JOC Article

Anomalous Intramolecular C−H Insertion Reactions of Rhodium Carbenoids: Factors Influencing the Reaction Course and Mechanistic Implications

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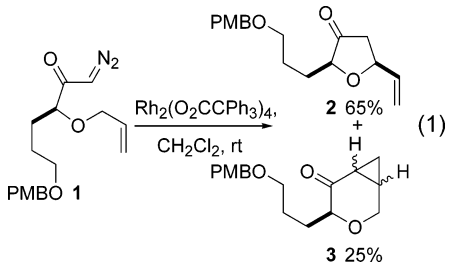
The intramolecular insertion of rhodium carbenoids into the α-C−H bonds of allylic ethers to give 3(2*H*)-furanones has been explored. Cyclopropanation is favored irrespective of the complex used for carbenoid generation or the substitution pattern of the allylic ether, unless a substituent is placed on the tether connecting the ether to the α-diazo ketone. Unusual acetal products resulting from an anomalous C−H insertion process are obtained in addition to the expected 3(2*H*)-furanones formed by conventional carbenoid C−H insertion. These acetals are the favored C−H insertion products in certain circumstances and particularly in cases where carbenoid generation is effected using an electron-deficient rhodium complex. Experiments with simple deuterium labeled substrates reveal that anomalous C−H insertion products arise by a mechanism that is distinct from that leading to the formation of conventional C−H insertion products. The formation of acetal products and the outcome of reactions performed using deuterium-labeled substrates suggest that a mechanism involving hydride migration to the rhodium center of the carbenoid is operative.

Introduction

Intramolecular C−H insertion reactions of metal carbenoids, generated from α-diazocarbonyl compounds, have been widely used for the stereoselective construction of substituted cyclopentanones, lactones, and lactams,[1] and the advent of asymmetric variants of these reactions has further extended the scope and general utility of the methodology.[2] The intramolecular insertion of a metal carbenoid into a C−H bond adjacent to an ether oxygen is a particularly favorable reaction, and Adams and co-workers have demonstrated that rhodium carbenoids generated from α-diazo ketones undergo efficient and stereoselective C−H insertion to give 3(2*H*)-furanones.[3] Taber and co-workers have used the corresponding reaction of α-diazo esters for the stereoselective synthesis of highly functionalized tetrahydrofurans,[4] and Lee has shown that the intramolecular insertion of a carbenoid into a C−H bond adjacent to a trialkylsilyl ether is especially favorable and that this reaction can be utilized to prepare medium-ring cyclic ethers.[5]

In the course of studies directed toward the synthesis of the sesquiterpene natural product neoliacinic acid,[6] we prepared the vinyl-substituted 3(2*H*)-furanone **2** from the α-diazo ketone **1** by generation of a rhodium carbenoid and subsequent intramolecular insertion of this reactive intermediate into the C−H bond of an allyl ether (eq 1). Although the yield for this transformation was reasonable and the furanone **2** was the major product, cyclopropanation of the alkene to give the pyranone **3** was found to be a significant competing process.[7] To gain a better understanding of the reaction and elucidate those factors controlling the selectivity of the C−H insertion process, we embarked on a study of the rhodium-catalyzed cyclization reactions of some simple α-diazo ketones related to **1**.[8]



Results and Discussion

Four α-diazo ketones (**17**−**20**) bearing variously substituted allylic ethers were chosen for our preliminary

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(1) For reviews concerning the C−H insertion reactions of metal carbenoids, see: (a) Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pattenden, G., Vol. Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 3, Chapter 4.2, pp 1045−1062. (b) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765. (c) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (d) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (d) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Hegedus, L. S., Vol. Ed.; Pergamon Press: New York, 1995; Vol. 12, Chapter 5.2, pp 421−468. (e) Doyle, M. P.; McKervey, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (f) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145. (g) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137.

(2) For an excellent recent review of asymmetric carbenoid C−H insertion reactions, see: Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.

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SCHEME 1

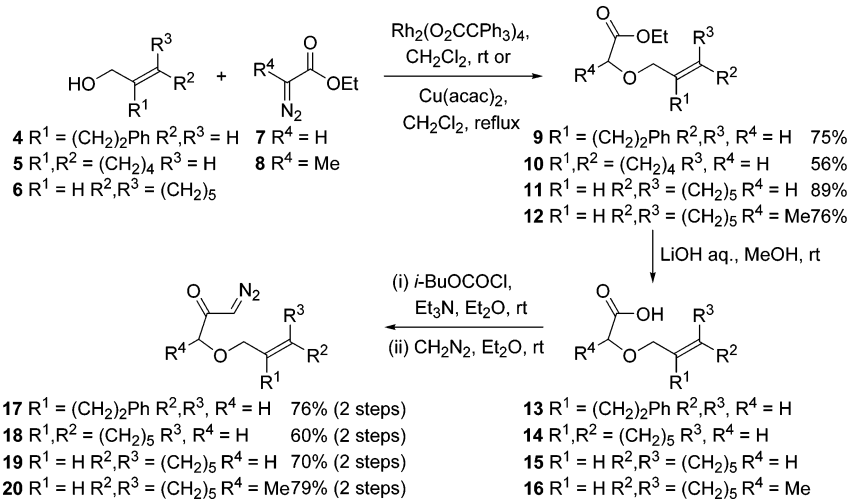
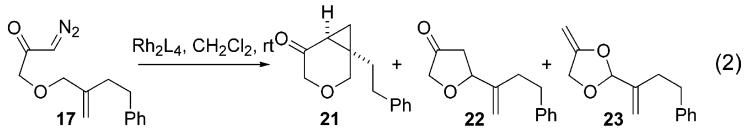


TABLE 1. Rhodium-Catalyzed Reactions of the α-Diazo Ketone 17



		product ratios (capillary GC)			isolated yields (%)		
entry	ligand (L)	**21**:**22**:**23**	**21**:(**22** + **23**)	**22**:**23**	**21**	**22**	**23**
1	O_2CCH_3	74:19:7	74:26	73:27	67	15	6
2	$O_2CC_7H_{15}$	83:14:3	83:17	81:19			
3	O_2CCPh_3	70:24:6	70:30	81:19			
4	O_2CCF_3	84:12:4	84:16	72:28			
5	$O_2CC_3F_7$	94:6:0	94:6				
6	$HNCOCH_3$	80:16:4	80:20	79:21			
7	$HNCOCF_3$	61:31:8	61:39	80:20			

studies concerning the scope of the reaction and those factors favoring C−H insertion over cyclopropanation. These carbenoid precursors were prepared from the appropriate allylic alcohols by a short and efficient route involving intermolecular carbenoid O−H insertion (Scheme 1).[1b,e,9] The route commenced with reaction of the appropriate allylic alcohol with a copper carbenoid (alcohol **4**) or rhodium carbenoid (alcohols **4**−**6**) generated by treatment of ethyl diazoacetate (**7**) or ethyl diazopropionate (**8**) with $Cu(acac)_2$ or $Rh_2(O_2CCPh_3)_4$, and the resulting esters **9**−**12** were then saponified to give the carboxylic acids **13**−**16**. The cyclization precursors **17**−**20** were obtained in good yield by conversion of the carboxylic acids **13**−**16** into mixed anhydrides using isobutyl chloroformate and subsequent treatment with diazomethane in diethyl ether.

The intramolecular C−H insertion reactions of each substrate were performed in dichloromethane at room temperature, and the carbenoids were generated using seven structurally diverse rhodium complexes: the standard relatively electron-rich complexes $Rh_2(O_2CCH_3)_4$ and $Rh_2(O_2CC_7H_{15})_4$; the electron-deficient complexes $Rh_2(O_2CCF_3)_4$ and $Rh_2(O_2CC_3F_7)_4$; the bulky complex $Rh_2(O_2CCPh_3)_4$; the carboxamide complexes $Rh_2(NHCOCH_3)_4$ and $Rh_2(NHCOCF_3)_4$. The crude reaction mixtures were analyzed by capillary gas chromatography, and in some cases, the products were isolated and purified for comparison purposes.

The α-diazo ketone **17** was selected as a test substrate because the alkene possesses the substitution pattern found in the substrate required for the synthesis of neoliacinic acid.[6] Treatment of this compound with the selected rhodium catalysts afforded the expected cyclopropane **21** and 3(2*H*)-furanone **22** in varying amounts (eq 2, Table 1). In contrast to the result obtained upon cyclization of the α-diazo ketone **1** (eq 1), the cyclopropane **21** predominated in all cases. In addition, we were

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(4) (a) Taber, D. F.; Song, Y. *Tetrahedron Lett.* **1995**, *36*, 2587. (b) Taber, D. F.; Song, Y. *J. Org. Chem.* **1996**, *61*, 6706.

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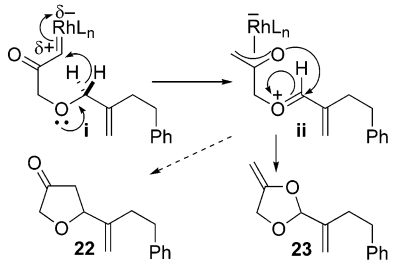
(7) (a) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Rosati, O. *Tetrahedron* **1992**, *48*, 9767. (b) Cox, G. G.; Moody, C. J.; Austin, D. J.; Padwa, A. *Tetrahedron* **1993**, *49*, 5109.

(8) For preliminary accounts of this work, see: (a) Clark, J. S.; Dossetter, A. G.; Russell, C. A.; Whittingham, W. G. *J. Org. Chem.* **1997**, *62*, 4910. (b) Clark, J. S.; Wong, Y.-S.; Townsend R. J. *Tetrahedron Lett.* **2001**, *42*, 6187.

(9) (a) Cox, G. G.; Kulagowski, J. J.; Moody, C. J.; Sie, E.-R. H. B. *Synlett* **1992**, 975. (b) Cox, G. G.; Miller, D. J.; Moody, C. J.; Sie, E.-R. H. B.; Kulagowski, J. J. *Tetrahedron* **1994**, *50*, 3195.

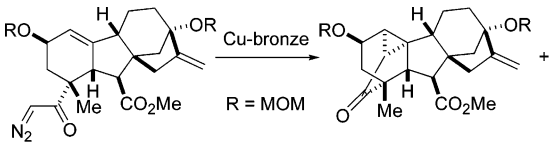
SCHEME 2



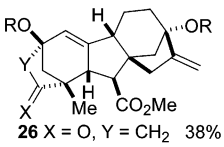
surprised to find that six of the seven reactions also delivered an unstable byproduct that we had not observed in previous studies. After complete characterization, it transpired that the new product was the cyclic acetal **23** arising from an abnormal C−H insertion reaction. The ratio of the cyclopropane **21** to the combined C−H insertion products was heavily dependent on the catalyst used and varied from 61:39 (entry 7, Table 1) up to 94:6 (entry 5, Table 1). In general, the use of rhodium complexes bearing strongly electron-withdrawing ligands resulted in high selectivity for cyclopropanation. The ratio of normal to abnormal C−H insertion product (**22**:**23**) was relatively insensitive to the catalyst used for carbenoid generation and ranged between 72:28 and 81:19. In contrast to the original reaction (eq 1), intramolecular C−H insertion was not the dominant process, even when $Rh_2(O_2CCPh_3)$ was employed as the catalyst (entry 3, Table 4).

