably adopts a chair conformation in which Y, the former substituent of the carbene function, could either be equatorial or axial. For Y = alkyl, aryl and X = O, one can assume that, as in six-membered ketones of similar structures,[62] the more favoured stereochemistry of Y is the equatorial one, especially in the case of a phenyl group (Scheme 42). Thus, for X = O, only one isomer in which the two hydrogen atoms H-7 and H-7a are *trans diaxial* should form, which is indeed observed. Moreover, according to calculations, this compound is the thermodynamically more stable isomer ($\Delta H_F = -42.68$ kcal·mol^{-1} vs. $\Delta H_F = -40.30$ kcal·mol^{-1} for the *trans* and the *cis* isomer, respectively).[63] In the case of a methyl group, it is likely that the energy difference between the two possible conformers is lower and that weak interactions with the solvent can change the stereochemical outcome of the reaction. This is also observed (vide supra).



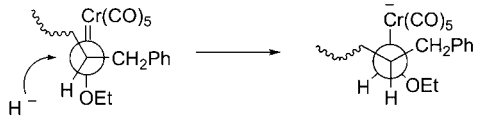
Scheme 42

However, the addition of nucleophiles bulkier than a hydride modified the stereochemical outcome: indeed, for Nu = methyl, two isomers were obtained. In the major product, as shown by X-ray diffraction studies, the phenyl group is still in an equatorial position. Nevertheless, 40% of a product in which this group is in an axial position are formed. For the butyl and trimethylsilylmethyl groups, the reaction is again highly selective. Nevertheless, small amounts (< 10%) of the second isomer could be detected by ^{1}H NMR spectroscopy, giving a singlet for the proton at the ring junction at about 5 ppm, downfield from the signal of the corresponding proton in the major isomer. We thus tentatively assigned a stereochemistry for these two compounds in which the introduced alkyl groups are axial. Thus, in all the cases examined, the phenyl group is equatorial in the major isomer.

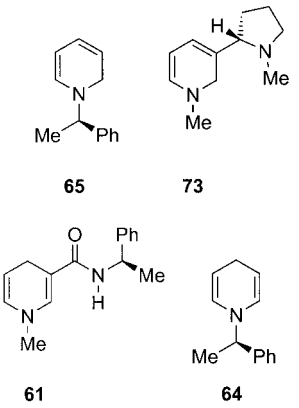
For Y = OR, X = CHR, other factors have to be considered: First, the anomeric effect and the oxygen-oxygen repulsion, which both favour the axial orientation of OR,[64] and second, steric hindrance between an axial Y group and the bulky ligands of the metal could also be critical and must be taken into account. It is thus not surprising to observe a balanced formation of the two isomers in this latter case, although according to the thermodynamics, the more stable product of the reaction has a *trans diaxial* geometry. ($\Delta H_F = -90.21$ kcal·mol^{-1} vs. $\Delta H_F = -88.40$ kcal·mol^{-1}) In the case of alkoxides, it is interesting to note that, according to the X-ray structure, the ethoxy group in compound **84** (Scheme 32, Figure 3) is in an axial position. This stereochemistry corresponds to that of the more stable product: due to the presence in the six-membered ring of an oxygen atom on the carbon bearing the alkoxy group, these two groups will be antiperiplanar as a result of the anomeric effect.[64]

For carbene complexes bearing a substituent on the alkyl chain, for example a benzyl group as in complex **48d**, a diastereoselectivity can already be expected in the first step, the reduction step. We can reason as for linear substituted carbonyl compounds: a Felkin−Anh model[65] might account for the formation of a major compound in which the benzyl substituent and the alkoxy group are *erythro*. Indeed, if the more bulky group, the benzyl of the alkyl chain, is antiperiplanar to the nucleophile, and the chain gauche with respect to the metal (Scheme 43), then the ethoxy and the benzyl groups in the resulting alkylmetalate will be *syn* in the major product, and thus the butenolide having an axially oriented ethoxy group and an equatorially oriented benzyl group will be the more abundant. Such an effect has already been observed by Cutler during the stepwise conversion of CO into poly(alkoxylethylene) acyl complexes.[66] For less-crowded substituents such as methyl groups, the distribution can again be reversed: since the chain can now be considered as the more crowded substituent, then the *trans* isomer will be the more abundant product, in agreement with the thermodynamic data ($\Delta H_F = -96.62$ kcal·mol^{-1} vs. $\Delta H_F = -93.91$ kcal·mol^{-1}). Finally, for the [5.5]-fused system, and in agreement with calculations ($\Delta H_F = -114.30$ kcal·mol^{-1} vs. $\Delta H_F = -113.44$

kcal·mol^{-1}), an equimolar amount of each isomer is formed during the insertion reaction, the enolate being almost planar and the protonation occurring with equal probability on the two sides of this intermediate.



Scheme 43



Chiral Dihydropyridines

Two important results have been observed: both dihydronicotinamides and dihydropyridines reduce carbene complexes and promote the cascade insertion reactions, although the yields are better in the case of simple dihydropyridines (75 vs. 37%). Moreover, both types of chiral analogues of NADH lead enantioselectively to butenolides. According to Scheme 41, a chiral hydride-transfer reagent should indeed be able to distinguish between the two faces of the carbene complex, as is the case for a ketone.[61] Two diastereomeric transition states might therefore form upon interaction of the chiral dihydropyridines with the carbene complexes, possibly giving rise to two enantiomers at different rates (stability control mechanism). There is, however, an important difference between carbene complexes and ketones which renders the discussion even more complicated: the alkoxycarbene complexes can exist as two different conformers around the oxygen atom at low temperature, their relative amounts depending on the nature of the substituents (Figure 5). According to the results gathered here, the following comments can tentatively be addressed. The best *ee*'s are achieved by the use of 1,2-dihydropyridines **65** and **73**. In both cases, the hydrides which can be transferred are on a carbon that is one atom away from the stereogenic centre — a carbon atom in **65** and a nitrogen atom in **73** — the difference between the two dihydropyridines being the presence of a second potential binding site in **73**, the nitrogen atom of the pyrrolidine substituent.

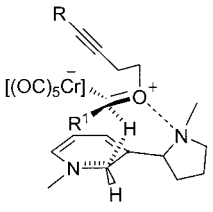
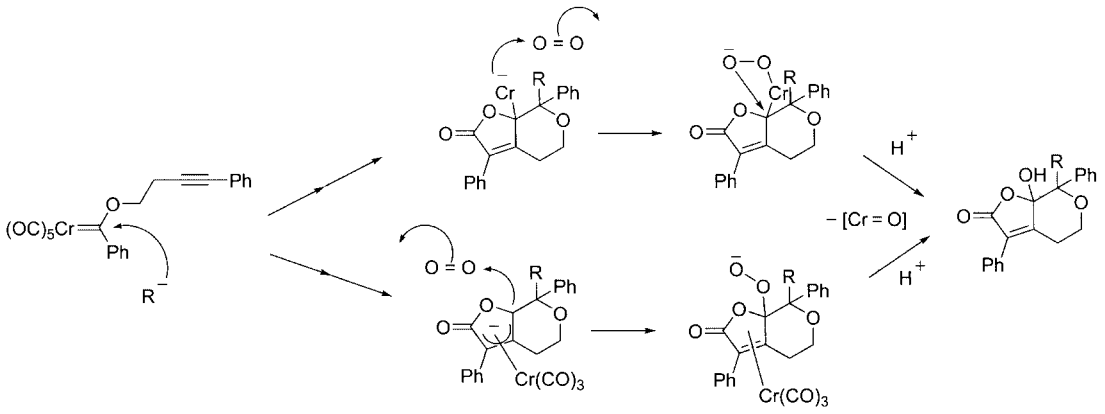


Figure 5. Transition-state model for the interaction of *N*-methyldihydronicotine with a carbene complex

The possibility for dihydronicotine to be coordinated to the carbene complex as a bidentate ligand prior to the hydride migration might thus be at the origin of the better enantioselection. According to calculations on the dihydronicotine **73**,[67] a preferential conformation exists in which the dihydropyridine and the pyrrolidine rings are almost perpendicular, as in nicotine.[68] A heteroatom substituent on the dihydropyridine might organize the transition state through coordination of the nitrogen atom of the pyrrolidine to the positive terminus of the carbene complex — the oxygen atom — as depicted in Figure 5. Moreover, a tight interaction between the pyridine ring, due to a developing positive charge on the nitrogen atom, and the negative terminus of the carbene, and thus with the substituents of the carbene carbon, can occur. It thus seems clear that the *ee*'s should be dependent on the nature of these substituents (vide supra).

Compound **63**, which is a dihydronicotinamide, appears in the third rank (*ee* 20%). Here the stereogenic centre is four atoms away from the carbon which bears the hydride. It might be compared to **64**, the efficiency of which is much lower (*ee* 1.4%). How can a more efficient interaction occur in this case? **63** contains a secondary amide with a rather acidic hydrogen atom. Thus a hydrogen bond between a carbonyl group of the complex and the hydrogen of the amide might form, which again might favour one transition state over the other. Such interactions have already been observed in the case of (arenetricarbonyl)chromium complexes and amides.[69]

To sum up, a transition state such as that depicted in Figure 5 would also be akin to the ternary ketone-dihydropyridine-Mg^{2+} complexes which have been proposed in the enantioselective reductions of ketones with analogues of NADH.[48] This reinforces the deep analogy which exists between carbene complexes and carbonyl compounds. Although no exceptional *ee*'s were observed up to now, the results are interesting and encouraging when compared to the efforts which have been devoted to the biomimetic enantioselective reduction of carbonyl compounds.[45,46] A way to perhaps improve the efficiency of the reducing dihydropyridines would be to either constrain the bicyclic system of nicotine or to add substituents on the pyrrolidine ring. Indeed, analogues of nicotine in which the rotation of the pyrrolidine ring is inhibited have been synthesised and



Scheme 44

are indeed much better haptens than nicotine for biological systems.[70] Other approaches to enantioselectivity would be to use chirally modified complex hydrides of the type $KHB(OR^*)_3$ as reducing agents or to carry out the reaction with other nucleophiles in conjunction with chiral additives. Work in this direction is underway.

Behaviour of Other Nucleophiles

We have clearly demonstrated that the addition of various nucleophiles to alkoxycarbene complexes of chromium is the key to the success of their general transformation into differently substituted butenolides. Crucial in this regard is the fact that no undesired interaction of the nucleophile with the various intermediates took place. A few points warrant a special comment: the behaviour of ethylmagnesium and -lithium derivatives, the formation of the unsaturated lactonols, and finally indications as to the limits of the method.

The formation of products due to a ''reduction'' of the starting carbene complexes upon their interaction either with ethylmagnesium or ethyllithium derivatives reflects again their analogy with carbonyl compounds as it is known that hindered carbonyl compounds can react with metal alkyl derivatives upon transfer of a hydride originating from the alkyl group, rather than of an alkyl group.[71]

The formation of lactonols along with the butenolides can easily be understood: The last step of the multiple insertion reactions is the protonation of a lactone enolate, one limiting form of which is a 2-oxyfuran. This may combine with triplet oxygen to afford a hydroperoxide which, in the presence of low-valent chromium species, will collapse into the lactonol and oxidized chromium. Conversely, direct interaction of oxygen with the metal of the final chromium enolate, a strong nucleophile, might lead to the same lactonol upon insertion of oxygen into the chromium−carbon bond (Scheme 44),[72a,72b] a radicalar pathway cannot, however, be excluded.[72c]

Nitrogen ylide complexes which are in fact ''internal'' tetraalkylammonium chromates, formed upon insertion of alkynes into aminocarbene complexes of chromium, behaved similarly and led to aminolactones upon oxidation with molecular oxygen.[73a,73c]

Behaviour of Sodium Thiophenolate and Ammonium Cyanide

In most of the intermediates obtained upon interaction of a nucleophile with the carbene complexes the metal bears a benzylic group. It is known that benzylic groups are not very prone to migrate to a coordinated carbon monoxide ligand to give an acylmetal derivative.[13,74] However, due to the presence of electron-rich substituents, such as alkoxy groups, the reaction takes place, although the presence of a nitrile, an electron-withdrawing group, inhibits the ''insertion'' of CO completely. Such a behaviour is also known from the literature: methoxycarbonyl substituents on an alkylmetal derivative inhibit the formation of metalacyl complexes.[74] The case of sodium thiophenolate is however less clear: since the electronegativities of sulfur and carbon are about the same, the alkylchromium intermediate should also insert a CO group and lead to a butenolide.That neither the CO nor the triple bond insertions were observed might be indicative of a direct interaction of the introduced functions(CN or SPh) with the metal.

Conclusion

In this paper we have demonstrated that a reaction which was interesting from a mechanistic point of view — the biomimetic reduction of carbene complexes with dihydropyridines — could be applied to the synthesis of highly functionalised unsaturated lactones by the use of various nucleophiles ranging from hydrides originating from dihydropyridines to alkyllithium derivatives and alkoxides. The analogy with biomimetic reactions allowed us to carry out the transformation in an enantioselective way with moderate, yet encouraging, success thanks to a new, efficient chiral reducing agent, *N*-methyldihydronicotine. The step which

triggers the rearrangement of these complexes is the transfer of a nucleophile to the carbene carbon giving a high energy electron-overloaded species which spontaneously leads to a new acyl complex. This new synthetic strategy led to the formation of six new bonds, up to four carbon−carbon bonds and two carbon−oxygen bonds, in a one-pot reaction involving alkoxycarbene complexes tethered to alkynes and various nucleophiles.

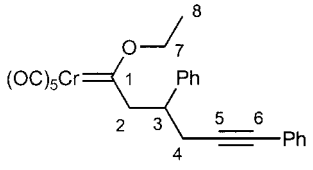
Experimental Section

General: Note that the experimental details for the preparation of some complexes can be found in the Supporting Information; for Supp. Inf. see also the footnote on the first page of this article.

