[4 + 3] Cycloadditions of Cyclic Oxyallyls and Cyclic 1,3-Dienes[1]

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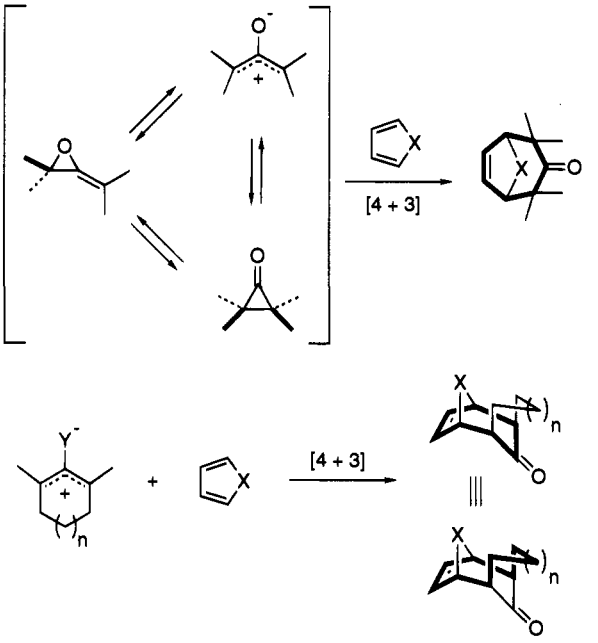
Abstract: The [4 + 3] cycloaddition of the oxyallyl intermediates, derived from 2-chlorocyclohexanone and related compounds, to cyclic 1,3-dienes under the Föhlisch conditions (Et_3N in CF_3CH_2OH) has been examined to assess its scope and limitations. Effects of substitution with alkyl or alkoxy groups on the cyclohexanone ring, along with variations of the base, solvent, or ring size have been investigated. Also included is a comparison between the Föhlisch cycloaddition and the Schmid cycloaddition (utilizing α′-chloroenamines). These reactions of cyclic oxyallyls afford tricyclic or tetracyclic cycloadducts of considerable molecular complexity with a well-defined stereochemical outcome and, thus, represent a new synthetic route to functionalized medium-sized carbocycles and heterocycles.

Introduction

Because of its exceptional reactivity, the oxyallyl−cyclopropanone−allene oxide triad has been of considerable interest to theoretical and synthetic chemists. Among the many known reactions involving these reactive molecules, the [4 + 3] cycloadditions to 1,3-dienes have received particular attention as a versatile synthetic method for seven-membered ring ketones (Scheme 1).[2−5] *Acyclic* oxyallyls have been utilized in the majority of the earlier investigations. A key variant of employing a *cyclic* oxyallyl, i.e., an oxyallyl embedded in a ring, would provide a convenient route to functionalized medium-sized carbocycles and heterocycles. In addition, the keto bridge present in the cycloadduct would be useful not only in providing a suitable functionality for further elaboration but also in rigidifying the otherwise flexible medium-sized ring.[6] Prior to our own work,[1] synthetic utility of these [4 + 3] cycloadducts of *cyclic* oxyallyls and cyclic 1,3-dienes had received surprisingly scant attention.

To date, only a few examples of the [4 + 3] cycloadditions involving *cyclic* oxyallyls have been reported (Scheme 2).[7−12]

Scheme 1



Under Noyori conditions using $Fe_2(CO)_9$, trapping of the oxyallyl cations derived from the cyclic dibromo ketones **1a−c** with furan (**2**) afforded the anti cycloadducts **3a−c** (35−54%), accompanied by substitution products **4a−c** (10−35%).[8] The corresponding cycloadditions with cyclopentadiene (**5**) proceeded in even lower yields,[9] which is in marked contrast to

[⊗] Abstract published in *Advance ACS Abstracts*, October 15, 1995.

(1) Part 6 in the series Synthetic Studies on [4 + 3] Cycloadditions of Cyclic Oxyallyls. (a) Part 1: Oh, J.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1992**, *57*, 6664. (b) Part 2: Oh, J.; Lee, J.; Jin, S.-j.; Cha, J. K. *Tetrahedron Lett.* **1994**, *35*, 3449. (c) Part 3: Lee, J.; Oh, J.; Jin, S.-j.; Choi, J.-R.; Atwood, J. L.; Cha, J. K. *J. Org. Chem.* **1994**, *59*, 6955. (d) Part 4: Oh, J.; Cha, J. K. *Synlett* **1994**, 967. (e) Part 5: Kim, H.; Ziani-Cherif, C.; Oh, J.; Cha, J. K. *J. Org. Chem.* **1995**, *60*, 792.

(2) For reviews on oxyallyls, see: (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (d) Hosomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, Chapter 5.1.

(3) For reviews on cyclopropanones, see: (a) Turro, N. J. *Acc. Chem. Res.* **1969**, *2*, 25. (b) Wasserman, H. H.; Berdahl, D. R.; Lu, T.-J. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Vol. 2, Chapter 23.

(4) For reviews on allene oxides, see: Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2269.

(5) For recent examples of related [4 + 3] cycloadditions, see *inter alia*: (a) Schultz, A. G.; Macielag, M.; Plummer, M. *J. Org. Chem.* **1988**, *53*, 391. (b) Harmata, M.; Fletcher, V. R.; Claassen, R. J., II. *J. Am. Chem. Soc.* **1991**, *113*, 9861. (c) West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795 and references cited therein.

(6) The successful implementation of the [4 + 3] cycloaddition of cyclic oxyallyls to natural product synthesis requires cleavage of the keto bridge to generate the requisite medium-sized ring system. We recently developed a practical method for oxidative cleavage of the keto bridge by employing β-fragmentation of an alkoxy radical.[1c,e]

(7) The term "cycloaddition" is used to indicate the overall bonding change rather than to imply a concerted mechanism.

(8) (a) Noyori, R.; Baba, Y.; Makino, S.; Takaya, H. *Tetrahedron Lett.* **1973**, 1741. (b) Takaya, H.; Makino, S.; Hayakawa, Y.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1765. (c) In case of **1c**, cycloadducts were obtained as a 3:1 mixture of *anti* and *syn* isomers. For clarity, only the *anti* isomer **3c** is shown in Scheme 2.

(9) Cf.: Siemionko, R. K.; Berson, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 3870.

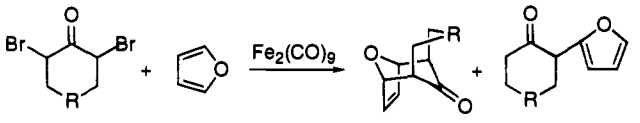
(10) (a) Vinter, J. G.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1973**, *95*, 3051. (b) Hoffmann, H. M. R.; Wagner, D.; Wartchow, R. *Chem. Ber.* **1990**, *123*, 2131. (c) Schottelius, T.; Hoffmann, H. M. R. *Chem. Ber.* **1991**, *124*, 1673.

(11) (a) Schmid, R.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 1883. (b) Schmid, R. Ph. D. Dissertation, University of Zürich, 1978. See also: (c) Ramos Tombo, G. M.; Pfund, R. A.; Ganter, C. *Helv. Chim. Acta* **1981**, *64*, 813.

0002-7863/95/1517-10914$09.00/0

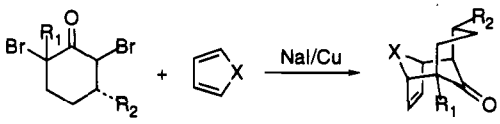
Scheme 2

1. Noyori (1973)[8]



1a: R = CH_2 **2** **3a** (35%) **4a** (35%)
1b: R = $(CH_2)_2$ **3b** (54%) **4b** (21%)
1c: R = $(CH_2)_3$ **3c** (37%)[8c] **4c** (10%)

2. Hoffmann (1973)[10]

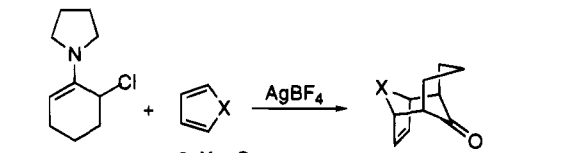


1a: $R_1 = R_2 = H$ **2**: X = O **3a**: $R_1 = R_2 = H$, X = O (10%)

6: R_1 = Me, $R_2 = H$ **5**: X = CH_2 **8a**: R_1 = Me, $R_2 = H$, X = O (25%)
8b: R_1 = Me, $R_2 = H$, X = CH_2 (20-25%)

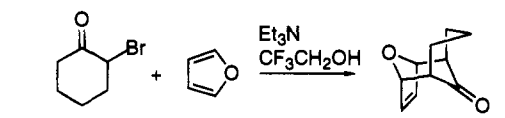
7: R_1 = *i*-Pr, R_2 = Me **9a**: R_1 = *i*-Pr, R_2 = Me, X = O (22%)
9b: R_1 = *i*-Pr, R_2 = Me, X = CH_2 (25-30%)

3. Schmid (1974)[11]



10 **2**: X = O **5**: X = CH_2 **3a**: X = O (68%) **11**: X = CH_2 (76%)

4. Föhlisch (1982)[12-14]

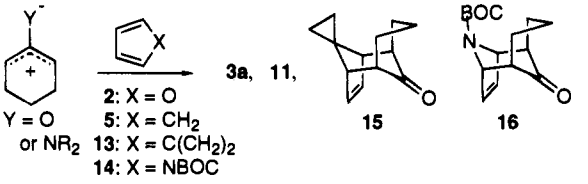


12 **3a** (84%)

the good yields obtained with open-chain dibromo ketones and both of these dienes. Similarly, poor yields were obtained for **1a** under Hoffmann conditions using NaI/Cu or $B(OEt)_3$/Zn. The presence of alkyl substituents (e.g., 2-alkyl-substituted 2,6-dibromocyclohexanones **6** and **7**) was found to slightly enhance yields, which can be attributed to increased stability of the oxyallyl intermediate conferred by the alkyl substituents.[10] Excellent yields for these sterically demanding cycloadditions became available by use of Schmid's "aminoallyl", which was prepared *in situ* by treatment of the α′-chloroenamine **10** with $AgBF_4$.[11] Subsequently, Föhlisch reported a remarkable [4 + 3] cycloaddition involving α-halo ketones (e.g., **12**) in the presence of Et_3N or $NaOCH_2CF_3$ in trifluoroethanol.[12-14] Most likely, the oxyallyl is generated by the Favorskii rearrangement.[15] Also effective was use of Et_3N in an ethereal $LiClO_4$ solution.[13b]

As part of our research program directed at developing a new, general method for preparing functionalized medium-sized carbocycles and heterocycles, we investigated the scope and limitations of the [4 + 3] cycloadditions of *cyclic* oxyallyls to cyclic 1,3-dienes under the Föhlisch and Schmid conditions.

