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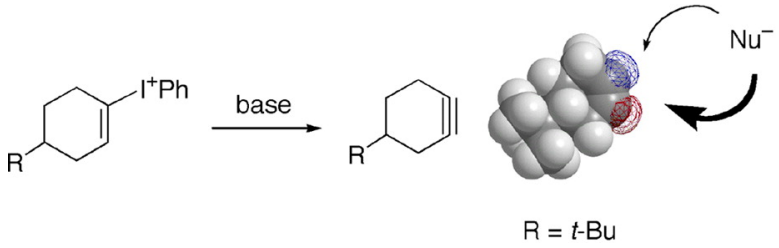

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Elimination−Addition Mechanism for Nucleophilic Substitution Reaction of Cyclohexenyl Iodonium Salts and Regioselectivity of Nucleophilic Addition to the Cyclohexyne Intermediate

Morifumi Fujita,*,† Wan Hyeok Kim,† Yuichi Sakanishi,† Koji Fujiwara,† Sayaka Hirayama,† Tadashi Okuyama,*,† Yasuhiro Ohki,‡ Kazuyuki Tatsumi,‡ and Yasunori Yoshioka§

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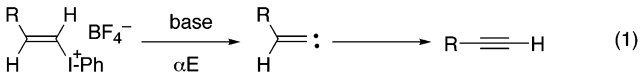
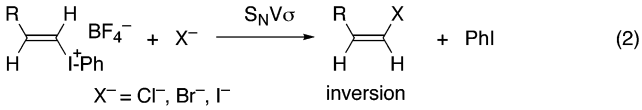
Abstract: The reaction of 4-substituted cyclohex-1-enyl(phenyl)iodonium tetrafluoroborate with tetrabutylammonium acetate gives both the *ipso* and *cine* acetate-substitution products in aprotic solvents. The isomeric 5-substituted iodonium salt also gives the same mixture of the isomeric acetate products. The reaction is best explained by an elimination−addition mechanism with 4-substituted cyclohexyne as a common intermediate. The cyclohexyne formation was confirmed by deuterium labeling and trapping to lead to [4 + 2] cycloadducts and a platinum−cyclohexyne complex. Cyclohexyne can also be generated in the presence of some other mild bases such as fluoride ion, alkoxides, and amines, though amines are less effective bases for the elimination. Kinetic deuterium isotope effects show that the anionic bases induce the E2 elimination ($k_H/k_D > 2$), while the amines allow formation of a cyclohexenyl cation in chloroform to lead to E1 as well as S_N1 reactions ($k_H/k_D \approx 1$). Bases are much less effective in methanol, and methoxide was the only base to efficiently afford the cyclohexyne intermediate. Nucleophiles react with the cyclohexyne to give regioisomeric products in the ratio dependent on the ring substituent. The observed regioselectivity of nucleophilic addition to substituted cyclohexynes is rationalized from calculated LUMO populations, which are governed by the bond angles at the acetylenic carbons: The less deformed carbon has a higher LUMO population and is preferentially attacked by the nucleophile.

Introduction

Vinyl iodonium salts are a class of very reactive compounds, which undergo nucleophilic substitution and base-induced elimination.[1,2] Main reactions of simple alk-1-enyliodonium salts are α-elimination (eq 1) and S_N2-type ($S_NV\sigma$)[3] substitution (eq 2) at the α position.[4−7] Some nucleophiles form a hypervalent



(1)



(2)

adduct, λ^3-iodane, in a rapid equilibrium in solution, and the adduct can lead to ligand coupling ($S_NV\pi$)[3,8,9] or an intramo-

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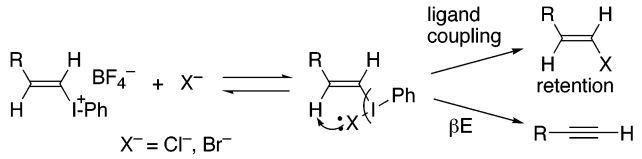
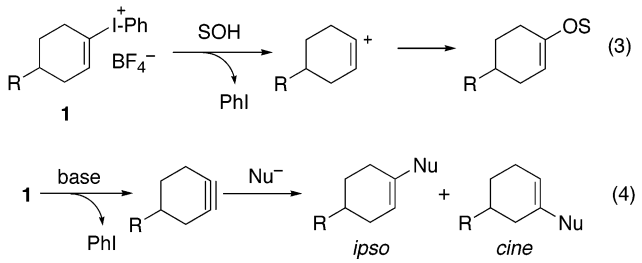
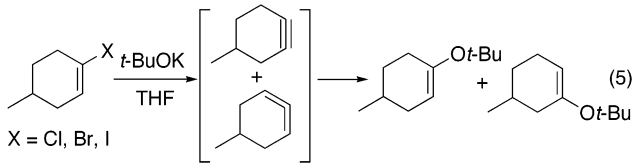
Scheme 1



lecular β-elimination (Scheme 1).[5−7] Cyclohex-1-enyliodonium tetrafluoroborate **1** undergoes an S_N1-type solvolysis via a cyclohexenyl cation intermediate in protic solvents (eq 3).[10] Reactions of this cyclic iodonium salt with nucleophiles/bases are now further investigated, and a new type of substitution via an elimination−addition (EA) mechanism with a cyclohexyne intermediate to give *ipso* and *cine* products[11] will be presented in this paper (eq 4).[12]



Chemistry of small-ring cycloalkynes has been studied for more than a century[13,14] but still remains as a challenging problem because of their constrained structure and high reactivity.[12−29] Among the angle-strained cycloalkynes, cycloheptyne has some lifetime in solution at −25 °C,[23a] while cyclohexyne is only isolable in matrixes at 77 K.[24a] They can be generated in solution as transient species by elimination reactions of appropriate precursors but readily undergo oligomerization and reactions with nucleophiles.[13,20,23] Regioselectivity of nucleophilic addition to cycloalkynes was previously noted in some examples,[13] and relatively careful examinations were made for methyl-substituted cyclohexynes, generated from the 1-halocyclohexenes with strong bases such as *t*-BuOK and *t*-BuONa−$NaNH_2$ (eq 5).[25,26] Under these reaction conditions,



cyclohexa-1,2-diene was also formed.[30,31] Cycloalkynes are known to isomerize to cycloalka-1,2-dienes under strongly basic conditions. The ratio of *ipso*/*cine* substitution products was found to change from 98/2 to 56/44 depending on the reaction conditions[25,26] probably due to the changing ratio of cyclohexyne/cyclohexa-1,2-diene intermediates. The intrinsic regioselectivity of nucleophilic addition to cyclohexyne is unknown for this reason. Thus, a mild and general method for selective generation of cyclohexyne is needed to permit study of its reactivity.[32]