The isolation of the abnormal C−H insertion product **23** as a minor product during the rhodium catalyzed reactions of the α-diazo ketone **17** (eq 2) was completely unexpected but was explicable by a mechanism involving hydride migration (Scheme 2). In this mechanism, oxygen-promoted hydride migration from the allylic ether position to the highly electrophilic rhodium carbenoid **i** occurs to give the intermediate **ii** which possesses a rhodium enolate and an oxenium ion. Nucleophilic attack of the highly reactive oxenium ion through the oxygen atom of the rhodium enolate then delivers the anomalous C−H insertion product **23**. It should be noted that if such a mechanism were operative, ring closure of the intermediate **ii** via the carbon of the rhodium enolate could deliver the expected C−H insertion product **22**, circumventing the generally accepted carbenoid C−H insertion mechanisms.[1]

Although both Doyle[10] and Lee[5] had isolated decomposition products from carbenoid C−H insertion reactions consistent with a hydride migration mechanism analogous to that in Scheme 2, at the time we published our preliminary results we believed that we were the first to have isolated an acetal such as **23** from a carbenoid C−H insertion reaction. However, it transpired that Mander and Owen had already observed the formation of an analogous product from a copper carbenoid reaction performed during their studies concerning the synthesis of the gibberellins[11] and had published this work prior to our preliminary communication.[8a] In the course of this work, Mander and Owen had observed the formation of the acetal **27** as a minor product along with the cyclopropane **25** and the expected C−H insertion product **26** upon generation of a copper carbenoid by treatment of the α-diazo ketone **24** with copper bronze (eq 3).[11] Following our initial report, several other research groups reported the isolation of anomalous C−H insertion products from metal carbenoid reactions.[12,13]



24 *Mander and Owen* **25** 46% (3)



26 X = O, Y = CH_2 38%
27 X = CH_2, Y = O 15%

We were intrigued by the isolation of the acetal **23**, and to explain its formation and probe the factors influencing the selectivity for C−H insertion versus cyclopropanation, the rhodium-catalyzed reactions of the other α-diazo ketones (**18**−**20**, Scheme 1) were explored. The reactions of carbenoids formed upon treatment of the α-diazo ketone **18** with a variety of rhodium complexes were investigated first (eq 4, Table 2). Analysis of the reaction products by capillary GC revealed that the cyclopropane **28** was the major product in all cases and that varying amounts of the expected 3(2*H*)-furanone **29** and the anomalous acetal **30** were also produced during these reactions (Table 2). The aldehyde **31** arising from decomposition of the acetal **30** was also detected by capillary GC. The highest ratio of C−H insertion products to cyclopropane (**28**) was obtained when $Rh_2(O_2CCPh_3)_4$ was employed as the catalyst (entry 3, Table 1), and the use of $Rh_2(NHCOCF_3)_4$ as the catalyst also furnished roughly equal amounts of products arising from C−H insertion and the cyclopropane **28**. Although a significant amount of the unstable acetal **30** was detected in each case, it was too unstable to fully characterize. The acetal **30** was identified on the basis of NMR analysis of partially purified material and by the fact that a substantial amount of the decomposition product **31** was produced upon attempted purification. When electron-rich rhodium complexes were used to catalyze the reaction (entries 1−3 and 6, Table 2), the relative amounts of the 3(2*H*)-furanone **29** and the anomalous C−H insertion product **30** produced in each reaction were similar with the former predominating. However, when complexes bearing strongly electron-withdrawing ligands were employed as catalysts (entries 4, 5, and 7, Table 2), there was a significant increase in the relative amount of the acetal **30**.

The rhodium-catalyzed reactions of two other allylic ether substrates (**19** and **20**) were also investigated (eq 5, Table 3, and eq 6). The rhodium-catalyzed reactions of the α-diazo ketone **19** delivered the cyclopropane **32**

(10) Doyle, M. P.; Dyatkin, A. B.; Autry, C. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 619.
(11) Mander, L. N.; Owen, D. J. *Tetrahedron Lett.* **1996**, *37*, 723.
(12) White, J. D.; Hrnciar, P. *J. Org. Chem.* **1999**, *64*, 7271.
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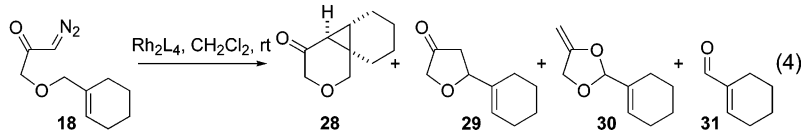
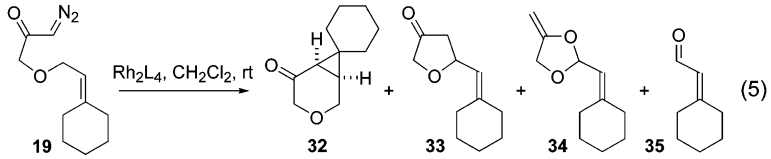
TABLE 2. Rhodium-Catalyzed Reactions of the α-Diazo Ketone 18



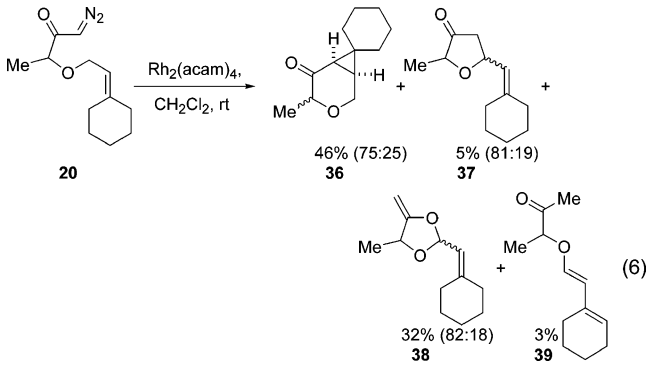
		product ratios (capillary GC)			isolated yields (%)	
entry	ligand (L)	**28**:**29**:**30**:**31**	**28**:(**29** + **30** + **31**)	**29**:(**30** + **31**)	**28**	**29**
1	O_2CCH_3	78:13:5:4	78:22	62:38	51	10
2	$O_2CC_7H_{15}$	82:13:5:0	82:18	73:27		
3	O_2CCPh_3	46:30:2:22	46:54	55:45	33	23
4	O_2CCF_3	75:8:7:10	75:25	30:70		
5	$O_2CC_3F_7$	79:7:5:9	79:21	30:70	72	8
6	$HNCOCH_3$	65:20:15:0	65:35	59:41		
7	$HNCOCF_3$	55:20:2:23	55:45	43:57		

TABLE 3. Rhodium-Catalyzed Reactions of the α-Diazo Ketone 19



		product ratios (capillary GC)			isolated yields (%)		
entry	ligand (L)	**32**:**33**:**34**:**35**	**32**:(**33** + **34** + **35**)	**33**:(**34** + **35**)	**32**	**33**	**34**
1	O_2CCH_3	75:11:0:14	75:25	45:55	64	1	13
2	$O_2CC_7H_{15}$	80:14:0:6	80:20	70:30			
3	O_2CCPh_3	81:13:3:3	81:19	68:32			
4	O_2CCF_3	84:0:5:11	84:16				
5	$O_2CC_3F_7$	89:0:6:5	89:11				
6	$HNCOCH_3$	90:10:0:0	90:10				
7	$HNCOCF_3$	84:4:0:12	84:16	36:64			

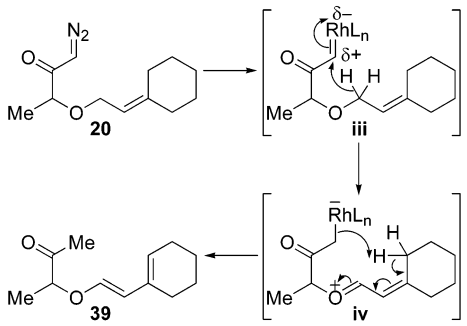
along with the C−H insertion products **33** and **34** and the aldehyde **35** arising by decomposition of the acetal **34**. Once again, cyclopropanation was the predominant reaction in each case. The ratio of cyclopropane **32** to the combined C−H insertion products was rather insensitive to the complex used for carbenoid generation, although complexes bearing electron-deficient ligands tended to give higher ratios in favor of cyclopropanation.



The presence of a substituent on the tether connecting the ether to the α-diazo ketone had a profound influence on the course of the reaction. The $Rh_2(HNCOCH_3)_4$-catalyzed reaction of the α-diazo ketone **20** delivered significantly increased amounts of the C−H insertion products (**37** and **38**) as diastereoisomeric mixtures (eq 6). Although a diastereoisomeric mixture of the cyclopropane **36** was obtained as the major product, the distribution of products was more consistent with that obtained from our preliminary experiment (eq 1). This result suggests that the presence of a substituent on the tether connecting the α-diazo ketone to the allylic ether is essential if one requires C−H insertion to be selected over cyclopropanation of the allylic ether. The isolation of a substantial amount of the acetal **38** arising from anomalous C−H insertion at the expense of the expected C−H insertion is also significant.

In addition to the cyclopropane **36** and the insertion products **37** and **38**, a small amount of the unstable ketone **39** was obtained and identified using mass spectrometry and NMR spectroscopy. The isolation of the ketone **39** may provide a mechanistic insight into the course of the C−H insertion reaction and can be accounted for by the mechanism shown in Scheme 3. Treatment of the α-diazo ketone **20** with a rhodium complex affords the electrophilic carbenoid **iii**. Oxygen-assisted hydride migration from the allylic ether then occurs to give the intermediate **iv** which contains a rhodium enolate and an oxenium ion. The enolate then abstracts a proton from the ring to produce a methyl ketone and the conjugated diene. It is also conceivable that proton loss from the intermediate **iv** and transfer to the rhodium enolate occurs in an intermolecular fashion. In addition, it is possible the ketone **39** could be produced from the acetal **38** by Lewis acid mediated elimination with ring opening.

SCHEME 3



SCHEME 4

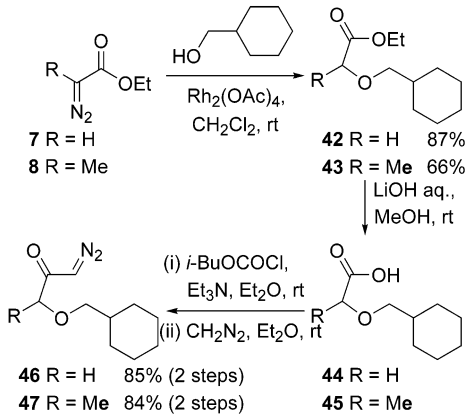
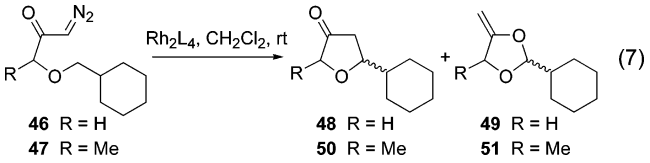


TABLE 4. Rhodium-Catalyzed Reactions of the α-Diazo Ketones 46 and 47



			isolated yields (%)	
entry	substrate	ligand (L)	**48/50**	**49/51**
1	**46**	O_2CCH_3	55	8
2	**46**	O_2CCF_3	35	40
3	**47**	O_2CCH_3	62	14
4	**47**	O_2CCF_3	18	40 (92:8)[a]

[a] Ratio of isomers determined by ^{1}H NMR analysis.

At this juncture, it was important to establish whether the formation of anomalous acetal products is a general phenomenon during the intramolecular C−H insertion reactions of ethers or is restricted to allylic ethers. It was also desirable to probe the competing C−H insertion reaction pathways without the complication of competitive cyclopropanation. To do this, the substrates **46** (the saturated analogue of the α-diazo ketone **18**) and **47** were prepared (Scheme 4), and their rhodium-catalyzed cyclization reactions were investigated (eq 7, Table 4). The synthesis of these substrates was straightforward and commenced with the reaction of cyclohexylmethanol with the rhodium carbenoid generated from either ethyl diazoacetate (**7**) or ethyl diazopropionate (**8**). The resulting esters (**42** and **43**) were saponified to give the carboxylic acids **44** and **45**, and these were converted into the α-diazo ketones **46** and **47** using the same protocol as before (Scheme 1).