Table 1



Y = O or NR_2 **2**: X = O **5**: X = CH_2 **13**: X = $C(CH_2)_2$ **14**: X = NBOC **3a**, **11**, **15**, **16**

method	**3a** (*yield*)	**11**	**15**	**16**
Noyori	35% (ref 8)	10%	0%	--[a]
Hoffmann	10% (ref 10)	0%	1%	--[a]
Schmid	68% (ref 11)	76%[11]	57%[b]	52%
Föhlisch	84% (ref 12)	51%	13%[b]	13%[c]

[a] No attempt was made to carry out these cycloadditions. [b] The corresponding substitution product was also isolated in 37% yield. [c] The α-substitution product was also isolated in 12% yield.

Results and Discussion

We first undertook the studies of comparison among the four [4 + 3] cycloaddition protocols employing an unsubstituted six-membered *cyclic* oxyallyl and furan (**2**), cyclopentadiene (**5**), spiro[2.4]hepta-4,6-diene (**13**), and *N*-BOC-pyrrole (**14**) to afford cycloadducts **3a**, **11**, **15**, and **16**, respectively. Our results, along with the literature data, are summarized in Table 1. When cyclic oxyallyls were employed (i.e., the oxyallyl functionality is embedded in a ring), synthetically useful yields of the [4 + 3] cycloadducts were available only with the Schmid and Föhlisch procedures. Moreover, Schmid's rarely-explored aminoallyl method appeared to be the best. Particularly noteworthy is the cycloaddition of **13**, a sterically demanding 1,3-diene; the resulting cycloadduct **15** can be readily prepared by the Schmid method in 57% yield and in mutligram quantities.[1a] On the other hand, when furan is employed as the 1,3-diene component, the Föhlisch method appears to be equally effective or superior. The practical aspects of convenience and simplicity of the Föhlisch reaction should also be emphasized. In the present work, particular emphasis was placed on the cycloadducts derived from furans, since the oxa bridge present in the cycloadducts would provide for subsequent stereoselective elaboration a well-defined stereochemical bias, as well as a latent hydroxyl group.[16]

Alkyl Substitution at the Oxyallyl Component: 2-Chlorocyclohexanone (17) vs 2-Methyl-2-chlorocyclohexanone (18). We next investigated the effect of a 2-alkyl substituent

(12) For [4 + 3] cycloadditions involving cyclic oxyallyls: (a) Föhlisch, B.; Gehrlach, E.; Herter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 137. (b) Föhlisch, B.; Joachimi, R. *Chem. Ber.* **1987**, *120*, 1951. (c) Föhlisch, B.; Joachimi, R.; Reiner, S. *J. Chem. Res. (S)* **1993**, 253. Cf.: (d) Harmata, M.; Elahmad, S. *Tetrahedron Lett.* **1993**, *34*, 789. (e) Harmata, M.; Elahmad, S.; Barnes, C. L. *J. Org. Chem.* **1994**, *59*, 1241. (f) Harmata, M.; Elahmad, S.; Barnes, C. L. *Tetrahedron Lett.* **1995**, *36*, 1397. (g) Harmata, M.; Gamlath, C. B.; Barnes, C. L.; Jones, D. E. *J. Org. Chem.* **1995**, *60*, 5077.

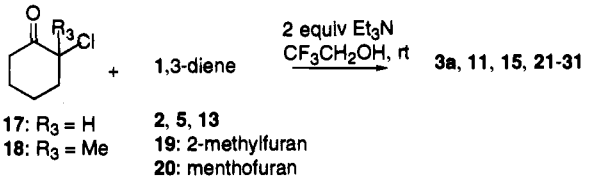
(13) For [4 + 3] cycloadditions involving acyclic oxyallyls, see: (a) Föhlisch, B.; Gottstein, W.; Kaiser, R.; Wanner, I. *Tetrahedron Lett.* **1980**, *21*, 3005. (b) Herter, R.; Föhlisch, B. *Synthesis* **1982**, 976. (c) Föhlisch, B.; Gehrlach, E.; Henle, G.; Boberlin, U.; Herter, R. *J. Chem. Res. (S)* **1991**, 136. (d) Föhlisch, B.; Herrscher, I. *Chem. Ber.* **1986**, *119*, 524. (e) Föhlisch, B.; Gehrlach, E.; Stezowski, J. J.; Kollat, P.; Martin, E.; Gottstein, W. *Chem. Ber.* **1986**, *119*, 1661. (f) Föhlisch, B.; Flogaus, R.; Oexle, J.; Schädel, A. *Tetrahedron Lett.* **1984**, *25*, 1773. (g) Föhlisch, B.; Herter, R.; Wolf, E.; Stezowski, J. J.; Eckle, E. *Chem. Ber.* **1982**, *115*, 355. (h) Föhlisch, B.; Herter, R.; Wolf, E. *J. Chem. Res. (S)* **1986**, 128. (i) Föhlisch, B.; Gehrlach, E.; Geywitz, B. *Chem. Ber.* **1987**, *120*, 1815. (j) Föhlisch, B.; Krimmer, D.; Gehrlach, E.; Käshammer, D. *Chem. Ber.* **1988**, *121*, 1585. (k) Föhlisch, B.; Sendelbach, S.; Bauer, H. *Liebigs Ann. Chem.* **1987**, 1.

(14) For intramolecular [4 + 3] cycloadditions under Föhlisch conditions, see: (a) Föhlisch, B.; Herter, R. *Chem. Ber.* **1984**, *117*, 2580. (b) Kaiser, R.; Föhlisch, B. *Helv. Chim. Acta* **1990**, *73*, 1504.

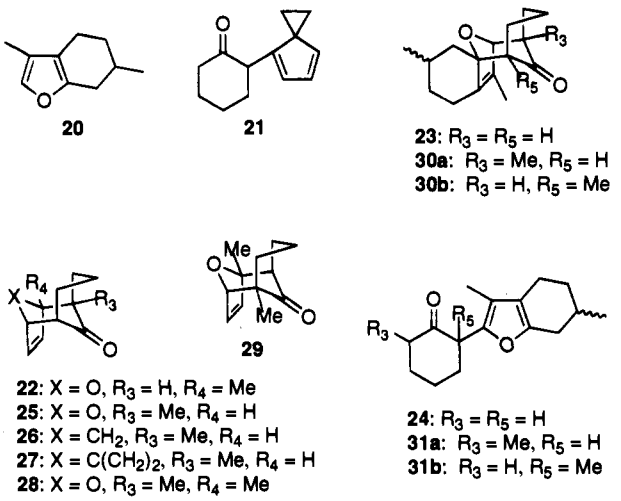
(15) (a) House, H. O.; Frank, G. A. *J. Org. Chem.* **1965**, *30*, 2948. (b) Bordwell, F. G.; Strong, J. G. *J. Org. Chem.* **1973**, *38*, 579. (c) Kende, A. S. *Org. React.* **1960**, *11*, 261. (d) Mann, J. In *Comprehensive Organic Synthesis*; Pattenden, G., Vol. Ed.; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 3, pp 839–859.

(16) (a) Application of **3a** in the synthesis of (+)-lauthisan has recently been reported.[1e] (b) Synthetic studies of structurally complex natural products of other structural types starting from **3a** are currently in progress.

Table 2



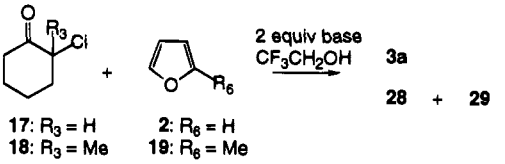
reactants	reaction time	product(s)	yield	stereo- or regioselectivity
17 + 2	3 d	3a	70%	
17 + 5	3 d	11	51%	
17 + 13	3 d	15 + 21	13% + 37%	
17 + 19	3 d	22	66%	
17 + 20	2 h	23	25%	2 : 1 ds
		24	75%	1 : 1 ds
18 + 2	12 h	25	56%	
18 + 5	3 d	26	17%	
18 + 13	12 h	27	0%	
18 + 19	3 h	28 : 29	60%	7 : 1 (regio)
18 + 20	2 h	30a,b	23%	5 : 3 (regio)
		31a,b	59%	



in the oxyallyl component by treating **17** and **18** with cyclic 1,3-dienes (**2**, **5**, **13**, **19**, and **20**). As summarized in Table 2, the presence of the methyl substituent appears to have no deleterious effect on the reaction yield, with the exception of the cycloaddition to cyclopentadiene (i.e., **18** + **5**). When progress of the cycloaddition was monitored by TLC, considerable enhancement in the reaction rate was observed for **18**. Formation of the corresponding oxyallyl intermediate from **18** must be more facile, which can be ascribed to additional stabilization provided by the methyl substituent. Competition experiments with equimolar amounts of dienes **2** and **5** with either **17** or **18** indicated that the resulting oxyallyl intermediates react with both dienes at about the same rate under Föhlisch conditions.

