Generation and Utilization of Carbonyl Ylides via the Tandem Cyclization–Cycloaddition Method

ALBERT PADWA

Department of Chemistry, Emory University, Atlanta, Georgia 30322

The stereoselective preparation of highly substituted oxygen heterocycles, especially structurally complex tetrahydrofurans and tetrahydropyrans, has attracted considerable attention in recent years.[1,2] These medium-size cyclic ethers are becoming increasingly recognized as common structural units in naturally occurring compounds such as the ionophores,[3] the brevetoxins,[4] and other marine natural products.[5] Due to the increasing interest in these bioactive molecules and the well-recognized problems in building midsize rings, the synthesis of such systems becomes a challenging objective.

Although a variety of methods exist for dihydro- and tetrahydrofuran synthesis,[1,6] few of these are based on an annulation strategy,[7] and of those that are, single-step procedures are uncommon.[8,9] Conceptually, the 1,3-dipolar cycloaddition of carbonyl ylides with π-bonds represents an attractive strategy for tetrahydrofuran formation.[10] Common methods for carbonyl ylide generation involve the thermolysis or photolysis of epoxides possessing electron-withdrawing substituents,[11-13] the thermal extrusion of nitrogen from 1,3,4-oxadiazolines,[14-16] and the loss of carbon dioxide from 1,3-dioxolan-4-ones.[17] One of the simplest routes for the generation of carbonyl ylides involves the addition of a carbene or carbenoid onto the oxygen atom of a carbonyl group. This can be readily achieved by the transition-metal-catalyzed decomposition of a diazo ketone in the presence of a carbonyl group.
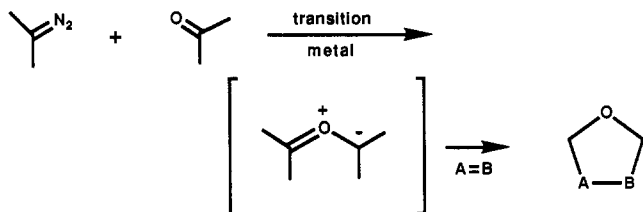
In recent years, a widespread upsurge of activity in the application of carbonyl ylides to new synthetic transformations has occurred.[10] This research has also stimulated interest in the use of carbenes and carbenoids as reactive intermediates for the generation of other types of ylides.[18] A diverse range of chemistry has already surfaced.[19] It is the intent of this Account to broadly define the boundaries of our present knowledge in this field. Such an overview will put into perspective what has been accomplished and will

Albert Padwa was born in New York City. He received both his B.A. and Ph.D. degrees (Cheves Walling) from Columbia University. After a NSF postdoctoral position with Howard E. Zimmerman at the University of Wisconsin, he was appointed Assistant Professor at the Ohio State University in 1963. He moved to SUNY Buffalo in 1966 as Associate Professor and was promoted to Professor in 1969. Since 1979 he has been the William Patterson Timmie Professor of Chemistry at Emory University. His research interests include heterocyclic chemistry, reactive intermediates, dipolar cycloadditions, the chemistry of strained molecules, and organic photochemistry.

hopefully provide impetus for further investigation of this general approach for organic synthesis.

Carbonyl Ylide Formation

Many studies support the intermediacy of carbonyl ylides in reactions involving the interaction of a carbene with a carbonyl oxygen.[20-25] Reactions of carbalkoxy-

(1) For general reviews, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 6. (c) Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825.

(2) For recent examples of stereoselective tetrahydrofuran syntheses, see: (a) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950. Rychnovsky, S. D.; Bartlett, P. A. *Ibid.* **1981**, *103*, 3963. (b) Williams, D. R.; Harigaya, Y.; Moore, J. L.; D'sa, A. *Ibid.* **1984**, *106*, 2641. (c) Dolle, R. E.; Nicolaou, K. C. *Ibid.* **1986**, *108*, 2105. Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *Ibid.* **1986**, *108*, 2106. (b) Noda, I.; Horita, K.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, 1917. (e) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748.

(3) Westley, J. W. *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Marcel Dekker: New York, 1982; Vols. I and II. Kishi, Y.; Schmid, G.; Fukuyama, T.; Akasaka, K. *J. Am. Chem. Soc.* **1979**, *101*, 259.

(4) (a) Lin, Y. Y.; Risk, M.; Ray, S. M.; Engen, D. V.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773. (b) Shimizu, Y.; Chou, H. N.; Bando, H.; Duyne, G. V.; Clardy, J. *J. Am. Chem. Soc.* **1986**, *108*, 514.

(5) Moore, R. E. *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978, Vol. I.

(6) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.

(7) Piers, E.; Karunaratne, V. J. *J. Org. Chem.* **1983**, *48*, 1774. Magnus, P.; Gange, D.; Bass, L.; Arnold, E. V.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 2134. Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746. Bruckner, C.; Reissig, H. U. *J. Org. Chem.* **1988**, *53*, 2440.

(8) For some examples, see: Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, 809. Eberbach, W.; Burchardt, B. *Chem. Ber.* **1978**, *111*, 3665. Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 627. Ochiai, H.; Nishihara, T.; Tamaru, Y.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 1343. Drewes, S. E.; Hoole, R. P. A. *Synth. Commun.* **1985**, *15*, 1067.

(9) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902.

(10) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984.

(11) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 572.

(12) Griffin, G. W.; Padwa, A. In *Photochemistry of Heterocyclic Compounds*; Buchart, O., Ed.; Wiley: New York, 1976; Chapter 2.

(13) Das, P. K.; Griffin, G. W. *J. Photochem.* **1985**, *27*, 317.

(14) Bekhazi, M.; Smith, P. J.; Warkentin, J. *Can. J. Chem.* **1984**, *62*, 1646. Warkentin, J. *J. Org. Chem.* **1984**, *49*, 343.

(15) Shimizu, N.; Bartlett, P. D. *J. Am. Chem. Soc.* **1978**, *100*, 4260.