The rhodium-catalyzed cyclization reactions of the α-diazo ketone **46** provided the expected C−H insertion product **48** along with the acetal **49**, but the outcome of this reaction was strongly influenced by the complex used for carbenoid generation (Table 4). When $Rh_2(O_2CCH_3)_4$ was used as the catalyst, the 3(2*H*)-furanone **48** was isolated in 55% yield along with only 8% of the acetal **49** (an isolated ratio of 87:13) (entry 1). However, when $Rh_2(O_2CCF_3)_4$ was employed as the catalyst, analysis of the crude reaction mixture by capillary gas chromatography indicated an approximately 1:2 ratio of products (**48**:**49**), although roughly equivalent amounts of the two products were isolated (entry 2). The acetal **49** proved to be relatively stable in comparison to the allylic ether derived acetals **23**, **30**, and **34** and could be isolated in good yield. The presence of the methyl substituent in substrate **47** was found to increase amount of acetal product **51** relative to 3(2*H*)-furanone product **50** obtained from both reactions (entries 3 and 4, Table 4) but especially from the reaction catalyzed by $Rh_2(O_2CCF_3)_4$ (entry 4).

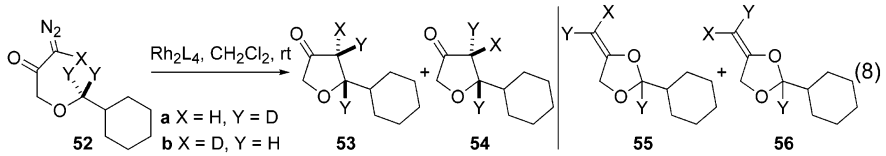
At this stage, the results suggested that the intramolecular insertion of metal carbenoids into C−H bonds adjacent to ethers may proceed by a more complex process than previously recognized and were consistent with the mechanism illustrated in Scheme 2.[8,11,12] In this mechanism, the acetal product arises by oxygen-assisted hydride transfer to the electrophilic carbon of the rhodium carbenoid to generate an oxenium ion **ii** (Scheme 2). The intermediacy of an oxenium ion is supported by the fact that the highest proportion of the anomalous C−H insertion product relative to the expected C−H insertion product is obtained upon cyclization of the α-diazo ketone **19**. This is consistent with our postulated reaction mechanism because the alkene substituents would stabilize development of incipient positive charge in the allyl system during formation of the oxenium ion. In addition, electron-deficient catalysts generally favor the formation of anomalous C−H insertion products, a fact that can be accounted for by an increased rate of hydride transfer to the more electrophilic carbenoid generated and stabilization of the resulting rhodium enolate (**ii**, Scheme 2) by electron withdrawal.

Experiments with Deuterium-Labeled Substrates. The formation of substantial amounts of the anomalous C−H insertion products obtained from the rhodium-catalyzed reactions of the α-diazo ketones **46** and **47** suggests that a zwitterionic intermediate is generated by hydride migration to the electrophilic metal carbenoid in each case. In principle, the ionic intermediate could also serve as an intermediate in the conventional C−H insertion product allowing the reaction to circumvent the generally postulated transition states for the reaction,[14,15] which involve H-migration to the rhodium or carbon

(14) (a) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686. (b) Taber, D. F.; You, K. K.; Rheingold A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547. (c) Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998**, *63*, 3717.

(15) (a) Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (b) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 8991. (c) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.

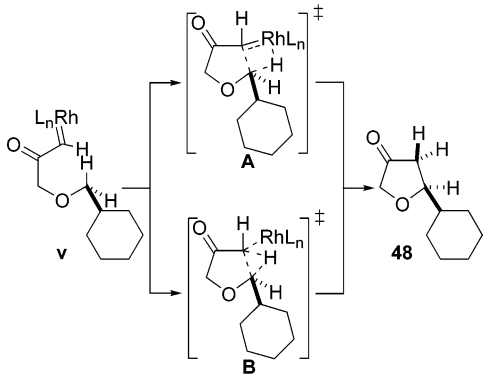
TABLE 5. Rhodium-Catalyzed Reactions of the α-Diazo Ketones 52a,b



substrate	ligand (L)	ratio **53**:**54**	ratio **53**/**54**	ratio **55**:**56**	ratio **55**/**56**
52a	O_2CCH_3	77:23	3.3		
52a	O_2CCF_3	71:29	2.4	75:25	3.0
52b	O_2CCH_3	75:25[a]	3.0[a]		
52b	O_2CCF_3	68:32[b]	2.1[b]	88:12[b]	7.1[b]

[a] The substrate **52b** had 96% deuterium incorporation, and the product ratio is corrected to account for this. [b] The substrate **52b** had 91% deuterium incorporation, and the product ratio is corrected to account for this.

SCHEME 5



center of the carbenoid **v** via the transition state **A** or **B** with concomitant C−C bond formation (Scheme 5).

To gain a better mechanistic understanding of the anomalous C−H insertion, we prepared deuterium-labeled derivatives of the α-diazo ketone **46** and investigated the product distribution obtained upon rhodium carbenoid generation. The simple α-diazo ketone **46** is a particularly good test substrate because there are no overlapping signals in the ^{1}H NMR spectrum of the conventional C−H insertion product **48** or the anomalous C−H insertion product **49** (Figure 1). This greatly simplifies peak assignment and means that accurate integration of signals for individual protons can be performed.

In preliminary studies, the reactions of the deuterium-labeled substrates **52a**,**b** (deuterated analogues of the substrate **46**) were explored. The substrate **52a** was prepared from dideuterated cyclohexane methanol using the route shown in Scheme 4, and the substrate **52b** was prepared by the reaction of CD_2N_2 with the acid chloride derived from the carboxylic acid **44**. Isomeric mixtures of the deuterated 3(2*H*)-furanones **53** and **54** and the deuterated acetals **55** and **56** were obtained upon treatment of either substrate with a substoichiometric amount of $Rh_2(O_2CCH_3)_4$ or $Rh_2(O_2CCF_3)_4$ in dichloromethane at room temperature (eq 8, Table 5). The ketone and acetal products were separated by careful chromatography, and the ratio of products arising from each reaction pathway was determined using ^{1}H NMR spectroscopy.[16] Analysis of the spectra of the mixtures of conventional C−H insertion products **53** and **54** revealed that the ketone **53** predominated in all cases and that there was a modest but significant dependence of product ratio on the catalyst used. Unfortunately, it was not possible to obtain

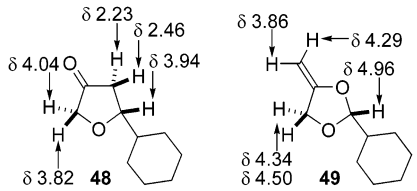


FIGURE 1. ^{1}H NMR peak assignments for the C−H insertion products **48** and **49**.

sufficient amounts of the anomalous products **55** and **56** from the $Rh_2(O_2CCH_3)_4$-mediated reactions. In the case of the $Rh_2(O_2CCF_3)_4$-mediated reaction of the α-diazo ketone **52a**, the isomeric acetals **55a** and **56a** were isolated and the isomer ratio was similar to but not identical with that of the conventional C−H insertion products (**53a** and **54a**) obtained from the same reaction. In contrast, the ratio of isomeric acetals **55b** and **56b** obtained from the $Rh_2(O_2CCF_3)_4$-mediated reaction of the α-diazo ketone **52b** was substantially higher than the ratio of the ketones **53b** and **54b** obtained from the same reaction.

In subsequent studies, cyclization reactions of the deuterated α-diazo ketone **52c** (derived from deuterated cyclohexane methanol) were studied and the deuterium isotope effects in both the conventional and anomalous C−H insertion reactions were calculated (Scheme 6). Previous work by Wang and Adams had shown that a kinetic isotope effect (k_H/k_D) of 1.2−2 was likely for the conventional intramolecular insertion reaction of a rhodium carbenoid into a deuterated ether,[17] and Sulikowski and Lee had obtained kinetic isotope effects of a similar magnitude during intramolecular insertion of rhodium and copper carbenoids into deuterated positions adjacent to tertiary amines.[18]

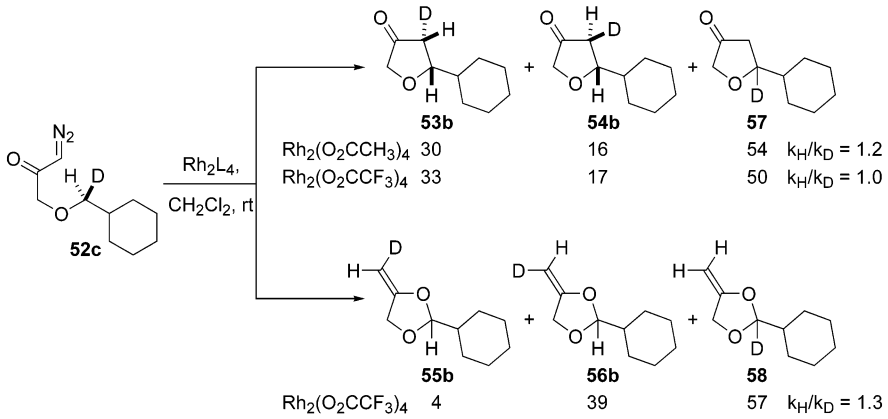
Treatment of the α-diazo ketone **52c** with $Rh_2(O_2CCH_3)_4$ in dichloromethane at room temperature and subsequent ^{1}H NMR analysis of the conventional C−H insertion products indicated a 65:35 ratio of the diastereoisomers **53b** and **54b** and a kinetic isotope effect (**57**/[**53b** + **54b**])

(16) The deuterated acetals **55b**, **56b**, and **58** were unstable to silica gel, and the deuterated 3(2*H*)-furanones **53b** and **54b** underwent significant deuterium−hydrogen exchange on exposure to alumina. To circumvent this problem, the crude reaction mixture was split and half was purified by flash column chromatography on silica gel while the other half was purified by flash column chromatography on neutral alumina prior to analysis by ^{1}H NMR spectroscopy.

(17) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296.

(18) Sulikowski, G. A.; Lee, S. *Tetrahedron Lett.* **1999**, *40*, 8035.

SCHEME 6



of 1.2. Unfortunately, it was not possible to isolate sufficient quantities of the products (**55b**, **56b**, and **58**) arising from the anomalous C−H insertion reaction for a comparison of the kinetic isotope effect with that of the conventional C−H insertion reaction to be made. However, both sets of products were isolable from the $Rh_2(O_2CCF_3)_4$-catalyzed reaction. In this case, the diastereoisomers **53b** and **54b** were obtained in a 66:34 ratio and the kinetic isotope effect (**57**/[**53b** + **54b**]) was 1.0.In contrast, the isomeric anomalous products **55b** and **56b** were obtained as a 9:91 mixture and the kinetic isotope effect (**58**/ [**55b** + **56b**]) was 1.3.

The temperature and solvent dependence of the reaction were also explored. The ratios of products obtained from the $Rh_2(O_2CCF_3)_4$-mediated reaction in dichloromethane were virtually identical at 0 °C, room temperature, or reflux.[19] To extend the temperature range, the same reaction was performed in 1,2-dichloroethane at 0 °C, room temperature, or reflux.[20] Although the ratio of products differed from those obtained in dichloromethane, there was little variation in the relative ratios of products within each reaction manifold between 0 and 83 °C.