The [4 + 3] cycloaddition of **18** and 2-methylfuran (**19**) proceeded with good (7:1) regioselectivity to give **28** as the major product, and this regiochemical preference closely parallels that of acyclic oxyallyls independently reported by Noyori[17] and Föhlisch.[13f] When a bicylic furan, menthofuran (**20**),[18] was employed, formation of the corresponding α-substitution products **24** and **31a,b** from **17** and **18**, respectively, was found to be the predominant pathway. The desired cycloadduct **23** was obtained in only poor (25%) yield as a 2:1 diastereomeric mixture from **17**. Compound **18** afforded a 5:3 mixture of the regioisomers **30a,b**, and the cycloadduct **30a** was a 3:1 mixture of the two possible epimers, whereas **30b** appeared to be predominantly a single isomer. Also, it was noted that the reactions with menthofuran proceeded considerably faster than those involving furan. Thus, when **17** was treated with equimolar amounts of dienes **2** and **20**, only the products from **20** were found in the reaction mixture as a 1:3 mixture of **23** and **24**.

Table 3



reactants	base	reaction time	yield	product(s) (regioselectivity)
17 + 2	Et_3N	3 d	70%	3a
17 + 2	*i*-Pr_2NEt	3 d	63%	3a
17 + 2	proton-sponge	3 d	32%	3a
18 + 19	Et_3N	3 h	60%	28 : 29 (7 : 1)
18 + 19	*i*-Pr_2NEt	1.5 h	47%	28 : 29 (20 : 1)
18 + 19	DBU	1.5 h	33%	28 : 29 (7 : 1)

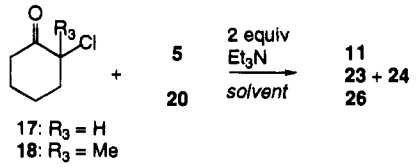
Base. The results of generating the oxyallyls from **17** and **18** with different tertiary amine bases, *i*-Pr_2NEt, DBU, or proton sponge, are summarized in Table 3. Use of a more hindered base resulted in lower yields, while the reaction rate was considerably increased. Interestingly, regioselectivity for the cycloaddition of **18** and **19** was greatly enhanced by the use of *i*-Pr_2NEt. Lower yields in the last two entries might be attributed to instability of the cycloadduct **28** toward the base. In a control experiment where cycloadduct **28** was resubjected to the identical cycloaddition conditions using DBU as a base, prolonged exposure gave rise to decomposition. Formation of the cycloadduct **28** was established to be irreversible; when **28** was subjected to the Föhlisch conditions in the presence of furan (**2**), no crossover product **25** was found in the reaction mixture. Overall, triethylamine appears to be the base of choice.

Solvent. Crucial to the success of the Föhlisch cycloaddition was the judicious choice of 2,2,2-trifluoroethanol as the solvent.[12a,13c] Also, 2,2,3,3-tetrafluoro-1-propanol proved to be an excellent solvent for the [4 + 3] cycloadditions.[13i] On the other hand, when 1,1,1,3,3,3-hexafluoro-2-propanol was used as the solvent, cycloaddition proceeded much more slowly; cycloaddition (2 equiv of Et_3N) of 2-chloro-3-pentanone with furan in $(CF_3)_2CHOH$ took 69 d (60%) in comparison to 6 d (80%) in CF_3CH_2OH![13e] Non-fluorinated alcohols of lower polarity were less effective.[13a,e] Alternatively, an ethereal solution of $LiClO_4$ has been successfully employed.[13b,14b] As summarized in Table 4, our results of the cycloadditions of cyclic oxyallyls derived from **17** and **18** to cyclopentadiene are in accord with the earlier observations found with acyclic oxyallyls and furan: better yields were obtained by use of 2,2,3,3-tetrafluoro-1-propanol in lieu of 2,2,2-trifluoroethanol. In the cycloadditions of the sterically demanding menthofuran (**20**), however, use of 2,2,3,3-tetrafluoro-1-propanol did not result in any significant change.

(17) Noyori, R.; Shimizu, F.; Fukuta, K.; Takaya, H.; Hayakawa, Y. *J. Am. Chem. Soc.* **1977**, *99*, 5196.

(18) Commerically available from Eastman Kodak Chemicals.

Table 4



reactants	solvent	reaction time	product (yield)
17 + 5	CF_3CH_2OH	3 d	**11** (51%)
17 + 5	$CHF_2CF_2CH_2OH$	3 d	**11** (65%)
18 + 5	CF_3CH_2OH	3 d	**26** (17%)
18 + 5	$CHF_2CF_2CH_2OH$	1 d	**26** (43%)
17 + 20	CF_3CH_2OH	1.5 h	**23** + **24** 23% + 59%
17 + 20	$CHF_2CF_2CH_2OH$	1.5 h	28% + 55%
17 + 20	$(CF_3)_2CHOH$	1.5 h	0% + 24%

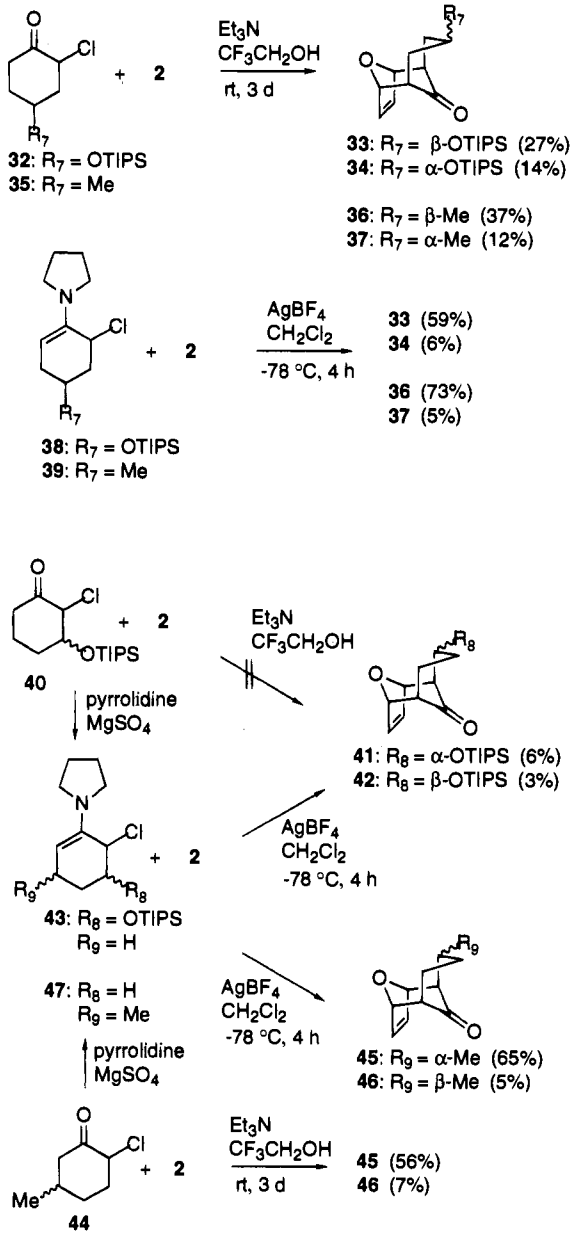
Functionalized Six-Membered Oxyallyls. As a preliminary study for synthetic applications of these [4 + 3] cycloadducts, we next investigated the generation of oxyallyls from functionalized 2-chlorocyclohexanones (Scheme 3). Treatment of 2-chloro-4-(triisopropylsiloxy)cyclohexanone (**32**)[1c] with furan under the Föhlisch conditions gave the cycloadducts **33** and **34** as a 2:1 mixture (41% yield). Similar results were obtained from the corresponding 4-methyl compound **35** (49%, a 3:1 mixture). In both cases, the major products (**33** and **36**) were shown to possess the *cis* relationship between the oxygen bridge and the C4 substituent. This stereochemical outcome is most likely a consequence of a preferred boat-shaped oxyallyl transition state structure having the C4 substituent in the pseudoequatorial position.[1c] In comparison with the Föhlisch reaction, the corresponding Schmid cycloadditions of **38** and **39** gave the corresponding cycloadducts in higher yields (65% and 78%, respectively) and with greater diastereoselectivity (10:1 and 15:1). The enhanced selectivity can be attributed to the lower reaction temperature (i.e., −78 °C) used in the Schmid procedure.

No cycloadduct was obtained from the Föhlisch reaction of 2-chloro-3-(triisopropylsiloxy)cyclohexanone (**40**)[19] with furan, and the Schmid protocol afforded the cycloadducts **41** and **42** in only small amounts (9% from **40**). Thus, the presence of an alkoxy group adjacent to the oxyallyl functionality appears to be deleterious. On the other hand, the corresponding methyl-substituted reactant **44** produced the cycloadducts **45** and **46** in 63% yield and with 8:1 diastereoselectivity. The corresponding Schmid cycloaddition of **47** also proceeded smoothly (70% yield) with enhanced (13:1) selectivity. The stereochemical assignments of **41**, **42**, **45**, and **46** were made by analogy to related literature examples.[10b]

More significantly, cycloaddition involving the α-chlorodecalones **48a,b** and furan or cyclopentadiene was found to furnish the tetracyclic cycloadducts **49** (61%, along with 9% of its stereoisomer) and **50** (38%), respectively, in synthetically useful yields (Scheme 4). Moreover, the yields based on pure *cis*-2-decalone are higher, since a commercially available sample of 2-decalone consisting of ca. 3:1 *cis* and *trans* isomers was employed.[20] The starting material **48a,b**, prepared by chlorination (with CF_3SO_2Cl)[21] of the lithium enolate derived from 2-decalone, was a mixture of regioisomers; no attempt was made

(19) (a) Compound **40** was prepared from 2,3-epoxycyclohexanone by the procedure of Grandi: Gehlfi, F.; Grandi, R.; Pagnoni, U. M. *J. Chem. Res. (S)* **1988**, 200. (b) Poor yield of the Schmid procedure was due to the difficulty of preparing the requisite enamine **43** from α-chloroketone **40**.

