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STUDY OF KETENE-ALKENE CYCLOADDITIONS AND CYCLOREVERSIONS OF CYCLOBUTANONES

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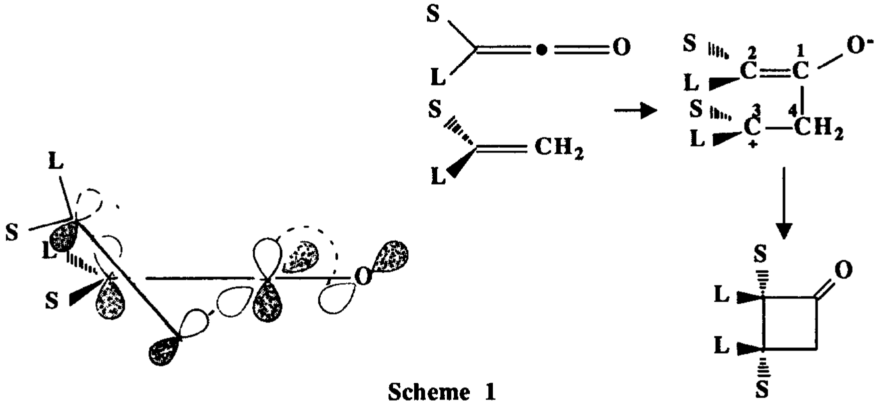
Abstract: A study of the addition reaction of tert-butylcyanoketene (TBCK) with several alkenes and thermal cycloreversion of various TBCK-alkene adducts in different solvents has been carried out Cycloreversions were usually found to follow a concerted pathway

INTRODUCTION

The [2+2] cycloaddition of ketenes and ketenophiles is an important chemical template to construct four membered carbo- or hetero-cyclic ring systems which are otherwise difficult to prepare [1] Even though the ketene chemistry has been started in the very beginning of this century[2] the pathway this pericyclic reaction traverses is still a subject of much speculation While a concerted [$\pi^2s + \pi^2a$] ketene-alkene cycloaddition[3], considered by Woodward and Hoffman, provides rationale for the stereochemical and kinetic evidence, several theoretical and practical studies[4] seem to agree with asynchronous (two-stage) and zwitterionic (two-step)[5] mechanisms A recent theoretical study[4c] on the ketene-alkene reaction analysis by correlation of localized molecular orbital suggests the reaction mechanism corresponding to the [$\pi^2s + (\pi^2s + \pi^2s)$] description, rather than to the [$\pi^2s + \pi^2a$] one In this description the reactants approach to one another in a perpendicular fashion twisted by some 50-60° C