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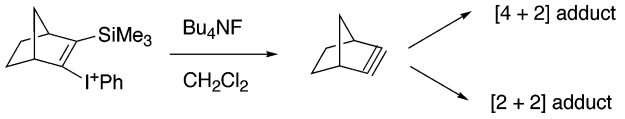
Scheme 2

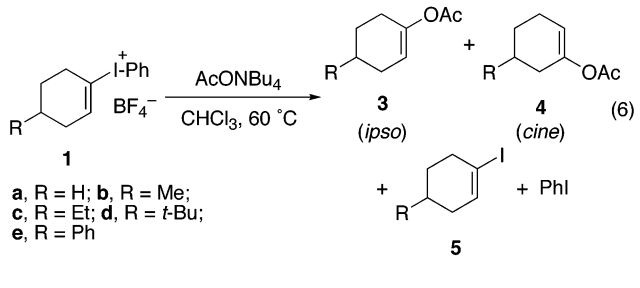


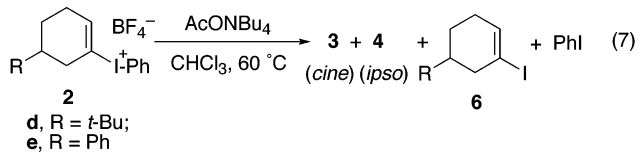
Selective formation of ring-strained triple-bond compounds has recently been achieved by using the 1,2-elimination of β-silylvinyl iodonium salts[15,16] or β-silylvinyl triflates.[27] Kitamura[15] and Gilbert[16] independently showed that norbornyne derivatives could be generated in a high yield from β-silyl iodonium salts (Scheme 2). This method combines the advantage of a facile fluoride-induced desilylation with that of the high nucleofugality of the iodonio group.[10] This strategy was also applied successfully to the generation of benzynes.[33,34] The regioselectivity of nucleophilic addition to substituted benzynes has been studied extensively to show a good correlation with the inductive parameters of the substituents of benzyne.[13a,35−38]

This paper is also concerned with the regioselectivity of nucleophilic addition to substituted cyclohexynes formed during the EA reaction of cyclohex-1-enyliodonium salts. The regioselectivity is compatible with the calculated LUMO populations at the acetylenic carbons of substituted cyclohexynes, which are controlled by the bond angle.

Results

Reaction with Acetate. The reactions of cyclohex-1-enyl(phenyl)iodonium tetrafluoroborate (**1a**) and 4- and 5-substituted derivatives (**1b**−**e** and **2d**,**e**) with tetrabutylammonium acetate were carried out in chloroform at 60 °C. The products include two regioisomers of 1-acetoxycyclohexene, **3** and **4**, which correspond to the *ipso* and *cine* substitution products of **1** or the *cine* and *ipso* products of **2**, respectively (eqs 6 and 7).





Iodobenzene and small amounts of 1-iodocyclohexenes, **5** and **6**, respectively from **1** and **2**, were also obtained. Yields of the products were determined by GC and are summarized in Table 1. The regioisomeric structures and the isomer ratios were also confirmed by the analysis of the cyclohexanones obtained upon acid-catalyzed hydrolysis of the acetate products. The *cine* substitution product was obtained in all the cases, and the isomeric iodonium substrates, **1** and **2**, resulted in similar product ratios of **3**/**4** (runs 8−17). Formation of a mixture of the *ipso* and *cine* products is in contrast to the selective formation of the *ipso* substitution product observed in the acetolysis of **1** and **2** in unbuffered acetic acid (see Supporting Information for experimental details).

Table 1. Reaction of **1** with Tetrabutylammonium Acetate[a]

			yield (%)				
run	substrate	[acetate] (M)	**3**	**4**	PhI	**5** (**6**)	**3**/**4**[b]
1	**1a**	0.01	50		82	2	
2	**1b**	0.10	37	44	69	15	46/54 (44/56)
3	**1b**	0.01	38	44	70	6	46/54
4[c]	**1b**	0.01	25	27	66	3	48/52
5	**1c**	0.10	21	33	74	7	39/61 (39/61)
6	**1c**	0.01	20	32	81	7	39/61 (39/61)
7[c]	**1c**	0.01	20	32	70	6	38/62
8	**1d**	0.10	20	52	89	11	28/72 (27/73)
9	**1d**	0.01	15	44	73	9	25/75
10[d]	**1d**	0.03 (THF)[d]	10	23	76	24	30/70
11[e]	**1d**	0.1 (AN)[e]	13[f]	39[f]	65	20	25/75
12	**2d**	0.10	15	55	78	(7)	21/79
13	**2d**	0.01	9	37	76	(5)	20/80
14	**1e**	0.10	36	27	67	28	57/43 (57/43)
15	**1e**	0.01	33	27	64	29	55/45 (57/43)
16	**2e**	0.10	31	30	60	(18)	51/49 (51/49)
17	**2e**	0.01	20	22	55	(18)	48/52 (49/51)
18[g]	**1d′**	0.01	11	45	76[h]	7	20/80
19[e,g]	**1d′**	0.01 (AN)[e]	4	12	56[h]	29	25/75

[a] Reactions were carried out in chloroform at 60 °C for 2 h, unless otherwise noted. [b] The ratio of **3**/**4** and the values in parentheses are those of the cyclohexanones (**11**/**12**) after hydrolysis of the products. [c] In the presence of methanol-*O*-*d* (1 vol %). [d] Tetrahydrofuran is used as a solvent. [e] Acetonitrile is used as a solvent. [f] Cyclohexanones were also obtained and sums of the yields of **3d** + **11d** and **4d** + **12d** are given. [g] Mesitylene was also detected in 6 and 29% yield for runs 18 and 19, respectively. [h] Yields of iodomesitylene.

In tetrahydrofuran or acetonitrile solution, the yields of the acetate products were lower with increasing yields of iodocyclohexene **5** (runs 10, 11, and 19), while the regioisomeric ratio of the acetate products **3**/**4** remained similar to that observed in chloroform. The ratio **3**/**4** depends on the substituent but is not much affected by the concentration of acetate ion, a small amount of added methanol (1 vol %) (runs 4 and 7), or the regiochemistry of the starting iodonium salt.