Complexes 37 and 48a,b

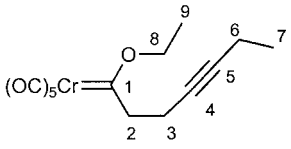
General Procedure: *tert*-Butyllithium (2.1 equiv. of a 1.7 M hexane solution) was added with a syringe over a period of 10 min to a solution of the corresponding iodide (1.0 equiv.) under argon at −78 °C in diethyl ether (7 mL/mmol of iodide) and pentane (10 mL/mmol of iodide). This solution was stirred at −78 °C for a period of 15 min and then transferred by cannula to a suspension of (hexacarbonyl)chromium [or (hexacarbonyl)tungsten; 1.0 equiv.] in diethyl ether (15 mL/mmol) at −78 °C. This mixture was warmed to room temperature and was stirred for 2.5 h. The solvent was removed on a rotary evaporator and the reaction mixture was cooled to 0 °C. Water (15 mL/mmol), petroleum ether (boiling fraction 40−65 °C, 15 mL/mmol), and then triethyloxonium tetrafluoroborate (1.1 equiv.) were added. The reaction mixture was warmed to room temperature and was extracted with petroleum ether. The organic layer was washed with sodium hydrogencarbonate solution, water, brine and dried with sodium sulfate. The solvent was removed on a rotary evaporator and final purification was achieved by chromatography on silica gel using pure petroleum ether as eluent.

Complex 48a: The general procedure was followed using (5-iodo-4-phenylpent-1-yn-1-yl)benzene (4.83 g; 13.96 mmol), *tert*-butyllithium (17.2 mL, 29.3 mmol), (hexacarbonyl)chromium (3.07 g, 13.95 mmol) and triethyloxonium tetrafluoroborate (2.92 g, 15.33 mmol). After chromatography on silica gel a reddish oil identified as complex **48a** was obtained (2.28 g, 4.87 mmol, 34.9%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38−7.18 (m, 10 H, arom. H), 4.92 (q, *J* = 7.0 Hz, 2 H, H^7), 3.96 (d, *J* = 7.3 Hz, 2 H, H^2), 3.44 (m, 1 H, H^3), 2.66 (m, 2 H, H^4), 1.40 (t, *J* = 7.0 Hz, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 357.5 (C^1), 223.2 (*trans* CO), 216.4 (*cis* CO), 142.9 (qC), 131.7 (qC), 128.6−127.3 (arom. HC), 123.6 (qC), 87.6, 83.1 (C^5 or C^6), 78.2 (C^3), 67.8 (C^8), 42.3 (C^2), 27.2 (C^4), 14.8 (C^9) ppm. HRMS [M + NH_4] calcd. for $C_{25}H_{24}CrNO_6$: 486.1069; found 486.1071.



48a

Complex 48b: The general procedure was followed using 1-iodohex-3-yne (4.16 g, 20.00 mmol), *tert*-butyllithium (24.7 mL), (hexacarbonyl)chromium (4.40 g, 20.00 mmol) and triethyloxonium tetrafluoroborate (4.20 g, 22.00 mmol). After chromatography on silica gel an orange oil identified as complex **48b** was obtained (3.50 g, 10.60 mmol, 53.0%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.11 (q, *J* = 7.0 Hz, 2 H, H^8), 3.50 (t, *J* = 6.0 Hz, 2 H, H^2), 2.30 (t, *J* = 6.0 Hz, 2 H, H^3), 2.11 (q, *J* = 8.0 Hz, 2 H, H^6), 1.64 (t, *J* = 7.0 Hz, 3 H, H^9), 1.07 (t, *J* = 8.0 Hz, 3 H, H^7) ppm. $C_{14}H_{14}CrO_6$ (330.3): calcd. C 50.90, H 4.24; found C 50.97, H 4.50.

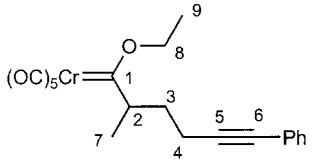


48b

Carbene Complex 48c

General Procedure: These compounds were prepared by catalytic phase-transfer alkylation of complex **37** with alkyl bromides or iodides. A mixture of the carbene complex (*n* mmol) and tetrabutylammonium bromide (0.1 N mmol) in dichloromethane (15 n mL) was treated with 50% aqueous NaOH and the halide (2−5 N mmol). The mixture was stirred at room temperature under argon until the starting material had been consumed. The reaction mixture was diluted with water, extracted with dichloromethane, dried, and concentrated under reduced pressure. The pure product was isolated by chromatography on silica gel by elution with petroleum ether.

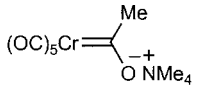
Complex 48c: The general procedure was followed using carbene complex **37** (4.24 g, 10.82 mmol), and methyl iodide (3.18 mL, 51 mmol), as starting material. After chromatography on silica gel a deep reed oil identified as complex **48c** was obtained (2.83 g, 6.97 mmol, 64.4%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40−7.24 (m, 5 H, arom. H), 5.08 (q, *J* = 7.0 Hz, 2 H, H^8), 4.17 (m, 1 H, H^2), 2.41 (m, 2 H, H^4), 1.88 (m, 1 H, H^3), 1.60 (t, *J* = 7.0 Hz, 3 H, H^9), 1.46 (m, 1 H, H^3), 1.06 (d, *J* = 6.6 Hz, 3 H, H^7) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 363.3 (C^1), 223.1 (*trans* CO), 216.4 (*cis* CO), 131.6−127.8 (arom. HC), 123.81 (qC), 89.1, 81.5 (C^5 or C^6), 78.1 (C^8), 64.5 (C^2), 31.9 (C^4), 17.6 (C^3), 16.1 (C^7), 14.9 (C^9) ppm. HRMS (EI^+), calcd. for $C_{20}H_{18}CrO_6$: 406.0508; found 406.0486.



48c

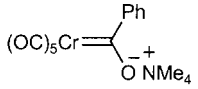
Salts A, B and C

Salt A: Methyllithium (15.05 mL, 1.33 M, 20 mmol) was added to a suspension of [$Cr(CO)_6$] (4.4 g, 20 mmol) in Et_2O (95 mL). After 10 minutes at room temperature, the solvent was evaporated in vacuo. Addition of water (100 mL) followed by filtration through celite and treatment with a saturated solution of tetramethylammonium bromide (6.16 g, 40 mmol) in water (10 mL) led to immediate formation of the ammonium salt. Dissolution in CH_2Cl_2 and addition of pentane gave the salt **A** as a yellow solid (5.19 g, 16.80 mmol, 84.0%).



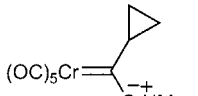
A

Salt B: Phenyllithium (30.5 mL, 0.65 M, 20 mmol) was added to a suspension of $[Cr(CO)_6]$ (4.4 g, 20 mmol) in Et_2O (95 mL). After 10 minutes at room temperature, the solvent was evaporated in vacuo. Addition of water (100 mL) followed by filtration through celite and treatment with a saturated solution of tetramethylammonium bromide (6.16 g, 40 mmol) in water (10 mL) led to the formation of the ammonium salt. The salt **B** was extracted with CH_2Cl_2 and dried with sodium sulfate. The solvent was removed on a rotary evaporator to give a red solid (6.83 g, 18.40 mmol, 92.0%).



B

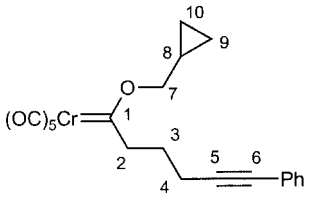
Salt C: A solution of *t*BuLi (24.7 mL, 1.7 M) in hexane was added slowly to a solution of bromocyclopropane (2.42 g, 20 mmol) in Et_2O (100 mL) at −78 °C. After 10 minutes at −78 °C, the resulting mixture was transferred to a flask containing a suspension of $[Cr(CO)_6]$ (4.4 g, 20 mmol) in Et_2O (200 mL) at −78 °C. After two hours at room temperature, the solvent was evaporated in vacuo. The crude product was dissolved in water (100 mL), filtered through celite and treated with a saturated aqueous solution of tetramethylammonium bromide (8.00 g/10 mL) to cause formation of a yellow precipitate. This material was dissolved in CH_2Cl_2 and crystallisation was induced by addition of pentane. Salt **C** was obtained as a yellow solid in 70.0% yield (4.69 g, 14.00 mmol).



C

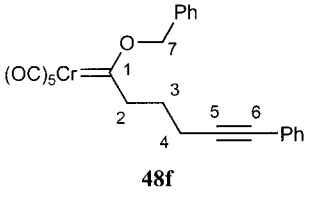
Carbene Complexes 48e,f

Complex 48e: Pivaloyl chloride (2.48 mL, 13.38 mmol) was added with a syringe to a solution of salt **A** (4.13 g, 13.38 mmol) in CH_2Cl_2 (25 mL) at −40 °C. The reaction mixture was stirred at −40 °C for one hour, then a solution of cyclopropylmethanol (963 mg, 13.38 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred for 2 h at this temperature before being allowed to reach room temperature. The resulting orange solution was evaporated to dryness and the crude product was purified by flash chromatography using PE as eluent giving a carbene complex as a orange oil (2.60 g, 8.96 mmol, 67%). *n*Butyllithium (5.38 mL, 8.62 mmol) was added to a solution of this complex (2.50 g, 8.62 mmol) in THF (100 mL) at −78 °C. After 10 minutes, a solution of the triflate derived from 4-phenylbut-3-yn-1-ol (2.86 g, 10.29 mmol) in THF (15 mL) was added and the reaction was warmed to −20 °C and stirred for two hours at this temperature. Column chromatography on silica gel gave the complex **48e** as a red oil (620 mg, 1.44 mmol, 16.7%). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.39−7.25 (m, 5 H, arom. H), 4.84 (d, *J* = 7.3 Hz, 2 H, H^7), 3.51 (t, *J* = 7.9 Hz, 2 H, H^2), 2.45 (t, *J* = 6.9 Hz, 2 H, H^4), 1.80 (dt *J* = 6.9−7.9 Hz, 2 H,, H^3), 1.43 (m, 1 H, H^8), 0.79−0.47 (m, 4 H, H^9 and H^{10}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 358.4 (C^1), 223.1 (*trans* CO), 216.5 (*cis* CO), 131.6−127.9 (arom. HC), 123.7 (qC), 88.8−81.8 (C^5 or C^6), 86.9 (C^7), 66.1 (C^2), 25.2 (C^4), 19.0 (C^3), 10.3 (C^8), 3.7 (C^9 and C^{10}) ppm. HRMS [M + NH_4] calcd. for $C_{21}H_{22}CrNO_6$ (436.4): 436.0852; found 43.0851.



48e

Complex 48f: *tert*-Butyllithium (24.7 mL, 42.00 mmol, 1.7 M) was added with a syringe over a period of 10 min to a solution of (5-iodopent-1-ynyl)benzene (5.40 g, 20 mmol) under argon at −78 °C in diethyl ether (140 mL) and pentane (200 mL). This solution was stirred at −78 °C for a period of 15 min and then transferred by cannula to a suspension of (hexacarbonyl)chromium (4.40 g, 20 mmol) in diethyl ether (300 mL) at −78 °C. This mixture was warmed to room temperature and was stirred for 2.5 h. The solvent was removed on a rotary evaporator, water was added (100 mL) and the resultant solution was filtered through celite and added to a solution of tetramethylammonium bromide (6.16 g, 40 mmol) in water (10 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL) and dried with sodium sulfate. The solvent was removed on a rotary evaporator giving the ammonium salt as a brownish oil (5.16 g, 11.82 mmol, 59.1%). The triflate derived from benzylic alcohol (1.18 g, 4.92 mmol) was added to a solution of this salt (1.80 g, 4.12 mmol) in CH_2Cl_2 (100 mL) at −20 °C and the reaction mixture was stirred for two hours before being allowed to reach room temperature. After column chromatography, the complex **48f** was obtained as a yellow solid (800 mg, 1.76 mmol, 42.8%), m.p. 35 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.28 (m, 10 H, arom. H), 6.06 (s, 2 H, H^7), 3.61 (t, *J* = 7.0 Hz, 2 H, H^2), 2.45 (t, *J* = 7.0 Hz, 2 H, H^4), 1.77 (qn, *J* = 7.0 Hz, 2 H, H^3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 360.2 (C^1), 223.1 (*trans* CO), 216.4 (*cis* CO), 131.6 (qC), 129.4−128.4 (arom. HC), 123.7 (qC), 88.7, 81.9 (C^5 or C^6), 83.7 (C^7), 62.3 (C^2), 25.3 (C^4), 19.1 (C^3) ppm. $C_{24}H_{18}CrO_6$ (454.4): calcd. C 63.44, H 3.99; found C 63.34, H 4.39.



48f

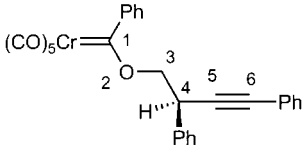
Carbene Complexes 49g,h

General Procedure 1: The pentacarbonyl[(tetramethylammonio)carbene]chromium salt (**A**, **B** or **C**; 1.0 molar equivalent) was dissolved in CH_2Cl_2 (20 mL/mmol) under argon. The flask was covered with aluminium foil, cooled to −20 °C and acetyl chloride (1.1 mol equivalent) was added dropwise over 5 min with a syringe to give a red solution. After the addition, the mixture was warmed to −10 °C and stirred for 10 min. The alkynol (1.0 mol equivalent) was

added as a solution in CH_2Cl_2 (1 mL/mmol) and the solution was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography to give the carbene complex.