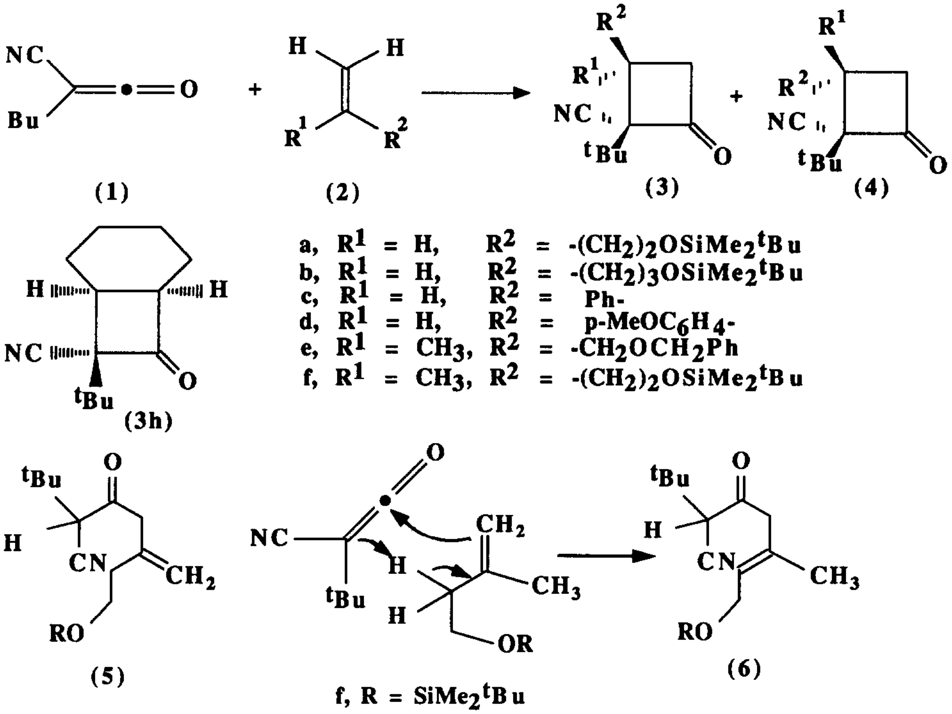
Scheme 1

In the transition state of this nonsynchronous concerted addition reaction the C_1-C_4 distance is substantially shorter than the C_2-C_3 There is appreciable charge separation in the transition state As shown in scheme 1, high regioselectivity is attributed to the electronic reasons and steric effects dictates the stereochemical outcome with cis-relationship of the bulky substituents in the resulting cyclobutanone Extreme cases of nonsynchroneity result in the ketene cycloaddition to enamines[6], vinyl ethers, or dienes and available experimental evidence points toward a stepwise mechanism involving zwitterionic intermediates[5]

In this report, we want to study the addition reactions of tert-butylcyanoketene (TBCK) with some mono- and di-substituted alkenes and aliphatic terminal alkynes We also want to examine the thermal cycloreversion of several substituted cyclobutanones to ketene and ketenophile Principle of microscopic reversibility suggests that every elementary reaction must be reversible and thermal studies of the cycloreversion process in different solvents would indeed be helpful in understanding certain important aspects of cycloaddition reactions.

RESULTS AND DISCUSSION

TBCK(1)[7] was generated in refluxing benzene (or toulene) and was allowed to react with several alkenes (Scheme 2) under different reaction conditions The addition reaction with tert-butyldimthylsilyl-3-butenyl ether



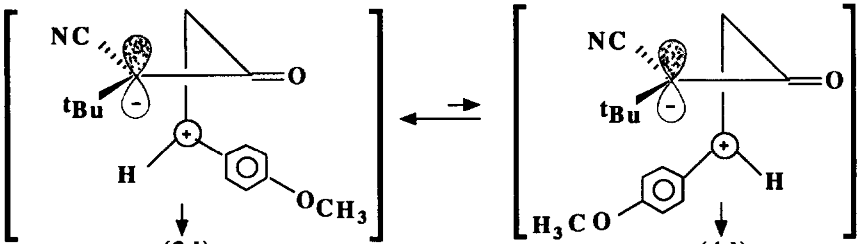
a, R^1 = H, R^2 = $-(CH_2)_2OSiMe_2{}^tBu$
b, R^1 = H, R^2 = $-(CH_2)_3OSiMe_2{}^tBu$
c, R^1 = H, R^2 = Ph-
d, R^1 = H, R^2 = p-$MeOC_6H_4$-
e, R^1 = CH_3, R^2 = $-CH_2OCH_2Ph$
f, R^1 = CH_3, R^2 = $-(CH_2)_2OSiMe_2{}^tBu$

f, R = $SiMe_2{}^tBu$

Scheme 2

(2a) in refluxing benzene afforded (3a) as the sole adduct in 70% yield with *cis* disposition of the bulky substituents at C-2 and C-3 We were unable to detect the formation of the thermodynamic adduct (4a) Similar cycloaddition of TBCK onto tert-butyldimethylsilyl-4-pentenyl ether (2b) gave both regiospecifically and stereoselectively the contrathermodynamic adduct (3b) as a crystalline solid (61%) yield The IR spectra had strong absorption at 1774 cm^{-1} due to the carbonyl group and CN absorption appeared at 2205 cm^{-1}

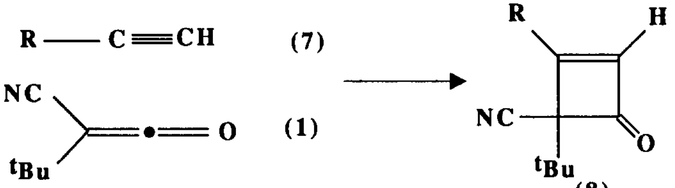
The TBCK-styrene[8] adduct (3c) and -cyclohexene[9] adduct (3h) were prepared in refluxing benzene and toluene respectively However the reaction of TBCK with p-methyoxystyrene (2d) was found to be nonselective. In refluxing benzene a mixture of adducts **(3d)** and **(4d)** was found to be in a ratio of 40 60, respectively Based on the proton NMR spectrra the stereochemistry was assigned to the adducts In **(3d)** the C-3 H, being cis to the C-2 cyanide group, appears at downfield (δ 4.38) compared to the C-3 H of **(4d)** which is shielded[10] by tert-butyl group Unlike styrene, the cycloaddition of p-methoxystyrene like vinylethers may involve zwitterionic intermediate The presence of p-methoxy group can stabilize such intermediate by resonance and kinetic adduct **(3d)** can equilibrate to the thermodynamic product **(4d)** via the zwitterionic intermediates