Attempts to prepare the 5-methyl derivative of cyclohexenyliodonium salt (**2b**) from 3-methylcyclohexanone resulted in a 1:1 mixture of **2b** and the 3-methyl isomer **7b**. The reaction of this mixture with acetate (0.1 M) in chloroform gave four methyl derivatives of 1-acetoxycyclohexene, **3b**, **4b**, **8b**, and

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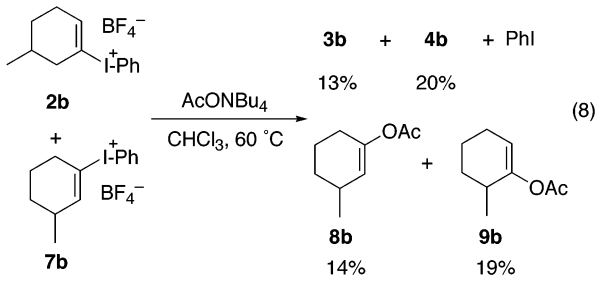
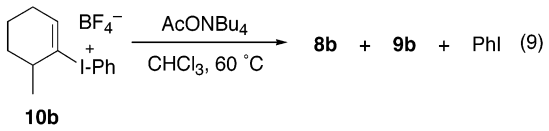
9b in 13%, 20%, 14%, and 19% yield, respectively (eq 8). The

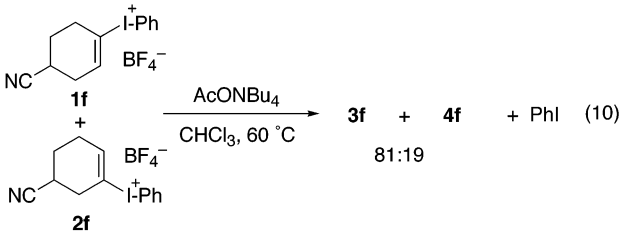


ratio of **3b**/**4b** (39/61) found here is close to that obtained from **1b** (46/54). The products **3b** and **4b** must be derived from **2b** of the substrate mixture, while **8b** and **9b** must be formed from **7b**.

The acetate reaction of 6-methylcyclohex-1-enyliodonium salt **10b** was also examined and found to give **8b** and **9b** in a ratio of 37:63 (eq 9). This ratio agrees with that obtained from the 3-methyl substrate **7b** of the above mixture (**8b**/**9b** = 42/58).



The cyano-substituted cyclohexenyl iodonium salt was prepared as a mixture of 4- and 5-substituted derivatives (**1f** and **2f**) and the 61:39 mixture of **1f** and **2f** was employed for the reaction with acetate ion (0.1 M) in chloroform to give 4- and 5-cyanocyclohex-1-enyl acetates (**3f** and **4f**) in a ratio of 81:19 (eq 10).



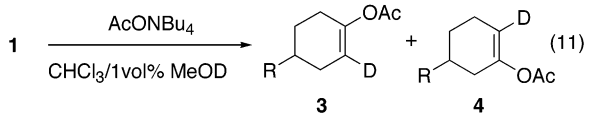
The acetate reaction was also examined with a substrate of a different leaving group, 4-*tert*-butylcyclohex-1-enyl(2,4,6-trimethylphenyl)iodonium tetrafluoroborate (**1d′**) (runs 18 and 19). The results are similar to those obtained for **1d**, but formation of some reduction product, mesitylene, was confirmed. Formation of benzene was also observed during the reaction of **1d** with acetate in acetonitrile-d_3 when the reaction was monitored by ^{1}H NMR. The amount of the reduction product corresponded to that of iodocyclohexene **5d**, and acetoxybenzene was not detected in the reaction of **1** (or **2**) with acetate.

Table 2. Product Yields in the Reaction of **1d** with Piperidine[a]

			yield (%)							
run	solvent	[base] (M)	**11d**	**12d**	PhI	**5d**	**13d**	**14d**	**15d**	**16d**
1	$CHCl_3$	0.01	5	9	65	2	6	27	18	13
2	$CHCl_3$	0.05	20	36	67	7	3	10	10	5
3	$CHCl_3$	0.10	25	45	69	9	2	7	10	3
4	$CHCl_3$	0.50	20	37	57	29	2	<1	5	<1
5	$CHCl_3$	1.0	19	35	55	31	2	<1	4	0
6	THF	0.10	7	14	71	28	17			
7	CH_3CN	0.10	14	4	57	30	6			

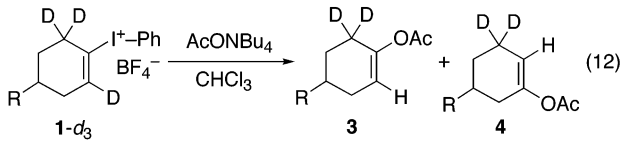
[a] At 60 °C for 2 h at the concentration of **1d** of 0.003 M.

Deuterium-Labeling Experiments. The reaction of **1b**−**d** with acetate in chloroform was carried out in the presence of CH_3OD (1 vol %) at 60 °C. The product ratios of **3**/**4** are similar to those obtained in the absence of CH_3OD, but deuterium was incorporated in the acetate products at the vinylic position (eq 11). The extents of deuterium incorporation of the products



from **1b**, **1c**, and **1d** were determined as 76, 75, and 64 atom %, respectively, by ^{1}H NMR analyses of the product mixture **3** and **4**. Although the separate NMR determinations of deuterium contents of **3** and **4** were difficult due to poor separation of the olefinic proton peaks, the GC-MS analysis of these product mixtures indicated that the deuterium is distributed in both **3** and **4**.

2,6,6-Trideuterated iodonium salts, **1a**-d_3 and **1d**-d_3, were prepared from the corresponding 2,2,6,6-tetradeuterated cyclohexanone at the isotopic purity of about 90 atom % and were employed for the reaction with acetate in chloroform without additional methanol. The reaction of **1d**-d_3 with acetate ion (0.01 M) gave **3d** and **4d** in a ratio of 35:65, and the protium is incorporated at the vinylic position of the acetate products (eq 12) to the extent of 84 atom % as deduced from the ^{1}H NMR spectra. The acetate reaction of **1a**-d_3 also gave the protium-incorporated **3a**, with the protium content at the vinylic position being 84%.



a, R = H; **d**, R = *t*-Bu

Reaction with Piperidine and Methoxide. The reaction of **1d** with a secondary amine, piperidine, was examined at varying concentrations of the amine in chloroform (and THF and acetonitrile) at 60 °C. A regioisomeric mixture of cyclohexanones **11d** and **12d** was obtained after aqueous workup (eq 13 and Table 2), along with various side products, including iodide **5d**, cyclohexene **13d**, fluoride **14d**, chloride **15d**, and