Scheme 3



to determine the exact composition. Encouraged by these results, we then examined the cycloadditions of angular methylated 2-decalone derivatives (**52a,b** and **55**). The *cis*-fused α-chlorodecalones **52a,b** were readily prepared by hydrogenation (10% Pd/C, EtOH) of 10-methyl-$\Delta^{1,9}$-octal-2-one (**51**),[22] followed by sequential treatment with LDA and CF_3SO_2Cl. The *trans*-fused α-chlorodecalone **55** was prepared, as a single isomer, by lithium−ammonia reduction of **51** and subsequent chlorination with SO_2Cl_2. Cycloaddition of **52a,b** and furan afforded the tetracyclic cycloadduct **53** as the sole product in 71% yield. Similarly, cycloaddition of **52a,b** and cyclopentadiene afforded the tetracyclic cycloadduct **54** in 68% yield, along with a small amount (6%) of its stereoisomer.[23] On the other hand, cycloaddition of **55** and furan proceeded very slowly (10

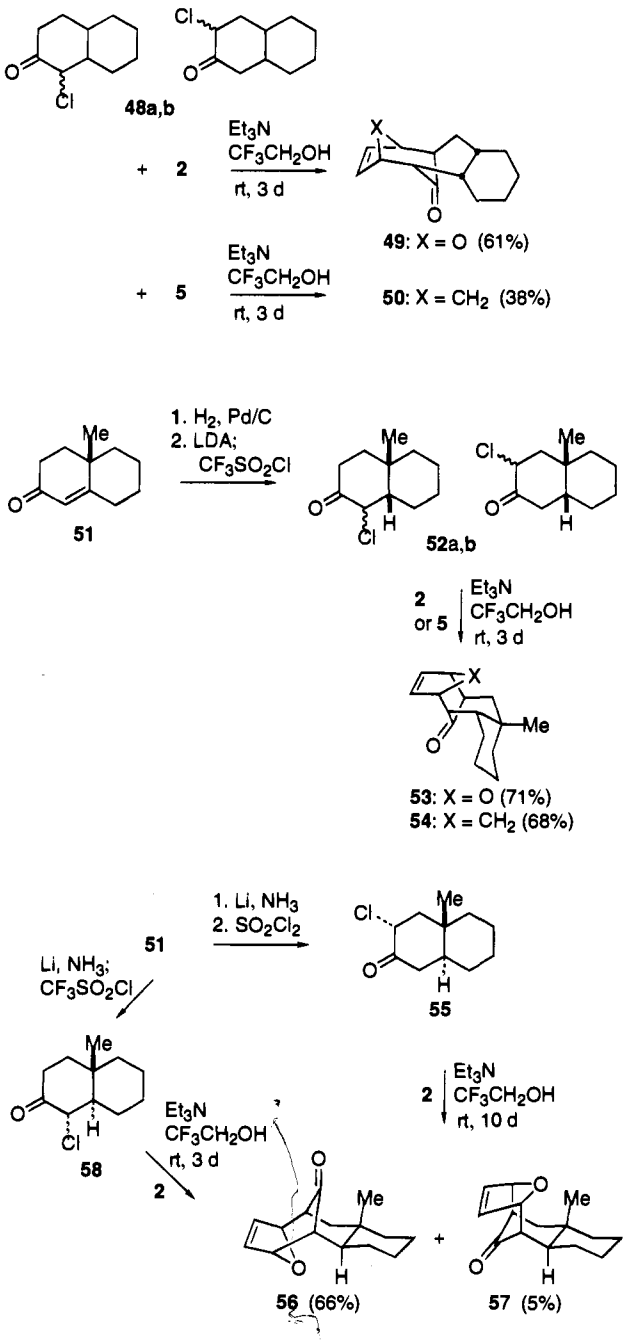
(20) (a) Based on the ^{13}C NMR spectrum. Cf.: Metzger, P.; Casadevall, E.; Pouet, M. J. *Org. Magn. Reson.* **1982**, *19*, 229. Gramain, J. C.; Quirion, J. C. *Magn. Reson. Chem.* **1986**, *24*, 938. (b) Purchased from Aldrich Chemical Co.

(21) Wender, P. A.; Holt, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 7771.

(22) Commerically available from Aldrich Chemical Co. in enantiomerically pure form.

(23) Use of a functionalized B-ring decalone derivative would provide a rapid, convenient synthetic entry to the congeners of taxol. Such studies will be a subject of future studies.

Scheme 4

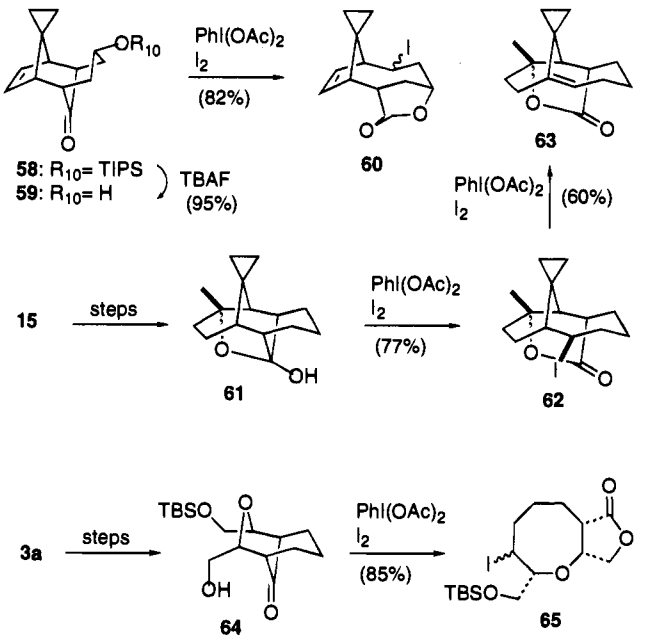


d) to give a ~12:1 mixture of **56** and **57** in 71% yield. The difficulty of generating the requisite chloro enolate at the $\Delta^{1,2}$ position of *trans*-fused angular methylated 2-decalones (i.e., the first step of the two-step oxyallyl-forming process) is likely responsible for the slower reaction rate of **55**. Indeed, cycloaddition of the regioisomeric chloroketone **58** was found to proceed faster (2−3 d) than that (10 d) of **55** under identical reaction conditions. The stereochemical assignment of the cycloadducts **56** and **57** was initially made by assuming that the bottom face of the oxyallyl intermediate, away from the angular methyl group, is sterically less encumbered and subsequently confirmed by X-ray single crystal analysis of a bis(benzoate) derived from **56**.[24]

Since the starting decalone derivatives are readily available in enantiomerically pure form, this [4 + 3] cycloaddition methodology lends itself to asymmetric synthesis. In fact,

(24) We thank Dr. Fook S. Tham at Rensselaer Polytechnic Institute for X-ray structure determination of a bis(benzoate) derivative, which was prepared by dihydroxylation (OsO_4, NMO) of cycladduct **56**, followed by perbenzoylation (BzCl, pyr).

Scheme 5



cycloadducts **53**, **54**, **56**, and **57** were prepared in enantiomerically pure form starting from commercially available, nonracemic **51**.

Other Ring Sizes. A brief study employing cyclic 1,3-dienes of a larger ring size such as 1,3-cyclohexadiene and 1,3-cycloheptadiene showed that little (<10%) of the desired cycloadducts was formed. Similarly, disappointing results (<10%) were obtained for cyclic oxyallyls derived from 2,7-dichlorocycloheptanone or 2,2-dichlorocycloheptanone.[25] Thus, it would appear that synthetically useful yields are available only for cycloadditions of six-membered oxyallyls and five-membered cyclic 1,3-dienes.

Synthetic Applications. As delineated in the present work, the [4 + 3] cycloaddition of cyclic oxyallyls allows a rapid assembly of the otherwise inaccessible medium-sized ring systems by virtue of the spectator cyclic skeleton in which the oxyallyl functionality is embedded. The resulting rigid, tricyclic or tetracyclic cycloadducts incorporate not only several functional groups but also clearly defined facial differentiation useful for subsequent elaboration. Thus, these cycloadducts should be of considerable utility in the synthesis of architecturally complex medium-sized carbocycles and heterocycles. The successful implementation of these cycloadducts to natural product synthesis, however, requires an efficient cleavage of the keto bridge present in the cycloadducts. As exemplified in the following examples previously reported by us (Scheme 5), a synthetically useful solution has recently been found in β-fragmentation (Suárez cleavage) of an alkoxy radical generated by the action of $PhI(OAc)_2-I_2$.[1] The required hydroxy group can be placed in either the same ring (i.e., **59**) or a different ring (i.e., **61** and **64**) to achieve the alkoxy-radical-induced fragmentation. The resulting products **63** and **65** should be valuable in the preparation of medium-sized carbocycles (i.e., taxanes) and heterocycles (i.e., oxocene marine natural products), respectively.[26] The tandem application of the cyclic oxyallyl [4 + 3] cycloaddition and Suárez cleavage offers a new, efficient synthetic method for many such natural products.