(3d) **(4d)**

Cycloaddition of TBCK with benzyl-2-methyl-2-propenyl ether **(2e)** afforded a mixture **(3e)** and **(4e)** in a respective ratio of of 60 40 The major adduct was assumed to have the stereochemistry as depicted in **(3d)** with the bulkier groups of C-2 and C-3 cis to each other Nonselective nature of this addition was attributed to the similar steric effects exerted by the two groups R^1 and R^2

The cycloaddition of TBCK with tert-butyldimethylsilyl-3-methyl-3-butenyl ether **(2f)** afforded acyclic products **(5f)** and **(6f)** in addition to normal adducts **(3f)** and **(4f)** in a ratio of 19 8 40 33, respectively The major product was assigned the stereochemistry as depicted in **(3f)** based on the least hindered approach of the addenda The formation of the acyclic products is presumably the result of ene-reaction as depicted in scheme 2 The E-geometry of the alkene **(6f)** is probably the outcome of the least hindered approach of TBCK towards the alkene **(2f)**

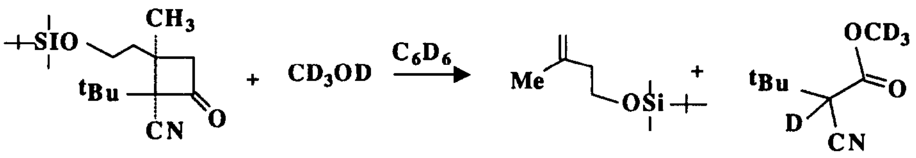


a, R = Ph ; **b**, R = $(CH_2)_3CH_3$; **c**, R = $(CH_2)_5CH_3$

d, R = $CH_2OSiMe_2{}^tBu$; **e**, R = $CMe_2OSiMe_2{}^tBu$; **f**, R = CH_2OCH_2Ph

Scheme 3

Next, we focussed our attention to the addition reaction of TBCK with several terminal alkynes (7) In refluxing benzene phenylacetylene (7a) afforded the cyclobutenone (8a)[11] in good yield The olefinic proton of (8a) appeared at δ 6 15 However, the corresponding addition reaction involving aliphatic alkynes (7b-7f) failed to yield appreciable quantities of any cycloadduct The reaction of TBCK with (7c) at 20°C, 50°C, or 80°C for shorter or longer duration gave cyclobutenone only in minute quantities as revealed by the presence of an olefinic proton at δ6.17 (t, J 1 8 Hz). We did not pursue the reaction further. Most probably the addition reactions with terminal aliphatic alkynes are either very slow at lower temperatures or the highly strained cyclobutenones (**8**) formed at higher temperature may not survive the relatively harsh reaction conditions Finally, we undertook the study of cycloreversion of several cyclobutanones to the TBCK and alkenes The results of the thermal study are included in the Table Cycloreversions are found to follow the kinetics of first-order reaction Cycloreversion of the adducts was followed by NMR technique which offers a convenient method for monitoring the progress of the reactions In the NMR tube was taken a C_6D_6 solution of the adduct (3f) containing CD_3OD, the trapping agent, which captures the ketene (TBCK) immediately upon its formation (Scheme 4)



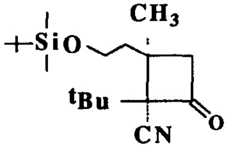
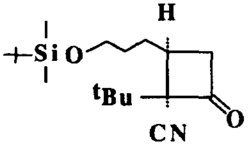
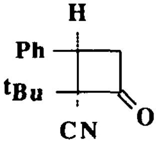
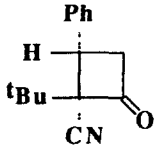
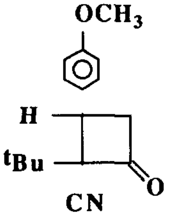
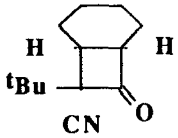
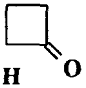
(3f) **(2f)** **(12)**