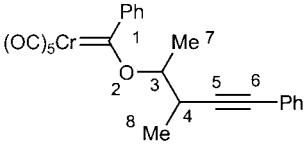
General Procedure 2: A solution of pentacarbonyl[(tetramethylammonio)carbene]chromium salt (**A**, **B** or **C**; 1 mmol) dissolved in CH_2Cl_2 (15 mL/mmol) in an oven-dried flask was put under argon and cooled to −40 °C with an acetone/dry ice bath. Pivaloyl chloride (1.1 mol equivalent) was added to the red solution with a syringe. The reaction mixture was stirred at −40 °C for one hour and the solution changed slowly to deep-red/brown. Then, a solution of alcohol (1.1 mol equivalent) in CH_2Cl_2 (5 mL/mmol) was added. The reaction was stirred for about 3 h at this temperature before being allowed to reach room temperature. The resulting red solution was evaporated and the crude product was purified by flash chromatography using mixtures of PE/CH_2Cl_2 as eluent giving, after evaporation of the solvents, the pure carbene complex.

Complex 49g: Salt **B** (1.52 g, 4.11 mmol), pivaloyl chloride (556 μL, 4.52 mmol) and (*R*)-2,4-diphenylbut-3-yn-1-ol (1.00 g, 4.52 mmol) were combined following the general procedure 2. Complex **49g** was obtained as a deep-red oil (932 mg, 1.86 mmol, 45.2%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.49−7.11 (m, 15 H, arom. H), 4.98 (br. s, 1 H, H^3), 4.58 (br. s, 1 H, H^4) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 350.0 (C^1), 224.5 (*trans* CO), 216.0 (*cis* CO), 153.1 (qC), 136.7 (qC), 131.8−128.3 (arom. HC), 122.7 (qC), 86.7, 85.4 (C^5 or C^6), 82.9 (C^3), 39.3 (C^4) ppm. HRMS calcd. for $C_{28}H_{18}CrO_6$: 502.0509; found 502.0499.



49g

Complex 49h: Salt **B** (3.20 g, 8.62 mmol), pivaloyl chloride (1.06 mL, 8.62 mmol) and 3-methyl-5-phenylpent-4-yn-2-ol (1.00 g, 5.75 mmol) were combined following the general procedure 2. Complex **49h** was obtained as a red solid (1.85 g, 4.08 mmol, 71.0%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40−7.25 (m, 10 H, arom. H), 5.28 (m, 1 H, H^3), 3.14 (m, 1 H, H^4), 1.60 (d, *J* = 5.9 Hz, 3 H, H^7), 1.40 (d, *J* = 6.9 Hz, 3 H, H^8) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 348.7 (C^1), 224.6 (*trans* CO), 216.2 (*cis* CO), 131.7−122.1 (arom. HC and qC), 89.7 (C^3), 89.2, 83.6 (C^5 or C^6), 33.2 (C^4), 19.1 (C^7), 17.0 (C^8) ppm. $C_{24}H_{18}CrO_6$ (454.4): calcd. C 63.44, H 3.99; found C 62.95, H 4.48.

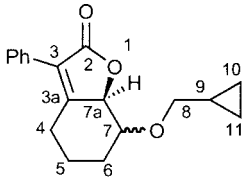


49h

Reaction of *N*-Methyldihydropyridine with Carbene Complexes 48a−c, 48e,f, 49c,d and 49g,h

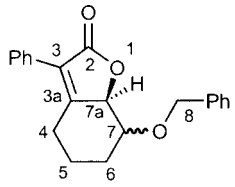
General Procedure: *N*-Methyldihydropyridine (**19**)[54] was prepared following the literature procedure. A solution of *N*-methyldihydropyridine (3 mol equiv.) in CH_2Cl_2 (0.5 mL/mmol of amine) was added dropwise from an addition funnel to a solution of the carbene complex (1 mol equiv.) in CH_2Cl_2 (25 mL/mmol of carbene) at −10 °C, under argon. After 15 min, the ice bath was removed and the mixture stirred at room temperature for 24 h. The solution slowly turned dark red. The solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel with mixture of PE/Et_2O as eluent.

With Complex 48e. 7-Cyclopropylmethoxy-3-phenyl-5,6,7,7a-tetrahydro-4*H*-benzofuran-2-one (50e and 51e): The general procedure was followed using carbene complex **48e** (600 mg, 1.43 mmol). Elution with PE/Et_2O (60:40) gave the butenolide. **50e:** (202 mg, 0.71 mmol, 49.7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.33 (m, 5 H, arom. H), 4.73 (d, *J* = 8.7 Hz, 1 H, H^{7a}), 3.66 (dd, *J* = 7.1−10.2 Hz, 1 H, H^8), 3.51 (dd, *J* = 7.1−10.2 Hz, 1 H, $H^{8'}$), 3.26 (ddd, *J* = 4.6, 8.7, 13.2 Hz, 1 H, H^7), 3.04 (m, 1 H, H^4), 2.26 (ddd, *J* = 6.1, 13.7, 13.7 Hz, 1 H, $H^{4'}$), 2.17 (m, 1 H, H^6), 2.01 (m, 1 H, H^5), 1.60 (m, 1 H, $H^{6'}$), 1.31 (m, 1 H, $H^{5'}$), 1.10 (m, 1 H, H^9), 0.59−0.21 (m, 4 H, H^{10}, H^{11}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (C^2), 160.9 (C^{3a}), 129.7 (Cq), 129.0−128.5 (arom. HC), 125.0 (qC), 85.7 (C^{7a}), 82.8 (C^7), 75.9 (C^8), 30.0 (C^6), 26.3 (C^4), 23.7 (C^5), 11.0 (C^9), 3.2 (C^{10} and C^{11}) ppm. $C_{18}H_{20}O_3$ (284.4): calcd. C 76.03, H 7.09; found C 76.05, H 7.19. **51e:** (51 mg, 0.18 mmol, 12.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49−7.29 (m, 5 H, arom. H), 4.79 (d, *J* = 3.6 Hz, 1 H, H^{7a}), 4.15 (m, 1 H, H^7), 3.40 (m, 2 H, H^8), 3.08 (m, 1 H, H^4), 2.28 (m, 1 H, $H^{4'}$), 2.01 (m, 1 H, H^6), 1.73 (m, 2 H, H^5), 1.59 (m, 1 H, $H^{6'}$), 0.94 (m, 1 H, H^9), 0.46−0.14 (m, 4 H, H^{10}, H^{11}) ppm.



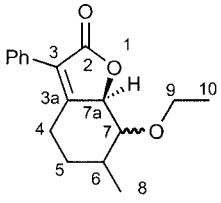
50e/51e

With Complex 48f. 7-Benzyloxy-3-phenyl-5,6,7,7a-tetrahydro-4*H*-benzofuran-2-one (50f and 51f): The general procedure was followed using carbene complex **48f** (780 mg, 1.72 mmol). The butenolide was obtained as two isomers: Elution with PE/Et_2O (60:40) gave the *trans* isomer **50f. 50f:** White solid (105 mg, 0.33 mmol, 19.2%), m.p. 76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59−7.18 (m, 10 H, arom. H), 4.98 (d, *J* = 11.8 Hz, 1 H, H^8), 4.86 (d, *J* = 8.4 Hz, 1 H, H^{7a}), 4.76 (d, *J* = 11.8 Hz, 1 H, $H^{8'}$), 3.41 (ddd, *J* = 4.6, 8.4, 15.3 Hz, 1 H, H^7), 3.06 (dd, *J* = 1.8−14.3 Hz, 1 H, H^4), 2.30 (dt, *J* = 7.5, 14.3 Hz, 1 H, H^4), 2.22 (m, 1 H, H^6), 2.03 (m, 1 H, H^5), 1.65 (m, 1 H, $H^{6'}$), 1.36 (m, 1 H, $H^{5'}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (C^2), 160.8 (C^{3a}), 138.0−128.9 (qC), 128.6−128.4 (arom. HC), 127.8 (qC), 85.7 (C^{7a}), 82.2 (C^7), 72.4 (C^8), 29.8 (C^6), 26.1 (C^4), 23.5 (C^5) ppm. $C_{21}H_{20}O_3$ (320.4): calcd. C 78.73, H 6.29; found C 79.20, H 6.54. Further elution with PE/Et_2O (70:30) gave the *cis* isomer **51f**. **51f:** (70 mg, 0.22 mmol, 12.8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53−7.28 (m, 10 H, arom. H), 4.88 (d, *J* = 3.5 Hz, 1 H, H^{7a}), 4.77 (d, *J* = 12.2 Hz, 1 H, H^8), 4.77 (d, *J* = 12.2 Hz, 1 H, $H^{8'}$), 4.28 (m, 1 H, H^7), 3.11 (m, 1 H, H^4), 2.36 (m, 1 H, $H^{4'}$), 2.10 (m, 1 H, H^6), 1.79 (m, 2 H, H^5 and $H^{5'}$), 1.63 (m, 1 H, $H^{6'}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.2 (C^2), 161.0 (C^{3a}), 138.7 (qC), 129.3 (qC), 128.9−127.7 (arom. HC), 125.4 (qC), 82.1 (C^{7a}), 75.6 (C^7), 73.3 (C^8), 28.3 (C^6), 26.9 (C^4), 20.8 (C^5) ppm.



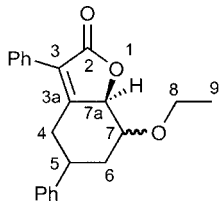
50f/51f

With Complex 48c. 7-Ethoxy-6-methyl-3-phenyl-5,6,7,7a-tetrahydro-4*H*-furan-2-one (50c and 51c): The general procedure was followed using carbene complex **48c** (2.03 g, 5.00 mmol). Elution with PE/Et_2O (70:30) gave the butenolide as a 4:3 mixture of two isomers (952 mg, 3.50 mmol 70.0%). **50c:** White solid, m.p. 58 °C, 534 mg, 1.96 mmol, 39.3%: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49−7.24 (m, 5 H, arom. H), 4.74 (d, *J* = 8.2 Hz, 1 H, H^{7a}), 4.06 (dq, *J* = 7.0, 9.2 Hz, 1 H, H^9), 3.60 (dq, *J* = 7.0, 9.2 Hz, 1 H, H^9), 2.98 (ddd, *J* = 1.8, 4.1, 14.1 Hz, 1 H, H^4), 2.81 (dd, *J* = 8.2, 10.2 Hz, 1 H, H^7), 2.32 (dt, *J* = 5.9, 14.1 Hz, 1 H, H^4), 1.56 (m, 1 H, H^5), 1.75 (m, 1 H, H^6), 1.24 (t, *J* = 7.0 Hz, 3 H, H^{10}), 1.09 (m, 1 H, H^5), 1.08 (d, *J* = 6.6 Hz, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (C^2), 161.2 (C^{3a}), 129.6 (qC), 128.8−128.2 (arom. HC), 124.45 (qC), 87.8 (C^7), 85.9 (C^{7a}), 68.0 (C^9), 36.0 (C^6), 32.4 (C^5), 25.7 (C^4), 17.4 (C^8), 15.5 (C^{10}). **51c:** 418 mg, 1.54 mmol, 30.7%. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49−7.24 (m, 5 H, arom. H), 4.82 (d, *J* = 3.4 Hz, 1 H, H^{7a}), 3.82 (br. s, 1 H, H^7), 3.72 (m, dq, *J* = 7.0, 9.4 Hz, 1 H, H^9), 3.57 (dq, *J* = 7.0, 9.4 Hz, 1 H, H^9), 3.01 (m, 1 H, H^4), 2.30 (m, 1 H, H^4), 1.80 (m, 1 H, H^6), 1.58 (m, 2 H, H^5), 1.13 (t, *J* = 9.0 Hz, 3 H, H^{10}), 1.08 (d, *J* = 6.3 Hz, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0 (C^2), 160.7 (C^{3a}), 130.3 (qC), 129.0−128.3 (arom. HC), 125.5 (qC), 82.7 (C^{7a}), 80.7 (C^7), 69.6 (C^9), 34.2 (C^6), 26.4 (C^5), 25.9 (C^4), 17.6 (C^8), 15.7 (C^{10}) ppm. HRMS calcd. for $C_{17}H_{21}O_3$: 273.1491; found 273.1495.



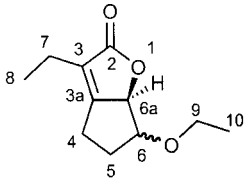
50c/51c

With Complex 48a. 7-Ethoxy-3,5-diphenyl-5,6,7,7a-tetrahydro-4*H*-benzofuran-2-one (50a and 51a): The general procedure was followed using carbene complex **48a** (1.15 g, 2.46 mmol). The butenolide was obtained as two isomers: Elution with PE/Et_2O (70:30) gave the *trans* isomer **50a** as white solid (227 mg, 0.68 mmol, 27.6%) m.p. 120 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42−7.14 (m, 10 H, arom. H), 4.79 (d, *J* = 8.1 Hz, 1 H, H^{7a}), 3.83 (dq, *J* = 6.9, 9.1 Hz, 1 H, H^8), 3.62 (dq, *J* = 6.9, 9.1 Hz, 1 H, H^8), 3.35 (ddd, *J* = 4.0−8.1−12.7 Hz, 1 H, H^7), 3.15 (m, 1 H, H^4), 2.65 (m, 1 H, H^5), 2.45 (m, 1 H, H^4), 2.28 (m, 1 H, H^6), 1.82 (m, 1 H, H^6), 1.18 (t, *J* = 6.9 Hz, 3 H, H^9) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (C^2), 159.5 (C^{3a}), 142.7 (qC), 129.2 (qC), 129.0−127.0 (arom. HC), 126.4 (qC), 85.3 (C^{7a}), 81.8 (C^7), 66.3 (C^8), 41.9 (C^5), 37.3 (C^6), 34.1 (C^4), 15.7 (C^9) ppm. HRMS [M + 1] calcd. for $C_{22}H_{23}O_3$: 335.1647; found 335.1652. Further elution with PE/Et_2O (60:40) gave the *cis* isomer **51a** as a white solid (118 mg, 0.35 mmol, 14.4%). m.p. 92 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45−7.18 (m, 10 H, arom. H), 4.89 (d, *J* = 4.0 Hz, 1 H, H^{7a}), 4.15 (m, 1 H, H^7), 3.58 (m, 2 H, H^8), 3.19 (m, 1 H, H^4), 3.10 (m, 1 H, H^5), 2.48 (m, 1 H, $H^{4'}$), 2.17 (m, 1 H, H^6), 1.84 (m, 1 H, $H^{6'}$), 1.09 (t, *J* = 7.0 Hz, 3 H, H^9) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0 (C^2), 159.6 (C^{3a}), 143.7 (qC), 129.9 (qC), 128.9−127.0 (arom. HC), 125.7 (qC), 81.4 (C^{7a}), 75.3 (C^7), 67.3 (C^8), 38.4 (C^5), 35.9 (C^6), 34.3 (C^4), 15.7 (C^9) ppm. HRMS [M + 1] calcd. for $C_{22}H_{23}O_3$ (335.4): 335.1647; found 335.1652.