(16) Hoffmann, R. W.; Luthardt, H. *J. Chem. Ber.* **1968**, *101*, 3861.

(17) Keus, D.; Kaminski, M.; Warkentin, J. *J. Org. Chem.* **1984**, *49*, 343. Bèkhazi, M.; Warkentin, J. *J. Am. Chem. Soc.* **1983**, *105*, 1289. Bèkhazi, M.; Smith, P. J.; Warkentin, J. *Can. J. Chem.* **1984**, *62*, 1646. Bèkhazi, M.; Warkentin, J. *Can. J. Chem.* **1983**, *61*, 619.

(18) Trost, B. M.; Melvin, L. S. *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic Press: New York, 1975.

(19) Maas, G. *Topics in Current Chemistry*; Srpinger-Verlag: Berlin, West Germany, 1987; Vol. 137, p 75.

(20) Tomioka, H.; Miwa, T.; Suzuki, S.; Izawa, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 753.

(21) Prakash, G. K. S.; Ellis, R. W.; Felberg, J. D.; Olah, G. A. *J. Am. Chem. Soc.* **1986**, *108*, 1341.

carbenes with carbonyl compounds were described as early as 1885,[26] and the structures of the dioxolane products were proposed in 1910.[27] Huisgen and de March were the first to examine the reaction in detail and to trap a carbonyl ylide with a number of reagents, including the carbonyl compound itself to produce a dioxolane.[28,29] The intramolecular carbene–carbonyl cyclization represents one of the most effective methods for generating carbonyl ylides. Ibata and co-workers[30] nicely demonstrated the utility of the method by studying the transition-metal-catalyzed decomposition of o-(alkoxycarbonyl)-α-diazoacetophenone in the presence of various dipolarophiles. A typical example involves treating o-(alkoxycarbonyl)-α-diazoaceto-phenone (1) with a catalytic amount of copper acetyl-acetonate. Evolution of nitrogen, followed by carbonyl ylide formation, generated a reactive dipole which could be trapped by N-phenylmaleimide to give cycloadduct 3 in high yield. Cycloadditions using the benzopyrylium oxide ylide 2 have been extensively studied by Ibata and his co-workers.[30]
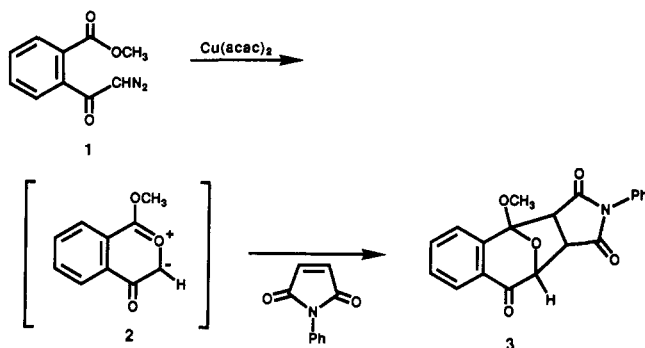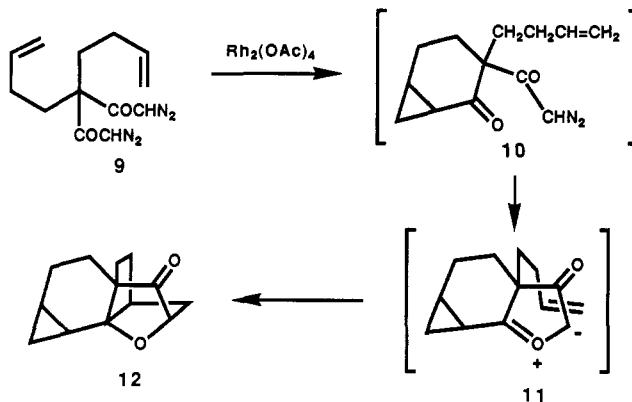

The tandem cyclization–cycloaddition methodology was further extended by the intramolecular trapping of the carbonyl ylide dipole with a C–C double bond suitably placed within the molecule. Bien and co-workers[31] reported on the transition-metal-catalyed decomposition of diazo ketone 4 to give 8-ethoxy-1-methyl-9-oxatricyclo[3.2.1.1]nonan-2-one (6) as the major product together with lesser quantities of 7 and 8. This result is consistent with the formation of a five-membered cyclic carbonyl ylide, which is followed by intramolecular trapping by the tethered olefin.

These same workers have also studied the catalytic decomposition of bis diazo ketone 9.[31] The formation of cycloadduct 12 is a unique case in which two diazo ketone moieties in the same molecule, under the influence of the same catalyst, reacted in different ways. One of the diazo groups underwent addition to the double bond to give bicyclo[4.1.0]heptane 10, which subsequently cyclized to generate the carbonyl ylide
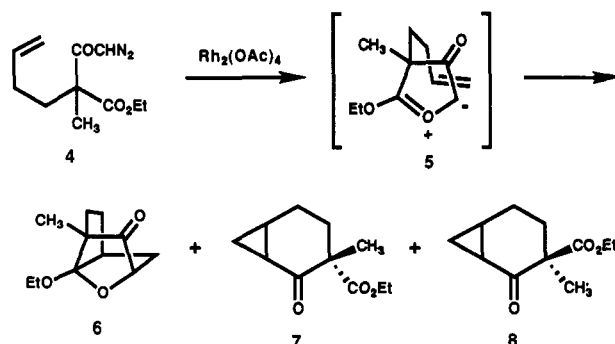
intermediate 11. Intramolecular trapping of this ylide ultimately afforded the isolated product 12.

