Dihydrofurans from α-diazoketones due to facile ring opening – cyclization of donor–acceptor cyclopropane intermediates

Elizabeth A. Lund, Isaac A. Kennedy, and Alex G. Fallis

Abstract: A series of α-diazoketones, **8**, **25**, **28**, **31**, and **34**, have been synthesized and their reaction with ethyl vinyl ether examined under various reaction conditions. In the presence of metal salts ($Rh_2(OAc)_4$, $Pd(OAc)_2$, CuCl) the ethoxydihydrofurans **12**, **37**, **39**, **41**, and **43** are produced. Sensitized irradiation of the α-diazoketone **8** afforded the dihydrofuran **12** plus cyclobutanone **7**, while direct photolysis of α-diazoketones **8**, **25**, **28**, **31**, and **34** gave the cyclobutanones **7**, **38**, **40**, **42**, and **44**, respectively. A sample of the cyclopropylketone **45** was isolated from the rhodium(II) acetate mediated reaction of **34** and its facile rearrangement to dihydrofuran **43** demonstrated. Collectively, these results indicate that the initial product from the reaction of an α-diazoketone with an electron-rich alkene such as ethyl vinyl ether is a cyclopropylketone. The donnor–acceptor substitution pattern of this intermediate results in spontaneous rearrangement to a dihydrofuran. Thus a direct dipolar cycloaddition mechanism is not involved when α-diazoketones react with enol ethers under metal-mediated conditions. Instead, these reactions follow a cyclopropanation rearrangement or, more accurately, cyclopropanation – ring opening – cyclization pathway.

Key words: diazoketone, rhodium acetate, dihydrofuran, cyclopropylketone, vinyl ether.

Résumé : On a synthétisé une série d'α-diazocétones **8**, **25**, **28**, **31** et **34** et on a étudié, dans différentes conditions, leur réaction avec l'éther éthylvinylique. En présence de sels métalliques ($RH_2(OAc)_4$, $Pd(OAC)_2$, CuCl) on obtient les éthoxydihydrofurannes **12**, **37**, **39**, **41** et **43**. L'irradiation sensibilisée de l'α-diazocétones **8** produit le dihydrofuranne **12** et la cyclobutanone **7**, tandis que la photolyse directe des α-diazocétones **8**, **25**, **28**, **31** et **34** donne les cyclobutanones **7**, **38**, **40**, **42** et **44** respectivement. On a isolé un échantillon de cyclopropylcétone **45** de la réaction du composé **34** en présence de l'acétate de rhodium et on démontre sa transposition facile en dihydrofuranne **43**. Collectivement, ces résultats indiquent que le produit initial de la réaction d'une α-diazocétone avec un alcène riche en électrons tel l'éther éthylvinylique est une cyclopropylcétone. Le modèle de substitution donneur–accepteur de cet intermédiaire provient d'une transposition spontanée en dihydrofuranne. Ainsi un mécanisme de cycloaddition dipolaire directe n'est pas impliqué lorsque une α-diazocétone réagit avec des éthers énoliques en présence d'un métal. Au lieu de cela ces réactions suivent une transposition cyclopropanique ou plus précisément un processus de cyclopropanation, d'ouverture du cycle du cyclopropane et de cyclisation.

Mots clés : diazocétone, acétate de rhodium, dihydrofuranne, cyclopropylcétone, éther vinylique.

[Traduit par la rédaction]

Introduction

Motivated by our interest in the total synthesis of the potent anti-tumor agent paclitaxel (Taxol®) (1) we initially envisaged a strategy that depended upon the successful application of an α-cyclopropyl radical ring opening – conjugate addition sequence (**1**–**3**, Scheme 1) for the construction of the congested tricyclo[9.3.1.$0^{3,8}$]pentadecene nucleus. This ring opening should install both the bridgehead double bond at C_{11}—C_{12} and generate a radical center in a relatively flat precursor suitably disposed to add in an 8-*endo* fashion to a ring C enone (2). We therefore required precursors that would give rise to a radical intermediate of type **A** (Scheme 2) in order to examine this strategy.

Initial results

A variety of standard Simmons–Smith based methods for cyclopropanation of appropriately substituted olefins to generate systems related to **A** were unsuccessful. Thus a different approach was investigated. The α-diazoketone **8** was synthesized from the cyclohexenone **4** (1*d*) as follows. Conjugate addition of lithium dimethylcuprate generated the enolate, which reacted in situ with ethyl formate to provide the ketone **5**. Diazo transfer was effected with tosylazide and triethylamine followed by treatment with potassium hydroxide to generate the α-diazoketone **8**. It was anticipated that treatment of this material with rhodium(II) acetate in the presence of ethyl vinyl ether would afford the requisite spiro cyclopropyl system **9**. However, treatment of **8** with $Rh_2(OAc)_4$ (2 mol %, 21°C) in the presence of excess ethyl vinyl ether afforded neither the expected cyclopropylcyclohexanone **9** nor the cyclobutanone **7** that would have arisen from Wolff rearrangement of **8** to the ketene **10** followed by conventional [2+2] cycloaddition. Instead, a new compound was isolated, whose spectra

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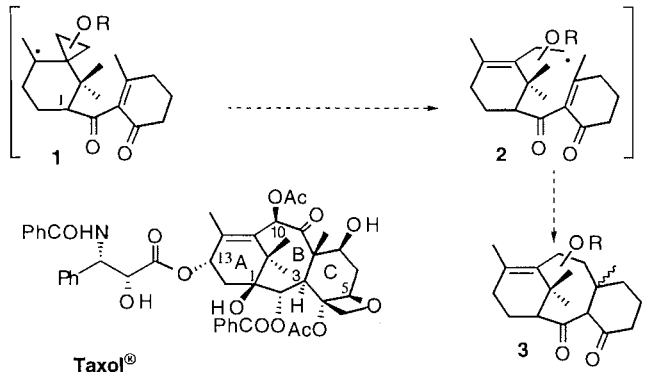
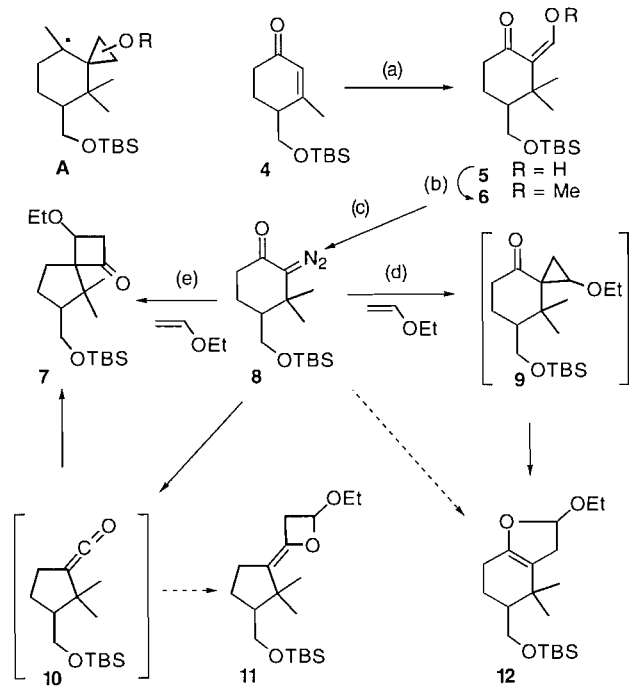
Scheme 1. Potential radical rearrangement – conjugate addition route to taxanes.



Scheme 2. Synthesis and reaction pathways for α-diazoketone **8**.

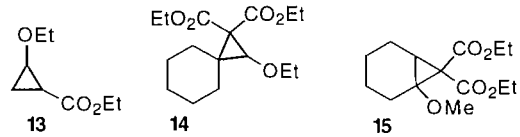


(a) Me_2CuLi, ether, 0 °C, 1.5 h, HCO_2Et, 0.5 h, 20%; (b) CH_2N_2, ether, 21 °C, 3 h, 83%; (c) Et_3N, TsN_3, CH_2Cl_2, -15 to 21 °C, 2 h; KOH (aq), 15 min; 20%; (d) $Rh_2(OAc)_4$ (cat), ether, $CH_2C{=}HOEt$, syringe pump, 21 °C, 4 h, 70%; (e) hv, $CH_2{=}CHOEt$, 2.5 h, 88%.

suggested the presence of two tertiary vinyl carbons (^{13}C NMR δ 102.4, 148.3 ppm) and an acetal carbon (δ 104.6 ppm) with an attached proton (^1H NMR δ 5.45 ppm). These features were consistent with both the oxetane structure **11** and the dihydrofuran system **12**. The oxetane could arise from the formal [2+2] addition of ethyl vinyl ether to the carbonyl group of the ketene **10**, while the dihydrofuran **12** could have been formed directly from a dipolar cycloaddition to ethyl vinyl ether or alternatively could have arisen from a ring opening – rearrangement – ring closure of the intermediate cyclopropyl ketone **9**. In spite of the visual difference between these two ring systems, various NMR experiments were inconclusive.

In addition, standard acid hydrolysis and oxidative cleavage

Scheme 3. Carbonyl-ether substituted cyclopropanes.