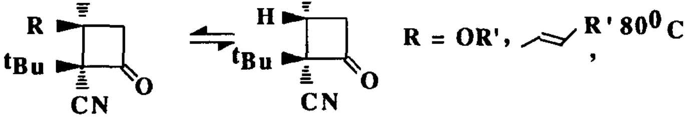
Scheme 4

The sealed NMR tube was then heated at the desired temperature and the proton NMR spectra were recorded from time to time. Using integration of several proton signals the ratio of the cyclobutanone (**3f**) and the product alkene (**2f**), hence the concentration of the adduct (**3f**), was determined and the first order rate constant was computed by linear regression analysis Likewise, rate constants for the cycloreversion of other cycloadducts were determined

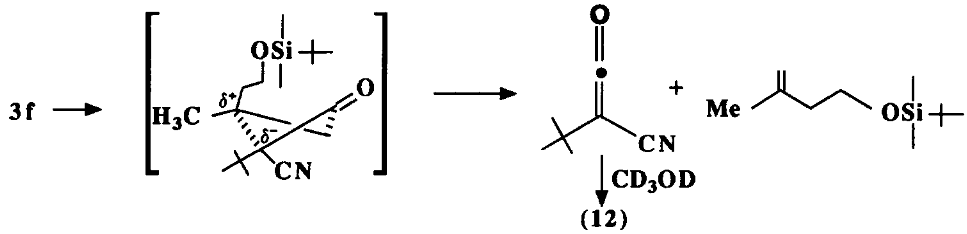
The rate constants for the cycloreversion of tetrasubstituted cyclobutanone (**3f**) in C_6D_6, DMSO-d_6, and CD_3OD at 92°C were found to be in a ratio of 1 0 1 8 2 4, respectively Such a small dependency of the rate constants on solvents with a wide difference in dielectric costants certifies the molecular nature of the cycloreversion process For the cycloaddition or cycloreversion process to follow stepwise pathway involving zwitterionic intermediate one would expect a much larger solvent effect The cycloreversion of the trisubstituted cyclobutanone (**3b**) was found to be very slow in compare to its tetrasubstituted counterpart (**3f**) Thermal decomposition did not occur at92°C Even at higher temperature (120°C) it was indeed a slow process It is presumable that the sever crowding in tetrasubstituted adduct (**3f**) would be relieved in the transition state leading to the formation of the ketene and alkene

Table. First order rate constants for cycloreversion of various cyclobutanones

Comp. No.	Cyclobutanones	Temp./°C	Solvent	$k_1/10^{-5}$ S^{-1}
3f		92 92 92	C_6D_6 DMSO-d_6 CD_3OD	9.2 17 22
3b		120	C_6D_6	0.68
3c		92 92	C_6D_6 CD_3OD	33 26
4c		120	C_6D_6	0.33
4d		120	C_6D_6	9.7
3h		103 120	C_6D_6 C_6D_6	1.1 5.8
9		368	bulk (vapor)	68



(10) (11)



In any nonsynchronous two-stage process with some charge separation, the transition state would inherit the stabilization of the apparent tertiary carbonium ion These factors may indeed be responsible for the much augmented rate of cycloreversion of the adduct (3f)

Rate of cycloreversion of the contrathermodynamic styrene adduct (3c) in C_6D_6 and CD_3OD was found to be approximately identical, thus indicating the concerted nature of the reaction As expected, the break down of the corresponding thermodynamic adduct (4c)[12] requires higher energy of activation and it was found to be much slower process even at 120°C Thermodynamic adduct (**4d**) of p-methoxystyrene undergoes decomposition approximately 30 times faster than the corresponding styrene adduct (**4c**). p-Methoxy substutuent stabilizes charge separated transition state and thus lower the energy of activation of the cycloreversion process

The homogeneous thermal decomposition of parent cyclobutanone (9) into ethylene and ketene was reported[13] to be very slow and the first order rate constant value was measured to be 68×10^{-5} s^{-1} at 368°C The rate constant for the cycloconversion of cyclohexene-TBCK adduct (3h) was found to be $1\ 1 \times 10^{-5}$ and $5\ 8 \times 10^{-5}$ s^{-1} at 103° and 120°C, respectively in C_6D_6 The contrathermodynamic ketene adduct (10), where R is usually an alkoxy or vinyl type substituent, are known to equilibrate to the more stable adduct (11) via zwitterionic intermediate[5] at 80-100°C

Rate constant values obtained for the cycloreversion of several cyclobutanones are of both theoretical and practical impotance For synthetic purposes our study provides useful information regarding the stability of several ketene adducts