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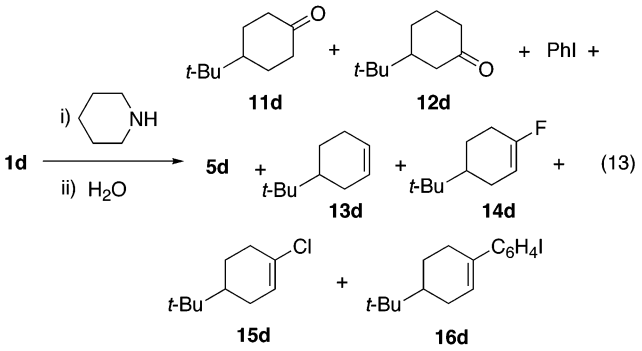
Table 3. Reactions of **1d** and **2d** in Methanol[a]

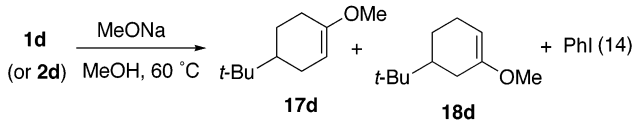
base (conc, M)	yield (%) 17d	18d	PhI	5d (6d)
(a) reaction of **1d**				
NaOAc (0.10)	82	0	76	0
piperidine (0.10)	29[b]	12[b]	61	20
Bu_4NCN[c] (0.03)	35	43	79	4
NaOMe (0.18)	17	48	47	4
(b) reaction of **2d**				
NaOAc (0.10)	0	65	84	(0)
Bu_4NCN[c] (0.03)	3	44	60	(0)
NaOMe (0.18)	20	51	88	(3)

[a] At 60 °C for 1 h. [b] The yields of the hydrolysis products **11d** (6%) and **12d** (9%) are included in those of **17d** and **18d**, respectively. [c] A regioisomeric mixture of cyanide substituted cyclohexenes was also detected but in <4% yield.

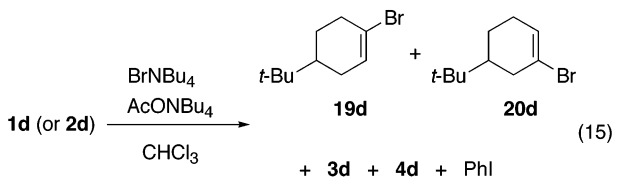
the Friedel−Crafts adduct **16d** (mainly of the *ortho* isomer).



Reaction of **1d** with a stronger base was carried out in methanol containing sodium methoxide (0.18 M) at 60 °C (eq 14). Both the *ipso* and *cine* methoxide substitution products **17d** and **18d** were obtained in a ratio of 26/74 (Table 3). A similar reaction of **2d** also gave **17d** and **18d** in the ratio of 28/72. Weaker bases were also employed for the reaction in methanol, but more of the *ipso* product was formed (Table 3). The acetate salt selectively gave the *ipso* methanolysis product, as was observed during solvolysis of **1d** in unbuffered methanol.[10]



Trapping Experiments. The acetate reactions of **1d** and **2d** in chloroform were carried out in the presence of bromide ion as an additional nucleophile (Table 4). The reaction products include two isomers of 1-bromocyclohexenes **19d** and **20d**, as well as the acetate products **3d** and **4d** (eq 15). This is in contrast



to the exclusive formation of the *ipso* bromide in the absence of acetate (runs 1 and 6), as summarized in Table 4. The addition of methanol (1 vol %) as a proton source increased the fraction of the bromide products over the acetate products (runs 3−5).

Table 4. Reactions of **1d** and **2d** with Bromide in the Presence of Acetate[a]

run	concentration (M) Br^-	AcO^-	yield (%) 19d	20d	3d	4d	PhI	5d (6d)
(a) reaction of **1d**								
1	0.10	0	92	0	0	0	100	0
2	0.094	0.007	23	27	6	9	78	7
3	0.070	0.029	5	6	15	34	75	13
4[b]	0.070	0.030	7	9	10	26	68	10
5[c]	0.070	0.030	19	29	7	12	80	3
(b) reaction of **2d**								
6	0.10	0	0	78	0	0	100	(0)
7	0.094	0.005	12	48	1	4	98	(2)
8[c]	0.096	0.005	13	54	1	2	100	(0)
9	0.081	0.021	7	10	4	16	61	(3)
10[c]	0.079	0.018	18	40	1	6	99	(1)

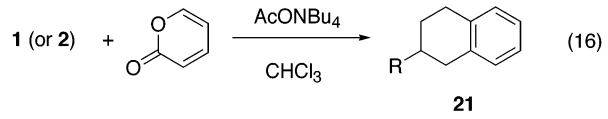
[a] In chloroform at 60 °C. [b] In the presence of 0.1 vol % (0.025 M) of methanol. [c] In the presence of 1 vol % (0.25 M) of methanol.

Table 5. Product Yields Determined by GC for the Reactions of **1b**, **1d** and **2d** with Acetate in the Presence of α-Pyrone[a]

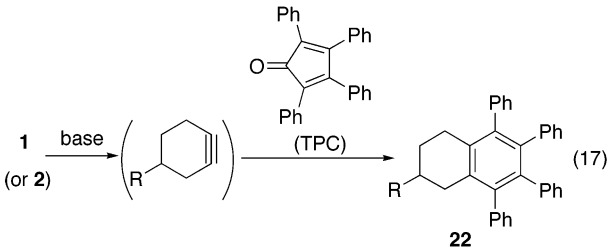
substrate	21	3	4	5 (6)	PhI
1b	32	6	3	3	58
1d	49	5	6	7	93
2d	91	∼0	6	(3)	78

[a] Reactions were carried out at [substrate] = ca. 0.004 M, [acetate] = 0.010 M, [pyrone] = 0.10 M, and 60 °C.

The acetate reactions of **1** and **2** were carried out in the presence of 2*H*-pyran-2-one (α-pyrone) as a trapping agent, and the product mixtures were analyzed by GC (eq 16). Tetrahydronaphthalene **21**, the adduct with cyclohexyne, was obtained together with some acetate products. The results are given in Table 5.



Trapping experiments were also carried out on a preparative scale using tetraphenylcyclopentadienone (TPC) under various conditions with different bases and solvents. The adduct **22** (eq 17) was isolated, and the yields obtained are summarized in Table 6. The yields are always good for acetate and fluoride in aprotic solvents, but amine bases afforded lower yields (at most 52%) of **22** due to the extensive side reactions.