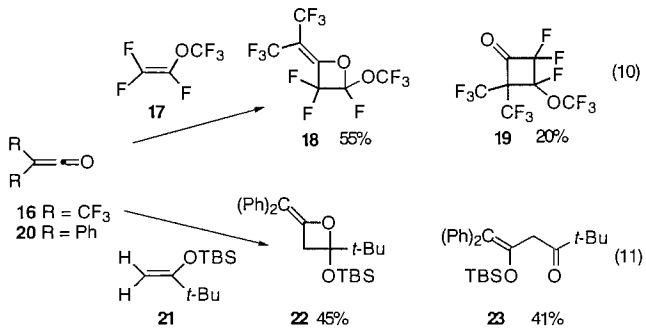
reactions (ozone, RuO_4) gave mixtures that did not permit a definitive structural assignment with only one compound available. As described below, the structures of **12** and related dihydrofurans were ultimately established by acid-catalyzed hydrolysis and in situ trapping to form a new keto-acetal. However, based on additional studies with related α-diazoketone systems, it is now clear that with electron-rich olefins such as ethyl vinyl ether, cyclopropylketones are formed initially but do not survive the standard reaction work-up at room temperature (21°C), and rapidly rearrange to dihydrofurans related to **12**. Thus, in contrast to literature examples that invoke dipolar cycloaddition mechanisms to rationalize dihydrofuran formation, with cyclopropanes containing both electron-donating and -withdrawing substituents the normal mechanism involves cyclopropanation followed by rearrangement (ring opening – cyclization) to afford the cyclic ethers (3).

Background

Donor–acceptor (push–pull) cyclopropanes have received considerable attention (4). Generally cyclopropanes with a single electron-donating and an electron-withdrawing group (e.g., 1-ethoxy-2-carboethoxycyclopropane, **13**) are stable at room temperature and require more forcing conditions for rearrangement to a dihydrofuran acetal, although cyclopropyl β-amino acids ring open readily, indicating the donating ability of the donor is a key feature (Scheme 3). Thus, for oxygen-substituted systems direct rearrangement usually requires either two donor or two acceptor groups. The ease with which the initial cyclopropane undergoes a 1,3-sigmatropic shift is therefore both substituent and substrate dependent (4). For example, the spirosystem **14** may be isolated, but the related cyclopropane **15** was not detected when dimethyl diazomalonate reacted in the presence of copper with 1-methoxycyclohexene (5). Other methoxy cyclopropanes also rearranged more readily than the corresponding ethoxy-substituted derivatives (6). However, the reaction conditions markedly influence the course of diazocarbonyl rearrangements, particularly solvent polarity (pentane versus CH_2Cl_2) (7) and the catalyst ($Rh_2(OAc)_4$ versus $Rh_2(OPiv)_4$) (8). Cyclopropanes were the presumed intermediates generated from cyclic β-diazodiketones in the presence of furans and rhodium carboxylate salts (9).

Discrete ketene carbonyl cycloadditions are rare and have received limited attention. The two previously reported cases involved strong electron-withdrawing groups in the ketene. One case involved the reaction of bis(trifluoromethyl)ketene (**16**) with vinyl ether **17** to give a mixture of the oxetane **18** and the expected [2+2] cycloaddition product **19** (Scheme 4) (10). A related example employed the sterically hindered silyl enol ether of *tert*-butyl methyl ketone (**21**) with diphenylketene (**20**) to provide the oxetane **22** and the ketone **23** from ring opening of the initial cyclobutanone adduct followed by silyl

Scheme 4. Ketene carbonyl cycloadditions.



migration (11). In addition, ab initio molecular orbital calculations have demonstrated that alkene addition to the ketene carbonyl is usually energetically disfavoured relative to cyclobutanone formation (12).

Results

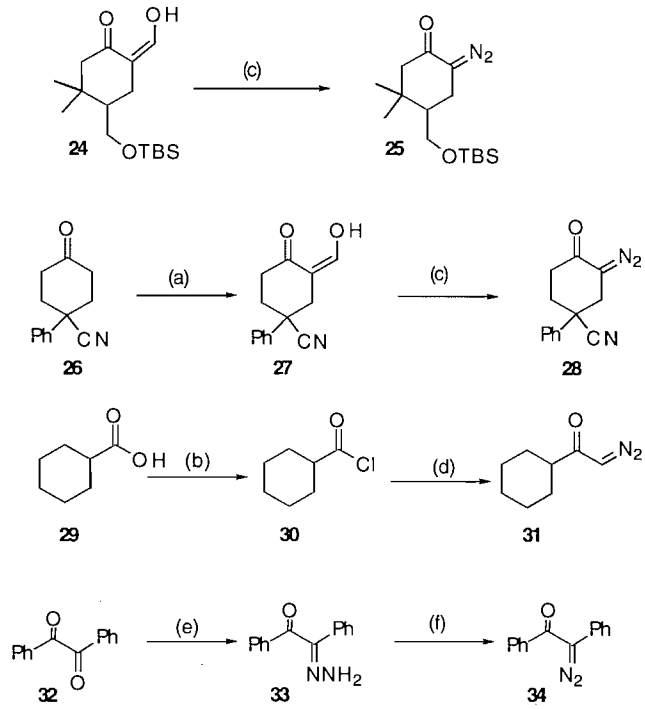
Is the dihydrofuran structure **12** correct, or do the methyl groups in the ketene **10**, derived from Wolff rearrangement of **8**, provide sufficient steric hindrance to alter the normal [2+2] cycloaddition reaction to give the oxetane **11** rather than the cyclobutanone **7**?

To learn more about the reactivity of the α-diazoketone **8**, other metal salts ($Pd(OAc)_2$, CuCl) were examined as well as its photolytic behaviour. In addition, other diazo ketones **25**, **28**, **31**, and **34** with various substitution patterns were synthesized (Scheme 5) and subjected to a parallel set of conditions. The initial enolate, derived from the conjugate addition of lithium dimethylcuprate to **4**, underwent rapid proton transfer to the sterically less hindered enolate when allowed to warm to 21°C, so that condensation with ethyl formate afforded the keto-aldehyde **24** directly. Diazo transfer as above generated the α-diazoketone **25**. Parallel reactions afforded **28** from **26**, while **31** was synthesized by treatment of acyl chloride **30** with diazomethane. The diphenyl system **34** (azibenzil, 2-diazo-1,2-diphenyl-1-ethanone) was prepared by silver oxide oxidation of **33** (13).

The results of the catalytic reactions and the irradiation experiments are summarized in Table 1. In the case of **8**, the major product from the metal-catalyzed reaction with ethyl vinyl ether was the dihydrofuran **12**, although the yield varied with the catalyst selected. Thus the reactions with $Pd(OAc)_2$ or CuCl afforded **12** in isolated yields of 72% and 30%, respectively. However, when standard alkenes, rather than electron-rich olefins, were used, the dihydrofuran products were not observed. Instead, cyclopropylketone **35** was isolated in 25% yield in the rhodium(II) acetate catalyzed reaction with 2,5-dihydrofuran in place of ethyl vinyl ether (Scheme 6). In a similar manner, addition to cyclohexene afforded **36** (25%). Clearly the methyl groups are not a major factor as the other α-diazoketones listed in Table 1 also afforded acetal products. In all cases direct irradiation generated the [2+2] cycloaddition products illustrated, which arise from Wolff rearrangement to the ketene followed by conventional cycloaddition.

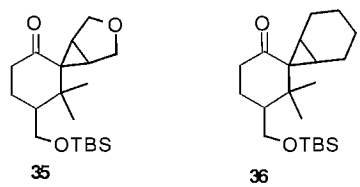
The dihydrofuran-acetal structures observed above in the metal-catalyzed reactions of the various α-diazoketones

Scheme 5. Synthesis of α-diazoketone substrates.



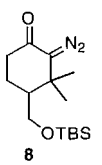
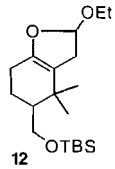
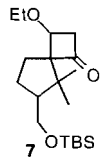
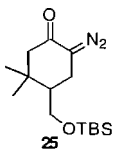
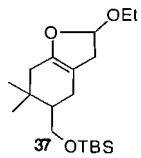
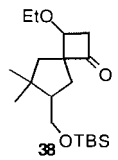
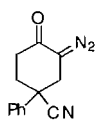
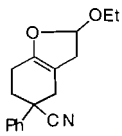
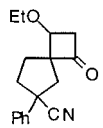
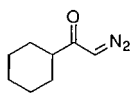
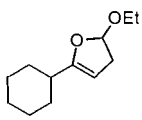
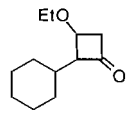
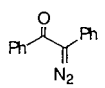
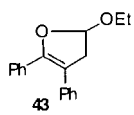
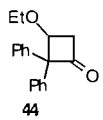
(a) NaH, ether, HCO_2Et; (b) $(COCl)_2$, C_6H_6, 21 °C, 97%; (c) Et_3N, TsN_3, CH_2Cl_2, -15 to 21 °C, 2 h; KOH (aq), 15 min; 40-70% (d) CH_2N_2, ether, 0 °C, 95%; (e) ref 13; (f) Ag_2O, THF, 67 °C, 5 h, 84%.

Scheme 6. Cyclopropane products with standard alkenes.



require additional experimental data to establish their structures unambiguously. To ascertain the decomposition pathways of these systems, the model system azibenzil (**34**) was examined in detail, particularly its behaviour with ethyl vinyl ether and rhodium(II) acetate. Direct pathways to the dihydrofuran **43** or the oxetane **48** from the α-diazoketone **34** (Scheme 7) are feasible after initial reaction of the carbenoid intermediate. Both of these products may arise from zwitterionic intermediates such as **46** or **47** that possess both enolate and oxacarbenium ion character. Surprisingly, the acetal product from the reaction could not be established from its spectral data. High-resolution mass spectroscopy confirmed the molecular formula ($C_{18}H_{18}O_2$). Both structures contain an equal number of CH, CH_2, CH_3, and quaternary carbons plus one methine attached directly to two ether oxygens, two methylene groups, and the methyl group of an ethoxy substituent. Unfortunately two-dimensional ^1H–^1H COSY, ^1H–^1H ROESY, and ^1H–^{13}C HETCOR experiments were inconclusive. A ^{13}C–^{13}C coupling INADEQUATE experiment should have allowed differentiation of the two different olefin substitution patterns, but the olefin carbon atoms had long relaxation

Table 1. Metal-catalyzed and photochemical reactions of α-diazoketones in ethyl vinyl ether.