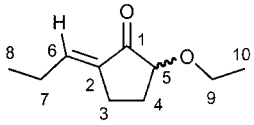


50a/51a

With Complex 48b. 6-Ethoxy-3-ethyl-4,5,6,6a-tetrahydrocyclopenta-[*b*]furan-2-one (50b, 51b) and 2-Ethoxy-5-propylidenecyclopentanone (52): The general procedure was followed using carbene complex **48b** (2.50 g, 7.58 mmol). Elution with PE/Et_2O (90:10) gave the cyclopentanone **52** as an oil (142 mg, 0.85 mmol, 11.1%). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.65 (m, 1 H, H^6), 3.91 (t, *J* = 8.0 Hz, 1 H, H^5), 3.83 (m, 1 H, H^9), 3.63 (m, 1 H, H^9), 2.65 (m, 1 H, H^3), 2.34 (m, 2 H, H^3 and H^4), 2.17 (m, 2 H, H^7), 1.77 (m, 1 H, H^4), 1.25 (t, *J* = 8.0 Hz, 3 H, H^{10}), 1.05 (t, *J* = 8.0 Hz, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7 (C^1), 140.1 (C^6), 133.7 (C^2), 81.6 (C^5), 65.8 (C^9), 27.2 (C^4), 22.8 (C^7), 22.4 (C^3), 15.4 (C^{10}), 12.9 (C^8) ppm. HRMS calcd. for $C_{10}H_{17}O_2$: 169.1229; found 169.1230. The butenolide was obtained as two isomers in 1:1 ratio (863 mg, 4.40 mmol, 58.1%). Elution with PE/Et_2O (85:15) gave **50b** (*trans*) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.66 (d, *J* = 8.0 Hz, 1 H, H^{6a}), 3.77 (m, 1 H, H^9), 3.56 (m, 2 H, H^6 and H^9), 2.75−2.00 (m, 6 H, H^4, H^5 and H^7), 1.20 (t, *J* = 7.0 Hz, 3 H, H^{10}), 1.06 (t, *J* = 7.4 Hz, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0 (C^2), 164.7 (C^{3a}), 127.8 (C^3), 88.4 (C^{6a}), 80.7 (C^6), 66.2 (C^9), 31.3 (C^5), 20.9 (C^4), 18.1 (C^7), 15.6 (C^{10}), 12.6 (C^8) ppm. Further elution with PE/Et_2O (80:20) gave **51b** (*cis*) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.89 (br. s, 1 H, H^{6a}), 3.95 (m, 1 H, H^6), 3.57 (m, 2 H, H^9), 2.62−2.14 (m, 6 H, H^4, H^5 and H^7), 1.18 (t, *J* = 7.4 Hz, 3 H, H^{10}), 1.05 (t, *J* = 7.0 Hz, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1 (C^2), 166.5 (C^{3a}), 133.9 (C^3), 86.0 (C^{6a}), 75.5 (C^6), 67.1 (C^9), 32.7 (C^5), 20.4 (C^4), 18.4 (C^7), 15.8 (C^{10}), 12.6 (C^8) ppm. HRMS calcd. for $C_{11}H_{17}O_3$: 197.1178; found 197.1181.



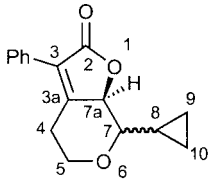
50b/51b



52

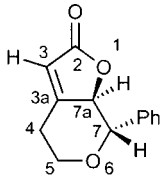
With Complex 49c: 7-Cyclopropyl-3-phenyl-4,5,7,7a-tetrahydro-furo[2,3-*c*]pyran-2-one (53c and 54c): The general procedure was followed using carbene complex **49c** (1.32 g, 3.38 mmol). The butenolide was obtained as two isomers: Elution with PE/Et_2O (70:30) gave **53c** the *trans* isomer as white solid (521 mg, 1.95 mmol, 57.6%), m.p. 89 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51−7.35 (m, 5 H, arom. H), 4.66 (d, *J* = 8.7 Hz, 1 H, H^{7a}), 4.20 (dd, *J* = 6.6, 11.5 Hz, 1 H, H^5), 3.28 (ddd, *J* = 2.0, 11.5, 11.5 Hz, 1 H, $H^{5'}$), 3.02 (dd, *J* = 2.0, 13.5 Hz, 1 H, H^4), 2.78 (ddd, *J* = 6.6, 11.5, 13.5 Hz, 1 H, $H^{4'}$), 2.63 (dd, *J* = 7.5, 8.7 Hz, 1 H, H^7), 1.21 (m, 1 H, H^8), 0.72−0.40 (m, 4 H, H^9 and H^{10}) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 171.2 (C^2), 159.9 (C^{3a}), 133.0 (qC), 129.4−128.7 (arom. HC), 124.0 (qC), 86.7 (C^7), 80.9 (C^{7a}), 67.4 (C^5), 29.3 (C^4), 14.2 (C^8), 2.2−2.0 (C^9 or C^{10}) ppm. HRMS [M + 1] calcd. for $C_{16}H_{17}O_3$: 257.1178; found 257.1182. Further elution with PE/Et_2O (80:20) gave the *cis* isomer **54c**. **54c:** (31 mg, 0.21 mmol, 6.1%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53−7.25 (m, 5 H, arom. H), 5.09 (d, *J* = 7.1 Hz, 1 H, H^{7a}), 3.94 (dd, *J* = 7.6,11.7 Hz, 1 H, H^5), 3.77 (ddd, *J* = 2.8, 11.7, 11.7 Hz, 1 H, $H^{5'}$), 3.62 (dd, *J* = 7.1, 9.7 Hz, 1 H, H^7), 3.04 (dd, *J* = 2.8, 13.5 Hz, 1 H, H^4), 2.81 (m, 1 H, $H^{4'}$), 1.18 (m, 1 H, H^8), 0.80−0.28 (m, 4 H, H^9 and H^{10}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5 (C^2), 157.8 (C^{3a}), 136.7 (qC), 129.4−128.7 (arom. HC), 125.3 (qC), 82.7 (C^7), 78.1 (C^{7a}), 59.5 (C^5), 28.9 (C^4), 14.3 (C^8), 6.0, 5.6 (C^9 or C^{10}) ppm.



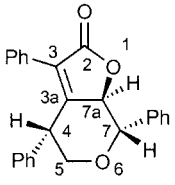
53c/54c

With Complex 49d. 7-Phenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (53d): The general procedure was followed using carbene complex **49d** (940 mg, 2.68 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53d** as white solid (365 mg, 1.69 mmol, 63.1%), m.p. 48 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48−7.25 (m, 5 H, arom. H), 5.93 (s, 1 H, H^3), 4.66 (d, *J* = 8.7 Hz, 1 H, H^{7a}), 4.42 (ddd, *J* = 6.5, 11.1, 11.1 Hz, 1 H, H^5), 4.05 (d, *J* = 8.7 Hz, 1 H, H^7), 3.51 (ddd, *J* = 2.7, 11.1, 11.1 Hz, 1 H, $H^{5'}$), 2.86 (dd, *J* = 2.7, 13.7 Hz, 1 H, H^4), 2.77 (ddd, *J* = 6.5, 11.1, 13.7 Hz, 1 H, $H^{4'}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7 (C^2), 167.6 (C^{3a}), 137.8 (qC), 128.7−128.3 (arom. HC), 126.5 (qC), 113.6 (C^3), 85.3 (C^7), 82.9 (C^{7a}), 68.1 (C^5), 30.4 (C^4) ppm. HRMS [M + 1] calcd. for $C_{13}H_{13}O_3$: 217.0865; found 217.0869.

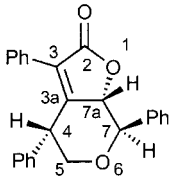


53d

With Complex 49g. (4*R*,7*R*,7a*S*)-3,4,7-Triphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (53g) and (4*R*,7*S*,7a*R*)-3,4,7-Triphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (55g): The general procedure was followed using carbene complex **49g** (820 mg, 1.63 mmol). The butenolide was obtained as two isomers: Elution with PE/Et_2O (80:20) gave the *trans-trans* isomer **53g. 53g:** Fluorescent solid (293 mg, 0.80 mmol, 48.9%), m.p. 97 °C. $[\alpha]_D^{20}$ = 171.43 (*c* = 2.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.58−7.25 (m, 15 H, arom. H), 4.96 (d, *J* = 9.0 Hz, 1 H, H^{7a}), 4.70 (d, *J* = 11.7 Hz, 1 H, H^5), 4.46 (d, *J* = 3.1 Hz, 1 H, H^4), 4.26 (d, *J* = 9.0 Hz, 1 H, H^7), 3.87 (dd, *J* = 3.1, 11.7 Hz, 1 H, H^5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (C^2), 161.2 (C^{3a}), 139.2 (qC), 138.3 (qC), 132.5−129.0 (arom. HC), 126.9 (qC), 126.2 (qC), 86.0 (C^7), 80.1 (C^{7a}), 72.7 (C^5), 44.5 (C^4) ppm. $C_{25}H_{20}O_3$ (368.4): calcd. C 81.50, H 5.47; found C 81.33, H 5.36. Further elution with PE/Et_2O (70:30) gave the *trans-cis* isomer **55g**. **55g:** Yellow solid (515 mg, 0.14 mmol, 8.60%), m.p. 174 °C, $[\alpha]_D^{20}$ = 90.93 (*c* = 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56−6.80 (m, 15 H, arom. H), 4.84 (d, *J* = 9.4 Hz, 1 H, H^{7a}), 4.39 (d, *J* = 9.4 Hz, 1 H, H^7), 4.33 (dd, *J* = 6.4, 11.0 Hz, 1 H, H^5), 4.22 (dd, *J* = 6.4, 11.0 Hz, 1 H, H^4), 3.69 (dd, *J* = 11.0, 11.0 Hz, 1 H, H^5) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8 (C^2), 160.0 (C^{3a}), 138.1 (qC), 134.0 (qC), 129.7−126.6 (arom. HC), 122.2 (qC), 84.3 (C^7), 81.7 (C^{7a}), 74.3 (C^5), 48.2 (C^4) ppm. HRMS [M + 1] calcd. for $C_{25}H_{21}O_3$: 369.1491; found 369.1485.

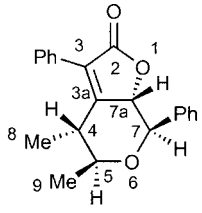


53g



55g

With Complex 49h. 4,5-Dimethyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (53h): The general procedure was followed using carbene complex **49h** (830 mg, 1.83 mmol). Elution with PE/Et_2O (60:40) gave the butenolide **53h** as a white solid (310 mg, 0.97 mmol, 52.9%). m.p. 168 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.51−7.25 (m, 10 H, arom. H), 4.68 (d, *J* = 9.2 Hz, 1 H, H^{7a}), 4.23 (d, *J* = 9.2 Hz, 1 H, H^7), 3.41 (dq, *J* = 6.1, 9.7 Hz, 1 H, H^5), 2.64 (dq, *J* = 6.8, 9.7 Hz, 1 H, H^4), 1.41 (d, *J* = 6.1 Hz, 3 H, H^9), 0.90 (d, *J* = 6.8 Hz, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1 (C^2), 163.1 (C^{3a}), 138.2 (qC), 130.7 (qC), 130.2−126.7 (arom. HC), 126.0 (qC), 83.9 (C^7), 82.0 (C^{7a}), 80.7 (C^5), 42.8 (C^4), 19.5 (C^9), 14.1 (C^8) ppm. $C_{21}H_{20}O_3$ (320.4): calcd. C 78.73, H 6.29; found C 78.57, H 6.45.



53h

Reaction of *N*-Benzyldihydropyridine 59 with Complexes 37, 48a and 48d

1,4-*N*-Benzyldihydropyridine **59** was synthesised following the literature procedure.[44]

General Procedure: A solution of *N*-benzyldihydropyridine (3 mol equiv.) in CH_2Cl_2 (0.5 mL/mmol of amine) was added dropwise from an addition funnel to a solution of the carbene complex (1 mol equiv.) in CH_2Cl_2 (25 mL/mmol of carbene) at −10 °C, under argon. After 15 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solution slowly turned dark red. The solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel with mixtures of PE/Et_2O as eluent.

With Complex 37. 7-Ethoxy-3-phenyl-3,6,7,7a-tetrahydro-4*H*-benzofuran-2-one (38 and 39): The general procedure was followed using carbene complex **7** (1.74 g, 4.44 mmol). Elution with PE/Et_2O (20:80) gave the butenolide as two isomers in 43.0% overall yield: *trans* isomer **38** (394 mg, 1.53 mmol, 34.4%), *cis* isomer **39** (98 mg, 0.38 mmol, 8.6%), *de* = 60%.