Several important findings emerge from the results obtained using deuterium-labeled substrates. First, in the case of the reaction of the α-diazo ketone **52c** mediated by $Rh_2(O_2CCF_3)_4$, there is a modest but significant difference between the kinetic isotope effect for the conventional reaction and that for the anomalous reaction. This finding rules out a common rate determining C−H bond cleavage step for the conventional and anomalous C−H insertion reactions. Second, the high level of diastereocontrol (**55b**:**56b**, 9:91) obtained from the anomalous C−H insertion reaction contrasts with the modest level of diastereocontrol (**53b**:**54b**, 66:34) obtained during the conventional C−H insertion reaction; a similar though less pronounced effect was observed during the cyclization of the α-diazo ketones **52a**,**b**. This result demonstrates that the stereochemistry-defining steps differ in the conventional and anomalous C−H insertion reactions. It also precludes the intermediacy of an equilibrating or freely rotating rhodium enolate generated by hydride transfer prior to C−C bond formation (as in Scheme 1) because this would produce a 1:1 mixture of the labeled acetals **55** and **56** (Scheme 1). Finally, the kinetic isotope effects for both the conventional and anomalous C−H insertion reactions are generally independent of the reaction temperature, a finding that is indicative of the nonlinear transition state required for intramolecular H-transfer.[21]

The most plausible explanation for the data obtained from the reactions of deuterium-labeled precursors is that conventional C−H insertion occurs by the generally accepted mechanism illustrated in Scheme 5 and that anomalous C−H insertion occurs by the mechanism shown in Scheme 7. In the case of anomalous C−H insertion, oxygen-assisted hydride migration to the rhodium center of the carbenoid results in enolate formation. Bond rotation then allows C−O bond formation by trapping of the oxenium ion with the enolate oxygen. Subsequent reductive elimination then delivers the acetal product and allows catalyst regeneration. In the mechanism shown in Scheme 7, the stereochemical outcome of the reaction (i.e. **55** > **56**, eq 8, and **56b** > **55b**, Scheme 6) is dictated by attack of hydride on the metal center of the carbenoid in the most favorable conformation.

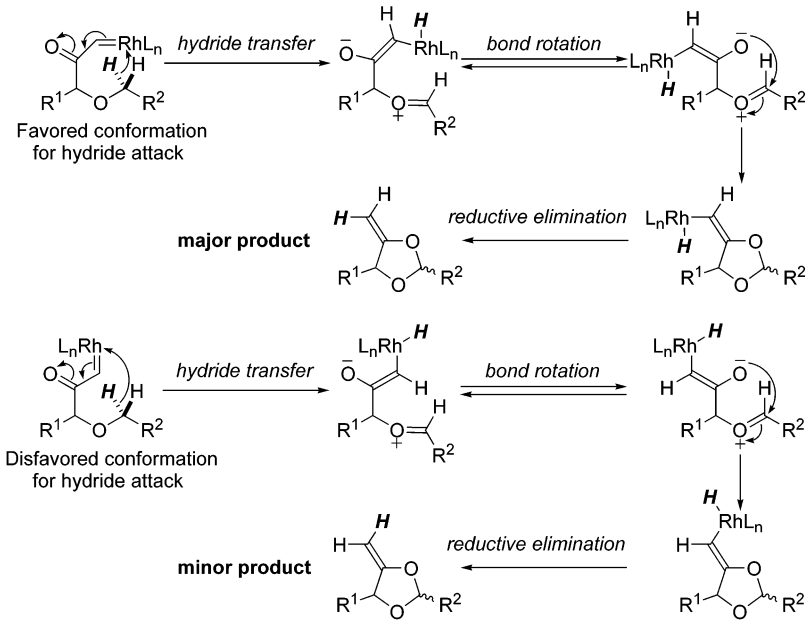
The hydride transfer mechanism outlined in Scheme 7 accounts for both the discrepancy in kinetic isotope effects between the anomalous and conventional C−H insertion reactions and for the high stereoselectivity observed in the anomalous C−H insertion reaction. It should be noted that an analogous hydride transfer step appears in the mechanism proposed by White and Hrnciar to explain the formation of anomalous (but nonacetal) products upon intramolecular C−H insertion of a rhodium carbenoid during their synthetic work on (+)-codeine.[12]

(19) The product ratios obtained from reactions performed with $Rh_2(O_2CCF_3)_4$ at various temperatures in dichloromethane were as follows: 0 °C, **53b**:**54b**:**57**, 33:16:51, and **55b**:**56b**:**58**, 5:39:56; room temperature, see Scheme 6; reflux, **53b**:**54b**:**57**, 34:15:51, and **55b**:**56b**:**58**, 5:39:56.

(20) The product ratios obtained from reactions performed with $Rh_2(O_2CCF_3)_4$ at various temperatures in 1,2-dichloroethane were as follows: 0 °C, **53b**:**54b**:**57**, 31:13:56, and **55b**:**56b**:**58**, 3:42:55; room temperature, **53b**:**54b**:**57**, 30:12:58, and **55b**:**56b**:**58**, 2:42:56; reflux, **53b**:**54b**:**57**, 29:14:57, and **55b**:**56b**:**58**, 5:40:55.

(21) (a) Kwart, H. *Acc. Chem. Res.* **1982**, *15*, 401. (b) Anhede, B.; Bergman, N.-Å. *J. Am. Chem. Soc.* **1984**, *106*, 7634. (c) Dakin, L. A.; Ong, P. C.; Panek, J. S.; Staples, R. J.; Stavropoulos, P. *Organometallics* **2000**, *19*, 2896.

SCHEME 7



Experimental Section

Preparation of 4-Phenyl-2-((trimethylsilyl)methyl)-but-1-ene.[22] Dry cerium(III) chloride (18.5 g, 75.1 mmol) was heated at 140 °C under vacuum (∼0.5 mmHg) in a 250 mL round-bottom flask for 2 h and then cooled to room temperature. The vacuum was released and the flask immediately flushed with N_2. Dry THF (100 mL) was added to the cerium(III) chloride at a steady rate with vigorous stirring to produce an even suspension. The mixture was stirred at room temperature for 3 h during which sonication was also applied for 1 h. The suspension was then cooled to −72 °C, and then ((trimethylsilyl)methyl)magnesium chloride (80 mL of 1.0 M solution in diethyl ether, 80 mmol) was added over a period of 45 min in 10 mL aliquots. The mixture was stirred for an additional 30 min, and then methyl 3-phenylpropionate (4.02 g, 2.44 mmol) in dry THF (10 mL) was added over 2 min. The mixture was kept at −72 °C for 2 h and then gradually allowed to come to room temperature and left to stir overnight. The reaction was cooled to 0 °C and quenched by the addition of saturated aqueous NH_4Cl solution (100 mL). The mixture was diluted with water (100 mL) and the products extracted into diethyl ether (3 × 200 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (100 mL) and then dried (Na_2SO_4 and then $CaCl_2$) and concentrated in vacuo. The residue was redissolved in CH_2Cl_2 (200 mL) and silica gel added (40 g), and the resultant slurry was stirred for 2 h and then filtered and concentrated to an oil in vacuo. Purification by flash column chromatography (petrololeum ether 40−60) gave 4-phenyl-2-((trimethylsilyl)methyl)but-1-ene (3.9 g, 73%) as a colorless oil: $R_f = 0.45$ (petroleum ether 40−60); IR (liquid film) 3068, 3028, 2953, 1940, 1742, 1693, 1631, 1603 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.30−7.13 (m, 5H), 4.65 (d, 1H, J = 0.9 Hz), 4.56 (d, 1H, J = 0.9 Hz), 2.78−2.72 (m, 2H), 2.28−2.22 (m, 2H), 1.58 (s, 2H), 0.03 (m, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 147.4 (C), 142.6 (C), 128.6 (CH), 128.5 (CH), 126.0 (CH), 107.4 (CH_2), 40.4 (CH_2), 34.7 (CH_2), 27.2 (CH_2), −1.1 (CH_3); HRMS (EI) for $C_{14}H_{22}Si$ [M^+] calcd 218.1491, found 218.1490. Anal. Calcd for $C_{14}H_{22}Si$: C, 76.99; H, 10.15. Found: C, 76.71; H 9.99.

Preparation of 4-Phenyl-2-(hydroxymethyl)but-1-ene.[23] Osmium tetroxide (2 mL of 1% solution in water) was added to a stirred solution of 4-phenyl-2-((trimethylsilyl)methyl)but-1-ene (3.00 g, 13.7 mmol), *N*-methylmorpholine *N*-oxide (6.00 g, 51.2 mmol), and pyridine (2 drops) in a mixture of acetone (30 mL), water (5 mL), and *tert*-butyl alcohol (5 mL). The mixture was stirred at room temperature for 16 h and then concentrated and rediluted with water (100 mL). The mixture was extracted into CH_2Cl_2 (4 × 100 mL), and the combined extracts were dried ($MgSO_4$) and concentrated to an oil in vacuo. Purification by flash column chromatography (EtOAc/petroleum ether 40−60, 1:4) gave the diol (3.06 g, 88%) as a colorless oil. The diol was immediately dissolved in methanol (40 mL), and glacial acetic acid (15 mL) was added. The mixture was heated at reflux for 2 h and then cooled, and the acid was quenched with concentrated ammonia solution (10 mL). The mixture was then concentrated (∼20 mL) and diluted with water (100 mL), and the products were extracted into diethyl ether (3 × 100 mL). The extracts were dried (Na_2SO_4 and then $CaCl_2$) and concentrated in vacuo to an oil. Purification by flash column chromatography (EtOAc/petroleum ether, 1:4) gave 2-methylene-4-phenyl-1-butanol (1.97 g, 99%) as a colorless oil: $R_f = 0.32$ (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 3363, 3027, 2928, 1703, 1649, 1602, 898 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.30−7.12 (m, 5H), 5.04 (s, 1H), 4.90 (s, 1H), 4.04 (s, 2H), 2.77 (t, 2H, J = 7.8 Hz), 2.35 (t, 2H, J = 7.8 Hz), 2.11 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 148.6 (C), 142.0 (C), 128.6 (CH), 128.6 (CH), 126.1 (CH), 110.0 (CH_2), 66.1 (CH_2), 34.8 (CH_2), 34.5 (CH_2); HRMS (EI) for $C_{11}H_{14}O$ [M^+] calcd 162.1045, found 162.1042.

General Procedure for the O−H Insertion of Carbenoids Generated from Ethyl Diazoacetate or Ethyl Diazopropionate. A solution of either ethyl diazoacetate or ethyl diazopropionate in dry CH_2Cl_2 was added by syringe pump over 1 h to a stirred solution of the alcohol and the catalyst in dry CH_2Cl_2 at the appropriate temperature under nitrogen. After the addition was complete, the mixture was left at the given temperature for a further 20 min and then concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether 40−60/diethyl ether, 10:1).

(22) Fleming, I.; Pearce, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 251.

(23) Charlton, J. L.; Williams, G. J.; Lypka, G. N. *Can. J. Chem.* **1980**, *58*, 1271.

Preparation of Ethyl (2-Methylene-4-phenylbutoxy)-acetate (9). Ethyl diazoacetate (0.970 mL, 9.22 mmol) in CH_2Cl_2 (100 mL) was added to 4-phenyl-2-(hydroxymethyl)-but-1-ene (1.50 g, 9.25 mmol) and $Cu(acac)_2$ (40 mg) in CH_2Cl_2 (30 mL) at reflux. The ester **9** (1.72 g, 75%) was isolated as a colorless oil: IR (liquid film) 3028, 2930, 1756, 1644, 1602, 1029 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.30−7.18 (m, 5H), 5.06 (s, 1H), 4.99 (s, 1H), 4.24 (q, 2H, J = 7.2 Hz), 4.05 (s, 2H), 4.03 (s, 2H), 2.80 (t, 2H, J = 7.4 Hz), 2.40 (t, 2H, J = 7.4 Hz), 1.28 (t, 3H, J = 7.2 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.4 (C), 144.5 (C), 141.8 (C), 128.3 (CH), 128.3 (CH), 125.8 (CH), 113.4 (CH_2), 74.4 (CH_2), 67.0 (CH_2), 60.8 (CH_2), 34.6 (CH_2), 34.0 (CH_2), 14.2 (CH_3); HRMS (CI, CH_4) for $C_{15}H_{20}O_3$ [M^+] calcd 247.1334, found 247.1344. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.60; H 8.29.