Diazo ketone	Catalyst	Yield (%)	Dihydrofuran	Photolysis yield (%)	Cyclobutanone
 **8**	$Rh_2(OAc)_4$	70	 **12**	88	 **7**
	$Pd(OAc)_2$	72			
	CuCl	30			
	$h\nu$,Ph_2CO	25		30, Ph_2CO	
 **25**	$Rh_2(OAc)_4$	75	 **37**	88	 **38**
	$Pd(OAc)_2$	72			
	CuCl	35			
 **28**	$Rh_2(OAc)_4$	40	 **39**	60	 **40**
	$Pd(OAc)_2$	36			
	CuCl	10			
 **31**	$Rh_2(OAc)_4$	71	 **41**	88	 **42**
	$Pd(OAc)_2$	37			
 **34**	$Rh_2(OAc)_4$	68	 **43**	77	 **44**
				44, Ph_2CO	

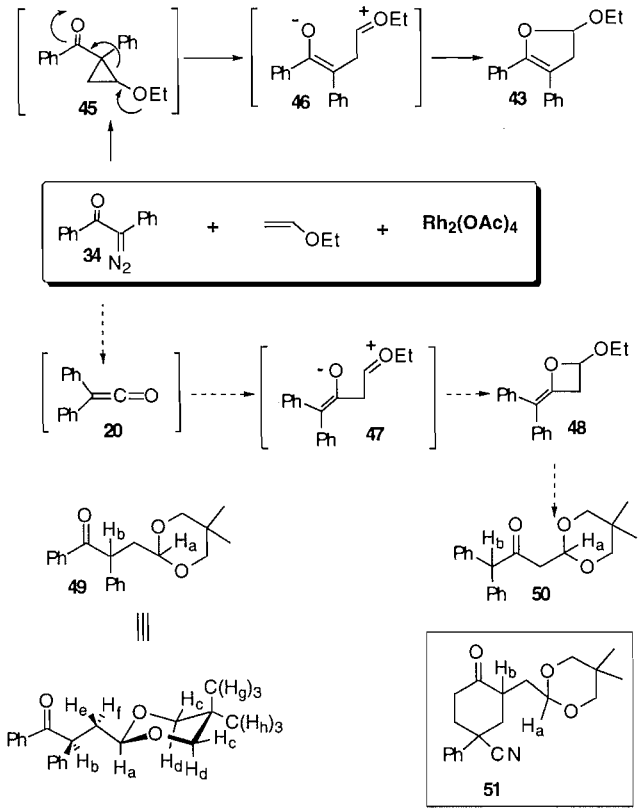
times (approximately 10 s), making it impossible to resolve the structural differences.

To establish the structure unambiguously the acetal product was subjected to acid-catalyzed hydrolysis with in situ trapping of the resulting keto-aldehyde with 2,2-dimethyl-1,3-propanediol. These experiments confirmed the upper pathway was followed (Scheme 7), since treatment of the presumed acetal **43** with *p*-toluenesulfonic acid in the presence of 3,3-dimethyl-1,3-propanediol afforded ketone **49** (68% yield), which could be distinguished from **50** by its ^1H NMR spectrum. The spectrum exhibited a characteristic one-proton doublet of doublets at δ 4.91 ppm (J = 7.8, 7.0 Hz) that was assigned to the acetal proton H_a coupled with each of the diastereotopic methylene protons. A second one-proton doublet of doublets at δ 4.31 ppm (J = 4.9, 5.6 Hz) was assigned to the methine proton H_b adjacent to the carbonyl group. The splitting pattern seen with this signal also arises from independent couplings with each of the diastereotopic methylene protons H_e and H_f. This type of coupling is only possible in structure **49**. Proton H_b in structure **50** has no adjacent carbons bearing protons and would therefore be expected to appear as a singlet in the ^1H NMR spectrum. In a similar manner the dihydrofuran **39** derived from diazoketone **28** afforded the keto-acetal **51** and thus established that the dihydrofurans are the final products of these α-diazoketones upon treatment with various metal catalysts in the presence of ethyl vinyl ether.

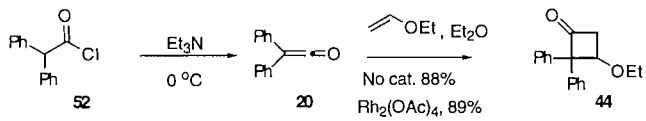
Diphenyl ketene, the putative Wolff rearrangement product from azibenzil (**34**) is relatively stable. It was synthesized independently to determine its reactivity with ethyl vinyl ether and its behaviour in the presence of rhodium(II) acetate and to establish with certainty that neither dihydrofuran **43** nor oxetane **48** were formed from the ketene. Diphenylketene (**20**) was prepared from acid chloride **52** upon treatment with triethylamine (Scheme 8) (14). For the thermal reaction a solution of diphenyl ketene (**20**) and ethyl vinyl ether in freshly distilled ether was stirred overnight under argon. Cyclobutanone **44** was obtained in 88% yield (IR, 1779 cm^{-1}). A metal-ketene intermediate, if formed, does not appear to alter the course of the reaction, as only the cyclobutanone **44** was isolated (89%) in the presence of $Rh_2(OAc)_4$.

The use of benzophenone as a triplet sensitizer during the photolysis of α-diazoketones is known to promote cyclopropane formation (15), although a large excess of sensitizer is required (16). It was anticipated that these conditions would allow detection of the cyclopropane. However, benzophenone (10 equiv.) sensitized photolysis of **8** failed to provide the cyclopropane **9**. A mixture of cyclobutanone **7** (30%) and dihydrofuran **12** (25%) was formed instead (Table 1). This

Scheme 7. Rearrangement pathways for α-diazoketone **34**.



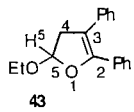
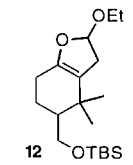
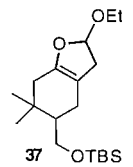
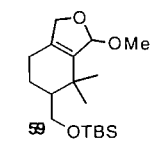
Scheme 8. Diphenylketene cycloadditions.



result was unexpected since Wolff rearrangement is considered to arise only from the singlet carbene (16, 17). Upon direct irradiation, no acetal products could be detected and clean conversion to the cyclobutanone **7** from [2+2] cycloaddition to the ketene double bond was observed. As mentioned above, this same pattern was observed with the other α-diazoketones **25**, **28**, **31**, and **34** to give **38**, **40**, **42**, and **44**, respectively. Decomposition of **8** under various conditions that are known to promote cyclopropanation ($Rh_2(OAc)_4$, pentane/ethyl vinyl ether, 30:1, 0°C; $Rh_2(OPiv)_4$, pentane/ethyl vinyl ether, 30:1, 0°C) (7, 8) also afforded **12** as the major product. A similar result was obtained with $Rh_2(OAc)_4$ in ethyl vinyl ether at −78°C, although immediate GC–MS analysis indicated the presence of a minor component (~10%) consistent with cyclopropylketone **9.**

A final attempt was made to prepare a sample related to **9**, the methoxy cyclopropane **B**, by addition of dimethyloxosulfonium methylide (18) to the enol ether ketone **6**. It was anticipated that conjugate addition would occur in accord with literature precedent (18, 19) to generate the methoxy cyclopropanone **B**. However, the product was a new methoxydihydrofuran system that differed from the dihydrofuran **12** by more than the substitution pattern. The ^1H NMR signal at δ 5.55 and

Table 2. NMR data for dihydrofurans.

Compound	δ H5 (ppm)	δ C2 (ppm)	δ C3 (ppm)
 43	5.62 (dd, J = 7.2, 2.6 Hz)	148.2	102.6
 12	5.45 (m)	148.3	102.4
 37	5.45 (m)	147.3	102.4
 59	5.55	148.2	113.2

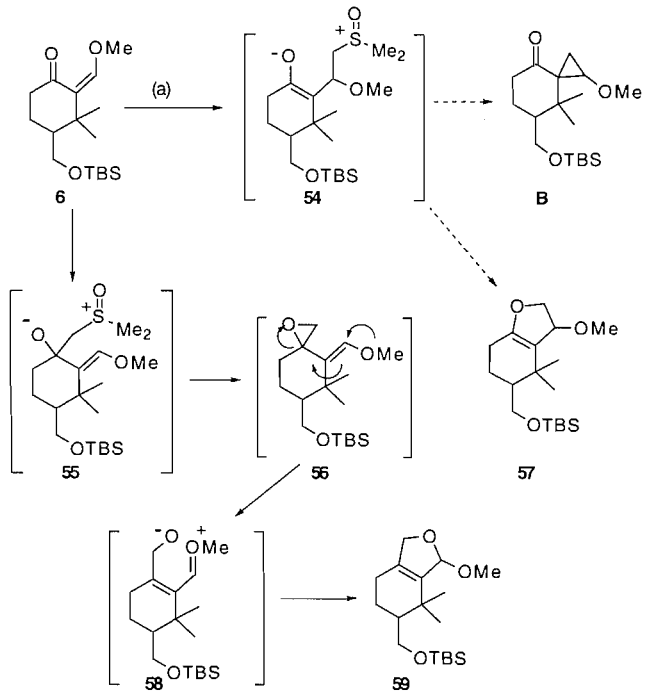
the olefinic carbon signals at δ 113.2 and 148.0 did not fit the chemical shift pattern observed for the other isomers, as tabulated in Table 2. In addition, it was not the product **57** from closure of the oxygen anion on the sulfinyl bearing carbon. In contrast to literature examples, the ylide adds preferentially to the carbonyl group, possibly as a consequence of the steric interference of the geminal dimethyl groups. Closure of **55** should afford the epoxide **56**, but this material was not detected. Instead it opens in a similar manner to the cyclopropanes to generate a dipolar zwitterionic species **58**, which collapses to give the observed product **59** (Scheme 9).