EXPERIMENTAL

Elemental analyses were performed on a Carl-Erba elemental analyser 1106 I R spectra were recorded on a Perkin-Elmer Model 237B instrument and are reported in cm^{-1} ^1H NMR spectra were recorded on a Bruker AC-80 using deuterochloroform, unless otherwise stated, as solvent and TMS as internal standard. All m p s are uncorrected, tert-Butylcyanoketene was generated by the procedure of Moore[7] The tert-buyldimethylsilyl ethers (**2a, b, f**) were prepared by treating the corresponding alcohols with one equivalent of tert-butyldimethylchorosilane and two equivalents of imidazole in dimethylformamide solvent The benzyl ether (**2e**) was prepared by treating sodium 2-methyl-2-propenoxide with benzyl bromide All the alkenes were distilled prior to use Benzene was freshly distilled from calcium hydride under nitrogen The addition reactions were performed under a positive pressure of dry argon Silica gel chromatrographic separations were performed with flash silica (Baker chemical co)

Reaction of the TBCK with tert-butyldimethylsilyl-3-butenyl ether (2a).- The TBCK (6 0 mmol) was reacted with (**2a**) (9 0 mmol) in refluxing benzene (50 mL) for 12 h under argon The reaction mixture was then concentrated and the residual liquid was purified by chromatography over silica gel using 5·1 hexane/ether mixture as the eluant to give (**3a**) (1 30g, 70%) as colorless liquid, (Found C, 66 12, H, 9 89, N,4 41

$C_{17}H_{31}NO_2Si$ requires C, 65 97, H, 10 10, N, 4 53%), υ_{max} (neat) 2930, 2840, 2235, 1794, 1469,1392, 1257, 1102, and 850 cm^{-1}, δ_H 0 06 (6H, s), 0 90 (9H, s), 1 23 (9H, s), 1 85-2 25 (2H, m), 2 85-3 50 (3H, m), and 3 70 (2H, t, J 6 0 Hz)

Reaction of the TBCK with tert-butyldimethylsilyl-4-pentenyl ether (2b) - The TBCK (6.0 mmol) and the alkene **(2b)** (9.0 mmol) in benzene (50 mL) was refluxed for 20 h under argon. Usual chromatographic purification over silica gel using 10 1 hexane/ether as the eluant afforded the sole adduct **(3b)** as colorless crystal (0 90 g, 61%), m.p 67-68^0 C (ether/hexane) (Found C, 66 53, H, 10 12, N, 4 28 $C_{18}H_{33}NO_2Si$ requires C, 66 82, H, 10 28, N, 4.33%), υ_{max} (KBr) 2848-2822, 2205, 1774, 1469, 1409, 1379, 1259, 1199, and 849 cm^{-1}, δH 0 05 (6H, s), 0 90 (9H, s), 1 22 (9H, s), 1 30-2 43 (4H, m), 2 75-3 45 (3H, m) and 3 67 (2H, t, J 6 0 Hz)

Reaction of the TBCK with p-methoxystyrene(2d) - Reaction of the TBCK (6 0 mmol) with p-methoxystyrene **(2d)** in refluxing benzene (50 mL) for 4 h resulted in the formation of **(3d)** and **(4d)** in a ratio of 40 60 as determined by the analysis of proton NMR of the crude reaction mixture However, we were able to isolate only (4d) as a colorless liquid in pure form by silica gel column chromatography using hexane/ether (10 1) as eluant. During chromatography the adduct **(3d)** either decomposed or rearranged to the thermodynamic adduct **(4d)** (Found C, 74 20, H, 7 22, N, 5 27 $C_{16}H_{19}NO_2$ requires C, 74 68, H, 7 44, N, 5 44%), δH(C_6H_6) 1 20 (9H, s), 3 14-4 12 (3H, m), 3 80 (3H, s) and 7 10 (4H, AB, J 9 0 Hz)

Reaction of the TBCK with benzyl-2-methyl-2-propenylether (2e) - A solution of the TBCK (6 0 mmol) and alkene **(2e)** (8 0 mmol) in benzene (50 ml) was refluxed under argon for 24 h After removal of the solvent the crude reaction mixture was purified by silica gel chromatography using hexane/ether (5 1) as the eluant to give a nonseparable mixture of adducts **(3e)** and **(4e)** as a colorless liquid (0 72 g, 42%) in a ratio of 55 45 as determined by the integration of the methyl singlets at δ1 53 and 1 67 The proton NMR signals of (3e) and **(4e)** were deduced from the spectrum of their mixture (Found C, 75 50, H, 7 95, H, 4 77 $C_{18}H_{23}NO_2$ requires C, 75 75, H, 8 12, N, 4 91%) υ_{max} (neat) 2930, 2842, 2207, 1783, 1104, and 752 cm^{-1}