Ethyl (1-Cyclohexen-1-ylmethoxy)acetate (10). Ethyl diazoacetate (0.380 mL, 3.60 mmol) in CH_2Cl_2 (20 mL) was added to 1-cyclohexenylmethanol (336 mg, 3.00 mmol) and $Rh_2(O_2CCPh_3)_4$ (10 mg) in CH_2Cl_2 (5 mL). The ester **10** (331 mg, 56%) was isolated as a colorless oil: R_f = 0.85 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2930, 1754, 921, 900, 857, 831, 802 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.71 (br, 1H), 4.22 (q, 2H, J = 7.2 Hz), 4.01 (s, 2H), 3.94 (s, 2H), 2.08−2.00 (m, 4H), 1.70−1.50 (m, 4H), 1.30 (t, 3H, J = 7.2 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.8 (C), 134.2 (C), 126.7 (CH), 76.4 (CH_2), 66.8 (CH_2), 60.9 (CH_2), 26.0 (CH_2), 25.2 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 14.4 (CH_3); HRMS (EI) for $C_{11}H_{18}O_3$ [M^+] calcd 198.1256, found 198.1247. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.39; H 9.35.

Ethyl (2-Cyclohexylideneethoxy)acetate (11). Ethyl diazoacetate (0.830 mL, 7.89 mmol) in CH_2Cl_2 (30 mL) was added to (2-cyclohexylidene)ethanol (1.00 g, 7.92 mmol) and $Rh_2(O_2CCPh_3)_4$ (20 mg) in CH_2Cl_2 (10 mL). The ester **11** (1.49 g, 89%) was isolated as a colorless oil: R_f = 0.81 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2930, 2854, 1754, 1665, 855 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.30 (t, 1H, J = 7.3 Hz), 4.22 (q, 2H, J = 7.3 Hz), 4.10 (d, 2H, J = 7.3 Hz), 4.10 (s, 2H), 2.23−2.10 (m, 4H), 1.60−1.45 (m, 6H), 1.30 (t, 3H, J = 7.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.8 (C), 146.6 (C), 116.8 (CH), 66.9 (CH_2), 66.8 (CH_2), 60.9 (CH_2), 37.2 (CH_2), 29.1 (CH_2), 28.5 (CH_2), 27.9 (CH_2), 26.8 (CH_2), 14.4 (CH_3); HRMS (CI, CH_4) for $C_{12}H_{21}O_3$ [$(M + H)^+$] calcd 211.1334, found 211.1337. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.55; H 9.66.

Ethyl 2-(2-Cyclohexylideneethoxy)propionate (12). Ethyl diazopropionate (1.22 g, 9.52 mmol) in CH_2Cl_2 (30 mL) was added to (2-cyclohexylidene)ethanol (1.00 g, 7.92 mmol) and $Rh_2(O_2CCPh_3)_4$ (20 mg) in CH_2Cl_2 (10 mL). The ester **12** (1.36 g, 76%) was isolated as a colorless oil: R_f = 0.85 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2930, 1747, 1665, 855 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.29 (t, 1H, J = 6.9 Hz), 4.25−4.08 (m, 3H), 4.03−3.94 (m, 2H), 4.01−3.94 (m, 1H), 2.10−2.07 (m, 4H), 1.58−1.45 (m, 6H), 1.40 (d, 3H, J = 6.9 Hz), 1.29 (t, 3H, J = 7.1 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.7 (C), 145.8 (C), 117.2 (CH), 73.6 (CH), 65.6 (CH_2), 60.8 (CH_2), 37.2 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 27.8 (CH_2), 26.8 (CH_2), 18.9 (CH_3), 14.4 (CH_3); HRMS (CI, CH_4) for $C_{13}H_{21}O_3$ [$(M - H)^+$] calcd 225.1491, found 225.1504. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.50; H 9.97.

Ethyl (Cyclohexylmethoxy)acetate (42). Ethyl diazoacetate (2.30 mL, 21.9 mmol) in CH_2Cl_2 (60 mL) was added to cyclohexylmethanol (2.50 g, 21.9 mmol) and $Rh_2(O_2CCH_3)_4$ (20 mg) in CH_2Cl_2 (20 mL). The ester **42** (3.84 g, 88%) was isolated as a colorless oil: R_f = 0.88 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2923, 1756 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.18 (q, 2H, J = 7.2 Hz), 4.02 (s, 2H), 3.29 (d, 2H, J = 6.5 Hz), 1.81−1.52 (m, 6H), 1.25 (t, 3H, J = 7.2 Hz), 1.28−1.10 (m, 3H), 0.98−0.85 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.7 (C), 77.7 (CH_2), 68.6 (CH_2), 60.7 (CH_2), 38.0 (CH), 30.0 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 14.3 (CH_3); HRMS (CI, CH_4) for $C_{11}H_{20}O_3$ [M^+] calcd 201.1490, found 201.1507. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.92; H 10.19.

Ethyl 2-(Cyclohexylmethoxy)propionate (43). Ethyl diazopropionate (1.00 g, 7.81 mmol) in CH_2Cl_2 (50 mL) was added to cyclohexylmethanol (892 mg, 7.81 mmol) and $Rh_2(O_2CCH_3)_4$ (20 mg) in CH_2Cl_2 (10 mL). The ester **43** (1.10 g, 66%) was isolated as a colorless oil: R_f = 0.88 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2920, 2852, 1738 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.19 (dq, 2H, J = 2.7, 7.3 Hz), 3.90 (q, 1H, J = 6.9 Hz), 3.36 (dd, 1H, J = 6.5, 8.9 Hz), 3.15 (dd, 1H, J = 6.7, 8.9 Hz), 1.80−1.52 (m, 6H), 1.38 (d, 3H, J = 6.9 Hz), 1.28 (t, 3H, J = 7.2 Hz), 1.25−1.12 (m, 3H), 0.98−0.86 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.9 (C), 76.4 (CH_2), 75.5 (CH_2), 61.0 (CH_2), 38.3 (CH), 30.3 (CH_2), 26.9 (CH_2), 26.1 (CH_2), 18.9 (CH_3), 14.5 (CH_3); HRMS (EI) for $C_{12}H_{22}O_3$ [M^+] calcd 214.1568, found 214.1575. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.28; H 10.25.

General Two Step Procedure for the Conversion of an Ester into an α-Diazo Ketone. A 2 M solution of aqueous lithium hydroxide (2 equiv) was added to a solution of the ethyl ester in methanol. The mixture was stirred at room temperature overnight and then diluted with 2 M aqueous NaOH (5 mL) and water (50 mL). The aqueous solution was washed with diethyl ether (2 × 50 mL) and then acidified to pH 2 with 2 M aqueous HCl. The product was then extracted into diethyl ether (3 × 75 mL), and the combined were extracts dried (Na_2SO_4 and then $CaCl_2$) and concentrated in vacuo. The crude carboxylic acid was used without further purification.

Isobutyl chloroformate (1 equiv) was added to a stirred solution of the crude acid and triethylamine (1 equiv) in dry diethyl ether at room temperature under nitrogen. The mixture was left to stir for 3 h and then filtered and added dropwise over 30 min to a solution of diazomethane (at least 2 equiv in diethyl ether) at room temperature. The α-diazo ketone was then left to form overnight. Excess diazomethane was quenched with acetic acid (1−2 mL) and the mixture diluted with diethyl ether (100 mL) and washed successively with saturated sodium bicarbonate solution (50 mL) and brine (50 mL). The yellow solution was dried (Na_2SO_4 and then $CaCl_2$) and concentrated in vacuo to an oil. Flash column chromatography on silica gel gave the required α-diazo ketone.

1-Diazo-3-(2-methylene-4-phenylbutoxy)-2-propanone (17). Ethyl (2-methylene-4-phenylbutoxy)acetate (**9**) (1.00 g, 4.03 mmol) was hydrolyzed by following the general procedure using 2 M aqueous lithium hydroxide (5 mL) and methanol (10 mL). The resulting carboxylic acid **13** was then converted into the α-diazo ketone by using the general protocol and by employing the following quantities of reagents and solvents: isobutyl chloroformate (0.52 mL, 4.0 mmol); triethylamine (0.56 mL 4.0 mmol); diethyl ether (40 mL); diazomethane (8 mmol in diethyl ether). Flash column chromatography on silica gel (hexane/diethyl ether, 5:1) gave the α-diazo ketone **17** (747 mg, 76% for two steps) as a yellow oil: R_f = 0.45 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2924, 2108, 1641, 909 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.31−7.16 (m, 5H), 5.72 (br, 1H), 5.06 (s, 1H), 5.00 (s, 1H), 3.96 (s, 4H), 2.79 (t, 2H, J = 8.0 Hz), 2.37 (t, 2H, J = 8.0 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 193.9 (C), 144.6 (C), 141.8 (C), 128.6 (CH), 128.5 (CH), 126.2 (CH), 113.2 (CH_2), 74.7 (CH_2), 73.8 (CH_2), 53.3 (CH), 34.8 (CH_2), 34.3 (CH_2); HRMS (CI, CH_4) for $C_{14}H_{17}O_2N_2$ [$(M + H)^+$] calcd 245.1290, found 245.1328.

1-(1-Cyclohexen-1-ylmethoxy)-3-diazo-2-propanone (18). Ethyl (1-cyclohexen-1-ylmethoxy)acetate (**10**) (771 mg, 3.89 mmol) was hydrolyzed by following the general procedure using 2 M aqueous lithium hydroxide (8 mL) and methanol (8 mL). The resulting carboxylic acid **14** was then converted into the α-diazo ketone by using the general protocol and by employing the following quantities of reagents and solvents: isobutyl chloroformate (0.50 mL, 3.9 mmol); triethylamine (0.54 mL 3.9 mmol); diethyl ether (15 mL); diazomethane (8 mmol in diethyl ether). Flash column chromatography on silica

gel (hexane/diethyl ether, 7:1 and then 5:1) gave the α-diazo ketone **18** (455 mg, 60% for two steps) as a yellow oil: R_f = 0.50 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 3128, 2928, 2104, 1641, 832, 802 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.78 (br, 1H), 5.71 (m, 1H), 3.94 (s, 2H), 3.88 (s, 2H), 2.10−1.95 (m, 4H), 1.70−1.53 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 194.3 (C), 133.9 (C), 126.6 (CH), 76.4 (CH_2), 73.3 (CH_2), 53.2 (CH), 26.0 (CH_2), 25.1 (CH_2), 22.6 (CH_2), 22.4 (CH_2); HRMS (CI, CH_4) for $C_{10}H_{15}O_2N_2$ [(M + H)$^+$] calcd 195.1134, found 195.1120.