Discussion

The experiments above have established that the major product isolated from the reaction of structurally diverse α-diazoketones in the presence of rhodium(II) acetate and related catalysts with an electron-rich olefin such as ethyl vinyl ether is a dihydrofuran. There are two possible mechanisms for this process. The dihydrofuran may arise from a concerted or stepwise dipolar cycloaddition to the enol ether or, alternatively, the ethoxy-substituted cyclopropylketone is a true intermediate that undergoes rapid fragmentation and subsequent ring closure to the dihydrofuran.

Doyle et al. (20) have examined cyclopropanations with ethyl diazoacetate. The regio- and stereochemical control in catalytic cyclopropanation reactions is derived from the transition metal, its associated ligands, the diazo compound, and the olefin. The influence of the olefin is the weakest, while the electronic influence of the transition metal provides the dominant regio- and stereochemical control. Studies with chiral catalysts confirmed (21–24) that the transition metal is directly involved in the product-forming step. The more stable *trans* cyclopropanes usually predominate and the stereoselec-

Scheme 9. Attempted synthesis of cyclopropylketone **B**.

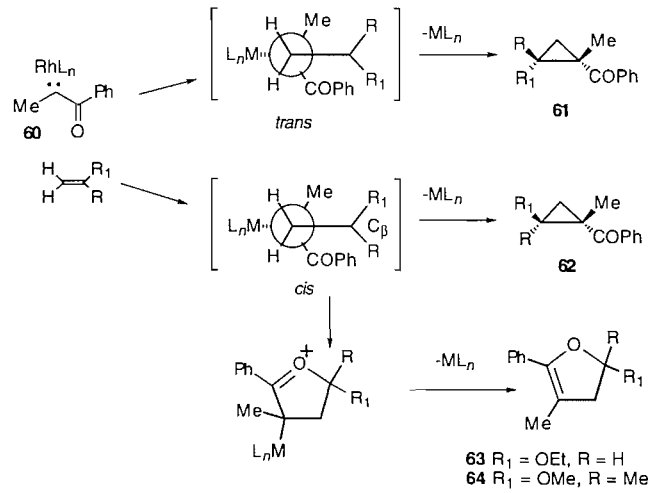


(a) Me_2SOCH_3I, NaH, DMF, 21 °C, 2h, 40%

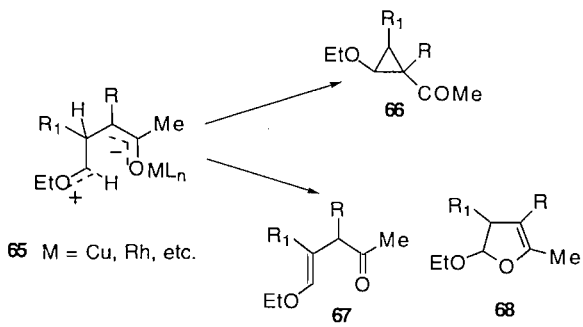
tivities are not altered by the catalyst concentration, the rate of addition of the diazo compound, or the molar ratio of olefin to diazo compound. The cyclopropanation process was proposed by Doyle et al. (6, 20, 25) to occur through an initial interaction between the olefinic π bond and the electrophilic centre of the metal carbenoid, followed by σ-bond formation with backside displacement of the catalyst (Scheme 10). As the reaction proceeds the π-complexed olefin may rotate around the electrophilic centre to place the C—C bond of the olefin parallel to the metal–carbon bond. Thus the substituted carbon of the olefin is oriented *anti* to the metal. Two transition states, *trans* and *cis*, are possible in which the energy difference due to the interactions between R/R_1 and COPh determines the predominant isomer **61** or **62**. A study by Noels, Hubert, and co-workers supports the existence of a free carbene–carbenoid equilibrium (26).

The product distribution is influenced by an increase in the nucleophilicity of the carbonyl oxygen and (or) the electrophilicity of the β-carbon in the metaloid complex. This favours the dihydrofuran products as a consequence of the increased stabilization provided by both the carbonyl group and the developing electrophilic centre on the vinyl ether (Scheme 10). Due to the absence of an ether oxygen this stabilization is less with a standard olefin. This influence is usually only observed with α-diazoketones, as α-diazoesters are less nucleophilic. Dihydrofurans have also been obtained from copper-catalyzed reactions of diazomalonates and related diazoketones with various vinyl ethers (27, 28). These subtle effects are illustrated by the finding that dihydrofuran **63** (9%) was the minor product (cyclopropane 83%) in the $Rh_2(OAc)_4$ catalyzed reaction of α-diazopropiophenone (**60**) with ethyl vinyl ether, but **64** was the major product (40%) with 2-methoxypropene (6).

Scheme 10. Possible combined cyclopropanation–dihydrofuran mechanism.



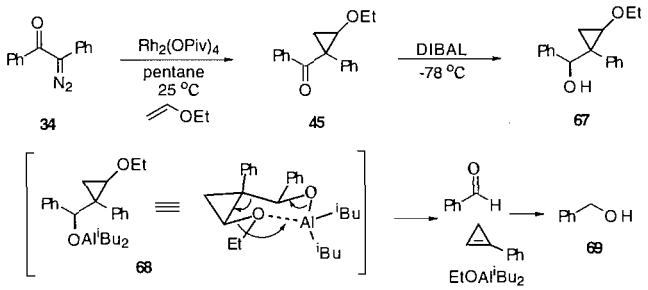
Scheme 11. Possible dipolar mechanism for dihydrofuran formation.



Alonso et al. (27) suggested a direct dipolar mechanism to explain the formation of dihydrofuran and acyclic products from various cyclopropanation reactions (Scheme 11) (27, 29). The dipolar intermediate **65** was proposed as the precursor to both the acyclic **67** and dihydrofuran **68** products. In this case, 1,3 ring closure to **66** is disfavoured with respect to the 1,5 ring closure. The stabilization of the dipolar intermediate is consistent with Doyle's mechanism where an increase in the nucleophilicity of the enolate oxygen increases the ease of 1,5-cyclization compared to 1,3-cyclization (6).

Variation of the catalyst ligands and solvent polarity has a significant effect on the outcome of rhodium(II) carboxylate catalyzed cyclopropanation reactions (7, 8, 30). Padwa, Doyle, and co-workers have established that the products that may arise from a dipolar mechanism are inhibited in pentane relative to dichloromethane (30). Competition experiments between cyclopropanation and bond insertion (tertiary C—H) provided a 44:56 product ratio with $Rh_2(OAc)_4$. More electrophilic metal carbenoids (perfluoroborate ligands) resulted in hydrogen insertion exclusively. In contrast, only cyclopropanation products were obtained with the less electrophilic rhodium(II) caprolactamate catalyst, which suppresses the carbene insertion into the C—H bond. Cyclopropanation is enhanced relative to dihydrofuran formation with rhodium(II) pivalate as catalyst (31, 32). Thus azibenzil (**34**) and ethyl vinyl ether

Scheme 12. Reduction of cyclopropylketone **45**.



were treated with $Rh_2(OAc)_4$ in ether and pentane in separate experiments to provide the dihydrofuran **43** in yields of 97% and 91%. However, unexpectedly, the use of rhodium pivalate also gave the same product **43** (93%) in each case.

Dowd et al. (33) found that $Rh_2(OAc)_4$ catalyzed reactions of ketene acetals with methyl diazoacetate yielded unstable cyclopropyl esters that were reacted in situ with lithium aluminum hydride, albeit in low yield. They concluded that with diazoacetone the cyclopropylketone was too reactive to be isolated and probably rearranged through a dipolar intermediate to yield a small amount of a dihydrofuran product.

It is standard practice to purify reaction products prior to spectroscopy by filtration and chromatography. To discern the influence of the work-up conditions on the presumed cyclopropylketone intermediates the following experiments were conducted. Reactions with **34** were conducted separately with $Rh_2(OAc)_4$–ether and $Rh_2(OPiv)_4$–pentane, excess solvent was evaporated under a stream of argon, and the crude material was dissolved in $CDCl_3$ (which had been passed through basic alumina immediately prior to use). The ^1H NMR spectrum of this material displayed the characteristic cyclopropane signals expected at δ 0.6–0.9 ppm and a ^{13}C NMR signal at δ 194.5 ppm. In addition, an IR absorption at 1675 cm^{-1} was consistent with the cyclopropyl ketone **45**. Storage at −15°C (24 h) or further purification resulted in complete conversion to dihydrofuran **43**. A further attempt was made to detect the cyclopropylketone by in situ reduction with DIBAL at −78°C (Scheme 12). GC–MS analysis of the red reaction solution indicated a new compound (23%) had been formed with a mass corresponding to that of cyclopropanol **67** (*m/z* 268). Aqueous work-up and chromatography afforded dihydrofuran **43** plus benzyl alcohol (**69**), which appears to result from a Grob-type fragmentation (34) to generate benzaldehyde from the intermediate aluminate **68** followed by further reduction (Scheme 12).