With Complex 48d. 6-Benzyl-7-ethoxy-3-phenyl-5,6,7,7a-tetrahydro-4*H*-benzofuran-2-one (50d and 51d): The general procedure was followed using carbene complex **48d** (1.50 g, 3.11 mmol). Elution with PE/Et_2O (30:70) gave the butenolide as two isomers in 45.0% overall yield: *trans* isomer **50d** (205 mg, 0.59 mmol, 21.0%), *cis* isomer **51d** (283 mg, 0.81 mmol, 24.0%), *de* = 16%.

With Complex 48a. 7-Ethoxy-3,5-diphenyl-5,6,7,7a-tetrahydro-4*H*-benzofuran-2-one (50a and 51a): The general procedure was followed using carbene complex **48a** (1.05 g, 2.24 mmol). Elution with PE/Et_2O (30:70) gave the butenolide as two isomers in 42.0% global yield: *trans* isomer **50a** (157 mg, 0.47 mmol, 21.0%), *cis* isomer **51a** (157 mg, 0.47 mmol, 21.0%), *de* = 0%.

Reaction of *N*,*N*-Diethyl-*N*-(methyl)dihydronicotinamide 60 with Complex 49a

Dihydronicotinamide **60**[44] was prepared following the literature procedure. A solution of nicotinamide **60** (3 mol equiv.) was added dropwise with a syringe to a solution of carbene complex **49a** (360 mg, 0.84 mmol) in CH_2Cl_2 (20 mL) at −10 °C, under argon. After 20 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solvent was evaporated under vacuum and the butenolide **53a** was obtained after silica gel chromatography as a white solid (91 mg, 0.31 mmol, 37.0%, *de* = 100%).

Reaction of the Chiral Nicotinamides 61, 62, and 63

Dihydronicotinamides **61**,[46a] **62**,[46i] **63**,[49a,49b] were prepared following the literature procedures

General Procedure: A solution of the appropriate nicotinamide (3 mol equiv.) was added dropwise with a syringe to a solution of carbene complexes **49e** or **49d** (1 mol equiv.) in CH_2Cl_2 (25 mL/mmol of carbene) at −40 °C, under argon. After 20 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solution slowly turned dark red. The solvent was evaporated under vacuum and the butenolides **53d** and **53e** were obtained after silica gel chromatography using mixtures of PE/Et_2O as eluent.

With Nicotinamide 61: The general procedure was followed using complex **49d** (350 mg, 1.00 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53d** (65 mg, 0.30 mmol, 30.1%, *de* = 100%, *ee* = 20%).

The general procedure was followed using complex **49e** (734 mg, 2.55 mmol). Elution with PE/Et_2O (70:30) gave the butenolide **53e** (216 mg, 1.40 mmol, 55.0%, *de* = 100%, *ee* = 1%).

With Nicotinamide 62: The general procedure was followed using complex **49d** (402 mg, 1.15 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53d** (32 mg, 0.15 mmol, 13.1%, *de* = 100%, *ee* = 2%).

With Nicotinamide 63: The general procedure was followed using complex **49e** (402 mg, 1.15 mmol). Elution with PE/Et_2O (70:30) gave the butenolide **53e** (20 mg, 0.13 mmol, 15.0%, *de* = 49%, *ee* = 11%).

Reactivion with the Chiral *N*-Alkyldihydropyridines 64, 65, 66, 67, and 68

Dihydropyridines **64**,[50a] **65**,[50b] **66**,[50c] **67**,[50b] and **68**[50a] were prepared following the literature procedures.

General Procedure: A solution of the appropriate *N*-alkyldihydropyridine (3 mol equiv.) was added dropwise with a syringe to a solution of carbene complexes (1 mol equiv.) in CH_2Cl_2 (25 mL/mmol of carbene) at −40 °C, under argon. After 20 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solution slowly turned dark red. The solvent was evaporated under vacuum and the corresponding butenolides were obtained after silica gel chromatography using mixtures of PE/Et_2O as eluent.

With Dihydropyridine 64: The general procedure was followed using complex **49d** (410 mg, 1.17 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53d** (151 mg, 0.70 mmol, 59.7%, *de* = 100%, *ee* = 4.3%).

The general procedure was followed using complex **49e** (746 mg, 2.57 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53e** (247 mg, 1.60 mmol, 62.5%, *de* = 100%, *ee* = 1.2%).

The general procedure was followed using complex **49f** (1.00 g, 3.18 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53f** (332 mg, 1.84 mmol, 58.0%, *de* = 100%, *ee* = 1.8%).

With Dihydropyridine 65: The general procedure was followed using complex **49d** (380 mg, 1.08 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53d** (167 mg, 0.77 mmol, 71.6%, *de* = 100%, *ee* = 27%).

The general procedure was followed using complex **49e** (480 mg, 1.67 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53e** (171 mg, 1.11 mmol, 66.7%, *de* = 100%, *ee* = 11.5%).

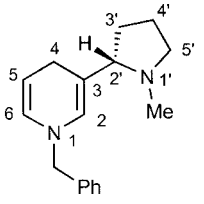
The general procedure was followed using complex **49f** (500 mg, 1.59 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53f** (172 mg, 0.95 mmol, 60.0%, *de* = 100%, *ee* = 1%).

With Dihydropyridine 66: The general procedure was followed using complex **49d** (396 mg, 1.13 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53d** (165 mg, 0.76 mmol, 67.5.%, *de* = 100%, *ee* = 18.0%).

With Dihydropyridine 67: The general procedure was followed using complex **49d** (600 mg, 1.71 mmol). Elution with PE/Et_2O (80:20) gave the butenolide **53d** (94 mg, 0.43 mmol, 25.3%, *de* = 100%, *ee* = 11.0%).

With Dihydropyridine 68: The general procedure was followed using complex **49e** (443 mg, 1.54 mmol). Elution with PE/Et_2O (70:30) gave the butenolide **53e** (118 mg, 0.77 mmol, 50.0%, *de* = 100%, *ee* = 7.6%).

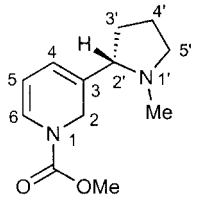
Synthesis of *N*-Benzyldihydronicotine (71): *N*-benzylnicotinium bromide (**70**)[53] was prepared following the literature procedure. An aqueous solution (25 mL) of *N*-benzylnicotinium bromide (**70**, 5 g, 15 mmol) was added from a dropping funnel to a suspension of sodium dithionite (15.66 g, 99 mmol) and potassium carbonate (12.43 g, 90 mmol) in toluene (80 mL) and water (90 mL). The resulting mixture was refluxed for 12 min. The organic phase was separated, washed with sodium hydrogencarbonate solution and water, and dried with sodium sulfate. After removal of the solvent, the *N*-benzyl-1,4-dihydronicotine (**71**) was obtained as a yellow oil in 24% yield (1.04 g, 4.1 mmol). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.33−7.14 (m, 5 H, arom. H), 5.8 (m, 2 H, H^6, H^2), 4.46 (m, 1 H, H^5), 4.16 (s, 2 H, Bn CH_2), 3.46 (m, 1 H, $H^{2'}$), 3.05 (m, 2 H, $H^{5'}$), 2.88 (m, 2 H, H^4), 2.40−1.50 (m, 7 H, $H^{4'}$, $H^{3'}$, $Me^{1'}$) ppm.



71

Synthesis of *N*-Methyldihydronicotine (73)

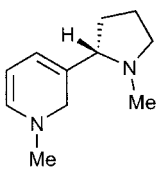
Formation of Methyl 3-(1-Methylpyrrolidin-2-yl)-2*H*-pyridine-1-carboxylate (72): A solution of methyl chloroformate (3.80 mL, 49.40 mmol) in Et_2O (16 mL) was added to a mixture of (*S*)-(−)-nicotine (**69**, 8.00 g, 49.40 mmol) and sodium borohydride (1.88 g, 49.40 mmol) in absolute ethanol (60 mL) at −78 °C. The temperature was not allowed to exceed −70 °C. The reaction mixture was warmed to −40 °C and stirred for an additional 1.5 h, then poured into ice water before being extracted three times with Et_2O (200 mL). The organic layers were combined, washed with brine and finally dried with sodium sulfate. The crude oil was purified by flash chromatography on silica gel using a mixture of PE/EtOAc (65:35) as eluent. After solvent removal compound **72** was obtained as a yellow oil in 76% yield (8.36 g, 37.64 mmol).



72

Mixture of two rotamers A and B (50:50). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 7.6 Hz, 0.5 H, H^{6A}), 6.60 (d, *J* = 7.6 Hz, 0.5 H, H^{6B}), 5.78 (d, *J* = 6.0 Hz, 1 H, H^4), 5.17 (m, 1 H, H^5), 4.32 (m, 1 H, H^2), 4.13 (m, 1 H, H^2), 3.76 (s, 3 H, OMe), 3.06 (m, 1 H, $H^{5'}$), 2.59 (m, 1 H, $H^{2'}$), 2.17 (s, 3 H, NMe), 2.16−2.01 (m, 2 H, $H^{2'}$ and $H^{5'}$), 1.89−1.27 (m, 4 H, $H^{3'}$ and $H^{4'}$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.8−153.8 (C=O), 132.6−131.3 (qC), 125.6−124.6 (C^6), 119.2−118.2 (C^4), 105.3−105.1 (C^5), 71.2−70.8 ($C^{2'}$), 56.8 ($C^{5'}$), 53.1 (OMe), 40.5 (NMe), 29.8−29.4 ($C^{3'}$), 22.7 ($C^{4'}$) ppm. $C_{12}H_{18}N_2O_2$ (222.3): calcd. C 64.84, H 8.16, N 8.16; found C 64.67, H 8.35, N 12.57. $[\alpha]_D^{20}$ = −83.3 (*c* = 2.33, $CHCl_3$).

Reduction of 72. 1-Methyl-3-(1-methylpyrrolidin-2-yl)-1,2-dihydropyridine (73): An Et_2O solution (25 mL) of methyl 3-(1-methylpyrrolidin-2-yl)-2*H*-pyridine-1-carboxylate (8.35 g, 37.60 mmol) was added to a suspension of lithium aluminium hydride (2.44 g, 1.7 equiv.) in Et_2O (120 mL) at 0 °C. After the addition the mixture was refluxed for 24 h. A 10% solution of sodium hydroxide (50 mL) was added slowly at 0 °C. The mixture was extracted three times with Et_2O (250 mL), washed with water and brine, and then dried with sodium sulfate. After removal of the solvent, the *N*-methyl-1,2-dihydropyridine **73** was obtained as a yellow oil in 90% yield (6.02 g, 33.82 mmol). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.93 (dd, *J* = 0.7, 7.0 Hz, 1 H, H^6), 5.77 (d, *J* = 5.5 Hz, 1 H, H^4), 4.68 (dd, *J* = 5.5, 7.0 Hz, 1 H, H^5), 3.66 (s, 2 H, H^2), 3.05 (m, 2 H, $H^{5'}$), 2.63 (s, 3 H, NMe), 2.58 (m, 1 H, $H^{2'}$), 2.17−2.0 (m, 5 H, $H^{3'}$ and NMe), 1.77 (m, 2 H, $H^{4'}$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.5 (C^6), 124.3 (qC), 121.6 (C^4), 95.2 (C^5), 72.0 ($C^{2'}$), 56.9 ($C^{5'}$), 49.2 (C^2), 42.5 (NMe), 40.6 (NMe), 29.0 ($C^{3'}$), 22.6 ($C^{4'}$) ppm. $[\alpha]_D^{20}$ = −92.6 (*c* = 2.42, $CHCl_3$).



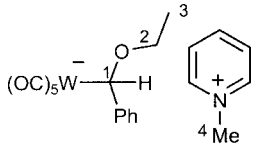
73

Reaction of *N*-Benzyldihydronicotine (71) with Complex 49e. 7-Methyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (53e): A solution of *N*-benzyldihydronicotine (**71**, 720 mg, 3 mmol) in CH_2Cl_2 (4 mL) was added dropwise from a syringe to a solution of carbene complex **49e** (576 mg, 2 mmol) in CH_2Cl_2 (40 mL) at −40 °C, under argon. After 20 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solvent was evaporated and, after silica gel chromatography, the butenolide **53e** was obtained as a colourless oil (157 mg, 1.02 mmol, 51.1%, *ee* = 4.3%).

Reaction of *N*-Methyldihydronicotine (73) with Complexes 49a−f

General Procedure: A solution of *N*-methyldihydronicotine (**73**, 3 mol equiv.) was added dropwise from a syringe to a solution of the appropriate carbene complex (1 mol equiv.) in CH_2Cl_2 (25 mL/mmol of carbene) at −40 °C, under argon. After 20 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solution slowly turned dark red. The solvent was evaporated under vacuum and the expected butenolide was obtained after silica gel chromatography using mixtures of PE/Et_2O as eluent.

Reaction of Complex 4b with KHB(O*i*Pr)$_3$ and 1-Methylpyridinium Iodide 74. Complex 75: At 0 °C, 4 mL of potassium triisopropoxyborohydride solution (0.83 M in THF) was added to a solution of the carbene complex **4b** (1.00 g, 2.67 mmol) in 30 mL of THF. The reaction turned immediately from red to yellow and, after five minutes, 2 mL of a 10% sodium hydroxide solution in water was added in order to destroy the unreacted hydride. Then 1-methylpyridinium iodide (1.18 g, 5.34 mmol) was added leading to the formation of the tungstenate complex **75** as a red oil (1.31 g, 2.38 mmol, 89.0%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.12 (d, *J* = 6.0 Hz, 2 H, H_o py.), 8.72 (t, *J* = 7.0 Hz, 1 H, H_p py.), 8.27 (m, 2 H, H_m py.), 8.00−7.01 (m, 5 H, arom. H), 5.05 (s, 1 H, H^1), 4.65 (s, 3 H, H^4), 3.42 (m, 1 H, H^2), 3.06 (m, 1 H, $H^{2'}$), 1.15 (t, *J* = 7.0 Hz, 3 H, H^3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 205.1 (*trans* CO), 192.4 (*cis* CO), 146.5−120.3 (arom. HC and qC), 97.4 (C^1), 67.2 (C^2), 49.7 (C^4), 16.6 (C^3) ppm.