A platinum complex, **23**,[39] of cyclohexyne was also obtained

(39) (a) Bennett, M. A.; Schwemlein, H. P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1296−1320. (b) Bennett, M. A.; Robertson, G. B.; Whimp, P. O.; Yoshida, T. *J. Am. Chem. Soc.* **1971**, *93*, 3797−3798. (c) Robertson, G. B.; Whimp, P. O. *J. Am. Chem. Soc.* **1975**, *97*, 1051−1059. (d) Bennett, M. A.; Yoshida, T. *J. Am. Chem. Soc.* **1978**, *100*, 1750−1759. (e) Bennett, M. A.; Rokicki, A. *Aust. J. Chem.* **1985**, *38*, 1307−1318. (f) Lu, Z.; Abboud, K. A.; Jones, W. M. *Organometallics* **1993**, *12*, 1471−1474.

Table 6. Isolated Yields of the Adduct **22** in the Reaction of **1a**−**e** and **2d** in the Presence of Tetraphenylcyclopentadienone (TPC)[a]

		isolated yield of **22** (%)					
base (conc, M)	solvent	**1a**	**1b**	**1c**	**1e**	**1d**	**2d**
$AcONBu_4$ (0.010)	$CHCl_3$	90	84	86	98	91	70
$AcONBu_4$ (0.010)	THF					81	
$AcONBu_4$ (0.010)	MeCN					75	
$FNBu_4$(0.010)	$CHCl_3$	81	100	95	98	94	63
$FNBu_4$(0.010)	THF					100	
MeONa(0.18)	MeOH				87	81	
t-BuOK (0.020)[b]	THF					89	
piperidine (0.020)	$CHCl_3$					36[c]	
piperidine (0.10)	$CHCl_3$					52[c]	
piperidine (0.020)	THF					20[c]	
Et_3N (0.020)	$CHCl_3$					26[c]	
Et_3N (0.10)	$CHCl_3$					29[c]	
Et_3N (0.50)	$CHCl_3$					25[c]	

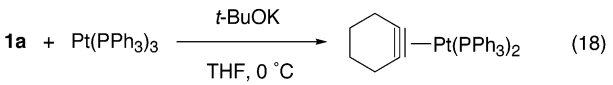
[a] Reactions were carried out at [**1** (or **2d**)] = 3−8 mM, [TPC] = 10 mM, and 60 °C for 1−2 h. [b] The reaction was carried out at room temperature. [c] Other products (**16d**, **14d**, and **15d**) were also detected or isolated for the amine bases.

Table 7. Pseudo-First-Order Rate Constants (k_H and k_D) for the Reactions of Iodonium Salts **1** and **1**-d_3 with Tetrabutylammonium Acetate or Piperidine in Chloroform at 60 °C

[base] (M)	10^3k_H (s^{-1})	10^3k_D (s^{-1})	k_H/k_D
(a) reaction of **1a** with acetate[a]			
0.001	10.4	4.05	2.6
0.010	10.5	3.48	3.0
0.025	10.9	3.76	2.9
0.050	9.59	3.56	2.7
0.10	9.65	3.37	2.9
(b) reaction of **1d** with acetate[a]			
0.001	4.62	2.03	2.3
0.010	4.44	1.81	2.5
0.050	4.73	1.98	2.4
0.10	4.97	1.86	2.7
(c) reaction of **1d** with piperidine			
0.010	0.57	0.50	1.14
0.050	0.81	0.64	1.27
0.10	0.98	0.90	1.09
0.50	1.64	1.52	1.08

[a] The ionic strength of the solution was maintained at 0.10 M with tetrabutylammonium perchlorate.

as colorless crystals from the base (*t*-BuOK) reaction of **1a** in the presence of $Pt(PPh)_3$ in THF at 0 °C (eq 18).



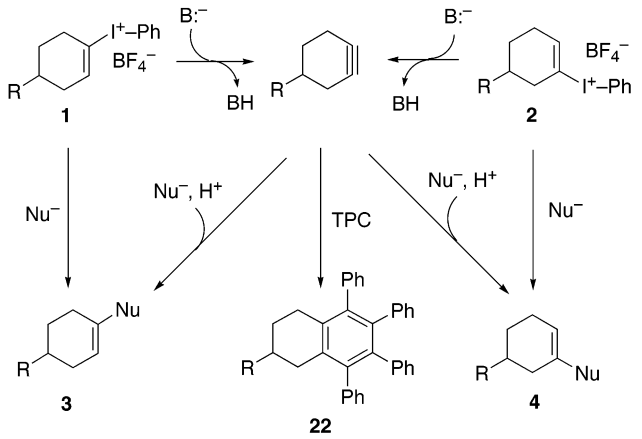
(18)

23

Kinetics of the Reaction. The acetate reactions of **1a** and **1d** and their deuterated analogues **1**-d_3 in chloroform were followed at 60 °C and the ionic strength of 0.10 (Bu_4NClO_4) by monitoring the decrease in absorbance at 280 nm due to the iodonium salt. The reaction followed reasonably well the pseudo-first-order kinetics, and the observed first-order rate constants are given in Table 7 as averages of at least three runs within ±5%. The unsubstituted idodonium salt **1a** is about 2 times more reactive than the *tert*-butyl derivative **1d**, and the observed rate constants are practically independent of the concentration of acetate. The rate constant (k_D) for the reaction of **1**-d_3 is smaller than that of **1** (k_H) by 2.3−3.0 times.

The reaction of **1d** with piperidine (0.01−0.1 M) in chloroform was slower, but **1d** and **1d**-d_3 showed similar rates (k_H/k_D = 1.1−1.3). The reaction in methanol containing NaOMe (0.1 M) was too fast at 60 °C, and the rate constants for **1d** determined at 25 °C were $k_H = 6.9 \times 10^{-4}$ s^{-1} and $k_D = 3.0 \times 10^{-4}$ s^{-1} (k_H/k_D = 2.3).

Scheme 3



Discussion

Mechanism for the *ipso* and *cine* Substitution by Acetate. Solvolysis of cyclohex-1-enyl(phenyl)iodonium tetrafluoroborate (**1**) in unbuffered alcohols and acetic acid gives solely the *ipso* substitution products via an S_N1-type mechanism with the cyclohexenyl cation as an intermediate (eq 3).[10] The reaction with bromide ion in chloroform also afforded the *ipso* bromocyclohexene (Table 4, runs 1 and 6) probably via a ligand coupling mechanism.[8,9] The *ipso* bromo product was reported to form via ligand coupling in the presence of copper(I) salt, though the reaction was occurring as the copper ligands.[40]

In contrast, the reaction of 4-substituted **1** with tetrabutylammonium acetate in chloroform gave the *cine* substitution product **4** in addition to the *ipso* acetate **3** (eq 6), with the ratio of **3**/**4** depending on the 4-substituent (Table 1). The same mixture of regioisomeric substitution products was also obtained from the 5-substituted isomeric substrate **2** (eq 7). The largest selectivity in favor of **4** was observed with the *tert*-butyl substrates **1d** and **2d**; **3d**/**4d** = 25/75−20/80 (runs 8−13). The formation of *ipso* and *cine* substitution products and the regioconvergent product ratio obtained from the isomeric substrates suggest the intervention of a common intermediate and are best interpreted by the elimination−addition (EA) mechanism with a cyclohexyne intermediate as illustrated in Scheme 3. A similar EA mechanism for the aromatic nucleophilic substitution via a benzyne intermediate is well-known, though under strongly basic conditions. In accord with the EA mechanism, the deuterium incorporation at the vinylic carbon of the acetate products **3** and **4** was observed in the reaction of **1** with acetate in the presence of methanol-*d* in chloroform (eq 11). Similar results were also obtained in the acetate reaction of the deuterated substrate **1**-d_3 under normal conditions; the protium was incorporated at the vinylic carbon of the products, **3** and **4** (eq 12).