Conclusions

The results of the acetal hydrolysis trapping experiments, together with the spectroscopic evidence for the formation of cyclopropane **45**, indicate that dihydrofuran **43** is not formed by either a direct concerted or a stepwise mechanistic pathway involving a dipolar cycloaddition. Rather the dihydrofuran arises from a facile rearrangement of the initially formed cyclopropane due to its donor–acceptor substitution pattern. This conclusion finds support in related metal-catalyzed systems (27) in which cyclopropanation of enol ethers or ketene acetals is followed by rearrangement as the preferred pathway (6, 35, 36). In addition, mild oxidation of 1-hydroxymethyl-2-ethoxycyclopropane to the corresponding ethoxy-aldehyde resulted in spontaneous rearrangement to a dihydrofuran (37). In the case of vinyl diazoester addition to vinyl ethers ($Rh_2(OAc_4)$, the initial vinyl cyclopropanes undergo a Et_2AlCl catalyzed rearrangement to cyclopentenes (36). Over 35 years ago D'Yakonov and Komendantov concluded that furans arose from copper-catalyzed cyclopropanations with ethyl diazoacetate and acetylenes by rearrangement of the initial cyclopropene (38). By analogy, the same conclusion can be extended to the other α-diazoketones in this study with ethyl vinyl ether. Indeed the majority of alkene–diazocarbonyl combinations produce cyclopropanes in good yields with standard alkenes. Only when the "electronics" of both the reacting partners are "tuned" to stabilize a dipolar intermediate due to their donor–acceptor or push–pull properties, are appreciable amounts of dihydrofuran formed (6, 8, 31, 33, 37).

Thus, in keeping with current knowledge, it is reasonable to suggest that the α-diazoketone initially forms a metal carbenoid intermediate, which adds to the olefin to form an α-cyclopropylketone. In the majority of cases with a standard olefin, the stable cyclopropane product is isolated. However, with electron-rich enol ethers the electronic substitution pattern precipitates further rearrangement, resulting in ring opening and subsequent cyclization to afford the observed dihydrofurans. In these cases, exposure to most purification conditions (filtration through a plug of Celite®, TLC, or standing at −10 to −15°C, ~24 h) assists the rearrangement. Variation in the polarity of the reaction medium has no significant effect on the outcome of the reaction, and it is therefore unlikely that a dipolar-type mechanism, as illustrated in Schemes 10 and 11, is involved. Thus, we favour the intermediacy of the cyclopropane in the majority of literature examples that involve electron-rich alkenes. Therefore, a common mechanism should be applied to most metal-catalyzed α-diazoketone cyclopropanations with all olefins. The product distribution reflects, in large measure, the relative stability of the three-membered ring system and its substitution pattern. Consistent with this conclusion, the literature experimental data are (naturally) not reported on crude reaction products before the dihydrofurans are formed but after purification, by which time, in most cases, the primary donor–acceptor substituted cyclopropanes have rearranged by ring opening and subsequent cyclization (Scheme 7). This implies that much of the mechanistic work and corresponding conclusions compiled to date concerned with cyclopropanation – dihydrofuran formation would benefit from further study under controlled, neutral conditions.

In summary, spontaneous dihydrofuran formation from α-diazoketones usually requires diactivated cyclopropyl carbonyl systems. This mild route from cyclic α-diazoketones via monoactivated cyclopropyl ketones provides an attractive sequence to generate compounds for further synthetic manipulation in view of the widespread occurrence of five-membered oxygen-containing heterocyclic ring systems in nature (39).[2]

Finally, it would be beneficial to have a standard, recognized nomenclature to describe this rhodium(II) mediated cyclopropanation–rearrangement process to afford dihydro-

[2] For a spiro-dihydrobenzofuran system see ref. 39*c*.

furans. This conversion has a formal resemblance to a dipolar cycloaddition. For example, in a nice synthesis of aflatoxin B_2, the intermolecular addition of an α-diazodiketone to 2,3-dihydrofuran via a cyclopropanation–rearrangement sequence is described as a "rhodium carbenoid dipolar cycloaddition", a "rhodium-mediated dipolar cycloaddition", or "the formal dipolar cycloaddition of cyclic diazodicarbonyl compounds with vinyl ethers mediated by dirhodium catalysts" (40). Clearly a cycloaddition is an addition reaction that forms a ring; however, this term also has mechanistic implications implying the reaction is either of a pericyclic or dipolar nature. In the present context these dihydrofuran-forming reactions may be characterized as a sequence involving a metal carbenoid or metal-mediated cyclopropanation – ring opening – cyclization pathway in which the cyclopropane cleavage step is similar to a Grob-type fragmentation,[3] which affords a dipolar intermediate that closes to the dihydrofuran.

Experimental (see ref. 1*d* for general procedures)

2-Formyl-3,3-dimethyl-4-*tert*-butyldimethylsilyloxymethylcyclohexanone (5)

Copper(I) iodide (3.80 g, 20 mmol) suspended in ether (200 mL) was cooled to 0°C and methyllithium (28.6 mL, 40 mmol) was added to the stirred suspension. After stirring for 15 min, an ether solution of the enone **4** (1*d*) (2.56 g, 20 mmol) was added dropwise over 10 min. After 90 min, ethyl formate (9 mL) was added and, after a further 20 min at 0°C, the reaction was poured into aqueous 10% NH_4Cl solution (150 mL). The organic layer was washed (3×) with dilute aqueous 1% HCl solution, dried, and concentrated. Chromatography (ethyl acetate/petroleum ether; 1:20) gave **5** (0.64 g, 20%). ^{1}H NMR (200 MHz) δ: 0.03 (s, 6H), 0.90 (s, 9H), 1.11 (s, 3H), 1.30 (s, 3H), 1.55 (m, 2H), 1.95 (m, 1H), 2.40 (m, 2H), 3.42 (dd, 1H, J = 8.4, 5.3 Hz), 3.83 (dd, 1H, J = 4.3, 8.7 Hz), 8.90 (d, 1H, J = 3.2 Hz), 15.22 (d, 1H, J = 3.2 Hz); ^{13}C (50.3 MHz) δ: 188.3, 185.6, 117.9, 62.5, 46.0, 33.3, 30.2, 29.0, 25.6, 19.9, 18.0, −5.7; HRMS calcd. for $C_{12}H_{21}O_3Si$ ($M^+ - C_4H_9$): 241.1259; found: 241.1252.

2-Formyl-5,5-dimethyl-4-*tert*-butyldimethylsilyloxymethylcyclohexanone (24)

This compound was a component of the reaction above and was prepared selectively when the reaction was allowed to warm to 21°C prior to adding the ethyl formate. After a further 4 h, work-up as above afforded **24** (2.5 g, 78%). ^{1}H NMR (200 MHz) δ: 0.02 (s, 6H), 0.85 (s, 12H), 0.98 (s, 3H), 1.55 (m, 1H), 2.09 (d, 2H, J = 11.4 Hz), 2.51 (dd, 1H, J = 5.8, 15.7 Hz), 3.41 (dd, 1H, J = 8.4, 5.3 Hz), 3.75 (dd, 1H, J = 4.3, 8.7 Hz), 8.73 (d, 1H, J = 1.6 Hz), 15.0 (d, 1H, J = 1.6 Hz); ^{13}C (50.3 MHz) δ: 188.3, 185.6, 117.9, 62.5, 46.0, 33.3, 30.2, 29.0, 25.6, 19.9, 18.0, −5.7. HRMS calcd. for $C_{12}H_{21}O_3Si$ ($M^+ - C_4H_9$): 241.1259; found: 241.1254.

2-(Methoxymethylidene)-3,3-dimethyl-4-*tert*-butyldimethylsilyloxymethylcyclohexanone (6)

Treatment of **5** (200 mg, 0.067 mmol) in ether (1 mL) at 22°C with excess diazomethane (prepared from *N*-nitrosomethylurea) in ether afforded **6** directly. Concentration followed by chromatography (20% acetone – petroleum ether) gave the product **6** (174 mg, 83%). ^{1}H NMR (acetone-d_6) (200 MHz) δ: 0.08 (s, 6H), 0.90 (s, 9H), 1.11 (s, 3H), 1.34 (s, 3H), 1.56–2.32 (m, 5H), 3.50 (dd, 1H, J = 8.15, 10 Hz), 3.85–3.92 (m, 4H), 7.22 (s, 1H); ^{13}C (50.3 MHz) δ: 201.8, 160.6, 123.5, 62.7, 61.9, 47.8, 37.1, 36, 26.9, 25.8, 21.1, 20.7, 18.2, −5.4; HRMS calcd. for $C_{13}H_{23}O_3$ ($M^+ - C_4H_9$): 255.1416; found: 255.1409.

2-Diazo-3,3-dimethyl-4-*tert*-butyldimethylsilyloxymethylcyclohexanone (8)

Standard diazo transfer procedure

2-Formyl-3,3-dimethyl-4-*tert*-butyldimethylsilyloxymethylcyclohexanone (**5**) (3.6 g, 12 mmol) was dissolved in dichloromethane (25 mL) and freshly distilled triethylamine (3.37 mL, 0.024 mmol) was added. The solution was cooled in an external ice–salt bath (−10°C) and *p*-toluenesulfonyl azide (1.8 g, 10 mmol, prepared from *p*-toluenesulfonyl chloride and sodium azide) was added with vigorous stirring over a period of approximately 1 h. Stirring was continued for an additional 2 h as temperature rose to 0°C. A solution of KOH (0.672 g, 12 mmol) in water (25 mL) was added and the mixture was stirred at 21°C for 15 min. The resulting emulsion was placed in a separatory funnel (100 mL), the dichloromethane layer separated, and the aqueous layer extracted twice with dichloromethane (5 mL). The combined dichloromethane extracts were washed with aqueous KOH solution (0.05 g in 15 mL water), water, and dried. Concentration and chromatography (5% ethyl acetate – petroleum ether) gave the product in 20% yield from **4**. IR (neat): 2100, 1740 cm^{-1}; ^{1}H NMR (200 MHz) δ: 3.85 (dd, 1H, J = 10.0, 4.4 Hz) 3.54 (dd, 1H, J = 10.0, 7.5 Hz), 2.41 (m, 2H), 2.1 (m, 1H), 1.71 (m, 2H), 1.39 (s, 3H), 11.17 (s, 3H), 0.93 (s, 9H), 0.1 (s, 6H); ^{13}C (50.3 MHz) δ: 193.9, 62.5, 62.2, 51.4, 44.2, 32.6, 28.4, 25.6, 22.3, 17.9, −5.8; HRMS calcd. for $C_{15}H_{28}O_2Si$: 268.1858; found: 268.1865.