An attractive feature of the above tandem cyclization–cycloaddition process is the opportunity to control the stereochemistry of the product at several different centers. The resulting product represents a highly functionalized rigid bicyclic system that is amenable to subsequent synthetic elaboration. This tandem cyclization–cycloaddition sequence has been extensively used in our laboratories as a method for synthesizing a variety of oxapolycyclic ring systems.[32-43] For example, treatment of o-[(alk-3-enyloxy)carbonyl]-α-diazo-acetophenone 13 with rhodium(II) acetate resulted in initial cyclization to produce a six-membered-ring carbonyl ylide, which underwent a subsequent intramolecular dipolar cycloaddition with the neighboring double bond to give cyclohepta[1,2-b]furanone 14 in 87% yield.[32] When the reaction was carried out in the presence of dimethyl acetylenedicarboxylate, the only product obtained was the bimolecular dipolar cyclo-adduct 15. In this case, the stabilized carbonyl ylide

(22) Wong, P. C.; Griller, D.; Scaiano, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 6631.
(23) Scaiano, J. C.; McGimpsey, W. G.; Casal, H. L. *J. Am. Chem. Soc.* **1985**, *107*, 7204.
(24) Janulis, E. P., Jr.; Arduengo, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 5929.
(25) Becker, R. S.; Bost, R. O.; Kolc, J.; Bertoniere, N. R.; Smith, R. L.; Griffin, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 1302.
(26) Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2371.
(27) Dieckmann, W. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1024.
(28) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4952.
(29) Huisgen, R.; de March, P. *J. Am. Chem. Soc.* **1982**, *104*, 4953.
(30) Ibata, T.; Toyoda, J.; Sawada, M.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1266. Ibata, T.; Toyoda, J. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2489 and references cited therein.
(31) Gillon, A.; Ovadia, D.; Kapon, M.; Bien, S. *Tetrahedron* **1982**, *38*, 1477.

(32) Padwa, A.; Carter, S. P.; Nimmesgern, H. *J. Org. Chem.* **1986**, *51*, 1157. Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. D. *J. Am. Chem. Soc.* **1988**, *110*, 2894.
(33) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Org. Chem.* **1988**, *53*, 2877.
(34) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.
(35) Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, 1491.
(36) Dean, D. C.; Krumpe, K. E.; Padwa, A. *J. Chem. Soc., Chem. Commun.* **1989**, 921.
(37) Padwa, A.; Chinn, R. L.; Hornbuckle, S. F.; Zhi, L. *Tetrahedron Lett.* **1989**, 301.
(38) Padwa, A.; Hornbuckle, S. F.; Hertzog, D. L.; Fryxell, G. E. *J. Org. Chem.*, in press.
(39) Padwa, A.; Krumpe, K.; Zhi, L. *Tetrahedron Lett.* **1989**, 2633.
(40) Padwa, A.; Chiacchio, U.; Garreau, Y.; Kassir, J. M.; Krumpe, K. E.; Schoffstall, A. M. *J. Org. Chem.* **1990**, *55*, 414.
(41) Padwa, A.; Hertzog, D. L.; Chinn, R. L. *Tetrahedron Lett.* **1989**, 4077.
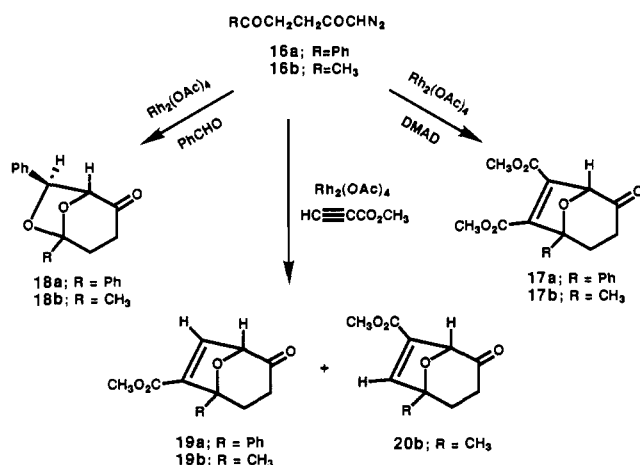(42) Padwa, A.; Dean, D. C.; Zhi, L. *J. Am. Chem. Soc.* **1989**, *111*, 6451.
(43) Padwa, A.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 2037.

prefers to cycloadd with the activated external dipolarophile as opposed to reacting with the unactivated internal π-bond.


13

14

15
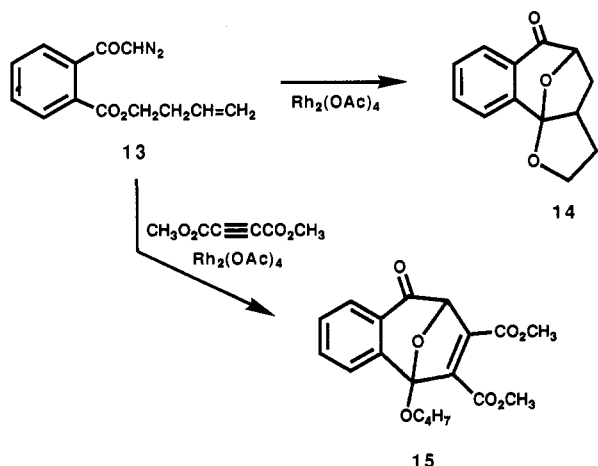
Most of the examples of intramolecular carbonyl ylide formation reported involve systems in which the keto metallocarbenoid and the remote ester carbonyl group are substituted ortho to one another on a benzene ring. This arrangement provides interatomic distances and bond angles that are ideal for dipole formation. To simultaneously test the geometric and electronic requirements of dipole formation, the 1-diazo-2,5-pentanedione system 16 was studied.[33,34] In this system, the dipole is formed by attack of a less nucleophilic ketonic carbonyl, and the tether is a simple dimethylene chain, introducing a conformational "floppiness" not available in the previously studied benzo systems. Diazo ketone 16 was treated with rhodium(II) acetate in the presence of various dipolarophiles. When dimethyl acetylenedicarboxylate was used as the trapping agent, cycloadduct 17 was produced in excellent yield. In the presence of benzaldehyde, only one regioisomer was formed (i.e., 18). The reaction of 16a with methyl propiolate afforded cycloadduct 19a whereas the cycloaddition of 16b with the same alkyne gave rise to a 4:1 mixture of two regioisomers (19b and 20b) in 78% overall yield. The major regioisomer formed is consistent with the expected product predicted by FMO theory. The most favorable FMO interaction is between the HOMO of the dipole and the LUMO of the dipolarophile.