75

Reaction of Complex 4b with *N*-Methyldihydropyridine (19). Complex 75: A solution of *N*-methyldihydropyridine (**19**, 650 mg, 6.80 mmol) in Et_2O (20 mL) was added to a solution of complex **4b** (1.00 g, 2.30 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The solution immediately turned dark red. After warming at 0 °C, the solvent was evaporated under vacuum to give the tungstenate complex **75** (1.09 g, 1.98 mmol, 86.0% yield).

Reaction of Complex 49a with KHB(O*i*Pr)$_3$. 3-Benzylidene-2-phenyltetrahydrofuran (79, 80), 3,7-Diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (53a) and 4-Phenylbut-3-yn-1-ol: At −10 °C, 845 μL of potassium triisopropoxyborohydride solution (0.83 M in THF) was added to a solution of the carbene complex **49a** (300 mg, 0.70 mmol) in 15 mL of THF. After 10 minutes at 0 °C the reaction was warmed to room temperature and then stirred for 15 h. After cooling to 0 °C the unreacted hydride was destroyed by addition of ice and then the THF was removed on a rotary evaporator. After extraction with CH_2Cl_2 (3 × 10 mL) the combined extracts were

washed with water and brine and dried with anhydrous Na_2SO_4. Chromatography on silica gel with mixtures of PE/Et_2O as eluent first gave 3-benzylidene-2-phenyltetrahydrofuran **79** and **80** as a clear oil (50 mg, 0.21 mmol, 30.2%) as a mixture of two isomers in a 6:4 ratio: one isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28−6.99 (m, 10 H, arom. H), 6.60 (d, J = 1.5 Hz, 1 H, H^6), 5.68 (s, 1 H, H^2), 3.83 (t, J = 6.8 Hz, 2 H, H^5), 2.95−2.76 (m, 2 H, H^4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.4 (C^3), 140.1 (qC), 137.1 (qC), 128.9−127.0 (arom. HC), 124.1 (C^6), 80.8 (C^2), 65.5 (C^5), 35.9 (C^4) ppm. HMRS [M + 1] calcd. for $C_{17}H_{17}O$ 237.1279; found 237.1273. Other isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−6.99 (m, 10 H, arom. H), 6.02 (d, J = 2.3 Hz, 1 H, H^6), 5.68 (d, J = 1.5 Hz, 1 H, H^2), 4.23 (m, 1 H, H^5), 3.87 (m, 1 H, H^5), 2.96−2.92 (m, 2 H, H^4) ppm. ^{13}C NMR(100 MHz, $CDCl_3$): δ = 144.7 (C^3), 141.9 (qC), 137.9 (qC), 128.8−127.1 (arom. HC), 123.2 (C^6), 85.3 (C^2), 68.4 (C^5), 32.2 (C^4) ppm.

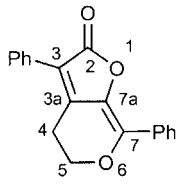
Further elution gave the butenolide **53a** in 20.9% yield as a single *trans* isomer. Finally, the alcohol 4-phenylbut-3-yn-1-ol was obtained as a colourless oil (33 mg, 0.22 mmol, 32.1%).

Reaction of Carbene Complex 49e with $NaBH_4$. 7-Methyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one(53e): Sodium borohydride (7 mg; 0.25 equiv.) was added in portions to a solution of carbene complex **49e** (199 mg; 0.69 mmol) in THF (10 mL) at −20 °C. The reaction mixture was slowly warmed to room temperature and stirred for 12 h. The starting material was completely reduced after 5 minutes (TLC monitoring). Addition of 2 mL of water followed by extraction with CH_2Cl_2 (3 × 15 mL), followed by drying over anhydrous sodium sulfate and evaporation of the solvents gave a brown residue. Silica gel chromatography gave the butenolide as a yellow oil and as two isomers in 7:3 ratio in 22.4% global yield (23.8 mg, 0.15 mmol). ***trans* Isomer 49e:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (s, 1 H, H^3), 4.30 (d, J = 8.6 Hz, 1 H, H^{7a}), 4.21 (dd, J = 6.7−11.3 Hz, 1 H, H^5), 3.31 (ddd, J = 2.6, 11.3, 11.3 Hz, 1 H, $H^{5'}$), 3.11 (dq, J = 6.1, 8.6 Hz, 1 H, H^7), 2.78 (dd, J = 2.9, 13.6 Hz, 1 H, H^4), 2.65 (m, 1 H, $H^{4'}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9 (C^2), 168.0 (C^{3a}), 112.7 (C^3), 83.2 (C^7), 80.1 (C^{7a}), 67.6 (C^5), 30.2 (C^4), 19.3 (C^8) ppm. $C_8H_{10}O_3$ (154.2): calcd. C 62.33, H 6.54; found C 62.42, H 6.56. ***cis* Isomer 53e′:** ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.85 (s, 1 H, H^3), 4.96 (d, J = 7.1 Hz, 1 H, H^{7a}), 4.66 (m, 1 H, H^5), 3.88 (m, 1 H, $H^{5'}$), 3.55 (dt, J = 3.6, 9.3 Hz, 1 H, H^4), 2.80−2.50 (m, 2 H, H^4 and H^7), 1.00 (d, J = 6.4 Hz, 3 H, C^8) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.1 (C^2), 168.1 (C^{3a}), 114.1 (C^3), 79.3 (C^7), 72.8 (C^{7a}), 58.9 (C^5), 29.7 (C^4), 19.9 (C^8) ppm.

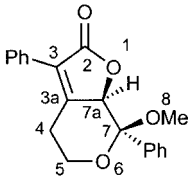
Reaction of Carbene Complex 49e with KHB(O*i*Pr)$_3$. 7-Methyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (53e): At −10 °C, 1.46 mL of potassium triisopropoxyborohydride solution (0.83 M in THF) was added to a solution of the carbene complex **49e** (349 mg, 1.21 mmol) in 15 mL of THF. After 10 minutes at 0 °C the reaction was warmed to room temperature and then stirred for 15 h. After cooling to 0 °C, the unreacted hydride was destroyed by addition of ice and then THF was removed on a rotary evaporator. After extraction with CH_2Cl_2 (3 × 10 mL) the combined extracts were washed with water and brine and dried with anhydrous Na_2SO_4. Chromatography on silica gel gave the butenolide **53e** as a mixture of two isomers (*trans*/*cis*: 90:10) in 12.5% yield (23 mg, 0.15 mmol).

Reaction of Carbene Complex 49e with 9-BBN and (*S*)-(−) Nicotine. 7-Methyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one 53e: A solution of complex **49e** (425 mg, 1.47 mmol) in THF (5 mL) was added to a mixture of (*S*)-(−)nicotine **69** (243 mg, 1.5 mmol) and 9-BBN (3.00 mL; 1.50 mmol, 0.5 M) in THF (3 mL) at −20 °C. The yellow solution turned red immediately. The mixture was allowed to reach room temperature and stirred for 24 h. The expected butenolide **53e** was obtained after silica gel chromatography as a mixture of two isomers in 6:4 ratio in 12.8% yield (29 mg, 0.19 mmol).

Reaction of Complex 49a with Sodium Methoxide. 3,7-Diphenyl-4,5-dihydrofuro[2,3-*c*]pyran-2-one (83) and 7-Methoxy-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (82): At 0 °C, 66 μL of a 30% MeO^-Na^+/MeOH solution was added with a syringe to a solution of carbene complex **49a** (153 mg; 0.36 mmol) in 15 mL of THF. The solution turned from red to yellow. The resulting mixture was stirred for 10 minutes at 0 °C and then warmed to room temperature and stirred for 15 h. Removal of the solvent left a brownish residue that was purified by silica gel chromatography with various mixtures of PE/Et_2O as eluent. Two butenolides **83** and **82** were obtained. **83:** (8 mg, 0.03 mmol, 7.7%), white solid, m.p. 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05−7.34 (m, 10 H, arom. H), 4.42 (t, J = 6.3 Hz, 2 H, H^5), 3.19 (t, J = 6.3 Hz, 2 H, H^4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0 (C^2), 143.4 (C^{7a}), 141.5 (qC), 135.2 (C^7), 130.9−127.9 (arom. HC and qC), 116.6 (C^3), 67.1 (C^5), 24.7 (C^4) ppm. HMRS [M + 1] calcd. for $C_{19}H_{15}O_3$ 291.1021; found 291.1013. **82:** (25 mg, 0.08 mmol, 21.6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71−7.37 (m, 10 H, arom. H), 4.88 (s, 1 H, H^{7a}), 4.11 (dd, J = 6.6, 7.4 Hz, 1 H, H^5), 3.76 (dd, J = 3.4, 11.7 Hz, 1 H, H^5), 3.13−2.78 (m, 2 H, H^4), 2.96 (s, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5 (C^2), 156.3 (C^{3a}), 137.5 (C^3), 130.8−125.0 (arom. CH and qC), 101.1 (C^7), 82.8 (C^{7a}), 59.8 (C^5), 49.8 (C^8), 28.3 (C^4) ppm.

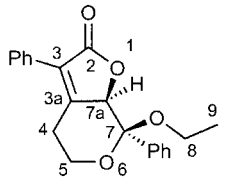


83



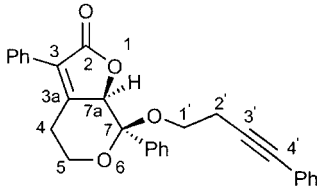
82

Reaction of Complex 11b with Sodium Phenylbutynolate. 3,7-Diphenyl-4,5-dihydrofuro[2,3-*c*]pyran-2-one (83) and 7-Ethoxy-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (84): A solution of 4-phenylbut-3-yn-1-ol (255 mg, 1.75 mmol, 1.1 equiv.) in THF (10 mL) was added to a suspension of NaH (210 mg, 60% oil, 5.25 mmol, 3.3 equiv.) in THF (15 mL) and the mixture was stirred at room temperature for 1 h. The resulting solution was transferred with a cannula to a solution of carbene complex **11b** (518 mg, 1.59 mmol, 1 equiv.) in THF (15 mL) at −40 °C. The mixture was stirred for 20 minutes at this temperature then warmed to room temperature and stirred for 15 h. Removal of the solvent left a brownish residue that was purified by silica gel chromatography. **83** (116 mg, 0.397 mmol, 25%) and **84** (134 mg, 0.397 mmol, 25%) were obtained. **84** as a white solid, m.p. 150 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.72−7.36 (m, 10 H, arom. H), 4.66 (s, 1 H, H^{7a}), 4.11 (dd, J = 5.5, 11.7 Hz, 1 H, H^5), 3.78 (dd, J = 2.9, 11.8 Hz, 1 H, H^5), 3.28−3.06 (m, 3 H, H^4 and H^8), 2.81 (m, 1 H, H^4), 1.06 (t, 3 H, H^9) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.6 (C^2), 156.3 (C^{3a}), 138.6 (C^3), 129.7−125.5 (arom. HC and qC), 100.8 (C^7), 82.8 (C^{7a}), 59.7 (C^5), 57.6 (C^8), 28.3 (C^4), 14.7 (C^9) ppm. HMRS [M + 1] calcd. for $C_{21}H_{21}O_4$ 337.1440; found 337.1437.



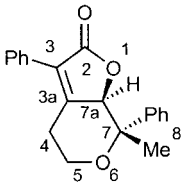
84

Reaction of Complex 49a with Sodium Phenylbutynolate. 3,7-Diphenyl-7-(4-phenylbut-3-ynyloxy)-4,5,7,7a-tetrahydrofuro[2,3-*c*]-pyran-2-one (85): A solution of 4-phenylbut-3-yn-1-ol (188 mg, 1.29 mmol, 1.1 equiv.) in THF (10 mL) was added to a suspension of NaH (154 mg, 60% oil, 3.9 mmol, 3.3 equiv.) in THF (15 mL) and the mixture was stirred for 1 hour at room temperature. The resulting solution was transferred with a cannula to a solution of carbene complex **49a** (500 mg, 1.17 mmol, 1 equiv.) in THF (15 mL) at −40 °C. The mixture was stirred for 20 minutes at this temperature then warmed to room temperature and stirred for 15 h. Removal of the solvent left a brownish residue that was purified by silica gel chromatography. Two butenolides were obtained: **83** (100 mg, 0.345 mmol, 29%) and **85** (44 mg, 0.101 mmol, 9%) as a white solid, m.p. 142 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.7−7.1 (m, 15 H, arom. H), 4.7 (s, 1 H, H^{7a}), 4.1 (m, 2 H, H^5), 3.4 (ddd, J = 6, 9, 9 Hz, 1 H, $H^{1'}$), 3.2 (dq, J = 5, 6.5, 9 Hz, 1 H, $H^{1'}$), 3.0 (dd, J = 2.8, 13.5 Hz, 1 H, H^4), 2.8 (ddd, J = 7.5, 11.5, 13.5 Hz, 1 H, H^4), 2.6 (m, 1 H, $H^{2'}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7 (C^2), 156.2 (C^{3a}), 138 (Cq), 131.5−123.4 (arom. and qC), 100.6 (C^7), 86.9 ($C^{3'}$), 82.7 (C^{7a}), 81.6 ($C^{4'}$), 60.3 ($C^{1'}$), 60.0 (C^5), 28.3 (C^4), 20.4 ($C^{2'}$) ppm. $C_{29}H_{25}O_4$ (437.5): calcd. C 79.8, H 5.54; found C79.4, H 5.73.