(25) For the cycloaddition of 2-chlorocyclopentanone, see: (a) Reference 12b. (b) Masters, A. P.; Parvez, M.; Sorensen, T. S.; Sun, F. *J. Am. Chem. Soc.* **1994**, *116*, 2804. (c) Cycloadditions of medium-sized (e.g., 11-, 12-, and 13-membered) cyclic α-chloroketones were reported by Noyori.[2a]

(26) Cycloadduct **65** has been successfully converted to (+)-lauthisan.[1e]

Conclusion

In summary, the Schmid [4 + 3] cycloaddition and the related *cyclic* variant of the Föhlisch cycloaddition have been found to proceed in good yields to give tricyclic or tetracyclic cycloadducts of considerable molecular complexity with a well-defined stereochemical bias. In particular, the [4 + 3] cycloaddition of the oxyallyl intermediates derived from α-chlorocyclohexanones and α-chlorodecalones with furan or cyclopentadiene should prove to be useful in an efficient preparation of functionalized medium-sized carbocycles and heterocycles. Further synthetic applications in natural product synthesis are currently in progress.

Experimental Section

General Procedure. All reactions were conducted under an atmosphere of dry nitrogen in oven-dried glassware. Unless noted otherwise, materials were obtained from commercial suppliers and used without further purification. All solvents were purified before use. Ether, tetrahydrofuran, and toluene were distilled under nitrogen from sodium benzophenone ketyl. Methylene chloride was distilled under nitrogen from CaH_2. The normal processing of organic extracts consisted of washing the extract with brine, drying over Na_2SO_4 or $MgSO_4$, filtration, and concentration under reduced pressure (aspirator) with a Büchi rotary evaporator.

Infrared spectra were recorded as thin films or as solutions. NMR spectra were measured as $CDCl_3$ solutions on commercially available spectrometers at 360 MHz for ^1H and at 90 MHz for ^{13}C. For ^1H spectra tetramethylsilane was used as the internal standard. ^{13}C NMR spectra were referenced with the δ 77.0 resonance of $CDCl_3$. Mass spectra were measured on a KRATOS Concept II HH four-sector mass spectrometer equipped with a cesium ion gun. The accurate mass spectra were run in electron impact (at 70 eV) or using a liquid secondary ion (LSI) probe with a matrix of 20% 3-nitrobenzyl alcohol and 20% glycerol in DMSO.

Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed by using Merck 60 F_{254} glass plates precoated with a 0.25-mm thickness of silica gel. Column chromatography was performed on Kieselgel 60 (70−230 mesh) silica gel. Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (>95% by ^1H NMR analysis) for use in subsequent reactions. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

2-Chloro-4-methylcyclohexanone (35). To a solution of 1.00 g (8.9 mmol) of 4-methylcyclohexanone in 5 mL of CH_2Cl_2 was added dropwise at 0 °C triethylamine (1.80 g, 17.8 mmol), followed by trimethylsilyl triflate (2.18 g, 9.8 mmol). The reaction mixture was stirred for 1 h and poured into water. The organic layer was washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford crude trimethylsilyl enol ether as a pale yellow oil, which was used immediately without further purification for the next step.

A solution of crude trimethylsilyl enol ether in 10 mL of CH_2Cl_2 was added dropwise to a solution of sulfuryl chloride (1.28 g, 9.5 mmol) in 20 mL of CH_2Cl_2 which was cooled to −78 °C. The reaction mixture was allowed to warm slowly to room temperature, and stirred for an additional 2 h. The reaction was quenched by adding cold water. The aqueous layer was extracted with methylene chloride (3 × 50 mL). The combined organic layers were washed with cold water (3 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude product as a pale yellow oil. Purification by column chromatography on silica gel (20:1 hexane−EtOAc) gave 720 mg (54%) of α-chloroketone **35** as a colorless oil: R_f 0.42 in 5:1 hexane−EtOAc; ^1H NMR δ 1.04 (d, J = 6.2 Hz, 3 H), 1.21−1.27 (m, 1 H), 1.41−1.59 (m, 2 H), 1.89−2.03 (m, 2 H), 2.48−2.58 (m, 1 H), 2.61−2.70 (m, 1 H), 4.43 (dd, J = 6.1, 11.7 Hz, 1 H).

3-Chloro-5-methyl-2-pyrrolidinocyclohexene (39). A 100-mL flask was charged with 160 mg (1.09 mmol) of chloroketone **35** and 5 mL of cyclohexane. To the stirred solution under nitrogen was added 720 mg of anhydrous magnesium sulfate in one portion. The mixture was cooled to 0 °C with an ice bath, and 393 mg (5.45 mmol) of pyrrolidine was added dropwise. The reaction mixture was stirred for an additional 30 min at 0 °C and then stirred overnight at room temperature. Magnesium sulfate was removed by filtration and rinsed thoroughly with hexane, and the filtrates were concentrated under reduced pressure without heating to afford crude α-chloroenamine **39** as an orange oil (195 mg, 90%): ^1H NMR δ 1.01 (d, J = 6.5 Hz, 3 H), 1.69−1.92 (m, 5 H), 2.12−2.34 (m, 4 H), 2.96−3.05 (m, 2 H), 3.13-3.24 (m, 2 H), 4.39 (dd, J = 5.4, 2.4 Hz, 1 H), 4.70 (t, J = 2.8 Hz, 1 H). The crude enamine was used immediately without further purification for the next step.

2-Chloro-3-(triisopropylsiloxy)cyclohexanone (40). To a solution of 1.45 g (10.8 mmol) of 2-chloro-3-hydroxycyclohexanone[19a] in 5 mL of DMF at 0 °C was added 1.84 g (27.1 mmol) of imidazole, followed by 2.50 g (13.0 mmol) of triisopropylsilyl chloride. The reaction mixture was stirred overnight at 0 °C and poured into cold water (100 mL). The aqueous layer was extracted with hexane (3 × 50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude product as a orange oil. Purification by column chromatography on silica gel (1:1 Et_2O−hexane) gave 2.55 g (81%) of silyl ether **40** as a colorless oil as a 1:1 mixture of the two diastereomers: R_f 0.90 in 1:1 Et_2O−hexane; IR (CCl_4) 1727 cm^{-1}; ^1H NMR δ 0.87 (m, 1 H), 1.03−1.09 (m, 21 H), 1.70−1.96 (m, 2 H), 2.03−2.18 (m, 1 H), 2.21−2.34 (m, 1 H), 2.68−2.85 (m, 1 H), 4.01 (d, J = 4.6 Hz, $^1/_2$ H), 4.30 (m, $^1/_2$ H), 4.45−4.51 (m, 1 H); ^{13}C NMR δ 12.2, 12.4, 17.6, 17.9, 20.1, 20.3, 28.2, 31.6, 36.7, 38.9, 62.3, 68.6, 74.8, 75.0, 201.6, 203.5.

1-Chloro-2-decalone and 3-Chloro-2-decalone (48a,b). To a solution of 768 mg (7.59 mmol) of *N,N*-diisopropylamine in 30 mL of THF was added dropwise at 0 °C 5.25 mL (7.59 mmol, 1.45 M in hexane) of *n*-butyllithium. After the mixture had been stirred for 30 min at 0 °C, the ice bath was removed and the mixture was cooled to −78 °C. The commercially available 2-decalone (1.05 g, 6.90 mmol) was then added dropwise. After the reaction mixture had been stirred at −78 °C for 40 min, a solution of trifluoromethanesulfonyl chloride (1.28 g, 7.59 mmol) in 5 mL of tetrahydrofuran was added slowly. The resulting mixture was stirred for 1 h at −78 °C and then poured into water. The aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography of the concentrate using 15:1 hexane−EtOAc as the eluent afforded 897 mg of chloroketones **48a,b** as a colorless oil: R_f 0.81 in 1:1 Et_2O−hexane; IR ($CHCl_3$) 1700 cm^{-1}.

α-Chloroketones 52a,b. To a solution of **51** (925 mg, 5.63 mmol) in 10 mL of ethanol was added 10% Pd/C (92.5 mg). The mixture was stirred at room temperature overnight under an atmosphere of hydrogen and then filtered through Celite. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (20:1 hexane−EtOAc) to give 486 mg (52%) of the corresponding *cis*-2-decalone as a colorless oil: R_f 0.67 in 5:1 hexane−EtOAc; IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 1.17 (s, 3 H), 1.20−1.31 (m, 2 H), 1.32−1.68 (m, 8 H), 2.06−2.18 (m, 2 H), 2.22−2.32 (m, 1 H), 2.35−2.48 (m, 1 H), 2.59 (dd, J =14.4, 5.6 Hz, 1 H); ^{13}C NMR δ 21.5, 24.9, 27.1, 28.8, 32.4, 32.9, 37.0, 37.7, 43.9, 44.1, 212.6.

A solution of the pure *cis*-ketone (260 mg, 1.56 mmol) in THF (1 mL) was added dropwise at −78 °C to a freshly prepared solution of LDA (2.35 mmol) in THF (5 mL). After the reaction mixture had been stirred at −78 °C for 40 min, a solution of trifluoromethanesulfonyl chloride (316 mg, 1.88 mmol) in THF (1 mL) was added slowly. The resulting mixture was stirred at −78 °C for 1 h and then poured into water. The aqueous layer was extracted with ether (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude product. Purification by column chromatography on silica gel (20:1 hexane−EtOAc) furnished 231 mg (74%) of α-chloroketones **52a,b** as a mixture of three isomers (a colorless oil): R_f 0.48 in 5:1 hexane−EtOAc; IR ($CHCl_3$) 1734 cm^{-1}; ^1H NMR δ 1.10 (s, $^3/_5$ H), 1.13 (s, $^6/_5$ H), 1.30 (s, $^6/_5$ H), 1.14−2.02 (m, 8 H), 2.21−2.92 (m, 5 H), 4.59−4.72 (m, 1 H).