RCOCH₂CH₂COCHN₂

16a; R=Ph
16b; R=CH₃

18a; R = Ph
18b; R = CH₃

17a; R = Ph
17b; R = CH₃

19a; R = Ph
19b; R = CH₃

20b; R = CH₃

This methodology has been applied to the synthesis of *exo-* and *endo-*brevicomin.[34,35] Thus, treatment of

1-diazo-2,5-hexanedione with rhodium(II) acetate in the presence of propionaldehyde afforded the 6,8-dioxabicyclo[3.2.1]octane ring system in 60% isolated yield as a 2:1 mixture of exo (21) and endo (22) isomers. The isomers were separated by silica gel chromatography and were subsequently carried on to *exo-* and *endo-*brevicomin (23 and 24) in good yield.

16b   21   22

exo-brevicomin   endo-brevicomin
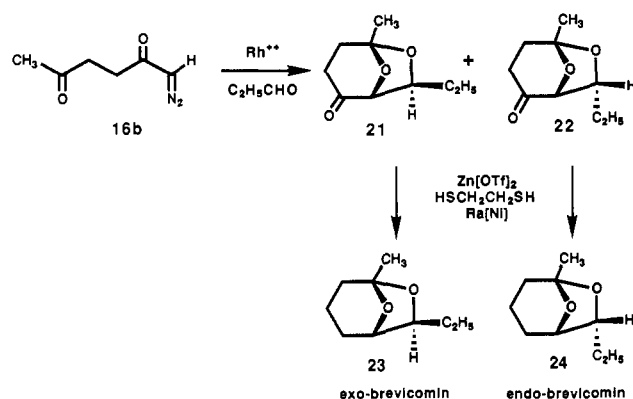
The use of aliphatic esters to form carbonyl ylides has also been examined.[44] Treatment of diazo keto ester 28 with a catalytic amount of rhodium(II) acetate in benzene led to the formation of 29 (53%) together with a complex mixture of products, none of which appeared to arise from cycloaddition of a carbonyl ylide intermediate. This result was found to be quite general for a series of aliphatic esters. In contrast, when the closely analogous keto system 25 was treated under identical conditions, the intramolecular cycloadduct 27 was produced in excellent yield. The results encountered with these two systems indicate that the differences between ketones and esters are not well understood.


25   26   27

28   29
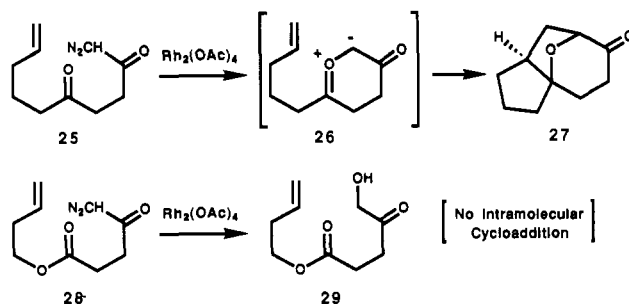
Replacement of a methylene group in the two-carbon tether with an oxygen atom would generate precursors for various dioxanones following the cyclization–cycloaddition reaction sequence.[36] However, when diazo ester 30 was treated with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate, cycloheptatriene 31 was the only product formed. No cy-


30   31
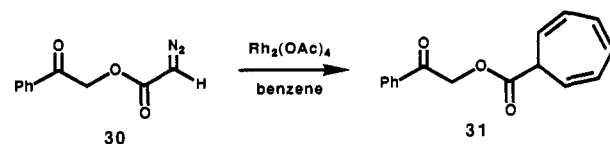
cloadduct resulting from carbonyl ylide formation was observed. One possible explanation for the differing reactivity of the α-diazoacetate system is the inherent decrease in electrophilic character conferred upon the intermediate rhodium carbenoid when the diazo ketone

(44) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* 1989, 54, 817.

is replaced by a diazoacetate functionality. This decrease in electrophilicity may attenuate the rate of carbenoid attack on the remote carbonyl group to the point where an alternative pathway can occur. To compensate for this diminished electrophilicity, the hydrogen of the diazo carbon atom was substituted with an electron-withdrawing group. Thus, treatment of ethyl diazomalonate **32** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate, methyl acrylate, or vinyl acetate afforded cycloadducts **33–35**, respectively.
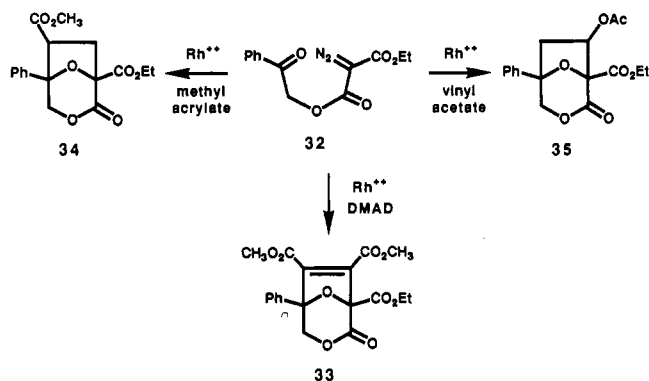
The primary spatial requirement for carbonyl ylide formation is that the distance between the two reacting centers should be sufficiently close so that effective overlap of the lone pair of electrons on the carbonyl group with the metallocarbenoid center can occur. The effect that variation in the spatial proximity between the carbonyl group and the diazo ketone would have on the course of the reaction was studied by varying the length of the methylene tether separating the two functionalities. The majority of systems examined in the literature have involved the formation of a six-membered-ring carbonyl ylide intermediate. Systems that are separated by a single methylene group should form five-membered-ring ylides. In fact, treatment of diazo ketone **36** with a catalytic amount of rhodium(II) acetate at 25 °C in benzene with dimethyl acetylenedicarboxylate afforded cycloadduct **37** in 85% yield.[37] The cycloaddition reaction proceeded with complete diastereofacial selectivity with approach of the dipolarophile from the α-face. Similar treatment of **36** with methyl propiolate produced cycloadduct **38** in 72% isolated yield. The tandem cyclization–cycloaddition reaction was also carried out in the presence of benzaldehyde to give the bicyclic ketal **39** in 66% yield. Approach from the α-face of the dipole is the preferred process because of the severe steric interaction with the bridgehead *gem*-dimethyl group associated with β-attack.
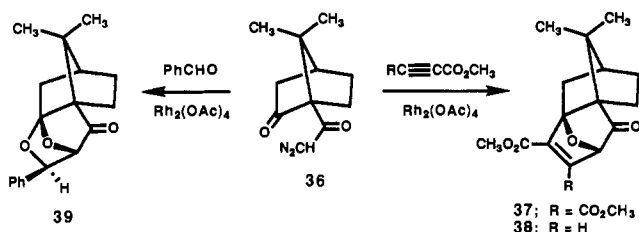