1-(2-Cyclohexylideneethoxy)-3-diazo-2-propanone (19). Ethyl (2-cyclohexylideneethoxy)acetate (**11**) (632 mg, 2.98 mmol) was hydrolyzed by following the general procedure using 2 M aqueous lithium hydroxide (3 mL) and methanol (5 mL). The resulting carboxylic acid **15** was then converted into the α-diazo ketone by using the general protocol and by employing the following quantities of reagents and solvents: isobutyl chloroformate (0.37 mL, 2.9 mmol); triethylamine (0.42 mL, 3.0 mmol); diethyl ether (15 mL); diazomethane (6 mmol in diethyl ether). Flash column chromatography on silica gel (hexane/diethyl ether, 7:1 and then 5:1) gave the α-diazo ketone **19** (434 mg, 70%) as a yellow oil: R_f = 0.51 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2930, 2854, 2107, 1641 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.77 (br, 1H,), 5.26 (t, 1H, J = 7.1 Hz), 4.04 (d, 2H, J = 7.1 Hz), 3.97 (s, 2H), 2.22−2.10 (m, 4H), 1.62−1.46 (m, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 194.5 (C), 146.7 (C), 116.6 (CH), 73.5 (CH_2), 67.2 (CH_2), 53.2 (CH), 37.2 (CH_2), 29.2 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 26.7 (CH_2); LRMS (CI, CH_4) 209.1 [(M + H)$^+$]; 181, 151, 137, 125, 109.

3-(2-Cyclohexylideneethoxy)-1-diazo-2-butanone (20). Ethyl 2-(2-cyclohexylideneethoxy)propionate (**12**) (1.27 g, 5.61 mmol) was hydrolyzed by following the general procedure using 2 M aqueous lithium hydroxide (6 mL) and methanol (12 mL). The resulting carboxylic acid **16** was then converted into the α-diazo ketone by using the general protocol and by employing the following quantities of reagents and solvents: isobutyl chloroformate (0.73 mL, 5.6 mmol); triethylamine (0.78 mL, 5.6 mmol); diethyl ether (25 mL); diazomethane (12 mmol in diethyl ether). Flash column chromatography on silica gel (hexane/diethyl ether, 7:1) gave the α-diazo ketone **20** (982 mg, 79% for two steps) as a yellow oil: R_f = 0.61 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 3126, 2930, 2856, 2105, 1642, 910, 854 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.78 (br, 1H), 5.31−5.24 (m, 1H), 4.12−3.97 (m, 2H), 3.88 (q, 1H, J = 6.9 Hz), 2.18−2.06 (m, 4H), 1.58−1.46 (m, 6H), 1.33 (d, 3H, J = 6.9 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 198.3 (C), 146.0 (C), 116.9 (CH), 79.5 (CH), 65.8 (CH_2), 51.9 (CH), 37.2 (CH_2), 29.2 (CH_2), 28.5 (CH_2), 27.9 (CH_2), 26.7 (CH_2), 19.0 (CH_3); HRMS (CI, CH_4) for $C_{12}H_{19}O_2N_2$ [(M + H)$^+$] calcd 223.1240, found 223.1233. Anal. Calcd for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N 12.60. Found: C, 64.53; H 8.13; N 12.19.

1-(Cyclohexylmethoxy)-3-diazo-2-propanone (46). Ethyl (cyclohexylmethoxy)acetate (**42**) (2.00 g, 0.999 mmol) was hydrolyzed by following the general procedure using 2 M aqueous lithium hydroxide (5 mL) and methanol (10 mL). The resulting carboxylic acid **44** was then converted into the α-diazo ketone by using the general protocol and by employing the following quantities of reagents and solvents: isobutyl chloroformate (1.30 mL, 10.0 mmol); triethylamine (1.39 mL, 9.97 mmol); diethyl ether (50 mL); diazomethane (20 mmol in diethyl ether). Flash column chromatography on silica gel (hexane/diethyl ether, 7:1) gave the α-diazo ketone **46** (1.66 g, 85% for two steps) as a yellow oil: R_f = 0.68 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 3129, 2925, 2853, 2108, 1642 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.76 (br, 1H), 3.97 (s, 2H), 3.29 (d, 2H, J = 6.7 Hz), 1.97−1.50 (m, 6H), 1.30−1.14 (m, 3H), 1.04−0.91 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 194.5 (C), 77.8 (CH_2), 75.0 (CH_2), 53.1 (CH), 38.1 (CH), 30.1 (CH_2), 30.1 (CH_2), 26.6 (CH_2), 26.0 (CH_2); HRMS (CI, CH_4) for $C_{10}H_{17}O_2N_2$ [(M + H)$^+$] calcd 197.1290, found 197.1293.

3-(Cyclohexylmethoxy)-1-diazo-2-butanone (47). Ethyl 2-(cyclohexylmethoxy)propionate (**43**) (1.10 g, 5.13 mmol) was hydrolyzed by following the general procedure using 2 M aqueous lithium hydroxide (6 mL) and methanol (6 mL). The resulting carboxylic acid **45** was then converted into the α-diazo ketone by using the general protocol and by employing the following quantities of reagents and solvents: isobutyl chloroformate (0.67 mL, 5.2 mmol); triethylamine (0.72 mL 5.2 mmol); diethyl ether (35 mL); diazomethane (10 mmol in diethyl ether). Flash column chromatography on silica gel (hexane/diethyl ether, 7:1) gave the α-diazo ketone **47** (846 mg, 78% for two steps) as a yellow oil: R_f = 0.74 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2978, 2924, 2852, 2105, 1643 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.73 (br, 1H), 3.89 (q, 1H, J = 6.8 Hz), 3.26 (d, 2H, J = 6.3 Hz), 1.52−1.81 (m, 6H), 1.31 (d, 3H, J = 6.8 Hz), 1.30−1.13 (m, 3H), 1.02−0.84 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 198.2 (C), 80.5 (CH), 76.0 (CH), 51.7 (CH), 38.1 (CH), 30.1 (CH_2), 29.8 (CH_2), 26.4 (CH_2), 25.7 (CH_2), 18.5 (CH_3); HRMS (CI, CH_4) for $C_{11}H_{19}O_2N_2$ [(M + H)$^+$] calcd 211.1447, found 211.1451. Anal. Calcd for $C_{11}H_{18}O_2N_2$: C, 62.83; H, 8.63; N 13.32. Found: C, 62.75; H 8.89; N 13.23.

General Procedure for the Rhodium(II)-Catalyzed Reactions of the α-Diazo Ketones. The rhodium(II) catalyst was added in one portion to a stirred solution of the α-diazo ketone in dry CH_2Cl_2 under N_2. The reaction was typically left to stir for 1 h at room temperature and then the solution concentrated in vacuo to give an oil. The reaction mixture was then purified by careful flash column chromatography on neutral alumina (Brockmann grade 3).

Reaction of 1-Diazo-3-(2-methylene-4-phenylbutoxy)-2-propanone (17). According to the general procedure, 1-diazo-3-(2-methylene-4-phenylbutoxy)-2-propanone (**17**) (368 mg, 1.51 mmol) was treated with $Rh_2(O_2CCH_3)_4$ (10 mg) in CH_2Cl_2 (200 mL). Flash column chromatography on neutral alumina (petroleum ether 40−60 and then 2%−10% diethyl ether in petroleum ether 40−60) gave three compounds.

1-(2-Phenylethyl)-3-oxabicyclo[4.1.0]heptan-5-one (21). This was isolated as a colorless oil (219.0 mg, 67% yield): R_f = 0.48 (petroleum ether 40−60/diethyl ether); IR (liquid film) 3014, 2923, 2858, 1700, 1602, 697 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.32−7.14 (m, 5H), 4.13 (d, 1H, J = 18.1 Hz), 4.01 (d, 1H, J = 11.3 Hz), 3.74 (d, 1H, J = 18.1 Hz), 3.03 (d, 1H, J = 11.3 Hz), 2.69 (t, 2H, J = 8.2 Hz), 1.95−1.63 (m, 4H), 1.09 (dd, 1H, J = 4.5, 9.8 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 205.6 (C), 141.3 (C), 128.8 (CH), 128.4 (CH), 126.4 (CH), 72.7 (CH_2), 66.5 (CH_2), 35.8 (CH_2), 33.1 (CH), 32.9 (CH_2), 28.0 (C), 16.8 (CH_2); HRMS (CI, CH_4) for $C_{14}H_{17}O_2$ [(M + H)$^+$] calcd 217.1229, found 217.1222. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.28; H 7.60.

Dihydro-5-(1-methylene-3-phenylpropyl)-3(2*H*)-furanone (22). This was isolated as a colorless oil (48.0 mg, 15% yield): R_f = 0.64 (petroleum ether 40−60/diethyl ether); IR (liquid film) 3088, 2991, 2924, 2852, 1766, 1651, 1603, 902 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25−7.01 (m, 5H), 5.11 (s, 1H), 4.97 (s, 1H), 4.63 (dd, 1H, J = 6.5, 9.1 Hz), 4.03 (d, 1H, J = 17.0 Hz), 3.82 (d, 1H, J = 17.0 Hz), 2.75 (m, 2H), 2.52 (dd, 1H, J = 6.5, 17.8 Hz), 2.41−2.24 (m, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 214.2 (C), 146.7 (C), 141.5 (C), 128.4 (CH), 128.3 (CH), 126.0 (CH), 111.5 (CH_2), 80.1 (CH), 71.2 (CH_2), 41.8 (CH_2), 34.2 (CH_2), 33.5 (CH_2); HRMS (EI) for $C_{14}H_{16}O_2$ [M$^+$] calcd 216.1150, found 216.1157.

4-Methylene-2-(1-methylene-3-phenylpropyl)-1,3-dioxolane (23). This was isolated as a colorless oil (20.4 mg, 6% yield): R_f = 0.83 (petroleum ether 40−60/diethyl ether); IR (liquid film) 3088, 2927, 2861, 1688, 1655, 904, 870 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.31−7.18 (m, 5H), 5.57 (s, 1H), 5.34 (s, 1H), 5.14 (s, 1H), 4.55 (ddd, 1H, J = 1.5, 1.6, 12.2 Hz), 4.42 (ddd, 1H, J = 1.9, 2.1, 12.2 Hz), 4.38−4.35 ("q", 1H, J = 2.1 Hz), 3.94−3.91 (m, 1H, J = 2.0 Hz), 2.82 (t, 2H, J = 7.3 Hz), 2.41 (t, 2H, J = 7.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 155.8 (C), 144.0 (C), 141.8 (C), 128.4 (CH), 128.3 (CH), 125.9 (CH),

116.4 (CH_2), 107.8 (CH), 78.3 (CH_2), 67.3 (CH_2), 34.1 (CH_2), 30.8 (CH_2); HRMS (EI) for $C_{14}H_{16}O_2$ [M^+] calcd 216.1150, found 216.1145.

Reaction of 1-(1-Cyclohexen-1-ylmethoxy)-3-diazo-2-propanone (18). According to the general procedure, 1-(1-cyclohexen-1-ylmethoxy)-3-diazo-2-propanone (**18**) (44.8 mg, 0.231 mmol) was treated with $Rh_2(O_2CCF_3)$ (2 mg) in CH_2Cl_2 (30 mL). Flash column chromatography on neutral alumina (petroleum ether 40−60 and then 10% diethyl ether in petroleum ether 40−60) gave three compounds.

Hexahydro-1*H*-benzo[1,3]cyclopropa[1,2-*c*]pyran-4(3*H*)-one (28). This was isolated as a colorless oil (27.0 mg, 72% yield): R_f = 0.64 (petroleum ether 40−60/diethyl ether); IR (liquid film) 3015, 2939, 1684 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.10 (d, 1H, J = 18.2 Hz), 3.85 (d, 1H, J = 11.3 Hz), 3.72 (dd, 1H, J = 0.8, 18.2 Hz), 3.56 (d, 1H, J = 11.3 Hz), 2.43−2.37 (m, 1H), 2.03−1.90 (m, 1H), 1.80−1.59 (m, 4H), 1.44−1.24 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 205.6 (C), 72.3 (CH_2), 68.0 (CH_2), 38.8 (CH), 28.3 (C), 24.2 (CH_2), 23.4 (CH), 22.9 (CH_2), 21.0 (CH_2), 20.3 (CH_2); HRMS (EI) for $C_{10}H_{14}O_2$ [M^+] calcd 166.0994, found 166.0990.