α-Chloroketone 55. Liquid ammonia (100 mL) was distilled into a dried two-neck (500 mL) flask immersed in a dry ice/*i*-PrOH bath. To the vigorously stirred solution was added 1.56 g of hexane-washed lithium wire cut into 1-in. pieces. After the mixture had been stirred at −33 °C for 0.5 h, a solution of **51** (970 mg, 5.90 mmol) in 2 mL of THF was added over a period of 5 min at −78 °C. The reaction mixture was stirred at −78 °C for an additional 0.5 h. Solid ammonium chloride was then added slowly at −78 °C until the blue color was discharged.

The resulting colorless mixture was brought to room temperature, and ammonia was allowed to evaporate overnight. The mixture was poured into water and extracted with chloroform (4 × 30 mL). The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure to give 0.81 g (87%) of the corresponding *trans*-2-decalone as a colorless oil: R_f 0.48 in 5:1 hexane−EtOAc; IR ($CHCl_3$) 1707 cm^{-1}; ^1H NMR δ 1.03 (s, 3 H), 1.05−1.39 (m, 4 H), 1.41−1.59 (m, 5 H), 1.62−1.76 (m 2 H), 2.05−2.35 (m, 2 H), 2.39−2.52 (m, 2 H); ^{13}C NMR δ 14.9, 21.5, 26.0, 28.9, 33.1, 38.2, 40.3, 41.0, 44.6, 45.0, 211.8.

To a solution of the *trans*-2-decalone (100 mg, 0.60 mmol) in 3 mL of CCl_4 at 0 °C was added a solution of sulfuryl chloride (162 mg, 1.20 mmol) in 1 mL of CCl_4. The reaction mixture was stirred overnight at room temperature and poured into water. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude product. Purification by column chromatography (20:1 hexane−EtOAc) on silica gel gave 79 mg (65%) of α-chloroketone **55** as a colorless oil: R_f 0.44 in 5:1 hexane−EtOAc; IR ($CHCl_3$) 1722 cm^{-1}; ^1H NMR δ 1.12 (s, 3 H), 1.15−1.30 (m, 3 H), 1.38−1.62 (m, 7 H), 1.71−1.81 (m, 1 H), 2.10−2.42 (m, 2 H), 4.62 (dd, J = 13.2, 6.4 Hz, 1 H); ^{13}C NMR δ 15.6, 20.8, 25.7, 28.4, 35.5, 39.7, 44.5, 45.6, 52.9, 61.8, 201.7.

General Procedure for the [4 + 3] Cycloadditions under Föhlisch Conditions. To a solution of α-chlorocycloalkanone (0.1 mmol) and 4 or 5 equiv of 1,3-diene (i.e., furan or cyclopentadiene) in 2 mL of trifluoroethanol was added dropwise at 25 °C 28 μL (0.2 mmol) of triethylamine with vigorous stirring. The reaction mixture was stirred at room temperature. After the starting material was consumed (as monitored by TLC), the reaction was quenched by addition of 2 mL of H_2O. The mixture was extracted four times with ether. The organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography using a mixture of EtOAc−hexane as the eluent.

General Procedure for the [4 + 3] Cycloadditions under Schmid Conditions. A 50-mL, two-neck flask, equipped with a magnetic stirring bar, was charged quickly with 366 mg (1.88 mmol) of silver tetrafluoroborate and wrapped in aluminum foil. The assembly was dried under vacuum and purged with nitrogen. Methylene chloride (5 mL) was added, followed by freshly distilled *N*-(butoxycarbonyl)pyrrole (503 mg, 3.02 mmol). To the resulting solution cooled to −78 °C was then added dropwise a solution of crude 3-chloro-2-pyrrolidinocyclohexene [prepared from 200 mg (1.51 mmol) of 2-chlorocyclohexanone and excess pyrrolidine in the presence of $MgSO_4$] in 2 mL of CH_2Cl_2. The reaction mixture was allowed to slowly warm to room temperature and stirred for an additional 8 h. The reaction mixture was filtered through Celite to remove the inorganic salts, and the solids were rinsed thoroughly with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to afford the immonium salt as a dark brown oil, which was then treated with 5 mL of methanol and 10 mL of deionized water, followed by 241 mg of NaOH. The mixture was stirred at room temperature for 2 h. After the bulk of methanol was removed under reduced pressure, the concentrate was extracted with ether (4 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude product as a dark orange oil. Purification by column chromatography on silica gel (10:1 hexane−EtOAc) gave 234 mg (52%) of cycloadduct **16** as a white solid: mp 110−111 °C; R_f 0.25 in 5:1 hexane−EtOAc; IR (CCl_4) 1715, 1690 cm^{-1}; ^1H NMR δ 1.49 (s, 9 H), 1.90−2.60 (m, 6 H), 2.45 (m, 2 H), 4.84 (br s, 1 H), 4.94 (br s, 1 H), 6.26 (br s, 1 H), 6.30 (br s, 1 H); ^{13}C NMR δ 19.3, 28.4, 29.2, 29.3, 51.1 (2C), 61.6, 62.6, 80.2, 135.9, 136.9, 153.0, 215.3; HRMS (M^+ + H) 264.1600 calcd for $C_{15}H_{22}NO_3$, found 264.1595. Anal. Calcd for $C_{15}H_{22}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.24; H, 8.03, N, 5.25.

***anti*-11-Oxatricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (3a).** Cycloadduct **3a** was a white solid: mp 46−47 °C (lit.[11a] 46 °C); R_f 0.32 in 5:1 hexane−EtOAc; IR (CCl_4) 1732 cm^{-1}; ^1H NMR δ 1.48 (m, 1 H), 1.98−2.12 (m, 2 H), 2.20−2.37 (m, 4 H), 2.53 (m, 1 H), 4.91 (br s, 2 H), 6.33 (br s, 2 H); ^{13}C NMR δ 20.8, 31.0, 53.0, 83.5, 135.4, 214.7.

***anti*-Tricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (11).** Cycloadduct **11** was a white solid: mp 86−87 °C (lit.[11a] 86−87 °C); R_f 0.26 in 7:1 hexane−EtOAc; IR (CCl_4) 1716 cm^{-1}; ^1H NMR δ 1.51−1.62 (m, 1 H), 1.66−1.75 (m, 1 H), 1.75−1.86 (m, 1 H), 1.98−2.18 (m, 4 H), 2.41 (m, 2 H), 2.76−2.81 (m, 3 H), 6.12 (br d, J = 0.8 Hz, 2 H); ^{13}C NMR δ 19.4, 29.0, 34.9, 46.1, 48.9, 137.6, 219.5; HRMS (M^+) calcd for $C_{11}H_{14}O$ 162.1045, found 162.1030.

***anti*-11-(*N*-(*tert*-Butoxycarbonyl)aza)tricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (16).** The Föhlisch [4 + 3] cycloaddition of 2-chlorocyclohexanone and *N*-(butoxycarbonyl)pyrrole afforded 13% yield of cycloadduct **16** (the spectral data of which is given above), along with 12% yield of the α-substitution product, 2-(*N*-(*tert*-butoxycarbonyl)-pyrrol-2′-yl)cyclohexanone: IR (CCl_4) 1738, 1715 cm^{-1}; ^1H NMR δ 1.54 (s, 9 H), 1.68−2.02 (m, 4 H), 2.16 (m, 1 H), 2.34−2.59 (m, 3 H), 4.32 (dd, J = 4.5, 12.6 Hz, 1 H), 6.03 (m, 1 H), 6.13 (t, J = 3.3 Hz, 1 H), 7.24 (m, 1 H); ^{13}C NMR δ 25.7, 28.0, 28.1, 32.6, 42.1, 50.6 (2C), 83.3, 109.9, 110.9, 121.6, 133.0, 149.4, 209.5.

2-(Spiro[2.4]hepta-4′,6′-dien-4′-yl)cyclohexanone (21). This α-substitution product was obtained as a pale yellow oil: R_f 0.21 in 7:1 hexane−EtOAc; IR (CCl_4) 1711 cm^{-1}; ^1H NMR δ 0.27 (m, 1 H), 1.30−1.42 (m, 2 H), 1.56 (m, 1 H), 1.66−1.77 (m, 1 H), 1.78−1.88 (m, 1 H), 1.94−2.05 (m, 2 H), 2.06−2.18 (m, 2 H), 2.28−2.36 (m, 1 H), 2.46−2.55 (m, 1 H), 2.77 (dd, J = 9.8, 5.4 Hz, 1 H), 6.04 (dd, J = 5.1, 1.5 Hz, 1 H), 6.40 (m, 1 H), 6.51 (dd, J = 5.1, 2.3 Hz, 1 H); ^{13}C NMR δ 12.5, 12.7, 24.7, 28.0, 34.1, 37.9, 41.6, 48.5, 126.4, 128.3, 138.7, 146.2, 210.5.

***anti*-11-Oxa-2-methyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (22).** Cycloadduct **22** was a pale yellow oil: R_f 0.50 in 5:1 hexane−EtOAc; IR (CCl_4) 1730 cm^{-1}; ^1H NMR δ 1.37 (m, 1 H), 1.43 (s, 3 H), 1.82−2.08 (m, 2 H), 2.13−2.30 (m, 4 H), 2.49 (m, 1 H), 4.92 (t, J = 1.6 Hz, 1 H), 6.14 (d, J = 5.7 Hz, 1 H), 6.28 (dd, J = 5.7, 1.6 Hz, 1 H); ^{13}C NMR δ 19.4, 20.5, 28.7, 31.3, 51.3, 56.5, 83.5, 87.4, 135.4, 139.0, 215.3; HRMS (M^+) calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0994.