2-Diazo-4-(*tert*-butyldimethylsilyloxy)methyl-5,5-dimethylcyclohexanone (25)

70% yield from **24**. IR (neat): 2100, 1740 cm^{-1}; ^{1}H NMR (200 MHz) δ: 3.82 (dd, 1H, J = 10.0, 4.4 Hz), 3.5 (dd, 1H, J = 10.0, 7.5 Hz), 2.85 (m, 1H), 2.60 (m, 1H) 2.08 (s, 2H), 1.68 (m, 1H,), 0.97 (s, 3H), 0.89 (s, 3H), 0.85 (s, 9H), 0.15 (s, 6H); ^{13}C (50.3 MHz) δ: 193.9, 62.5, 62.2, 51.4, 44.2, 32.6, 28.4, 25.6, 22.5, 17.9, −5.8; HRMS calcd. for $C_{15}H_{28}O_2Si$: 268.1858; found: 268.1865.

2-Diazo-4-cyano-4-phenylcyclohexanone (28)

40% yield from the parent ketone **26**. IR (CCl_4) 2238, 2110, 1727 cm^{-1}; ^{1}H NMR (200 MHz) δ: 2.34 (dd, 2 H, J = 8.1, 4.2 Hz), 2.57 (dt, 1 H, J = 18.4, 4.1 Hz), 2.80 (dt, 1 H, J = 18.4, 9.5 Hz), 3.22 (s, 2 H), 7.42 (m, 5 H); ^{13}C (50.3 MHz) δ: 190.4, 137.7, 129.5, 129.0, 125.5, 120.8, 62.5 (C-2), 41.2, 34.3, 33.7, 32.2; MS *m/z*: 225, 197, 168, 154, 141, 129.

2-Diazo-1-cyclohexyl-1-oxoethane (31)

Oxalyl chloride (4.8 mL, 54.6 mmol) was added dropwise to a stirred solution of cyclohexanecarboxylic acid (1 g, 7.8 mmol)

[3] For a Grob-type fragmentation in cyclopropanone acetals see ref. 41.

in benzene (40 mL). Concentration gave the acid chloride (97%), which was reacted directly with an ethereal solution of diazomethane to generate the diazoketone **31** (95%). IR (neat): 2104, 1636 cm^{-1}; ^1H NMR (200 MHz) δ: 1.25 (m, 6H), 1.71 (m, 4H), 5.22 (s, 1H), 2.10 (br, 1H); ^{13}C (50 MHz) δ: 198.5, 29.1, 25.6; HRMS calcd. for $C_8H_{12}N_2O$: 152.0950; found: 152.0942.

2-Diazo-1,2-diphenyl-1-ethanone (34)

A suspension of benzil monohydrazone **33** (2.0 g, 8.92 mmol) in THF (200 mL) was heated at reflux until the mixture became homogeneous. Powdered Ag_2O (2.26 g, 9.75 mmol) was added in small portions over 15 min and the resulting mixture was heated at reflux for 5 h with vigorous stirring. The silver residue was removed by hot filtration (gravity, over Celite®) and washed with two 5 mL portions of THF. The filtrate was concentrated to give ~2 g of oily orange crystals. Recrystallization from pentane yielded 1.66 g (84%) of azibenzil **34** as bright orange crystals, mp 66–67°C (lit. (13*b*) mp 67–67.5°C); IR (KBr pellet): 3051, 2075,1605 cm^{-1}; ^{13}C NMR (50.3 MHz): δ: 182.5, 132.0, 125.9, 125.7, 123.4, 123.1, 122.6, 122.1, 121.5, 120.1 ppm.

2-Formyl-4-cyano-4-phenylcyclohexanone (27)

A stirred mixture of sodium hydride (0.376 g, 12.5 mmol, 80% in mineral oil, Aldrich), anhydrous ether (100 mL), and ethyl alcohol (0.25 mL) was cooled (0°C) and a solution of ketone **26** (2.5 g, 12.5 mmol) and redistilled ethyl formate (1.52 mL, 18.8 mmol) was added dropwise over 1 h. After 66 h, ethanol (1 mL) and water (10 mL) were added and the mixture was poured into a separatory funnel (500 mL). The organic layer was separated, washed with water (5 mL), and the combined aqueous extract was washed with ether (100 mL). The aqueous layer was acidified with 6 N HCl (4 mL) and the mixture extracted twice with ether (30 mL). The combined ether solutions were washed with brine (25 mL), dried, filtered, and concentrated to give the product **27** (2.5 g), which was used directly in the diazo transfer step.

2,2-Dimethyl-3-*tert*-butyldimethylsilyloxymethyl-7-oxa-8-ethoxybicyclo[4.3.0]non-1,6-ene (12)

Standard catalytic procedure

An anhydrous diethyl ether (1.5 mL) solution of α-diazoketone **8** (100 mg, 0.34 mmol) was added over 4 h by syringe pump (Sage model 341A) to a stirred solution (dichloromethane, anhydrous ether, pentane, or benzene) of the catalyst ((1 mg, 4.5 mmol, palladium(II) acetate) or (0.7 mg, 1.7 mmol, rhodium(II) acetate or rhodium(II) pivalate) or (1.7 mg, 16.8 mmol, cuprous chloride)) and excess alkene (1 mL) at room temperature (21°C). The needle of the syringe was placed just below the surface of the reaction solution. Once the addition was complete, the mixture was concentrated, flushed through a small amount of silica gel (70–230 mesh) or Celite®, and reconcentrated. The product was purified by chromatography (5% ethyl acetate – petroleum ether) to give **12** in 70% yield (rhodium(II) acetate). IR (neat): 1100 cm^{-1}; ^1H NMR (200 MHz) δ: 0.15 (s, 6H), 0.85 (s, 9H), 1.05 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 1.27 (s, 3H), 1.71–2.80 (m, 7H), 3.35 (m, 1H), 3.50 (m, 1H), 3.75 (m, 2H), 5.45 (m, 1H); ^{13}C (50.3 MHz) δ: 148.3, 104.6, 102.4, 63.4, 63.2, 45.7, 39.5, 39.4, 32.6, 28.8, 25.7, 23.8, 23.0, 18.0, 15.0, −5.7; DEPT (50.3 MHz) δ: 104.6 (CH), 63.4 (CH_2), 63.2 (CH_2), 45.7 (CH), 39.5 (CH_2), 38.4 (CH_2), 28.8 (CH_3), 25.7 (CH_3), 23.8 (CH_2), 23.0 (CH_3), 15.0 (CH_3), −5.7 (CH_3); HRMS calcd. for $C_{19}H_{36}O_3Si$: 340.2433; found: 340.2433.

4,4-Dimethyl-3-*tert*-butyldimethylsiloxymethyl-7-oxa-8-ethoxybicyclo[4.3.0]non-1,6-ene (37)

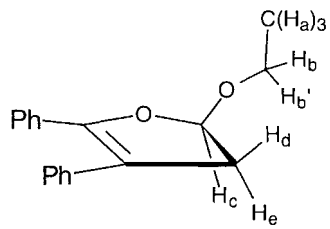
75% yield from diazoketone **25** with rhodium(II) acetate catalyst. IR (neat): 1100 (vs, C-O) cm^{-1}; ^1H NMR (200 MHz) δ: 0.14 (s, 6H), 0.85 (s, 9H), 0.86 (s, 3H), 0.96 (s, 3H), 1.19 (t, 3H, J = 7.1 Hz), 1.70–2.60 (m, 7H), 3.35 (m, 1H), 3.53 (m, 1H), 3.75 (m, 2H), 5.50 (m, 1H); ^{13}C (50.3 MHz) δ: 147.3, 105.0, 102.4, 63.6, 63.2, 45.5, 39.4, 39.2, 31.6, 28.6, 25.5, 23.8, 22.9, 18.0, 15.1, −5.6; HRMS calcd. for $C_{19}H_{36}O_3Si$: 340.2433; found: 340.2425.

3-Cyano-3-phenyl-7-oxa-8-ethoxybicyclo[4.3.0]non-1,6-ene (39)

40% yield from cyclohexanone **27** with rhodium(II) acetate catalyst. IR (CCl_4): 1098, 2241 cm^{-1}; ^1H NMR (200 MHz) δ: 1.23 (t, 3H, J = 7.1 Hz), 2.40 (m, 8H), 3.71 (m, 2H), 5.55 (m, 1H), 7.33 (m, 5H); ^{13}C (50.3 MHz) δ: 149.3, 139.9, 129.0, 102.0, 64.0, 39.3, 35.9, 32.8, 21.2, 14.9; HRMS calcd. for $C_{17}H_{19}NO$: 269.1411; found: 269.1382.

2,3-Diphenyl-5-ethoxy-4,5-dihydrofuran (43)

The $Rh_2(OAc)_4$ catalyzed addition of ethyl vinyl ether to **34** (21°C) (500 mg, 2.25 mmol) followed the general method described above. The ^1H NMR spectrum of the crude product showed no remaining starting material and GC–MS analysis indicated a 97% conversion to the dihydrofuran **43**. Analysis (TLC, silica gel, 20:1 petroleum ether/ethyl acetate) indicated rapid decomposition of the acetal. Dihydrofuran **43** was decomposed on exposure to $CDCl_3$ that had not been passed through basic alumina immediately prior to use. A purified sample was obtained by flash chromatography (20:1, hexanes/ether) to give **43** (68%) as a pale yellow oil.