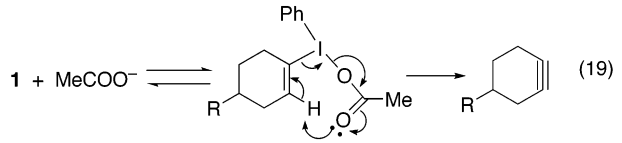
Trapping experiments confirmed the formation of the cyclohexyne intermediate during the acetate reaction (as well as other basic reactions). The reactions of **1** or **2** in the presence of

(40) Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095−4112.

trapping agents, α-pyrone and tetraphenylcyclopentadienone (TPC), gave effectively the adducts **21** and **22** of cyclohexyne (eqs 16 and 17), respectively. Trapping of cyclohexyne was also observed with bromide. The reaction of **1d** in the presence of both acetate and bromide in chloroform gave the *cine* bromide substitution product **20d** in addition to the *ipso* bromide **19d** as well as the acetate products (eq 15, Table 4). This is in contrast to the selective *ipso* substitution of the bromide reaction in the absence of acetate ion. The preferential formation of **20d** over **19d** was observed from both **1d** and **2d** in the presence of varying concentrations of acetate ion. This regioselectivity is in accord with that of the acetate substitution, **3d** < **4d**.[41]

Intermediacy of the cyclohexyne is now established, but the mechanism of formation is another problem. Rates for the reactions of **1a** and **1d** and their deuterated counterparts **1**-d_3 with acetate were determined in chloroform at 60 °C (Table 7). The reactions of the deuterated substrates are significantly slower than the corresponding protium substrates, $k_H/k_D = 2.3-3.0$. The observed primary kinetic isotope effects are consistent with a mechanism involving the rate-determining deprotonation at C2, i.e., the E2 mechanism for the formation of the cyclohexyne intermediate.

The observed rate was unexpectedly independent of the concentration of acetate base (Table 7). Yields of the products were also not dependent on the concentration of acetate. These observations may be explained by a mechanism involving the initial equilibrium formation of the adduct (λ^3-iodane) followed by an intramolecular elimination within the adduct (eq 19). The



(19)

formation constant of the adduct must be large in chloroform. A similar mechanism of β-elimination was proposed for the reaction of alk-1-enyl(phenyl)iodonium salts with chloride and bromide (Scheme 1)[5,6] and also that with carboxylates.[7] In the latter case, a stronger base-like acetate preferentially induces α-elimination, but a less basic carboxylate like trifluoroacetate can induce the intramolecular-type β-elimination.[7] In the present case, the acetate can participate in the intramolecular β-elimination within the λ^3-iodane due to the lack of α-hydrogen, but the competing bimolecular elimination cannot be excluded. Such an intramolecular elimination may contribute to efficient formation of cyclohexyne during the reaction with acetate and fluoride ions in chloroform. In any case, the deprotonation is involved in the rate-determining step, and the mechanism can be taken as an E2 elimination.

Reaction with Piperidine. The reaction of **1d** with piperidine provides the two isomeric cyclohexanones **11d** and **12d** on aqueous treatment of the reaction mixture obtained in chloroform (eq 13). These products must come from hydrolysis of the primary products of isomeric enamines, hydrolysis of which is known to be very fast.[42] The *ipso* and *cine* substitutions by the amine must occur via the EA mechanism with the cyclohexyne intermediate. However, the formation of various byproducts is apparent in this reaction (eq 13, Table 2). The byproducts, **14d**, **15d**, and **16d**, are typical of those derivable from a cyclohexenyl cation intermediate and were found in the thermal decomposition of the iodonium salts[43] and during the solvolysis.[10] The Friedel−Crafts recombination product, cyclohexenyliodobenzene **16d**, is considered to be derived from the contact cyclohexenyl cation−iodobenzene pair.[10] These results implicate that the EA mechanism of the piperidine reaction proceeds via the E1 elimination.

The kinetic isotope effects observed are in fact very small in the reaction with piperidine (Table 7). The fraction of the EA route is found to be over 50% when [piperidine] = 0.05−0.5 M (Table 2), and the expected overall kinetic isotope effect k_H/k_D would be greater than 1.5 provided that the k_H/k_D for the E2 reaction of **3** is operative (Table 7). The observed values (1.08−1.27) are differentiated from this value, although the present kinetic measurements are not perfectly precise due to the side reactions and the isotopic purity of the substrate **1**-d_3 (90% D). It can be concluded that the EA pathway of the piperidine reaction in chloroform does not show appreciable primary kinetic isotope effect, and the elimination proceeds mainly via the E1 mechanism as implied from the product analysis.

The iodocyclohexene product, **5** from **1** or **6** from **2**, formed from the cleavage of the aromatic carbon−iodine bond is also apparent at higher concentrations of piperidine (Table 2, runs 4 and 5). This product was found also in the acetate reaction, especially in more polar aprotic solvents (Table 1, runs 10, 11, and 19; Table 2, runs 6 and 7), and with the phenyl-substituted iodonium salts, **1e** and **2e** (Table 1, runs 14−17). However, acetoxybenzene was not detected as its counterpart product. The product observed was benzene (or mesitylene from **1d′**), a reduction product. The possibility of reduction product formation via benzyne intermediate can be eliminated: a similar reduction was observed in both cases of **1d** and **1d′**, although **1d′** cannot give the benzyne type intermediate. The pair of iodocyclohexene and benzene is evidently derived from homolysis of the C−I bond, and the reaction may involve electron transfer from the nucleophile to the iodonium ion.[44,45]