Cycloadduct 23. This pale yellow oil was obtained as an inseparable 2:1 mixture of the two diastereomers: R_f 0.35 in 10:1 hexane−EtOAc; IR (CCl_4) 1722, 1710 cm^{-1}; ^1H NMR δ 0.75−0.87 (m, 1 H), 0.95 (d, J = 6.3 Hz, 3 H), 1.22−1.50 (m, 2 H), 1.60 (s, 3 H), 1.67−1.79 (m, 2 H), 1.83−2.17 (m, 4 H), 2.17−2.31 (m, 4 H), 2.32−2.46 (m, 2 H), 4.51 (br s, 1/3 H), 4.55 (d, J = 1.6 Hz, 2/3 H); ^{13}C NMR (major isomer) δ 10.4, 20.5, 22.2, 23.0, 28.5, 28.8, 31.1, 33.5, 39.5, 49.4, 51.9, 86.1, 88.4, 133.6, 139.0, 214.7; ^{13}C NMR (minor isomer) δ 10.4, 18.7, 20.3, 20.5, 27.2, 29.6, 30.1, 31.2, 38.9, 49.8, 56.1, 85.8, 88.3, 134.4, 139.9, 215.4; HRMS (M^+ + H) calcd for $C_{16}H_{23}O_2$ 247.1698, found 247.1704.

α-Substitution Product 24. This pale yellow oil was obtained as an inseparable 1:1 mixture of the diastereomers: R_f 0.45 in 10:1 hexane−EtOAc; IR (CCl_4) 1716, 1621 cm^{-1}; ^1H NMR δ 0.80−0.91 (m, 1/2 H), 1.05 (d, J = 6.6 Hz, 3/2 H), 1.06 (d, J = 6.6 Hz, 3/2 H), 1.26−1.42 (m, 3/2 H), 1.63−1.97 (m, 4 H), 1.81 (s, 3 H), 1.98−2.43 (m, 7 H), 2.55−2.69 (m, 2 H), 3.60 (t, J = 8.2 Hz, 1 H); ^{13}C NMR (extra peaks due to the diastereomer are shown in parentheses) δ 8.1, 20.1 (20.2), 21.5, 24.6, 27.2, 29.5, 29.7, 31.2 (31.3), 32.1, 41.7, 49.3, 115.7, 117.9, 144.9, 148.8, 208.8.

***anti*-11-Oxa-1-methyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (25).** Cycloadduct **25** was a pale yellow oil: R_f 0.52 in 7:1 hexane−EtOAc; IR (CCl_4) 1733 cm^{-1}; ^1H NMR δ 0.83 (s, 3 H), 1.40−1.50 (m, 1 H), 1.64−1.73 (m, 1 H), 1.94−2.05 (m, 1 H), 2.20-2.26 (m, 2 H), 2.33−2.36 (m, 1 H), 2.49−2.63 (m, 1 H), 4.57 (s, 1 H), 4.91 (br s, 1 H), 6.35 (br s, 2 H); ^{13}C NMR δ 18.2, 21.0, 30.8, 40.1, 52.0, 53.8, 83.8, 87.3, 134.9, 136.2, 215.1; HRMS (M^+) calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0995.

***anti*-1-Methyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (26).** Cycloadduct **26** was a pale yellow oil: R_f 0.29 in 5:1 hexane−EtOAc; IR (CCl_4) 1720 cm^{-1}; ^1H NMR δ 0.93 (s, 3 H), 1.43−1.64 (m, 2 H), 1.67−1.83 (m, 2 H), 1.92−2.11 (m, 2 H), 2.19−2.27 (m, 1 H), 2.45 (m, 2 H), 2.71 (m, 1 H), 2.75 (m, 1 H), 6.12 (br s, 2 H); ^{13}C NMR δ 19.4, 23.3, 28.5, 36.7, 38.5, 46.1, 48.4, 49.9, 52.3, 137.0, 138.4, 219.2; HRMS (M^+) calcd for $C_{12}H_{16}O$ 176.1201, found 176.1201.

***anti*-11-Oxa-1,2-dimethyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (28).** This cycloadduct was obtained as an inseparable 7:1 mixture of **28** and **29** as a colorless oil: R_f 0.50 in 7:1 hexane−EtOAc; IR (CCl_4) 1729 cm^{-1}; ^1H NMR δ 0.88 (s, 3 H), 1.43 (s, 3 H), 1.50−1.61 (m, 1 H), 1.98−2.10 (m, 1 H), 2.20−2.34 (m, 3 H), 2.37 (m, 1 H), 2.46−2.63 (m, 1 H), 4.91 (dd, J = 1.8, 1.6 Hz, 1 H), 6.19 (d, J = 5.8 Hz, 1 H), 6.30 (dd, J = 5.8, 1.6 Hz, 1 H); ^{13}C NMR δ 16.8, 18.0, 21.2, 31.2,

37.6, 51.5, 55.6, 83.6, 87.5, 136.1, 138.6, 215.8; HRMS (M^+) calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1148.

The minor isomer **29** has the following ^{13}C NMR spectrum: δ 18.1, 19.4, 20.8, 28.6, 30.9, 40.5, 56.2, 87.7, 90.2, 135.0, 140.0, 215.8.

Tetracyclic Adduct 30a. It was obtained as a colorless oil: R_f 0.40 in 10:1 hexane−EtOAc; IR (CCl_4) 1730, 1712 cm^{-1}; ^1H NMR δ 0.92 (s, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 1.29−1.54 (m, 3 H), 1.58−1.69 (m, 2 H), 1.71 (d, J = 1.7 Hz, 3 H), 1.75 (m, 1 H), 1.85−1.96 (m, 1 H), 2.17 (m, 1 H), 2.21−2.32 (m, 3 H), 2.33−2.53 (m, 3 H), 4.26 (br s, 3/8 H), 4.31 (br s, 5/8 H); ^{13}C NMR (major isomer) δ 12.4, 17.8, 21.3, 22.2, 23.1, 28.6, 28.9, 33.7, 39.5, 41.3, 51.4, 51.9, 88.5, 90.5, 134.0, 140.8, 215.8; ^{13}C NMR (minor diastereomer) δ 12.5, 17.7, 19.0, 21.3, 20.4, 27.2, 28.6, 30.4, 39.2, 41.3, 51.7, 56.1, 88.6, 90.2, 135.1, 141.6, 216.3; HRMS (M^+ + H) calcd for $C_{17}H_{25}O_2$ 261.1855, found 261.1855.

Tetracyclic Adduct 30b. The adduct was obtained as a colorless oil: R_f 0.33 in 10:1 hexane−EtOAc; IR (CCl_4) 1713 cm^{-1}; ^1H NMR δ 0.92 (d, J = 6.3 Hz, 3 H), 0.96 (s, 3 H), 1.03−1.08 (m, 1 H), 1.34−1.51 (m, 2 H), 1.63 (d, J = 1.7 Hz, 3 H), 1.68−1.82 (m, 4 H), 1.85−1.99 (m, 1 H), 2.01−2.12 (m, 1 H), 2.17−2.34 (m, 2 H), 2.35−2.49 (m, 3 H), 4.50 (br d, J = 1.6 Hz, 1 H); ^{13}C NMR δ 18.9, 21.5, 22.8, 24.7, 29.7, 30.1, 31.4, 33.8, 38.5, 39.6, 50.0, 55.9, 86.0, 90.2, 135.5, 140.0, 216.2.

***anti*-11-Oxa-8-(β-triisopropylsiloxy)tricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (33) and *anti*-11-Oxa-8-(α-triisopropylsiloxy)tricyclo[4.3.1.1^{2,5}]-undec-3-en-10-one (34).** These cycloadducts were obtained as a pale yellow oil: R_f 0.42 in 5:1 hexane−EtOAc; IR (CCl_4) 1738 cm^{-1}; ^1H NMR δ 0.78−0.88 (m, 1/3 H), 0.90−1.10 (m, 21 H), 1.62−1.68 (m, 1/3 H), 1.95 (m, 2/3 H), 2.27−2.40 (m, 4 H), 2.52 (dd, J = 13.6, 7.1 Hz, 2/3 H), 3.86 (m, 2/3 H), 4.75 (d, J = 1.1 Hz, 4/3 H), 4.86 (br s, 2/3 H), 5.07 (m, 1/3 H), 6.25 (s, 4/3 H), 6.30 (s, 2/3 H); ^{13}C NMR (**33**) δ 18.0, 36.8, 50.0, 65.2, 82.6, 133.4, 212.0; ^{13}C NMR (**34**) δ 12.2, 40.5, 52.7, 65.8, 82.9, 134.1, 212.2; HRMS (M^+ + H) calcd for $C_{19}H_{33}O_3Si$ 337.2199, found 337.2194.

***anti*-11-Oxa-8-β-methyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (36) and *anti*-11-Oxa-8-α-methyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (37).** These cycloadducts were obtained as a pale yellow oil: R_f 0.26 in 7:1 hexane−EtOAc; IR (CCl_4) 1726 cm^{-1}; ^1H NMR δ 0.82 (d, J = 6.5 Hz, 1/2 H), 0.91 (d, J = 6.3 Hz, 5/2 H), 1.58−1.72 (m, 5/6 H), 1.91−2.06 (m, 4 H), 2.25−2.40 (m, 2 H), 3.00−3.12 (m, 1/6 H), 4.68 (s, 5/3 H), 4.91 (s, 1/3 H), 6.24 (s, 5/3 H), 6.33 (s, 1/3 H); ^{13}C NMR (**36**) δ 21.6, 27.8, 35.8, 51.0, 82.7, 134.0, 215.5; ^{13}C NMR (**37**) δ 23.0, 27.0, 39.8, 52.8, 83.1, 135.2, 215.5; HRMS (M^+) calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0989.