43

43: IR (film, NaCl): 1011, 760, 694 cm^{-1}; ^1H NMR (200 MHz) δ: 7.53–7.10 (m, 10H, aromatic protons), 5.62 (dd, H_c, $J_{c,e}$ = 7.2 Hz, $J_{c,d}$ = 2.6 Hz), 3.97 (dq, H_b, $J_{b,a}$ = 9.6 Hz, $J_{b,b'}$ = 7.1 Hz), 3.66 (dq, $H_{b'}$, $J_{b',a}$ = 9.6 Hz, $J_{b',b}$ = 7.1 Hz), 3.41 (dd, H_e, $J_{e,d}$ = 16.4 Hz, $J_{e,c}$ = 7.2 Hz), 2.93 (dd, H_d, $J_{d,e}$ = 16.4 Hz, $J_{d,c}$ = 2.6 Hz), 1.06 (dd, $3H_a$, $J_{a,b}$ = $J_{a,b'}$ = 9.6 Hz); ^{13}C NMR (50.3 MHz, DEPT) δ: 148.2 (s, Ph(O)*C*=C), 135.1 and 131.7 (s, phenyl *ipso* C), 128.5, 128.2, 128.1, 127.9, 127.5, 126.1 (d, phenyl *C*H), 109.3 (s, C=*C*Ph(CH_2)), 102.6 (d, O*C*HO), 63.7 (t, CCH_2CH(O)(O)), 42.3 (t, OCH_2CH_3), 15.3 (q, CH_2CH_3) ppm; HRMS calcd. for $C_{18}H_{18}O_2$: 266.1307; found: 266.1331.

3,3-Dimethyl-4-*tert*-butyldimethylsilyloxymethyl-2-(spiro-3-oxabicyclo[3.1.0]hexyl)cyclohexanone (35)

The standard reaction with **8** and rhodium(II) acetate with 2,5-dihydrofuran afforded the cyclopropyl product **35** (25%). IR (neat): 1710 cm^{-1}; ^1H NMR (200 MHz) δ: 0.0 (s, 6H), 0.81 (s, 3H), 0.87 (s, 9H), 1.21 (s, 3H), 1.23–1.50 (m, 2H), 1.9 (m, 1H), 2.1–2.7 (m, 4H), 3.31–3.60 (m, 2H), 3.70–3.85 (m, 2H), 4.21 (m, 1H), 4.70 (m, 1H); ^{13}C (50.3 MHz) δ: 210.2, 75.0, 62.7, 54.0, 46.0, 38.5, 36.1, 33.0, 29.5, 26.0, 21.2, 18.0, −6.4; HRMS calcd. for $C_{19}H_{34}O_3Si$ ($M^+ - H_2O$): 320.2099; found: 320.2097.

3,3-Dimethyl-4-*tert*-butyldimethylsilyloxymethyl-2-(spiro[4.1.0]heptanyl)cyclohexanone (36)

The standard reaction with rhodium(II) acetate and **8** plus cyclohexene gave the product **36** in 25% yield. IR (neat): 1710 1093 cm^{-1}; ^1H NMR (200 MHz) δ: 0.04 (s, 6H), 0.88 (s, 12H), 1.03 (s, 3H), 1.06–2.31 (m, 15H), 3.84 (m, 1H); HRMS calcd. for $C_{21}H_{38}O_2Si$: 350.2641; found: 350.2661.

Diphenylketene (20) (ref. 14)

A Schlenk flask (100 mL) containing a solution of diphenyl acyl chloride **52** (4.2 g, 5.64 mmol) in Et_2O (50 mL) was cooled to 0°C. Triethylamine (2.36 mL, 16.9 mmol, 3 equiv.) was added dropwise over 5 min to give a canary-yellow solution. The flask was sealed under argon and placed in the fridge overnight to precipitate $Et_3N{\cdot}HCl$. The salt was removed by filtration through a medium glass frit under an atmosphere of argon. Concentration under vacuum followed by flash vacuum distillation gave **20** as a thick yellow oil (0.91 g, 83%), bp 120–122°C at 0.15 Torr (1 Torr = 133.3 Pa). The distillation must be done rapidly to avoid formation of the ketene dimer. IR (KBr): 1762 cm^{-1}; IR (film, NaCl): 2097 (s) cm^{-1}; ^1H NMR (200 MHz) δ: 7.1–7.8 (m, 10H).

2,2-Diphenyl-3-ethoxycyclobutanone (44)

Standard photolysis procedure

A solution of α-diazoketone **34** (100 mg, 0.45 mmol) in ethyl vinyl ether (5 mL, 52.3 mmol) was placed in an oven-dried quartz tube (15 mm × 120 mm) that had been cooled under a stream of argon. The solution was degassed with dry deoxygenated argon (20 min) and irradiated with a medium-pressure Hanovia mercury lamp for 2.5 h until TLC analysis indicated that the starting material was consumed. Concentration and chromatography (11:1 petroleum ether/ethyl acetate) gave the cyclobutanone **44** (103 mg, 87%). IR (film): 1779 cm^{-1}; ^1H NMR (200 MHz) δ: 7.5–7.1 (m, 10H, aromatic protons), 4.82 (m, 1H), 3.6–3.11 (m, 4H), 1.06 (t, 3H); HRMS calcd. for $C_{18}H_{18}O_2$: 266.1307; found: 266.1316.

*Sensitized photolysis of α-diazoketone **34** with ethyl vinyl ether*

The procedure above was modified by the addition of benzophenone (0.813 g, 4.46 mmol, 10 equiv.) to the solution of α-diazoketone **34** (100 mg, 0.446 mmol) and ethyl vinyl ether (5 mL, 52.3 mmol). The mixture was degassed and irradiated (4.5 h). Concentration and chromatography (11:1 petroleum ether/ethyl acetate) gave 63 mg of cyclobutanone **44** and 8 mg of crude dihydrofuran **43** (7%)). Further radial chromatography (silica gel, 4 mm plates, 20:1 petroleum ether/ethyl acetate) afforded cyclobutanone **44** (52 mg, 44%).

Thermal reaction, no catalyst: Ethyl vinyl ether (246 μL, 2.57 mmol), diphenylketene **20** (200 mg, 1.03 mmol), and freshly distilled ether (25 mL) were placed in a 5 mL round-bottom flask and stirred under argon overnight. The IR of the reaction mixture contained no diphenylketene absorption (2096 cm^{-1}). Excess ethyl vinyl ether was removed under vacuum and the last traces of the ether were removed under a stream of argon. Chromatography (silica gel, 5:1 petroleum ether/ethyl acetate) gave **44** (241 mg (88%) as a bright yellow oil. The less polar product was the dimer of diphenylketene (IR (neat): 1814 (s) cm^{-1}; ^1H NMR (200 MHz) δ: 7.84–7.72 (m, 1.5H), 7.62–7.38 (m, 2H), 7.3–7.1 (m, 1.5H) 7.84–7.10 (m, aromatic protons)).

With catalyst: A solution of diphenylketene **20** (200 mg, 1.03 mmol) and freshly distilled ether (9 mL) was added by syringe pump to a mixture of ethyl vinyl ether (~1 mL, excess) and $Rh_2(OAc)_4$ (9 mg, 2 mol %) over a period of 7 h. The reaction mixture, after column chromatography (silica gel, 5:1 petroleum ether/ethyl acetate), yielded cyclobutanone **44** (206 mg, 89%).

5,5-Dimethyl-3-ethoxy-6-*tert*-butyldimethylsilyloxymethylspiro[3.4]heptan-1-one (7)

Direct photolysis of **8** in ethyl vinyl ether gave **7** in 88% yield. IR (neat): 1780, 1100 cm^{-1}; ^1H NMR (200 MHz) δ: 0.15 (s, 6H), 0.85 (s, 12H), 1.05 (s, 3H), 1.20 (m, 3H), 1.71 (m, 4H), 2.11 (m, 1H), 3.02 (m, 2H), 3.45 (m, 4H), 3.87 (m, 1H); HRMS calcd. for $C_{19}H_{36}O_3Si$: 283.1734; found: 283.1715.

6-Phenyl-6-cyano-3-ethoxyspiro[3.4]heptan-1-one (40)

Direct photolysis of **28** in ethyl vinyl ether gave **40** in 60% yield. IR (CCl_4): 2234, 1779 cm^{-1}; ^1H NMR (200 MHz) δ: 1.23 (m, 3H), 2.52 (m, 6H), 3.19 (m, 2H), 3.63 (m, 2H), 4.11 (m, 1H), 7.34 (m, 5H); HRMS calcd. for $C_{17}H_{19}O_2N$: 269.1411; found: 269.1411.

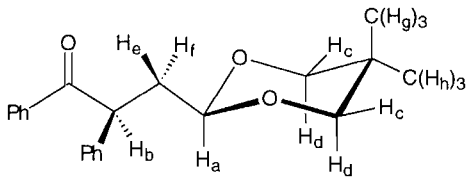
2-Cyclohexyl-3-ethoxycyclobutanone (42)

Direct photolysis of **31** in ethyl vinyl ether gave **42** in 80% yield. IR (neat): 1780 cm^{-1}; ^1H NMR (200 MHz) δ: 1.00 (m, 9H), 1.83 (m, 5H), 2.91 (m, 3H), 3.45 (m, 2H), 4.15 (m, 1H); MS *m/z*: 197, 196, 168, 154, 150, 132, 122, 108, 80, 67.