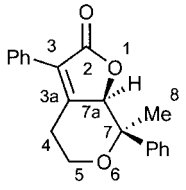


85

Reaction of MeLi with Carbene Complex 49a. 7-Methyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (86a, 87a): Methyllithium (520 μL, 1.6 M, 0.82 mmol) was added with a syringe to a solution of carbene complex **49a** (350 mg, 0.82 mmol) in THF (20 mL) at −40 °C and the resulting mixture was stirred for 30 minutes at this temperature before being allowed to reach room temperature. After 12 h, the solution was hydrolysed with aqueous 10% HCl and then extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine and finally dried with sodium sulfate. The residue was purified by thin layer chromatography (elution with 10% EtOAc/cyclohexane) and the butenolide was obtained as two isomers (*de* = 22%). **86a** (100 mg, 0.33 mmol, 40.2%) as a white solid, m.p. 132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74−7.35 (m, 10 H, arom. H), 4.96 (s, 1 H, H^{7a}), 4.21 (dd, J = 7.6, 11.7 Hz, 1 H, H^5), 3.82 (dd, J = 3.5, 11.7 Hz, 1 H, H^5), 3.12 (dd, J = 3.5, 14.2 Hz, 1 H, H^4), 2.87 (ddd, J = 7.6, 11.7, 14.2 Hz, 1 H, H^4), 1.40 (s, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (C^2), 158.2 (C^{3a}), 145.5 (qC), 129.4−124.9 (arom. HC and qC), 83.2 (C^{7a}), 80.5 (C^7), 60.1 (C^5), 28.7 (C^4), 17.5 (C^8) ppm. $C_{20}H_{18}O_3$: calcd. C 78.41, H 5.92; found C 78.44, H 5.89. **87a** (65 mg, 0.21 mmol, 25.6%) as a white solid, m.p. 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72−7.23 (m, 10 H, arom. H), 5.08 (s, 1 H, H^{7a}), 4.00 (ddd, J = 2.5, 6.2, 11.7 Hz, 1 H, H^5), 3.64 (ddd, J = 5.5, 9.7, 11.7 Hz, 1 H, H^5), 2.98−2.88 (m, 2 H, H^4), 1.81 (s, 3 H, H^8). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.4 (C^2), 158.3 (C^{3a}), 139.6 (qC), 129.3−124.8 (arom. HC and qC), 85.1 (C^{7a}), 80.7 (C^7), 60.8 (C^5), 32.6 (C^8), 28.1 (C^4) ppm. $C_{20}H_{18}O_3$ (306.4): calcd. C 78.41, H 5.92; found C 78.51, H 6.05.

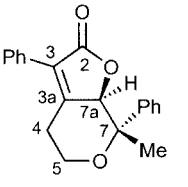


86a

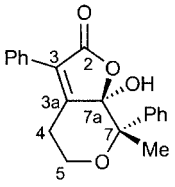


87a

Reaction of MeLi with Carbene Complex 49a. 7-Methyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (86a) and 7a-Hydroxy-7-methyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (88): Methyllithium (1.6 M, 1.23 mL, 1.97 mmol, 1.05 equiv.) was added with a syringe to a solution of carbene complex **49a** (800 mg, 1.87 mmol) in THF (30 mL) at −40 °C, under an argon. After 30 minutes the ice bath was removed and the mixture was stirred at room temperature for 24 h. The solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel with mixture of EP/Et_2O as eluent. The butenolide **86a** (107 mg, 0.35 mmol, 19%), then **88** (120 mg, 0.37 mmol, 20%) as a white solid, m.p. 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.8−7.4 (m, 10 H, arom. H), 4.2 (ddd, J = 11.3, 6.5, 1.8 Hz, 1 H, H^5), 3.9 (dt, J = 11.3, 4 Hz, 1 H, $H^{5'}$), 3.2 (s, 1 H, OH), 3.1−3 (m, 2 H, H^4), 1.6 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (C^2), 155.8 (C^{3a}), 139.5 (qC), 128.9−126.6 (arom. HC and qC), 102.1 (C^{7a}), 82.7 (C^7), 60.6 (C^5), 26.9 (C^4), 19.8 (Me) ppm. HRMS [M + 1] calcd. for $C_{20}H_{19}O_4$: 323.1283, found 323.1279.



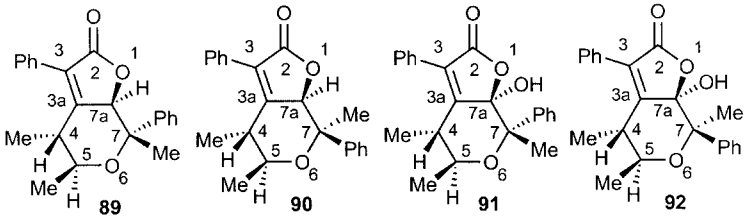
86a



88

Reaction of MeLi with Carbene Complex 49a under O_2. 7a-Hydroxy-7-methyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (88): Methyllithium (1.4 mL, 1.6 M, 2.24 mmol) was added with a syringe to a solution of carbene complex **49a** (804 mg, 1.89 mmol) in THF (30 mL) cooled to −40 °C and the resulting mixture was stirred for 30 minutes at this temperature before being allowed to reach room temperature. The flask was purged with O_2 and the solution stirred for 12 h. Silica gel was introduced and the solvent was evaporated under reduced pressure. The residue was purified by chromatography (elution EP/Et_2O). The lactonol **88** (89 mg, 0.28 mmol, 14.5%) was obtained.

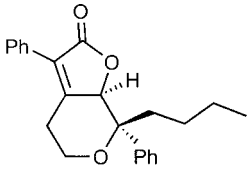
Reaction of MeLi with Carbene Complex 49h. 4,5,7-Trimethyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (89, 90). 7a-Hydroxy-4,5,7-trimethyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]-pyran-2-one (91, 92): Methyllithium (1.4 mL, 1.6 M, 2.22 mmol) was added with a syringe to a solution of carbene complex **49h** (839 mg, 1.82 mmol) in THF (30 mL) at −40 °C. After 30 minutes the ice bath was removed and the mixture stirred at room temperature. After 24 h, silica gel was added to the flask and the solvent was



evaporated under reduced pressure. The residue was purified by chromatography (elution EP/Et_2O) and the butenolide was obtained as two isomers (*de* = 8%). **89** (136 mg, 0.41 mmol, 22%) as a white solid, m.p. 168 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.6−7.2 (m, 10 H, arom. H), 5.3 (d, *J* = 1.3 Hz, 1 H, H^{7a}), 3.5 (dq, *J* = 6, 9.6 Hz, 1 H, H^5), 3.1 (dq, *J* = 7, 9.6 Hz, 1 H, H^4), 1.4 (d, *J* = 6 Hz, 3 H, Me^5), 1.3 (s, *J* = 6 Hz, 3 H, Me^7), 1.1 (d, *J* = 7 Hz, 3 H, Me^4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4 (C^2), 164.8 (C^{3a}), 146.4 (qC), 133.9−124.7 (arom. HC and qC), 82.0 (C^{7a}), 81.5 (C^7), 73.1 (C^5), 40.6 (C^4), 25.6 (Me^7), 19.4 (Me^5), 15.7 (Me^4) ppm. HRMS [M + 1] calcd. for $C_{22}H_{23}O_3$: 335.1647, found 335.1643.

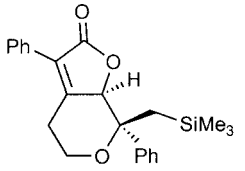
90: (159 mg, 0.48 mmol, 26%) as a white solid, m.p. 146 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.7−7.3 (m, 10 H, arom. H), 4.8 (s, 1 H, H^{7a}), 3.6 (dq, *J* = 9.4, 5.8 Hz, 1 H, H^5), 2.5 (dq, *J* = 9.4, 6.8 Hz, 1 H, H^4), 1.42 (s, 3 H, Me^7), 1.40 (d, *J* = 5.8 Hz, 3 H, Me^5), 0.90 (d, *J* = 6.8 Hz, 3 H, Me^4) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.6 (C^2), 161.7 (C^{3a}), 145.5 (qC), 130.2−125.0 (arom. HC and qC), 84.0 (C^{7a}), 79.7 (C^7), 72.6 (C^5), 42.5 (C^4), 19.8 (Me^5), 17.9 (Me^7) 14.1 (Me^4) ppm. Further elution furnished lactonol as two isomers (*de* = 20%). **91:** (24 mg, 0.068 mmol, 3.7%) as a white solid, m.p. 140 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.7−7.3 (m, 10 H, arom. H), 4.1 (dq, *J* = 9.5, 6 Hz, 1 H, H^5), 3.4 (s, 1 H, OH), 3.0 (dq, *J* = 9.5, 7 Hz, 1 H, H^4) 1.46 (s, 3 H, Me^7), 1.42 (d, *J* = 6 Hz, 3 H, Me^5), 1.2 (d, *J* = 7 Hz, 3 H, Me^4) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.8 (C^2), 161.0 (C^{3a}), 140.0 (qC), 129.5−125.6 (arom. HC and qC), 103.0 (C^{7a}), 84.6 (C^7), 72.5 (C^5), 40.1 (C^4), 27.9 (Me^7), 19.5 (Me^5), 16.2 (Me^4) ppm. **92:** (16 mg, 0.046 mmol, 2.5%) as an oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.8−7.3 (m, 10 H, arom. H), 3.8 (dq, *J* = 9.5, 6 Hz, 1 H, H^5), 3.2 (s, 1 H, OH), 2.8 (dq, *J* = 9.5, 7 Hz, 1 H, H^4) 1.6 (s, 3 H, Me^7), 1.43 (d, *J* = 6 Hz, 3 H, Me^5), 0.90 (d, *J* = 7 Hz, 3 H, Me^4) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.3 (C^2), 159.8 (C^{3a}), 139.6 (qC), 130.1−126.7 (arom. HC and qC), 102.8 (C^{7a}), 82.0 (C^7), 73.1 (C^5), 40.3 (C^4), 20.4 (Me^7), 19.7 (Me^5) 13.8 (Me^4) ppm.

Reaction of BuLi with Carbene Complex 49a. 7-Butyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (86c, 87c): Butyllithium (470 μL, 2.5 M, 1.17 mmol) was added with a syringe to a solution of carbene complex **49a** (500 mg, 1.17 mmol) in THF (30 mL) cooled to −40 °C and the resulting mixture was stirred for 30 minutes at this temperature before being allowed to reach room temperature. After 24 h, the solution was hydrolysed with aqueous 10% HCl and then extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine and finally dried with sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by chromatography (elution EP/Et_2O). The butenolide was obtained as two isomers **86c** and **87c** (*de* > 90%). **86c** *trans* isomer, viscous oil (173 mg, 0.5 mmol, 43%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.61−7.16 (m, 10 H, arom. H), 4.73 (s, 1 H, H^{7a}), 4.08 (dd, *J* = 7.6, 11.7 Hz, 1 H, H^5), 3.54 (dt, *J* = 3.0, 11.7 Hz, 1 H, $H^{5'}$), 3.01 (dd, *J* = 3.0, 14.2 Hz, 1 H, H^4), 2.76 (ddd, *J* = 7.6, 11.7, 14.2 Hz, 1 H, $H^{4'}$), 1.72 (m, 1 H, H^8), 1.6 (m, 1 H, $H^{8'}$), 1.02 (m, 3 H, H^9, $H^{9'}$, H^{10}), 0.78 (m, 1 H, $H^{10'}$), 0.67 (t, *J* = 7.5 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5 (C^2), 158.2 (C^{3a}), 143.7 (qC), 129.5−125.2 (arom. HC and qC), 84.1 (C^{7a}), 82.3 (C^7), 58.8 (C^5), 28.7 (C^4), 27.1 (C^8), 23.3 (C^{10}), 22.8 (C^9), 14.1 (CH_3) ppm. HRMS [M + 1] calcd. for $C_{23}H_{25}O_3$: 349.1804, found 349.1801.



86c/87c

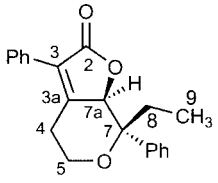
Reaction of (Trimethylsilylmethyl)lithium with Carbene Complex 49a. 3,7-Diphenyl-7-trimethylsilylmethyl-4,5,7,7a-tetrahydrofuro-[2,3-*c*]pyran-2-one (86d, 87d): Butyllithium (2.34μL, 1 M, 4.4 mmol) was added with a syringe to a solution of carbene complex **49a** (500 mg, 1.17 mmol) in THF (30 mL) at −40 °C. After 30 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solution was hydrolysed with aqueous 10% HCl and extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine and finally dried with sodium sulfate. The solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel with mixture of EP/Et_2O as eluent. The butenolide was obtained as a mixture of isomers **86d** and **87d** (*de* > 90%). **86d** *trans* isomer (151 mg, 0.4 mmol, 34%), as a yellow solid, m.p. 97 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70−7.29 (m, 10 H, arom. H), 4.69 (s, 1 H, H^{7a}), 4.14 (dd, *J* = 7.0, 11.7 Hz, 1 H, H^5), 3.68 (dt, *J* = 3.0, 11.7 Hz, 1 H, $H^{5'}$), 3.06 (dd, *J* = 3.0, 13.5 Hz, 1 H, H^4) 2.80 (ddd, *J* = 7.0, 11.7, 13.5 Hz, 1 H, $H^{4'}$), 1.27 (d, *J* = 16 Hz, 1 H, H^8), 1.1 (d, *J* = 16 Hz, 1 H, $H^{8'}$), −0.3 (s, 9 H, 3 CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.6 (C^2), 157.9 (C^{3a}), 145.2 (qC), 129.6−125.1 (arom. HC and qC), 84.7 (C^{7a}), 83.1 (C^7), 60.1 (C^5), 28.7 (C^4), 16.5 (C^8), −0.34 (3 CH_3) ppm. HRMS [M + 1] calcd. for $C_{23}H_{27}O_3Si$: 379.1716, found 379.1718.