Reaction in Methanol. The reaction of **1** in methanol usually gives simply the *ipso* 1-methoxycyclohexene **17**,[10] but in the presence of a strong base, sodium methoxide, the products include those of both *ipso* and *cine* substitution (eq 14 and Table 3). The isomeric iodonium salts **1d** and **2d** gave a similar mixture of the products **17d** and **18d**. Again, the intermediary formation of cyclohexyne is strongly suggested, and it was

(41) Effects of added methanol on the relative amounts of bromide and acetate products (Table 4, runs 4, 5, 8, and 10) may be worth mentioning here, since the acetate reactions summarized in Table 1 are not affected by added methanol. A small amount of methanol increases the yields of bromide products **19d** and **20d**, while reducing the acetate products **3d** and **4d**, keeping the relative preference for the regioisomer (**20d** > **19d** and **4d** > **3d**). The results may be rationalized from the effect of methanol on the relative nucleophilicity of acetate and bromide toward the cyclohexyne. A more effective hydrogen-bonding solvation of acetate reduces more effectively its reactivity than that of bromide. Alternatively, the increased yields of the bromide products could be ascribed to the reversibility of the bromide addition to the cyclohexyne: The interception of the β-bromovinyl anion with methanol would increase the contribution from the bromide addition without affecting the irreversible acetate addition.

(42) Maas, W.; Janssen, M. J.; Stamhuis, E. J.; Wynberg, H. *J. Org. Chem.* **1967**, *32*, 1111−1115.

(43) Okuyama, T.; Fujita, M.; Gronheid, R.; Lodder, G. *Tetrahedron Lett.* **2000**, *41*, 5125−5129.

(44) (a) Tanner, D. D.; Reed, D. W.; Setiloane, B. P. *J. Am. Chem. Soc.* **1982**, *104*, 3917−3923. (b) Grushin, V. V.; Demkina, I. I.; Tolstaya, T. P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 505−511. (c) Ochiai, M.; Shu, T.; Nagaoka, T.; Kitagawa, Y. *J. Org. Chem.* **1997**, *62*, 2130−2138. (d) Chen, D.-W.; Ochiai, M. *J. Org. Chem.* **1999**, *64*, 6804−6814.

(45) One of the referees pointed out the possibility of formation of cyclohexyne via the E2 reaction of **5**. This possibility is excluded since the cyclohexyne products always accompany the formation of iodobenzene and **5** is much less reactive toward elimination than **1**.

actually trapped by TPC under these conditions (Table 6). The observed kinetic isotope effect of $k_H/k_D = 2.3$ for the methoxide reaction suggests the E2 mechanism of the elimination.

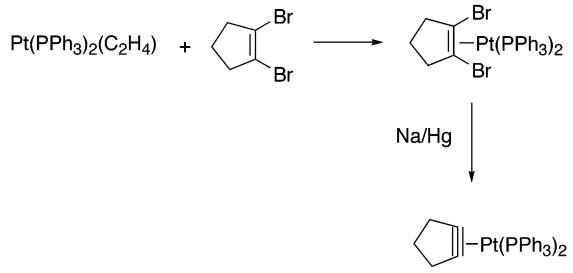
In contrast, acetate cannot effect the *cine*-substitution at all in methanol. Only the normal S_N1-type methanolysis to give the *ipso* methoxy product occurs. Piperidine and cyanide gave the *cine* methoxy product as well as the *ipso* methoxide, but the ratio is heavily biased to the side of the *ipso* product. The ratios of **17d**/**18d** obtained from **1d** and **2d** are significantly different, that is, a poor convergence of regioselctivity was observed. The *cine* product must come from the cyclohexyne intermediate (via the EA mechanism), but a considerable part of the reaction occurs via a competing *ipso* route, probably the S_N1 solvolysis through the cyclohexenyl cation intermediate. The mechanism of the elimination step in the EA pathway can be E1 or E2, but due to a small fraction of the elimination route, the kinetic isotope effect cannot clearly differentiate these mechanisms.

The reaction of **1d** with alkoxide in trifluoroethanol and hexafluoro-2-propanol (HFIP) was examined to see if the elimination reaction can lead to formation of the *cine*-substitution product, but no sign of the *cine* substitution was found. The alkoxides in these acidic alcohols are not basic enough to induce the elimination to afford highly strained cyclohexyne. This is in contrast to the efficient cycloheptyne formation via the E1-type mechanism with alkoxide in HFIP,[29] where the cycloheptenyl cation is formed from a cyclohexylidenemethyl derivative via participation and is deprotonated.

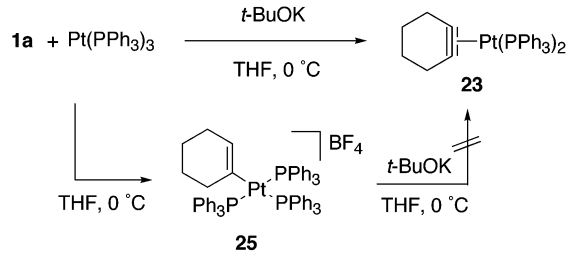
Trapping of the Cyclohexyne. Efficiency of formation of cyclohexyne was compared by trapping experiments with TPC under various conditions with changing bases and solvents. As summarized in Table 6, acetate and fluoride are the most effective for formation of cyclohexyne in chloroform and yields of isolated adducts **22** are more than 80% for various substrates **1** (and **2d**) with different alkyl and phenyl groups, practically quantitative in many cases. The basic reaction seems to be less effective in more polar solvents such as THF and acetonitrile, but it still provides sufficiently good access to cyclohexyne (>75% yield) under mild conditions. Strong bases such as methoxide in methanol and *tert*-butoxide in THF afforded satisfactory yields of the adducts of cyclohexynes at lower temperature.

In contrast, amines are not good bases for this reaction. Low yields of the cyclohexyne adducts using amine bases are due to the formation of various byproducts as discussed for the piperidine reaction. The contrasting tendency in efficiency of the cyclohexyne formation with ionic and neutral bases in chloroform can be rationalized by different mechanisms of elimination: E2 for the former and E1 for the latter bases. This contrasting conclusion on the mechanism for the elimination step induced by acetate and piperidine is rather unexpected on the basis of general knowledge of basicity: pK_a of acetic acid = 4.76 and pK_a of dialkylammonium ion = ca. 10 but in aqueous solution. In aprotic solvents, the basicity of an ionic base increases enormously, while that of a neutral base remains essentially unchanged, e.g., pK_a's in DMSO of acetic acid and triethylammonium ion are 12.6 and 9.0, respectively.[46] These effects would be still greater in chloroform, and acetate is a stronger base than piperidine in chloroform. This must be a main reason the former can induce the E2 reaction of the cyclohexenyliodonium salt while the latter can only work on the cyclohexenyl cation intermediate, which was allowed to form in the poorly basic medium, to lead to the E1 reaction. The intramolecularity of the acetate reaction may be another reason for the ease of the E2-type elimination.