Cyclopropyl-substituted diazo ketone **40** was also treated with rhodium(II) acetate in the presence dimethyl acetylenedicarboxylate, methyl propiolate, *N*-phenylmaleimide, ethyl cyanoformate, and methyl

propargyl ether. This produced the analogous cyclo-adducts **41–45** in high yield.[37] It would appear that decreasing the methylene side chain by one carbon atom does not significantly affect the facility by which diazo ketones undergo the cyclization reaction.
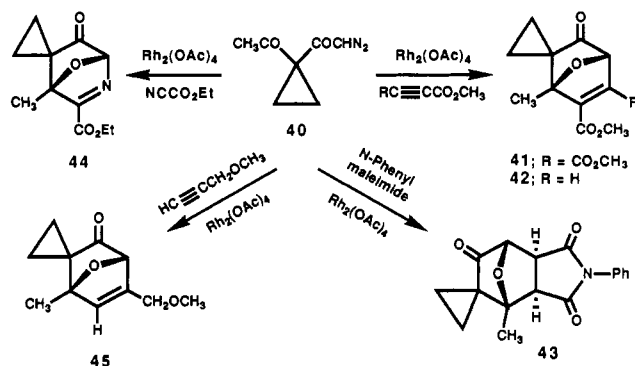

When the connecting chain contains three methylene units, a seven-membered-ring carbonyl ylide intermediate should form.[37] Indeed, the rhodium(II)-catalyzed reaction of 1-diazo-6-phenyl-2,6-hexanedione (**46**) in benzene with dimethyl acetylenedicarboxylate (or methyl propiolate) afforded a 2:1 mixture of products. The major product corresponded to the expected cycloadduct **47** whereas the minor component was identified as cycloheptatriene **48**. This compound is derived from a bimolecular addition of the rhodium carbenoid onto benzene, followed by ring tautomerization. The formation of a mixture of products in this case indicates that extending the tether to three methylene groups sufficiently retards the rate of intramolecular cyclization so as to allow the bimolecular reaction with benzene to occur.
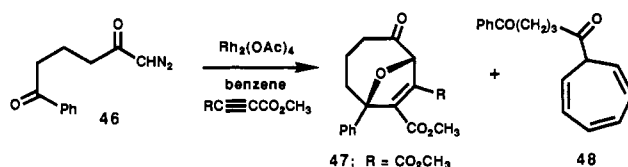

Trapping the carbonyl ylide dipole intramolecularly has proven to be an effective method for synthesizing complex polycyclic heterocycles. Varying the length of the tether that separates the olefin from the carbonyl ylide dipole allows for the synthesis of a variety of interesting oxopolycyclic ring systems. Olefinic double bonds tethered to the carbonyl group by three methylene units were shown to cyclize most efficiently. Thus, when diazo ketone **49** was treated with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate, cycloadduct **53** was the only product formed.[38] The intramolecular trapping reaction occurs at such a fast rate that the bimolecular cycloaddition reaction cannot compete with it. The homologous diazo ketone **50** was also treated with catalytic rhodium(II) acetate in benzene at 25 °C, producing cycloadduct **54** in 50% yield. In this case, the carbonyl ylide could be readily trapped with dimethyl acetylenedicarboxylate, giving the bimolecular cycloadduct **55** as the exclusive cycloadduct. Increasing the length of the tether to five methylene units gave no internal cycloadduct. Apparently, the π-bond is not close enough to the dipole to allow the cycloaddition to occur. Diazo ketone **51**, which contains only two methylene units in the tether, produced none of the internal cycloadduct. Clearly the

intramolecular trapping of carbonyl ylides by tethered olefins occurs best when the tether contains three or four methylene units. The internal cycloaddition fails to occur when the tether contains fewer than three or more than four methylene carbons.