***anti*-11-Oxa-7-(α-triisopropylsiloxy)tricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (41).** Cycloadduct **41** was a pale yellow oil: R_f 0.21 in 7:1 hexane−EtOAc; IR (CCl_4) 1731 cm^{-1}; ^1H NMR δ 1.03 (m, 21 H), 1.55−1.63 (m, 1 H), 2.05−2.27 (m, 2 H), 2.31−2.39 (m, 1 H), 2.48 (d, J = 1.9 Hz, 1 H), 2.65−2.78 (m, 1 H), 4.64 (m, 1 H), 4.89 (t, J = 3.2 Hz, 2 H), 6.33 (br s 2 H); ^{13}C NMR δ 12.2, 18.0, 26.0, 31.8, 52.6, 62.1, 74.9, 80.0, 84.0, 134.5, 135.3, 209.8; HRMS (M^+ + H) calcd for $C_{19}H_{33}O_3Si$ 337.2199, found 337.2193.

***anti*-11-Oxa-7-(β-triisopropylsiloxy)tricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (42).** Cycloadduct **42** was as a pale yellow oil: R_f 0.26 in 7:1 hexane−EtOAc; IR (CCl_4) 1727 cm^{-1}; ^1H NMR δ 1.03 (m, 21 H), 1.64−1.75 (m, 1 H), 1.93 (td, J = 7.4, 14.2 Hz, 1 H), 2.11 (dd, J = 8.6, 14.2 Hz, 1 H), 2.28 (m, 1 H), 2.60 (m, 1 H), 2.64−2.76 (m, 1 H), 4.22 (ddd, J = 5.2, 7.4, 10.2 Hz, 1 H), 4.90 (d, J = 2.2 Hz, 1 H), 5.22 (d, J = 1.8 Hz, 1H), 6.36 (br s, 2 H); ^{13}C NMR δ 12.2, 18.0, 25.4, 32.0, 51.9, 61.2, 72.7, 79.2, 83.3, 135.2, 135.7, 210.5.

***anti*-11-Oxa-7-α-methyltricyclo[4.3.1.1^{2,5}]undec-3-en-10-one (45).** The [4 + 3] cycloaddition of **44** and furan under Föhlisch conditions gave a 8:1 mixture of **45** and **46** as a pale yellow oil: IR (CCl_4) 1727 cm^{-1}; ^1H NMR δ 1.00 (d, J = 7.0 Hz, 3 H), 1.13−1.23 (m, 1 H), 2.04−2.14 (m, 2 H), 2.16−2.25 (m, 1 H), 2.28−2.34 (m, 1 H), 2.40−2.50 (m, 1 H), 2.55−2.61 (m, 1 H), 4.86 (dd, J = 2.3, 7.8 Hz, 2 H), 6.32 (br s, 2 H); ^{13}C NMR (for **45**) δ 22.4, 27.5, 28.8, 36.6, 52.1, 60.0, 82.8, 83.5, 134.9 (2 C), 213.4; HRMS (M^+) calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0989.

The ^{13}C NMR spectrum of the minor product **46**: 19.2, 29.7, 30.1, 37.7, 52.4, 58.4, 79.5, 83.4, 135.3, 135.9, 214.9.

Tetracyclic Adduct 49. Cycloadduct **49** was a white solid: mp 142−143 °C; R_f 0.23 in 10:1 hexane−EtOAc; IR ($CHCl_3$) 1737 cm^{-1}; ^1H NMR δ 1.10−1.34 (m, 3 H) 1.36−1.70 (m, 5 H), 1.91−2.22 (m, 3 H), 2.31−2.50 (m, 2 H), 3.46 (m, 1 H), 4.97 (m, 2 H), 6.36 (s, 2 H); ^{13}C NMR δ 20.7, 25.9, 29.3, 30.0, 30.8, 32.9, 43.1, 53.5, 60.0, 83.2, 83.7, 135.4, 135.5, 213.5; HRMS (M^+ + H) calcd for $C_{14}H_{19}O_2$ 219.1385, found 219.1383. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.92; H, 8.33.

Tetracyclic Adduct 50. Cycloadduct **50** was a pale yellow oil: R_f 0.26 in 10:1 hexane−EtOAc; IR ($CHCl_3$) 1716 cm^{-1}; ^1H NMR δ 0.87 (m, 1 H), 1.19−1.87 (m, 11 H), 2.08−2.23 (m, 2 H), 2.41 (m, 1 H), 2.52 (m, 1 H), 2.78 (m, 2 H), 6.11 (br s, 2 H); ^{13}C NMR δ 14.1, 22.1, 24.6, 30.8, 32.1, 32.9, 34.6, 36.4, 41.2, 46.9, 48.6, 56.1, 137.5, 137.8, 219.3; HRMS (M^+ + H) calcd for $C_{15}H_{21}O$ 217.1592, found 217.1591.

Tetracyclic Adduct 53. Cycloadduct **53** was a white solid: mp 88−89 °C; R_f 0.34 in 5:1 hexane−EtOAc; IR (CCl_4) 1717 cm^{-1}; ^1H NMR δ 0.91−1.00 (m, 1 H), 1.05 (s, 3 H), 1.13−1.75 (m, 8 H), 2.07 (m, 1 H), 2.20 (dd, J = 13.5, 2.0 Hz, 1 H), 2.42 (m, 1 H), 2.50 (br s, 1 H), 4.66 (br s, 2H), 6.22 (dd, J = 6.2, 1.2 Hz, B of AB q, 1 H), 6.24 (dd, J = 6.2, 1.2 Hz, A of AB q, 1 H); ^{13}C NMR δ 20.7, 22.2, 27.6, 30.0, 33.0, 34.5, 42.9, 45.7, 52.0, 58.8, 83.7, 83.9, 133.7, 133.9, 214.9; HRMS (M^+ + H) calcd for $C_{15}H_{21}O_2$ 233.1541, found 233.1536.

Tetracyclic Adduct 54. Cycloadduct **54** was a pale yellow oil: R_f 0.33 in 15:1 hexane−EtOAc; IR ($CHCl_3$) 1711 cm^{-1}; ^1H NMR δ 0.91−0.99 (m, 1 H), 1.07 (s, 3 H), 1.19−1.50 (m, 5 H), 1.55−1.75 (m, 4 H), 1.92 (dd, J = 14.4, 1.6 Hz, 1 H), 2.06 (m, 1 H), 2.23 (m, 1 H), 2.43 (m, 1 H), 2.52 (d, J = 11.5 Hz, 1 H), 2.71 (m, 2 H), 6.05 (dd, J = 5.8, 2.4 Hz, B of AB q, 1 H), 6.06 (dd, J = 5.8, 2.4 Hz, A of AB q, 1 H); ^{13}C NMR δ 20.7, 22.5, 27.9, 30.8, 31.8, 35.8, 36.1, 44.3, 46.7, 47.4, 47.5, 48.5, 55.7, 136.5, 136.8, 219.6; HRMS (M^+ + H) calcd for $C_{16}H_{23}O$ 231.1749, found 231.1748.

Tetracyclic Adduct 56. Cycloadduct **56** was a white solid: mp 90−92 °C; R_f 0.37 in 5:1 hexane−EtOAc; IR ($CHCl_3$) 1708 cm^{-1}; ^1H NMR δ 0.78−0.90 (m, 1 H), 0.91 (s, 3 H), 1.24−1.60 (m, 6 H), 1.72 (m, 1 H), 1.83 (dd, J = 13.0, 10.3 Hz, 1 H), 1.99 (m, 1 H), 2.12 (dd, J = 13.0, 1.6 Hz, 1 H), 2.46−2.56 (m, 2 H), 4.71 (br s, 2 H), 6.24 (dd, J = 6.1, 1.1 Hz, B of AB q, 1 H), 6.25 (dd, J = 6.1, 1.1 Hz, A of AB q, 1 H); ^{13}C NMR δ 19.7, 21.4, 26.3, 29.1, 35.0, 41.9, 43.3, 47.9, 53.0, 59.5, 83.4, 83.6, 133.8, 134.2, 214.8; HRMS (M^+ + H) calcd for $C_{15}H_{21}O_2$ 233.1541, found 233.1535.

Tetracyclic Adduct 57. Cycloadduct **57** was a white solid: R_f 0.47 in 5:1 hexane−EtOAc; IR ($CHCl_3$) 1734 cm^{-1}; ^1H NMR δ 0.81−0.93 (m, 1 H), 0.95 (s, 3 H), 1.22−1.54 (m, 7 H), 1.74 (m, 1 H), 2.14 (d, J = 14.0 Hz, 1 H), 2.37 (m, 2 H), 2.85 (d, J = 14.0 Hz, 1 H), 4.71 (br s, 1 H), 4.75 (br s, 1 H), 6.32 (dd, J = 6.0, 1.2 Hz, B of AB q, 1 H), 6.33 (dd, J = 6.0, 1.2 Hz, A of AB q, 1 H); ^{13}C NMR δ 19.4, 20.9, 26.2, 28.6, 29.7, 35.8, 41.3, 47.3, 56.1, 59.3, 83.4, 87.6, 133.2, 135.5, 204.5.

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Supporting Information Available: Characterization data (^1H and ^{13}C NMR spectra) for **3a**, **11**, **16**, **22**−**26**, **28**, **29**, **30a**,**b**, **33**, **34**, **36**, **37**, **41**, **42**, **45**, **46**, **49**, **50**, **53**, **54**, **56**, **and 57** (48 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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