86d/87d

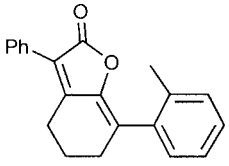
Reaction of Ethyllithium with Carbene Complex 49a. 7-Ethyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (86b, 87b) and 53a: Ethyllithium (282 μL, 0.5 M, 2.8 mmol, 2 equiv.) was added with a syringe to a solution of carbene complex **49a** (600 mg, 1.4 mmol) in THF (25 mL) at −40 °C, under argon. After 30 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solvent was evaporated under vacuum and the

residue was purified by chromatography on silica gel with mixtures of EP/Et_2O as eluent. Two butenolides **86b** and **87b** (*de* >90%) were obtained. **86b** (113 mg, 0.35 mmol, 25%) as a white solid, m.p. 127 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.7−7.3 (m, 10 H, arom. H), 4.8 (s, 1 H, H^{7a}), 4.15 (ddd, *J* = 0.9, 6.5, 11.5 Hz, 1 H, H^5), 3.6 (dt, *J* = 3, 11.5 Hz, 1 H, H^5), 3.1 (dd, *J* = 3, 14 Hz, 1 H, H^4), 2.85 (m, 1 H, H^4), 1.8 (m, 2 H, H^8), 0.6 (t, *J* = 7 Hz, 3 H,H^9 ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5 (C^2), 158.2 (C^{3a}), 143.3 (qC), 129.5−124.4 (arom. HC and qC), 84 (C^{7a}), 82.5 (C^7), 59.7 (C^5), 28.7 (C^4), 20.3 (C^8), 5.5 (C^9) ppm. HRMS [M + 1] calcd. for $C_{21}H_{21}O_3$: 321.1491; found 321.1486. And **53a** (40 mg, 0.14 mmol, 10%).



86b/87b

Reaction of Phenylpentynyllithium with Carbene Complex 95. 3-Phenyl-7-(*o*-tolyl)-5,6-dihydro-4*H*-benzofuran-2-one (96): At −78 °C, 2.6 mL of *tert*-butyllithium solution (1.6 N, 4.4 mmol, 3 equiv.) was added to a solution of (5-iodo-pent-1-ynyl) benzene (600 mg, 2.2 mmol, 1.5 equiv.) in pentane (19 mL) and diethyl ether (10 mL). The mixture was stirred for 15 min and was then transferred with a cannula into a solution of carbene complex (500 mg, 1.47 mmol) in diethyl ether (20 mL) at −78 °C. The mixture first became clear red then gradually deep purple. After 1−2 h, the mixture was allowed to reach room temperature and stirred for 12 h. After hydrolysis and extraction with dichloromethane, the residue was purified by thin layer chromatography (elution with 10% EtOAc/cyclohexane): the UV fluorescent stripe under the unreactive carbene complex furnished **96** (70 mg, 0.231 mmol, 16%) as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.69−7.20 (m, 10 H, arom. H), 2.93 (t, *J* = 6 Hz, 2 H, H^4or H^6), 2.61 (t, *J* = 6 Hz, 2 H, H^4or H^6), 2.23 (s, 3 H, CH_3), 1.97 (qt, *J* = 6 Hz, 2 H, H^5) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.3 (C^2), 148.0 (C^{7a}), 145.1 (qC), 136.4−125.7 (arom. HC and qC), 124.5 (C^3), 121.2 (C^7), 30.6 (C^4), 24.6 (C^6), 23.4 (C^5), 20.3 (CH_3) ppm. HRMS [M + 1] calcd. for $C_{21}H_{19}O_2$: 303.1385, found 303.1384.

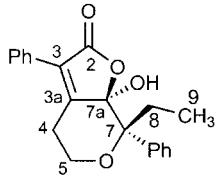


96

Reaction of Ethylmagnesium Bromide with Carbene Complex 49a

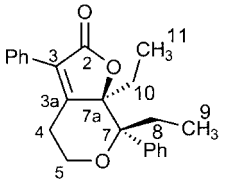
General Procedure: Ethylmagnesium bromide (3 M in diethyl ether, *x* mol equiv.) was added with a syringe to a solution of carbene complex **49a** (1 mol equiv.) in THF (25 mL/mmol) at −40 °C, under argon. After 20 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solution was hydrolysed with a saturated solution of NH_4Cl and extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine and finally dried with sodium sulfate. The solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel with mixture of EP/Et_2O as eluent.

Formation of Butenolides 93. 7-Ethyl-7a-hydroxy-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (93) and 53a: The general procedure was followed using carbene **49a** (300 mg, 0.704 mmol) and 1.2 equivalents of ethylmagnesium bromide (0.845 mmol, 282 μL). Butenolide **53a** was obtained (5 mg, 0.017 mmol, 2%) then **93** (21 mg, 0.062 mmol, 9%) as a white solid, m.p. 138 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ : 7.5−7.2 (m, 10 H, arom. H), 4.2 (ddd, *J* = 0.7, 3.2, 4 Hz, 1 H, H^5), 3.7 (dt, *J* = 2, 5 Hz, 1 H, H^5), 3.2 (s, 1 H, OH), 3 (m, 2 H, H^4), 2 (m, 1 H, H^8), 1.9 (m, 1 H, H^8), 0.5 (t, *J* = 3.5 Hz, 3 H, H^9) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.2 (C^2), 156.2 (C^{3a}), 137.3 (qC), 128.9−126.8 (arom. HC and qC), 102.2 (C^{7a}), 85.3 (C^7), 60.1 (C^5), 26.8 (C^4), 22.5 (C^8), 6.1 (C^9) ppm. HRMS [M + 1] calcd. for $C_{21}H_{21}O_4$: 337.1440; found 337.1442.



93

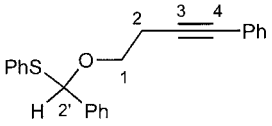
Formation of Butenolides 93 and 7,7a-Diethyl-3,7-diphenyl-4,5,7,7a-tetrahydrofuro[2,3-*c*]pyran-2-one (94): The general procedure was followed using carbene **49a** (655 mg, 1.54 mmol) and two equivalents of ethylmagnesium bromide (3.08 mmol, 1.03 mL). Butenolide **94** (79 mg, 0.23 mmol, 15%) was obtained as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.5−7.2 (m, 10 H, arom. H), 4.5 (q, *J* = 8 Hz, 1 H, H^5), 4.1 (dt, *J* = 3, 11 Hz, 1 H, H^5), 2.9 (m, 1 H, H^4), 2.4 (ddd, *J* = 3, 8, 12.4 Hz, 1 H, H^4), 2.2 (m, 1 H, H^8 or H^{10}), 2.1 (m, 1 H, H^8 or H^{10}), 1.4 (m, 1 H, H^8 or H^{10}), 1.2 (m, 1 H, H^8 or H^{10}), 1.0 (t, *J* = 7.5 Hz, 3 H, H^9 or H^{11}), 0.4 (t, *J* = 7.5 Hz, 3 H, H^9 or H^{11}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6 (C^2), 155.2 (C^{3a}), 139.3 (qC), 130.0−125.5 (arom. HC and qC), 113.9 (C^{7a}), 90.3 (C^7), 64.5 (C^5), 33.0 (C^4), 29.7 (C^{10}) 19.7 (C^8), 11.5 (C^{11}), 7.4 (C^9) ppm. HRMS [M + 1] calcd. for $C_{23}H_{25}O_3$: 349.1804; found 349.1800. Then **93** (23 mg, 0.07 mmol, 5%).



94

Reaction of Methylmagnesium Bromide with Complex 49a: Methylmagnesium bromide (3 M in diethyl ether, 2.8 mmol, 950 μL) was added with a syringe to a solution of carbene complex **49a** (600 mg, 1.4 mmol) in THF (25 mL) at −40 °C, under argon. After 20 min the ice bath was removed and the mixture stirred at room temperature for 24 h. The solution was hydrolysed with a saturated solution of NH_4Cl and extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine and finally dried with sodium sulfate. The solvent was evaporated under vacuum and the residue was purified by chromatography on silica gel with mixture of EP/Et_2O as eluent and the butenolide was obtained as two isomers (*de* = 46%) **86a** (93 mg, 0.3 mmol, 22%) and **87a** (33 mg, 0.10 mmol, 8%).

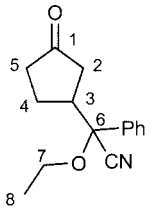
Reaction of Sodium Phenylthiolate with Complex 49a. Formation of 98a: Thiophenol (0.2 mL, 2 equiv.) was added with a syringe to a suspension of sodium hydride (80 mg, 60% oil, 1.64 mmol, 2 equiv.) in THF (25 mL), and the mixture was stirred at room temperature during 15 min. A solution of carbene complex **49a** (350 mg, 0.82 mmol) in THF (5 mL) was added with a cannula to the resulting mixture at −40 °C, which was stirred for 30 min at this temperature and then allowed to reach room temperature. After one hour, the mixture was heated to reflux and stirred at this temperature for 12 h. After hydrolysis and extraction with dichloromethane, the residue was purified by thin layer chromatography (elution with 5% EtOAc/cyclohexane). The first stripe at the top of the plate gave PhSSPh (168 mg, 0.77 mmol). The second one furnished **98a** as an oil (129 mg, 0.37 mmol, 46%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53−7.12 (m, 15 H, arom. H), 5.89 (s, 1 H, $H^{2'}$), 4.01 (q, J = 7, 8.8 Hz, 1 H, H^1), 3.73 (q, J = 7, 8.8 Hz, 1 H, H^1), 2.76 (t, J = 7 Hz, 2 H, H^2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.1−126.4 (arom.), 89.5 ($C^{2'}$), 86.7−83.57 (C^3, C^4), 67.0 (C^1), 20.7 (C^2) ppm. HRMS [M + 1] calcd. for $C_{23}H_{21}OS$: 345.1313, found 345.1309.



98a

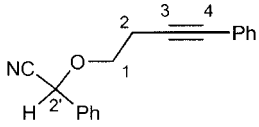
Reaction of Tetramethylammonium Cyanide with Carbene Complex 11b. Ethoxy(phenyl)acetonitrile (100): Tetramethylammonium cyanide (156 mg, 1 mmol) was added at room temperature to a solution of carbene complex **11b** (326 mg, 1 mmol) in THF (20 mL). The red solution became slowly greenish. After 12 h the solution was hydrolysed with aqueous NH_4Cl then extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine and finally dried with sodium sulfate. The solvent was evaporated under reduced pressure and the residue purified by chromatography (elution EP/EtOAc). The first product eluted was ethyl benzoate (66 mg, 0.44 mmol, 44%). Further elution furnished **100b** as an oil (31 mg, 0.19 mmol, 19%).

Reaction of Tetramethylammonium Cyanide with Carbene Complex 11b and 2-Cyclopentenone. Ethoxy(3-oxocyclopentyl)(phenyl)acetonitrile (101). Tetramethylammonium cyanide (312 mg, 2 mmol) was added at room temperature to a solution of carbene complex **11b** (652 mg, 2 mmol) and 2-cyclopentenone (300 μL, 4 equiv.) in THF (50 mL) and the resulting mixture was refluxed for 12 h. The solution was hydrolysed with aqueous NH_4Cl then extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine and finally dried with sodium sulfate. The solvent was evaporated under reduced pressure and the residue purified by chromatography (elution EP/EtOAc). Compound **101** was obtained as a colourless liquid, a mixture of diastereoisomers (*de* = 30%) (228 mg, 0.94 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48−7.37 (m, 5 H, arom. H), 3.61 (m, 1 H, H^7), 3.32 (m, 1 H, $H^{7'}$), 2.72 (m, 1 H, H^3), 2.50−1.73 (m, 6 H, H^5, H^4, H^2) 1.22 and 1.20 (t, 3 H, H^8) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.3 and 215.8 (C^1), 136.2 (qC), 129.4−125.7 (arom. HC), 117.6 (CN), 84.4 and 83.7 (C^6), 62.8 (C^7), 48.5 (C^3), 40.9 and 40.6.38.2 and 38.1, 24.7 (C^5,C^2 and C^4), 14.9 (C^8) ppm. HRMS (EI^+), calcd. for $C_{15}H_{18}NO_2$: 244.1338; found 244.1315.



101

Reaction of Tetramethylammonium Cyanide with Complex 49a. Phenyl(4-phenylbut-3-ynyloxy)acetonitrile (98b): Tetramethylammonium cyanide (128 mg, 0.82 mmol) was added at 0 °C to a solution of carbene complex **49a** (350 mg, 0.82 mmol) in anhydrous CH_2Cl_2 (10 mL). The solution turned from red to yellow. After 15 min the solution was allowed to reach room temperature and stirred for 24 h. Water was then added. After extraction three times with CH_2Cl_2, the organic layers were combined, washed with brine and finally dried with sodium sulfate. The solvent was evaporated under reduced pressure and the residue purified by chromatography (elution EP/Et_2O). **98b** was obtained as an oil (50 mg, 0.19 mmol, 23%). IR: $\tilde{\nu}$ = 1947 (CN) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53−7.29 (m, 10 H, arom. H), 5.40 (s, 1 H, $H^{2'}$), 3.85 (m, 2 H, H^1), 2.77 (t, J = 6.5 Hz, 2 H, H^2) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 133.2−123.3 (arom.), 117.1 (CN), 85.7 (C^4), 82.1 (C^3), 70.9 ($C^{2'}$), 67.9 (C^1), 20.7 (C^2) ppm. HRMS [M + 1] calcd. for $C_{18}H_{16}NO$: 262.1232, found 262.1230.



98b

CCDC-227184 (for **53g**), -227185 (for **53h**), -161753 (for **53k**), -227186 (for **57a**), -227187 (for **83**), -227188 (for **84**), -184028 (for **86a**), -227189 (for **88**) and -227190 (for **91**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk].

Supporting Information Available (see also the footnote on the first page of this article): Experimental details describing the synthesis of the carbene complexes and their transformation into butenolides.

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