49; n=3
50; n=4
51; n=2

52

53; m=1
54; m=2

55; n=4
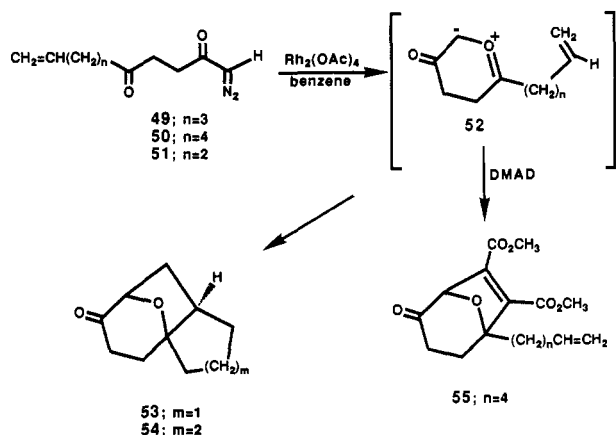
A similar cyclization–cycloaddition reaction was also found to occur with the vinylogous keto carbenoid **58**. Treatment of diazo ketone **56** with rhodium(II) acetate in the presence of N-phenylmaleimide gave adduct **60** in 60% yield. This result is consistent with intramolecular cyclopropenation of the alkyne by the rhodium carbenoid to give the highly strained cyclopropene **57**, which undergoes spontaneous ring opening to produce vinyl carbenoid **58**. Interaction of this species with the adjacent carbonyl oxygen generates the resonance-stabilized dipole **59**, which then cycloadds across the activated π-bond of N-phenylmaleimide to produce product **60**. This structure was established by an X-ray single-crystal structure analysis.[39]

56

57

58

59

N-Phenyl maleimide

60
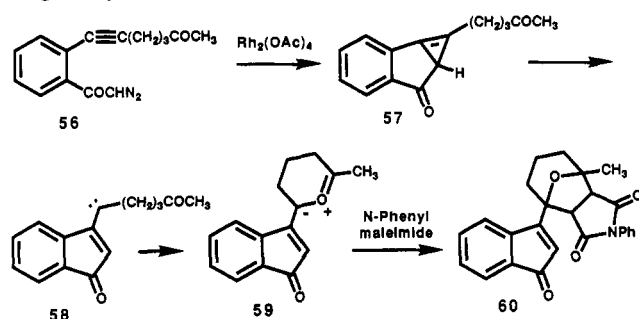
Carbonyl Ylide Formation from Imides, Carbamates, Amides, and Anhydrides

Although carbonyl ylides have been postulated as intermediates in many reactions, very few of these dipoles have actually been isolated and characterized. One of the earliest examples involving the isolation of a stable carbonyl ylide was reported by Ibata and Hamaguchi in 1974.[45] Diazo amide **61** was heated in benzene at 80 °C under a nitrogen atmosphere in the presence of Cu(acac)$_2$, producing N-methyl-2-phenyl-5-(p-nitrophenyl)anhydro-4-hydroxy-1,3-oxazolium hydroxide (**62**) in 85% yield as a red crystalline solid, which was stable in air for several weeks. Mesoionic oxazolium ylides such as **62** have been termed isomünchnones, and they correspond to the cyclic equivalents of a carbonyl ylide. Dipole **62** was found to react with dimethyl fumarate in benzene at 80 °C,
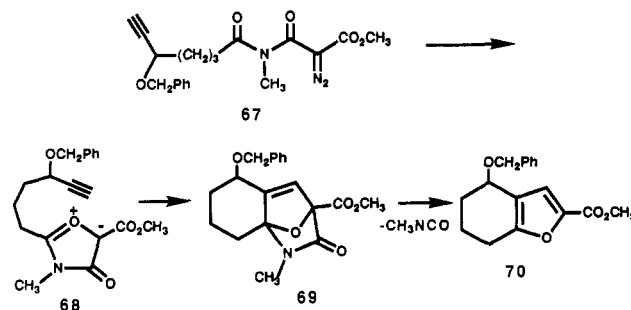
(45) Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1975,** 499. Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974,** 4475.

giving rise to cycloadduct **63** in only a few minutes in quantitative yield.

61
R = p-NO$_2$C$_6$H$_4$

62

Dimethyl fumarate

63
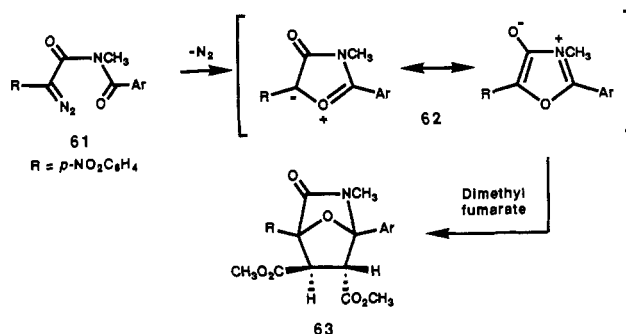
Intramolecular cycloadditions of isomünchnones, formed by the rhodium(II) acetate decomposition of N-(diazoacetylacetyl)alkeneamides, have been independently realized by Maier[46] and Padwa.[41,47] A solution of diazo amide **64** in toluene was added dropwise to a refluxing mixture of rhodium(II) acetate in toluene, producing cycloadduct **66** in 91% yield. The intermediate isomünchnone **65** was not isolated in this case. The relative stereochemistry of cycloadduct **66** was established by X-ray analysis, which showed that the addition of the olefin took place endo with regard to the 1,3-dipole and anti to the methyl group on the π-bond chain.

64

65

66
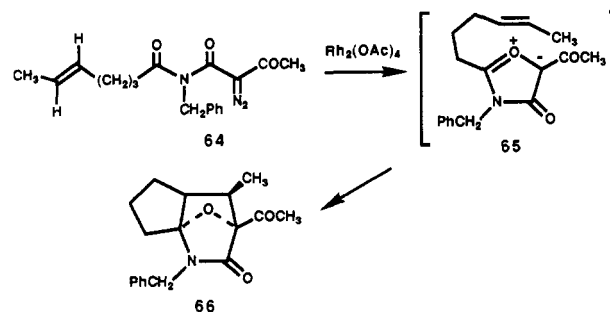
The cycloadducts derived from the intramolecular cycloaddition reactions of acetylenic isomünchnones fragment spontaneously under the reaction conditions to afford annulated furans.[41,46] Thus, treatment of acetylenic diazo amide **67** under the same conditions as used above produced 4,5,6,7-tetrahydrobenzofuran **70** in 60% yield. This result was interpreted in terms of carbonyl ylide formation (**68**) followed by 1,3-dipolar cycloaddition across the tethered acetylene to give cycloadduct **69**, which then underwent a subsequent cycloreversion reaction to give furan **70**.