5-(1-Cyclohexen-1-yl)dihydro-3(2*H*)-furanone (29). This was isolated as a colorless oil (3.2 mg, 8% yield): R_f = 0.70 (petroleum ether 40−60/diethyl ether); IR (liquid film) 3017, 2932, 1758 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.79 (br, 1H), 4.59 (dd, 1H, J = 6.7, 9.0 Hz), 4.08 (d, 1H, J = 17.0 Hz), 3.87 (d, 1H, J = 17.0 Hz), 2.52 (dd, 1H, J = 6.7, 18.0 Hz), 2.41 (dd, 1H, J = 9.1, 18.0 Hz), 2.00−2.06 (m, 4H), 1.54−1.72 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 215.4 (C), 135.7 (C), 125.5 (CH), 81.7 (CH), 71.5 (CH_2), 41.2 (CH_2), 25.1 (CH_2), 23.9 (CH_2), 22.6 (CH_2), 22.5 (CH_2); HRMS (EI) for $C_{10}H_{14}O_2$ [M^+] calcd 166.0994, found 166.0989.

2-(1-Cyclohexen-1-yl)-4-methylene-1,3-dioxolane (30). R_f = 0.92 (petroleum ether 40−60/diethyl ether). Partial data: ^1H NMR (270 MHz, $CDCl_3$) δ 4.33 ("q", 1H, J = 2.0 Hz), 4.39 ("dt", 1H, J = 2.0, 12.2 Hz), 4.54 ("dt", 1H, J = 1.5, 12.2 Hz), 5.44 (s, 1H), 5.81−5.99 (m, 1H); GC-MS peak at R_t = 2.88 min; LRMS (EI) calcd for $C_{10}H_{14}O_2$ 166, mass found 166, 137, 108, and 93.

Reaction of 1-(2-Cyclohexylideneethoxy)-3-diazo-2-propanone (19). According to the general procedure, 1-(2-cyclohexylideneethoxy)-3-diazo-2-propanone (**19**) (500 mg, 2.40 mmol) was treated with $Rh_2(O_2CCH_3)_4$ (20 mg) in CH_2Cl_2 (120 mL). Flash column chromatography on neutral alumina (petroleum ether 40−60 and then 10% diethyl ether in petroleum ether 40−60) gave three compounds.

Spiro[cyclohexane-1,7′-[3]oxabicyclo[4.1.0]heptan]-5′-one (32). This was isolated as a colorless oil (278 mg, 64% yield): R_f = 0.63 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 3013, 2932, 2855, 1681 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.21 (dd, 1H, J = 1.6, 12.2 Hz), 4.03 (dd, 1H, J = 3.3, 12.2 Hz), 3.89 (d, 1H, J = 17.8 Hz), 3.76 (d, 1H, J = 17.8 Hz), 1.95−1.89 (m, 2H), 1.76−1.69 (m, 1H), 1.62−1.49 (m, 6H), 1.43 (ddd, 1H, J = 1.6, 3.5, 7.8 Hz), 1.36−1.31 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 205.5 (C), 71.9 (CH_2), 62.9 (CH_2), 39.3 (CH_2), 35.9 (C), 34.8 (CH), 27.6 (CH_2), 27.3 (CH), 26.2 (CH_2), 25.8 (CH_2), 25.7 (CH_2); HRMS (EI) for $C_{11}H_{16}O_2$ [M^+] calcd 180.1150, found 180.1140. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95. Found: C, 72.75; H 9.03.

5-(Cyclohexylidenemethyl)dihydro-3(2*H*)-furanone (33). This was isolated as a colorless oil (5.1 mg, 1% yield): R_f = 0.74 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2937, 2856, 1759, 1669, 858 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.26 (ddd, 1H, J = 0.9, 1.1, 9.4 Hz), 4.98 (ddd, 1H, J = 6.0, 6.8, 9.4 Hz), 4.13 (d, 1H, J = 17.0 Hz), 3.84 (d, 1H, J = 17.0 Hz), 2.55 (dd, 1H, J = 6.0, 18.0 Hz), 2.25 (dd, 1H, J = 6.8, 18.0 Hz), 2.28−2.14 (m, 4H), 1.65−1.56 (m, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 215.6 (C), 147.3 (C), 120.3 (CH), 73.9 (CH), 71.3 (CH_2), 43.8 (CH_2), 37.0 (CH_2), 29.5 (CH_2), 28.3 (CH_2), 27.8 (CH_2), 26.5 (CH_2); HRMS (EI) for $C_{11}H_{16}O_2$ [M^+] calcd 180.1150, found 180.1149.

2-(Cyclohexylidenemethyl)-4-methylene-1,3-dioxolane (34). This was isolated as a colorless oil (55.6 mg, 13% yield): R_f = 0.90 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 3017, 2936, 2858, 1673, 919, 869 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.90 (d, 1H, J = 7.4 Hz), 5.23 (ddd, 1H, J = 1.1, 1.1, 7.4 Hz), 4.56 (ddd, 1H, J = 1.5, 1.6, 12.2 Hz), 4.38 (ddd, 1H, J = 2.0, 2.2, 12.2 Hz), 4.33 (ddd, 1H, J = 1.5, 1.8, 2.0 Hz), 3.90 (ddd, 1H, J = 1.6, 1.8, 2.2 Hz), 2.28−2.22 (m, 2H), 2.18−2.14 (m, 2H), 1.65−1.54 (m, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 156.2 (C), 151.0 (C), 117.0 (CH), 102.1 (CH), 78.2 (CH_2), 67.5 (CH_2), 37.1 (CH_2), 29.7 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 26.6 (CH_2); HRMS (EI) for $C_{11}H_{16}O_2$ [M^+] calcd 180.1150, found 180.1142.

Reaction of 3-(2-Cyclohexylideneethoxy)-1-diazo-2-butanone (20). According to the general procedure, 3-(2-cyclohexylideneethoxy)-1-diazo-2-butanone (**20**) (401 mg, 1.80 mmol) was treated with $Rh_2(HNCOCH_3)_4$ (10 mg) in CH_2Cl_2 (200 mL). Flash column chromatography on neutral alumina (petroleum ether 40−60 and then 2%−10% diethyl ether in petroleum ether 40−60) gave four fractions.

4′-Methylspiro[cyclohexane-1,7′-[3]oxabicyclo[4.1.0]-heptan]-5′-one (36). This was isolated as a colorless oil (160.0 mg, 46% yield, 75:25 mixture of diastereoisomers). Data for major isomer: R_f = 0.49 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2928, 2854, 1694 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.23 (dd, 1H, J = 4.7, 12.2 Hz), 3.85 (dd, 1H, J = 2.5, 12.2 Hz), 3.75 (q, 1H, J = 7.0 Hz), 1.70−1.85 (m, 2H), 1.60−1.51 (m, 7H), 1.37−1.25 (m, 3H), 1.31 (d, 3H, J = 7.0 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 208.1 (C), 76.3 (CH), 58.8 (CH_2), 39.1 (CH_2), 35.5 (C), 32.2 (CH), 28.1 (CH), 27.4 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 25.4 (CH_2), 16.3 (CH_3); HRMS (EI) for $C_{12}H_{18}O_2$ [M^+] calcd 194.1307, found 194.1291.

5-(Cyclohexylidenemethyl)dihydro-2-methyl-(2*H*)-furan-3-one (37). This was isolated as a colorless oil (18.0 mg, 5% yield, 81:19 mixture of diastereoisomers). Data for the major isomer: R_f = 0.60 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2938, 2858, 1762, 1671 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.23 (d, 1H, J = 8.4 Hz), 4.87 (ddd, 1H, J = 5.5, 8.4, 10.6 Hz), 3.83 (q, 1H, J = 6.8 Hz), 2.57 (dd, 1H, J = 5.5, 18.1 Hz), 2.28−2.10 (m, 4H), 2.24 (dd, 1H, J = 10.6, 18.1 Hz), 1.64−1.42 (m, 6H), 1.33 (d, 3H, J = 6.8 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 216.7 (C), 146.9 (C), 120.5 (CH), 77.5 (CH), 71.4 (CH), 43.4 (CH_2), 37.0 (CH_2), 29.5 (CH_2), 28.1 (CH_2), 27.7 (CH_2), 26.5 (CH_2), 15.9 (CH_3); HRMS (EI) for $C_{12}H_{17}O_2$ [$(M - H)^+$] calcd 193.1487, found 193.1488.

2-(Cyclohexylidenemethyl)-5-methyl-4-methylene-1,3-dioxolane (38). This was isolated as a colorless oil (112 mg, 32% yield, 82:18 mixture of diastereoisomers). Data for major isomer: R_f = 0.87 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2931, 2856, 1674, 970, 800 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.02 (d, 1H, J = 7.8 Hz), 5.24−5.20 (m, 1H), 4.78 (ddq, 1H, J = 1.4, 1.6, 6.5 Hz), 4.30 (dd, 1H, J = 1.6, 2.2 Hz), 3.84 (dd, 1H, J = 1.4, 2.2 Hz), 2.32−2.22 (m, 2H), 2.19−2.12 (m, 2H), 1.64−1.54 (m, 6H), 1.37 (d, 3H, J = 6.5 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 161.2 (C), 149.9 (C), 117.5 (CH), 100.0 (CH), 78.0 (CH_2), 73.8 (CH), 37.1 (CH_2), 29.5 (CH_2), 28.2 (CH_2), 27.9 (CH_2), 26.6 (CH_2), 19.7 (CH_3); HRMS (EI) for $C_{12}H_{19}O_2$ [$(M + H)^+$] calcd 195.1385, found 195.1385.

(*E*)-[2-(1-Cyclohexen-1-yl)ethenyloxy]propanone (39). This was isolated as a colorless oil (9.4 mg, 3% yield). Partial data: ^1H NMR (270 MHz, $CDCl_3$) δ 6.32 (d, 1H, J = 12.8 Hz), 5.60 (d, 1H, J = 12.8 Hz), 5.54 (t, 1H, J = 4.1 Hz), 4.18 (q, 1H, J = 7.0 Hz), 2.19 (s, 3H), 2.18−1.99 (m, 4H), 1.70−1.53 (m, 4H), 1.38 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4 (C), 143.0 (CH), 132.2 (C), 125.4 (CH), 112.7 (CH), 81.1 (CH), 25.7 (CH_2), 24.9 (CH_3), 24.7 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 17.4 (CH_3); LRMS (CI, CH_4) 196 [$(M + H)^+$] 195 [M^+].

Reaction of 1-(Cyclohexylmethoxy)-3-diazo-2-propanone (46). According to the general procedure, 1-(cyclohexylmethoxy)-3-diazo-2-propanone (**46**) (500 mg, 2.55 mmol) was treated with $Rh_2(O_2CCF_3)_4$ (10 mg) in CH_2Cl_2 (140 mL). Flash column chromatography on neutral alumina (petroleum ether

40−60 and then 2%−10% diethyl ether in petroleum ether 40−60) gave two fractions.