3,4-Diphenylbutan-4-oxo-(2,2-dimethylpropylenedioxy) acetal (49)

Dihydrofuran **43** (17 mg, 0.064 mmol) and 2,2-dimethyl-1,3-propanediol (20 mg, 0.192 mmol, 3 equiv.) were dissolved in dry benzene (10 mL) and a single crystal of PPTS was added. The mixture was stirred at room temperature until there was no remaining dihydrofuran by TLC analysis. The crude reaction mixture was concentrated and chromatographed (5:1 petroleum ether/ethyl acetate) to give acetal **49** (14 mg, 68%). ^1H NMR (500 MHz, COSY) δ: 8.00–7.98 (m), 7.97–7.20 (m) (10H, phenyl protons), 4.91 (dd, H_a, J = 7.8, 7.0 Hz), 4.31 (dd, H_b, J = 5.6, 4.9 Hz), 3.38 (ddd, $2H_c$, J = 18.8, 10.9, 2.7 Hz), 3.29 (dd, $2H_d$, J = 17.2, 11.0 Hz), 2.60 (ddd, H_e, J = 13.8, 7.9, 5.8 Hz), 2.15 (ddd, H_f, J = 13.8, 6.8, 4.8 Hz), 1.14 (s, $3H_g$), 0.67 (s, $3H_h$); ^{13}C NMR (125 MHz, DEPT) δ: 199.2 (s, C=O),

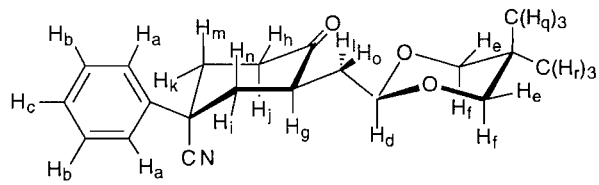
139.0 (s), 136.6 (s), 134.8 (d), 132.7 (d), 129.8 (d), 128.9 (d), 128.9 (d), 128.6 (d), 128.3 (d), 128.2 (d), 127.0 (d), 100.0 (d, C_a), 77.71 (t, $C_{c,d}$), 48.1 (d, C_b), 38.5 (t, $C_{e,f}$), 30.0 (s, $C(CH_3)_2$), 22.9 (q, C_g), 21.7 (q, C_h) ppm; HRMS calcd. for $C_{21}H_{24}O_3$: 324.1726; found: 324.1741.



49

Ethan-2-(4-cyano-4-phenyl-2-ethyl-1-oxocyclohexyl)-2,2-dimethylpropylenedioxy acetal (51)

Compound **39** (18 mg, 0.067 mmol) and 2,2-dimethyl-1,3-propanediol (35 mg, 0.33 mmol, 5 equiv.) were dissolved in anhydrous benzene (4 mL). A single crystal of PPTS was added and the solution was stirred at 21°C for 13 h. Chromatography (5:1 petroleum ether/ethyl acetate) provided **51** (12.3 mg, 56%).



51

51: ^{1}H NMR (500 MHz, COSY) δ: 7.50–7.48 (m, $2H_a$), 7.42–7.39 (m, $2H_b$), 7.36–7.34 (m, H_c), 4.58 (dd, H_d, J = 5.9, 3.9 Hz), 3.56 (dm, 2H, J = 11.3 Hz, H_e), 3.40 (d, 1H, J = 11.3 Hz, H_f), 3.37 (d, 1H, J = 11.3 Hz, H_f'), 3.24 (m, H_g), 2.97 (m, H_h), 2.67 (ddd, H_i, J = 13.6, 5.4, 3.7 Hz), 2.57 (ddd, H_j, J = 14.3, 4.2, 2.5 Hz), 2.450 (m, H_k), 2.32 (ddd, H_l, J = 3.91, 6.14, 14.31 Hz), 2.25 (ddd, H_m, J = 14.0, 14.0, 4.2 Hz), 1.98 (ddd, H_n, J = 13.6, 13.6, 13.6 Hz), 1.45 (ddd, H_o, J = 5.9, 5.9, 14.3 Hz), 1.16 (s, $3H_q$), 0.69 (s, $3H_r$). In ^{1}H–^{1}H decoupling experiments, irradiation of the methine proton at δ 3.24 (H_g) caused the collapse of the following signals: δ 2.67 (H_i) to a dd, J = 13.6, 3.7 Hz; δ 2.32 (H_l) to a dd, J = 14.3, 3.9 Hz; δ 1.98 (H_n) to a dd, J = 13.6, 13.6 Hz; and δ 1.45 (H_o) to a dd, J = 14.3, 5.9 Hz. Irradiation of the acetal methine proton at δ 4.58 (H_d) caused the collapse of the signal at δ 2.32 (H_l) to a dd, J = 14.3, 6.1 Hz and the signal at δ 1.45 (H_o) to a dd, J = 14.3, 5.9 Hz; ^{13}C NMR (125 MHz, DEPT) δ: 208.4 (s, *C*=O), 138.7 (s, phenyl=*C*(C)(C)), 129.2 (d, C_b), 128.5 (d, C_c), 125.5 (d, C_a), 121.6 (s, *C*N), 100.1 (d, C_d), 77.2 (t, $C_{e,f}$), 76.7 (t, $C_{l,o}$), 44.6 (s, *C*-CN), 42.9 (d, C_g), 39.0 (t, $C_{k,m}$), 38.0 (t, $C_{n,l}$), 33.5 (t, $C_{h,j}$), 30.1 (s, $C(CH_3)(CH_3)$), 23.0 (q, C_q), 21.8 (q, C_r); MS (EI) *m/z*: 326 (M−1, 1.0%), 283 (M−44, 8.1%), 197 (20.3%), 149 (74%), 129 (43%), 115 (37%), 105 ($C_6H_5C{=}O^+$, 16%), 77 (22%, $C_6H_5^+$), 57 (base peak), 41(81%); HRMS calcd. for $C_{20}H_{24}NO_3$ (M^+ −H): 326.1834; found: 326.1801.

9-Methoxy-2,2-dimethyl-3-*tert*-butyldimethylsilyloxymethyl-8-oxabicyclo[4.3.0]non-1,6-ene (59)

Trimethyloxosulfonium iodide (38.2 mg, 0.17 mmol) in DMF (0.5 mL) was added to a suspension of NaH (4 mg) in DMF (1 mL) at 21°C. After stirring for 20 min, a solution of **6** (53 mg, 0.17 mmol) in DMF (0.5 mL) was added in one portion and stirring was continued for 2 h. Cold water was added and the reaction mixture was extracted several times with ether. The combined ether extracts were washed with water and brine, dried, and chromatographed (5% Et_2O – petroleum ether) to give **59** (22 mg, 40%). ^{1}H NMR (300 MHz) δ: 0.02 (s, 6H), 0.86 (s, 3H), 0.87 (s, 9H), 1.1 (s, 3H), 1.43–1.50 (m, 2H), 1.90–1.96 (m, 1H), 2.04–2.09 (m, 2H), 2.38–2.35 (m, 1H), 2.64–2.68 (m, 1H), 3.40 (dd, 1H, J = 8.8, 10 Hz), 3.42 (s, 3H), 3.75 (dd, 1H, J = 3.6, 10 Hz), 5.34 (dd, 1H, J = 2.6, 7.2 Hz); ^{13}C (75 MHz) δ: 148.2, 113.2, 105.6, 63.5, 55.4, 47, 35.4, 26.9, 25.9, 22.4, 22.18, 22, 21.8, −5.3; DEPT (75 MHz) δ: 105.6 (CH), 63.5 (CH_2), 55.4 (CH_3), 47 (CH), 35.4 (CH_2), 26.9 (CH_3), 25.9 (CH_3), 22.4 (CH_2), 22.2 (CH_2), 22 (CH_3), −5.3 (CH_3); HRMS calcd. for $C_{18}H_{34}O_3$: 326.2276; found: 326.2285.

1-Phenacyl-1-phenyl-2-ethoxycyclopropane (45)

Trapping experiment with DIBAL

Diazo compound **34** (0.050 g, 0.223 mmol) in pentane (30 mL) with $Rh_2(OPiv)_4$ (2 mol%) as the catalyst was reacted as above. After the addition of **34** was complete the lime-green reaction mixture was cooled to −78°C and DIBAL (1.5 M in toluene, 300 μL, 0.446 mmol) added in one portion. The solution immediately turned bright red. This mixture was allowed to stir at −78°C for 15 min. GC–MS analysis indicated the presence of a new peak (23% of the mixture) with a mass corresponding to the α-cyclopropyl alcohol **67**. The reaction was quenched with a saturated aqueous solution of sodium potassium tartrate (5 mL). This mixture was extracted with ether (3 × 10 mL). The combined extracts were washed with brine, filtered, dried, and concentrated to give 54 mg of crude product as a thick red-brown oil. Chromatography (5:1 petroleum ether/ethyl acetate) afforded benzyl alcohol (6 mg) and the cyclopropyl alcohol **67** (10 mg).

The standard reaction rhodium(II) acetate reaction was conducted with ethyl vinyl ether and **34** but filtration was bypassed and the lime-green crude solution was concentrated directly under a stream of argon. It was dissolved in $CDCl_3$ that had been passed through basic alumina immediately prior to use. The ^{1}H and ^{13}C NMR and IR spectra of this opaque suspension were recorded immediately. The sample was stored in the freezer, without solvent, under an atmosphere of argon. Attempts to purify cyclopropane **45**, other than by filtration under an inert atmosphere, resulted in either partial or complete conversion to dihydrofuran **43**. Slow conversion of **45** to **43** occurred on storage (−10–15°C) in a sealed flask under an inert atmosphere. Compound **45**: IR (film, NaCl): 3062, 1722 cm^{-1}; ^{1}H NMR (200 MHz) δ: 7.92–7.78 (m, 5H), 7.62–6.90 (m, 5H), 3.38 (q, 2H), 1.41–0.90 (m, 5H, overlapping t at 1.12), 0.90–0.62 (m, 1H) ppm; ^{13}C NMR (50.3 MHz) δ: 194.5, 134.8, 132.9, 129.9, 129.1, 129.0, 128.7, 128.6, 128.2, 128.1, 128.0, 65.8, 32.4, 29.7, 23.2, 15.3 ppm.

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