67

68

69

70

(46) Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988,** 1677. Maier, M. E.; Schoffling, B. *Chem. Ber.* **1989,** *122,* 1081.
(47) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.,* in press.

Treatment of diazo imide **71** (*n* = 1) with rhodium(II) acetate at 80 °C in benzene produced an isomünchnone dipole **75**. 1,3-Dipolar cycloaddition of this species with dimethyl acetylenedicarboxylate gave cycloadduct **77**, which subsequently fragmented via a retro-Diels–Alder reaction into furan **78** in 85% yield. Trapping of dipole **75** with *N*-phenylmaleimide gave cycloadduct **76** in 78% yield. The generality of this method was demonstrated by varying the structure of the cyclic imide to probe any geometric effects of ring size on the outcome of the cyclization–cycloaddition reaction. The ring size was reduced to a four-membered ring (**72**; *n* = 0) (61%) and enlarged to a six-membered ring (**73**; *n* = 2) (85%) and a seven-membered ring (**74**; *n* = 3) (75%). In all cases, high yields of the expected cycloadducts derived from *N*-phenylmaleimide were obtained. Interestingly, the cyclic cases where *n* = 1 and *n* = 3 showed little exo/endo selectivity, but the cases of *n* = 0 and *n* = 2 resulted in formation of single stereoisomers. The conformational rigidity imposed by the cyclic imide ring was demonstrated to be inconsequential by carrying out the tandem cyclization–cycloaddition sequence using acyclic amides.
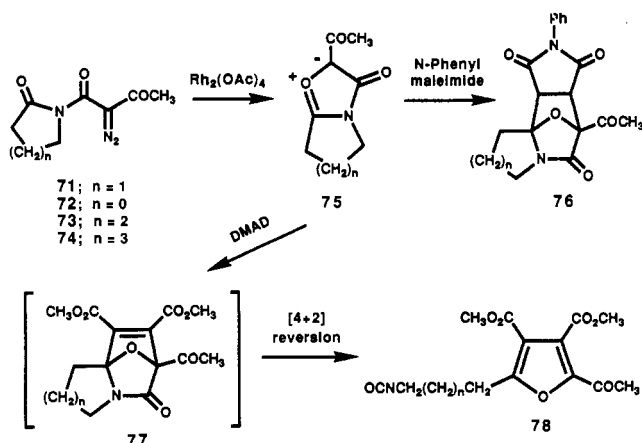

Extending the length of the tether by one methylene unit gives rise to a six-membered-ring carbonyl ylide that is not stabilized by any isomünchnone type delocalization.[41] Thus, treatment of diazo phthalimido ester **79** with rhodium(II) acetate in refluxing benzene in the presence of *N*-phenylmaleimide afforded cycloadduct **82** in 87% yield. Similar treatment of the less activated diazo phthalimido ester **80** with rhodium(II) octanoate at 25 °C in the presence of *N*-phenylmaleimide gave the related cycloadduct **83**, which is derived from dipole **81**.

Dipole Cascade

1,3-Dipoles are extremely valuable intermediates in synthetic organic chemistry. Their best known reaction is a 1,3-dipolar cycloaddition reaction. Less attention, however, has been placed on the interconversion of one dipole into another. A new method for azomethine ylide formation was recently developed which involves a cascade of dipoles. This novel process was uncovered during an examination of the reaction of (*S*)-1-acetyl-2-(1-diazoacetyl)pyrrolidine (**84**) with 1.5 equiv of dimethyl acetylenedicarboxylate in the presence of a catalytic quantity of rhodium(II) acetate. Very little (<10%) of the expected carbonyl ylide derived cyclo-adduct **86** was obtained.[42] Instead, the major product (90%) was structure **89**. A mechanism that rationalizes
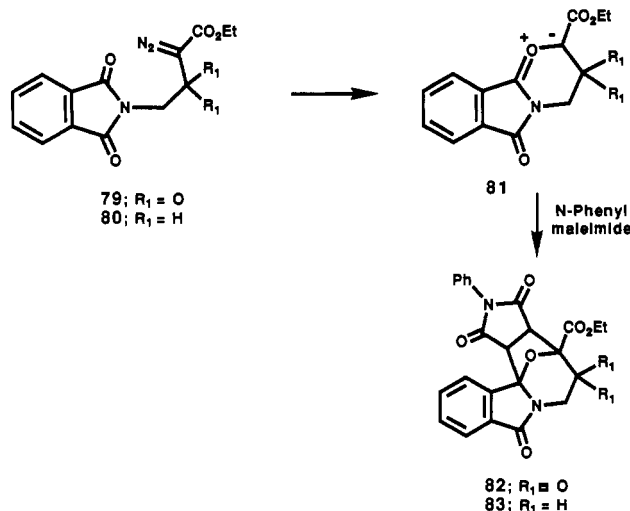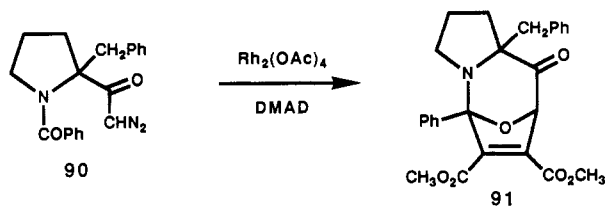