Adduct **(3e)** δ_H 1 28 (9H, s), 1 53 (3H, s), 3 05 (2H, AB, J 18 0 Hz), 3 67 (2H, AB, J 12 0 Hz), 4 62(2H, AB, J 12 0 Hz) and 7 30 (5H, s)

Adduct **(4e)** δ_H 1 20 (9H, s), 1 67 (3H, s), 3 00 (2H, s), 3 71 (2H, AB, J 12 0 Hz), 4 65 (2H, AB, J 12 0 Hz), and 7 30 (5H, s)

Reaction of the TBCK with tert-butyldimethylsilyl-3-methyl-3-butenyl ether (3f) A solution the TBCK (12 0 mmol) and the alkene **(3f)** (14 0 mmol) in benzene (50 mL) was refluxed under argon for 24 h After removal of the solvent the yellow residue was chromatographed using hexane/ether (10 1) as the eluant to give the following fractions

The first component eluted contained compound **(3f)** followed by a mixture of **(3f)** and **(4f)**, then continued elution gave a mixture of **(4f)** and **(5f)** Further elution afforded **(5f)** and finally **(6f)** Thus, we were able to isolate **(3f)**, **(5f)**, and **(6f)** in pure form as colorless liquids However, the NMR spectrum of **(4f)** was deduced from the spectrum of its mixture with other isomers Detailed analysis of NMR spectra and the mass of several fractions isolated revealed that the compounds **(3f)-6(f)** were formed in a ratio of 40 33 19 8, respectively The isolated yield of the products was 73%

Compound (3f) (Found C, 66 62, H, 10 07, N, 4 39 $C_{18}H_{33}NO_2Si$ requires C, 66 82, H, 10 28, N, 4 33%) υ_{max} (neat) 2925, 2905, 2830, 2208, 1780, 1487, 1406 and 1137 cm^{-1}, δ_H 0 07 (6H, s), 0 90 (9H, s), 1 25 (9H, s), 1 51 (3H, s), 2 20 (2H, m), 2 78 (1H, d, J 17 5 Hz), 3 38 (1H, d, J 17 5 Hz), and 3 83 (2H, dd, J 5 0, 7 0 Hz)

Compound (4f) δ_H 0 07 (6H, s), 0 90 (9H, s), 1 28 (9H, s), 1 54 (3H, s), 2 20 (2H, m), 2 75 (1H, d, J 18 0 Hz), 3 41 (1H, d, J 18 0 Hz), and 3 80 (2H, dd, J 5 0, 7 0 Hz)

Compound (5f) (Found C, 66 47, H, 10 35, N, 4 17 $C_{18}H_{33}NO_2Si$ requires C, 66.82, H, 10 28, N, 4 33%), υ_{max} (neat) 2928, 2923, 2823, 2228, 1788, 1725, 1473, 1379, 1263, 1106 and 856 cm^{-1}, δH 0 07 (6H, s), 0 90 (9H, s), 1 15 (9H, s), 2 29 (2H, t with fine splitting J 6 5 Hz), 3 38 (3H, apparent s), 3 73 (2H, t, J 6 5 Hz), 4 92 (1H, bs), and 5 07 (1H, m)

Compound (6f): υ_{max} (neat) 2940, 2925, 2240, 1724, 1444, 1389, 1259, 1114, 1074, and 847 cm^{-1}, δ_H 0 07 (6H, s), 0.90 (9H, s), 1 13 (9H, s), 1 65 (3H, bs), 3 38 (3H, apparent s), 4 22 (2H, apparent d, J 6 5 Hz), and 5 44 (1H, apparent t, J 6 5 Hz)

Kinetics of cycloreversion process. A generalized procedure - The cyclobutanone **(3f)** (60 mg), CD_3OD (30 mg) and C_6D_6 (1.0 mL) were taken in a dry NMR tube and was sealed under N_2 atmosphere The sealed tube was heated at a constant temperature bath at 92± 0.5°C The progress of the reaction was monitored by NMR spectroscopy at various intervals of time The ratio of the alkene **(2f)** and the adduct **(3f)** was determined by integration of the olefinic and C-4 proton of **(3f)** First order rate constant was determined by linear regression analysis

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12 Preparation of several thermodynamic TBCK-alkene adducts including the TBCK-styrene adduct **(4c)** will be published elsewhere

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