5-Cyclohexyldihydro-3(2*H*)-furanone (48). This was isolated as a colorless oil (149 mg, 35% yield): R_f = 0.66 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2926, 2853, 1762 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.01 (d, 1H, J = 17.1 Hz), 3.94 (ddd, 1H, J = 6.0, 7.3, 9.8 Hz), 3.82 (d, 1H, J = 17.1 Hz), 2.46 (dd, 1H, J = 6.0, 17.8 Hz), 2.23 (dd, 1H, J = 9.8, 17.8 Hz), 2.05−1.95 (m, 1H), 1.83−1.50 (m, 6H), 1.38−0.92 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4 (C), 82.6 (CH), 71.5 (CH_2), 42.8 (CH), 41.0 (CH_2), 28.9 (CH_2), 28.7 (CH_2), 26.3 (CH_2), 25.8 (CH_2), 25.6 (CH_2); HRMS (EI) for $C_{10}H_{16}O_2$ [M$^+$] calcd 168.1150, found 168.1153.

2-Cyclohexyl-4-methylene-1,3-dioxolane (49). This was isolated as a colorless oil (172 mg, 40% yield): R_f = 0.88 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2928, 2855, 1685, 886 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.96 (d, 1H, J = 5.1 Hz), 4.50 (ddd, 1H, J = 1.6, 1.6, 12.2 Hz), 4.34 (ddd, 1H, J = 2.0, 2.0, 12.2 Hz), 4.29 (ddd, 1H, J = 1.6, 1.9, 2.0 Hz), 3.86 (ddd, 1H, J = 1.6, 1.9, 2.0 Hz), 1.87−1.56 (m, 6H), 1.58−1.02 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 156.4 (C), 110.1 (CH), 77.7 (CH_2), 67.4 (CH_2), 41.6 (CH), 26.9 (CH_2), 27.0 (CH_2), 26.4 (CH_2), 25.7 (CH_2); HRMS (EI) for $C_{10}H_{17}O_2$ [(M+H)$^+$] calcd 169.1228, found 169.1236.

Reaction of 3-(Cyclohexylmethoxy)-1-diazo-2-butanone (47). According to the general procedure, 3-(cyclohexylmethoxy)-1-diazo-2-butanone (**47**) (311 mg, 1.48 mmol) was treated with $Rh_2(O_2CCF_3)_4$ (5 mg) in CH_2Cl_2 (120 mL). Flash column chromatography on neutral alumina (petroleum ether 40−60 and then 2%−10% diethyl ether in petroleum ether 40−60) gave two compounds.

5-Cyclohexyldihydro-2-methyl-3(2*H*)-furanone (50). This was isolated as a colorless oil (47.5 mg, 18% yield): R_f = 0.63 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2979, 2925, 2852, 1760 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.88−3.74 (m, 2H), 2.45 (dd, 1H, J = 5.5, 18.0 Hz), 2.18 (dd, 1H, J = 10.7, 18.0 Hz), 2.04−1.92 (m, 1H), 1.83−1.48 (m, 6H), 1.30 (d, 3H, J = 6.8 Hz), 1.31−0.91 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 216.7 (CH), 80.2 (CH), 77.7 (CH_2), 42.8 (CH), 40.6 (CH_2), 29.1 (CH_2), 28.6 (CH_2), 26.4 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 15.8 (CH_3); HRMS (EI) for $C_{11}H_{18}O_2$ [M$^+$] calcd 182.1307, found 182.1312.

2-Cyclohexyl-4-methyl-5-methylene-1,3-dioxolane (51). This was isolated as a colorless oil (109 mg, 40% yield, 92:8 mixture of diastereoisomers of a colorless oil). Data for major isomer: R_f = 0.83 (petroleum ether 40−60/diethyl ether, 1:1); IR (liquid film) 2977, 2927, 2854, 1684, 998, 886 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.07 (d, 1H, J = 5.2 Hz), 4.69 (ddq, 1H, J = 1.5, 1.5, 6.5 Hz), 4.26 (dd, 1H, J = 1.5, 2.2 Hz), 3.79 (dd, 1H, J = 1.5, 2.2 Hz), 1.80−1.50 (m, 6H), 1.33 (d, 3H, J = 6.5 Hz), 1.30−1.00 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 161.3 (C), 108.0 (CH), 77.2 (CH), 73.7 (CH_2), 41.9 (CH), 26.8 (CH_2), 26.7 (CH_2), 26.2 (CH_2), 25.5 (CH_2), 25.5 (CH_2), 19.8 (CH_3); HRMS (EI) for $C_{11}H_{18}O_2$ [M$^+$] calcd 182.1307, found 182.1304.

General Method for the Preparation of Mono- and Dideuterated Analogues of the Carboxylic Acid 44. The deuterated ester was dissolved in THF, and 2 M aqueous lithium hydroxide was added at room temperature. The mixture was then heated at reflux for a period of 1.5 h. Aqueous 2 M HCl was added, and the solvents (THF and water) were evaporated in vacuo. (Final traces of water were removed azeotropically with toluene.) The resulting viscous white precipitate was triturated with ethyl acetate, and the organic solutions were combined and filtrated through a pad of silica gel using ethyl acetate. After evaporation, the product was obtained as a white solid.

(Cyclohexyl[^{2}H,^{2}H]methoxy)acetic Acid. Following the general procedure, ethyl (cyclohexyl[^{2}H,^{2}H]methoxy)acetate (1.13 g, 5.22 mmol) was dissolved in THF (6 mL) and 2 M aqueous lithium hydroxide (5 mL) was added at room temperature. The carboxylic acid (784 mg, 80%) was obtained as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 2H), 1.88−1.59 (m, 6H), 1.31−1.11 (m, 3H), 1.02−0.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C), 76.6 (quintet, J = 21.4 Hz, CD_2), 71.7 (CH_2), 67.6 (CH_2), 37.3 (CH), 29.5 (CH_2), 26.3 (CH_2), 25.5 (CH_2); HRMS (CI, CH_4) for $C_9H_{15}D_2O_3$ [(M + H)$^+$] calcd 175.1303, found 175.1288.

(Cyclohexyl[^{2}H]methoxy)acetic Acid. Following the general procedure, ethyl (cyclohexyl[^{2}H]methoxy)acetate (289 mg, 1.34 mmol) was dissolved in THF (3 mL) and 2 M aqueous lithium hydroxide (2 mL) was added at room temperature. The carboxylic acid (227 mg, 90%) was obtained as a white solid: mp 29−30 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 2H), 3.34 (d, 1H, J = 6.4 Hz), 1.86−1.59 (m, 6H), 1.34−1.10 (m, 3H), 1.03−0.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (C), 77.2 (t, J = 21.8 Hz, CHD), 67.8 (CH_2), 37.6 (CH), 29.7 (CH_2), 26.4 (CH_2), 25.7 (CH_2); LRMS (CI, CH_4) 174 [(M + H)$^+$, 57], 98 (100); HRMS (CI, CH_4) for $C_9H_{16}DO_3$ [(M + H)$^+$] calcd 174.1240, found 174.1229.

General Method for Preparing the Deuterated α-Diazo Ketones 52a−c from the Corresponding Carboxylic Acids. The carboxylic acid was dissolved in a mixture (1:1) of dried CH_2Cl_2 and diethyl ether under nitrogen. Oxalyl chloride and DMF (one drop) were added at room temperature, and the mixture was stirred for 2 h. The solvent and excess of oxalyl chloride were removed in vacuo, and the resulting yellow oil was diluted with dried CH_2Cl_2. The solution was cooled to 4 °C (ice bath), and an excess of cold CH_2N_2 or CH_2D_2 in diethyl ether was added in one portion with vigorous stirring. After 2 h at 4 °C, the excess CH_2N_2 or CH_2D_2 was destroyed by the careful addition of acetic acid. The solvent and acetic acid were evaporated in vacuo, and the residue was purified by flash chromatography on silica gel (hexanes−ethyl acetate, 9:1) to give the α-diazo ketone as a yellow oil.

1-(Cyclohexyl[^{2}H,^{2}H]methoxy)-3-diazopropanone (52a). Following the general procedure, (cyclohexyl[^{2}H,^{2}H]methoxy)-acetic acid (780 mg, 4.46 mmol) was dissolved in a mixture (1:1) of dried CH_2Cl_2 and diethyl ether (15 mL) and reacted with oxalyl chloride (1.4 g, 11 mmol). The resulting acid chloride was diluted with dried CH_2Cl_2 (10 mL) and added to an excess of CH_2N_2 in diethyl ether. Purification gave the α-diazo ketone **52a** (658 mg, 74%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (br, 1H), 3.97 (s, 2H), 1.97−1.50 (m, 6H), 1.35−0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9 (C), 74.5 (quintet, J = 21 Hz, CD_2), 52.6 (CH), 37.5 (CH), 29.6 (CH_2), 26.2 (CH_2), 25.5 (CH_2); LRMS (CI, CH_4) 199 [(M + H)$^+$, 100], 99 (32), 97(9); HRMS (CI, CH_4) for $C_{10}H_{15}D_2O_2N_2$ [(M + H)$^+$] calcd 199.1416, found 199.1407.

3-[^{2}H]-1-(Cyclohexylmethoxy)-3-diazopropanone (52b). Following the general procedure, (cyclohexylmethoxy)acetic acid (**44**) (2.03 g, 11.8 mmol) was dissolved in a mixture (1:1) of dried CH_2Cl_2 and diethyl ether (30 mL) and reacted with oxalyl chloride (2.9 g, 23 mmol). The resulting acid chloride was diluted with dried CH_2Cl_2 (20 mL) and added to an excess of CD_2N_2 in diethyl ether. Purification gave the α-diazo ketone **52b** as a yellow oil. Dideuteriodiazomethane (CD_2N_2) was prepared according to the procedure of Gassman.[24]

IR ($CHCl_3$): 2913, 2847, 2226, 2116, 1644, 974, 890 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.88 (s, 2H), 3.28 (d, J = 6.4 Hz, 2H), 1.79−1.55 (m, 6H), 1.31−1.13 (m, 3H), 1.02−0.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.1 (C), 77.5 (CH_2), 74.6 (CH_2), 52.5 (t, J = 30 Hz, CDN_2), 37.8 (CH), 29.7 (CH_2), 26.3 (CH_2), 25.6 (CH_2). LRMS (CI, CH_4): 198 ([M + H]$^+$, 12), 197 (73), 97 (95), 84 (89). HRMS (CI, CH_4) for $C_{10}H_{15}DO_2N_2$ [M$^+$]: calcd, 197.1275; found, 197.1280.

1-(Cyclohexyl[^{2}H]methoxy)-3-diazopropanone (52c). Following the general procedure, (cyclohexyl[^{2}H]methoxy)-acetic acid (225 mg, 1.29 mmol) was dissolved in a mixture (1:1) of dried CH_2Cl_2 and diethyl ether (5 mL) and reacted with oxalyl chloride (0.7 g, 6 mmol). The resulting acid chloride was diluted with dried CH_2Cl_2 (5 mL) and added to an excess of CH_2N_2 in diethyl ether. Purification gave the α-diazo ketone

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52c (186 mg, 72%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (br, 1H), 3.96 (s, 2H), 3.27 (d, 1H, J = 6.3 Hz), 1.84−1.55 (m, 6H), 1.33−1.11 (m, 3H), 1.05−0.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2 (C), 77.5 (t, J = 21 Hz, CHD), 74.7 (CH_2), 52.8 (CHN_2), 37.8 (CH), 29.8 (CH_2), 26.4 (CH_2), 25.7 (CH_2); LRMS (CI, CH_4) 198 [$(M + H)^+$, 100], 98 (58); HRMS (CI, CH_4) for $C_{10}H_{16}DO_2N_2$ [$(M + H)^+$] calcd 198.1353, found 198.1343.

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Supporting Information Available: General experiment methods, preparation of starting materials, and ^{1}H and ^{13}C NMR spectra for compounds **17**−**23**, **28**, **29**, **32**−**34**, **36**−**38**, and **46**−**51**. This material is available free of charge via the Internet at http://pubs.acs.org.

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