the formation of this product requires generation of the expected carbonyl ylide dipole **85** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. Isomerization of **85** to the thermodynamically more stable azomethine ylide **87** occurred via proton exchange with a small amount of water that was present in the reaction mixture. 1,3-Dipolar cycloaddition with dimethyl acetylenedicarboxylate provides cycloadduct **88**, which undergoes a subsequent 1,3-alkoxy shift to generate the tricyclic dihydropyrrolizine **89**. We refer to this overall process as a *dipole cascade*. MNDO calculations show that cyclic carbonyl ylides of type **85** have higher heats of formation (ca. 15 kcal/mol) than the corresponding azomethine ylides **87**. Some of this energy difference is presumably responsible for the facility with which the dipole reorganization occurs.
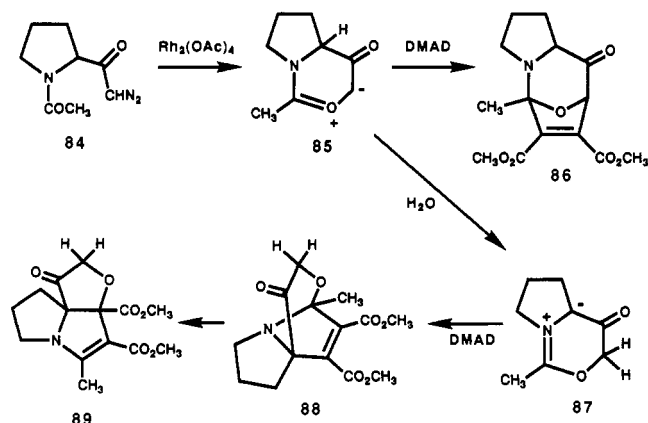

In the *dipole cascade* reaction, a proton must be removed from the α-carbon atom in order to generate the azomethine ylide. When the α-position of the pyrrolidine ring was blocked by a benzyl group, formation of the azomethine ylide dipole could not occur. In fact, treatment of diazo ketone **90** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate afforded only the carbonyl ylide derived cycloadduct **91** in 95% yield.[42]

In the case of α-diazo keto amide **92**, the carbonyl ylide dipole is sufficiently stabilized by resonance to be trapped by dimethyl acetylenedicarboxylate to give cycloadduct **94** in 90% yield.[43] No signs of any material derived from azomethine ylide cycloaddition were observed. The closely related α-diazo keto amide **93** was

also examined. Most interestingly, treatment of **93** with rhodium(II) acetate in the presence of dimethyl acetylenedicarboxylate afforded cycloadduct **95** in 60% yield.
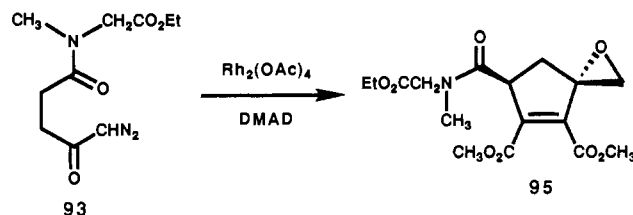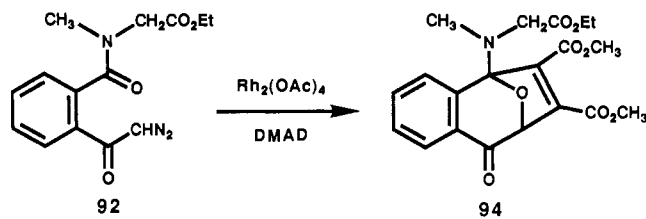
The initial reaction involves generation of the expected carbonyl ylide dipole **97** by intramolecular cyclization of the keto carbenoid onto the oxygen atom of the amide group. This highly stabilized dipole does not readily undergo 1,3-dipolar cycloaddition, but rather transfers a proton to produce the cyclic ketene N,O-acetal **98**. This material reacts further with the activated π-bond of the dipolarophile to produce zwitterion **99**. The anionic portion of **99** adds to the adjacent carbonyl group, affording a new zwitterionic intermediate **100**. Under anhydrous conditions, epoxide formation occurs with charge dissipation to give the observed cycloadduct **101**.

The high efficiency of the dipole cascade, in conjunction with the intriguing chemistry of the resulting cycloadducts, presents numerous synthetic possibilities
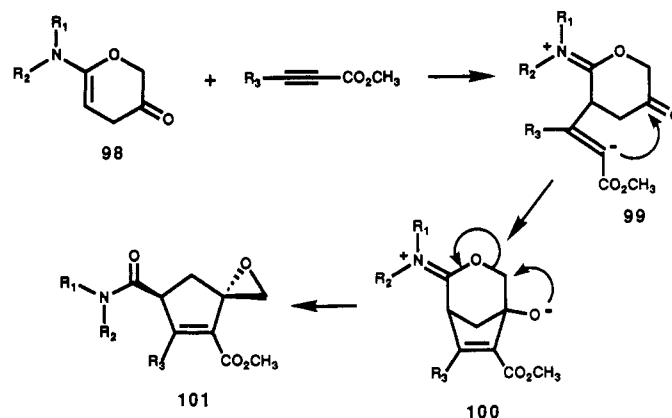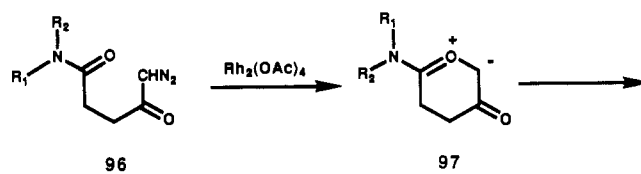
for the preparation of complex heterocycles.

Conclusion

Carbonyl ylide generation from the reaction of carbenes and carbenoids with carbonyl compounds continues to be of great interest both mechanistically and synthetically. Certainly, many important applications of this method remain undiscovered. In particular, extension to more highly substituted carbonyl ylide precursors remains to be studied. At the moment, relatively little use has been made of this procedure for the synthesis of complex natural products. In view of the mild conditions, the carbenoid route seems most promising for intramolecular ylide trapping and for reactions involving complex structures. Given the recent explosion of research in this field, one can only assume that additional work will be forthcoming.