Scheme 4

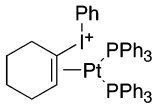


Scheme 5



Trapping Cyclohexyne by Platinum. While cyclohexyne is labile and exists only in matrixes at 77 K,[24a] group 10 transition metals are known to form stable complexes with distorted alkynes.[39] In fact, when the iodonium salt **1a** was treated with $Pt(PPh_3)_3$ in the presence of *t*-BuOK in THF at 0 °C, the cyclohexyne complex **23** of platinum(0) was obtained in 69% yield as colorless crystals (eq 18). This can be taken as another experiment for trapping cyclohexyne. However, for the synthesis of the related platinum(0) cyclopentyne complex from 1,2-dibromocyclopentene, the reduction by Na/Hg to give cyclopentyne was reported to occur after coordination of the olefin to platinum, as shown in Scheme 4.[39a] It was also suggested that free cyclohexyne is not involved in the analogous synthesis of **23** from 1,2-dibromocyclohexene.[39a]

To gain mechanistic insights into the formation of **23** from **1a**, the reaction of **1a** with $Pt(PPh_3)_3$ was examined in the absence of the base, *t*-BuOK. From this reaction, the olefin complex of platinum shown by **24** was not isolated, which is



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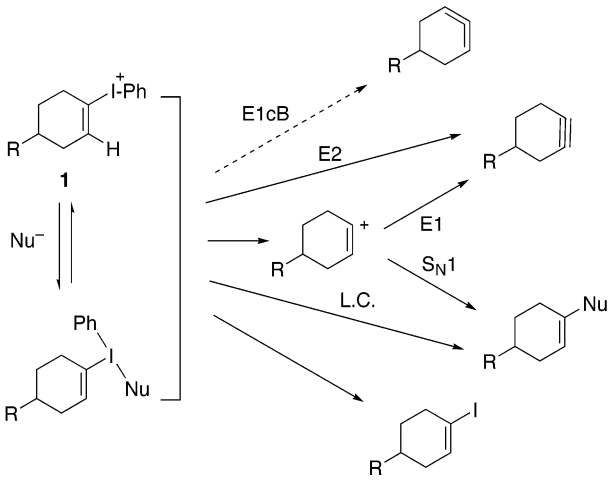
analogous to the preformed cyclopentene complex in the reaction of Scheme 4. Instead, the cationic cyclohexenyl platinum(II) complex **25** was produced in 85% yield as colorless crystals (Scheme 5). Complex **25** is stable toward oxygen and moisture in solid, and the combustion analysis and NMR spectra are consistent with the formulation. The molecular structure of **25** was determined by X-ray crystallographic analysis, in which the 1-cyclohexenyl ligand is situated approximately perpen-

(46) Maskill, H. *The Physical Basis of Organic Chemistry*; Oxford University Press: Oxford, 1985; p 185.

Scheme 6



dicular to the coordination plane consisting of platinum and phosphorus atoms (Figure S3).

If *t*-BuOK deprotonates **25** at the vinylic position, this complex could be regarded as a potential intermediate leading to the cyclohexyne complex **23**. However, it turns out not to be the case. Treatment of **25** with *t*-BuOK in THF at 0 °C resulted in a complex mixture containing a small amount of $Pt(PPh_3)_3$. In the mixture, the cyclohexyne complex **23** was not discernible as a product. Therefore, it is likely that $Pt(PPh_3)_3$ trapped transient cyclohexyne generated from the deprotonation of **1a** by *t*-BuOK. It is interesting to note that iodobenzene formed as a side product does not hamper the synthesis of the cyclohexyne complex **23**. The oxidative addition reaction of $Pt(PPh_3)_3$ with iodobenzene would be fast, probably more facile than coordination of the olefin portion of **1a**. This observation also indicates that the highly reactive free-cyclohexyne indeed reacted with $Pt(PPh_3)_3$.

Some Notes on the Mechanism. The elimination step of the EA mechanism for the reaction of the cyclohexenyliodonium salts is always subject to competition with other reactions (Scheme 6). The conceivable first steps include the E2 (with a base), ligand coupling (with a nucleophile), and spontaneous heterolysis (to lead to E1 and S_N1) as well as the cleavage of the aromatic C−I bond.[47] Strong bases are good for the E2 pathway (as observed with acetate and fluoride in chloroform and with alkoxides). If the spontaneous heterolysis to give the cyclohexenyl cation is allowed in poorly basic media, the selection of the E1 and S_N1 routes occurs on the cationic intermediate depending on the basicity/nucleophilicity of the reagents working in the reaction medium.

The possibility of formation of cyclohexa-1,2-diene cannot be neglected in the elimination step of the reaction of the iodonium salt. Formation of the 1,2-diene has usually been observed during the elimination of 1-halocyclohexene with strong bases,[30,31] and moreover cyclohexa-1,2-diene is more stable than cyclohexyne. Nonetheless, no sign of formation of the 1,2-diene was found during the acetate reaction of the iodonium salt in chloroform: 1-acetoxy-3-alkylcyclohexene **8** was not formed from **2**. The concerted E2 reaction requires the coplanarity of the orbitals involved in the bondings of both the electrofuge and the nucleofuge, which strongly favors formation of cycloalkyne over 1,2-diene from the cycloalkenyl substrate due to the restricted rotation of the skeletal C−C bonds. In contrast, the ElcB mechanism involving a vinylic anion intermediate may be at work in the elimination of 1-halocyclohexene due to the lower nucleofugality of the halide and use of the strong base. In this reaction, the deprotonation would provide the more stable carbanion, allylic anion, leading to the 1,2-diene. The E2 reaction of the iodonium salt should be more E1-like rather than E1cB-like due to the nucleofugality.

Table 8. Regioselectivity of Nucleophilic Addition to Substituted Cyclohexynes

		product ratio, **3**/**4**[a]	
substituent	σ_I[b]	reaction of **1**	reaction of **2**
H	0.00	50/50	50/50
4-Me	−0.04	46/54	39/61
4-Et	−0.05	39/61	
4-*t*-Bu	−0.07	28/72	21/79
4-Ph	0.10	57/43	49/51
4-CN	0.56	81/19[c]	
3-Me	−0.04	42/58[d]	37/63[e]

[a] The product ratio obtained from the acetate reaction at [acetate] = 0.10 M (Table 1). [b] Inductive substituent constants.[48] [c] The product ratio of **3f**/**4f** obtained from a 61:39 mixture of **1f** and **2f**. [d] The product ratio of **8b**/**9b** obtained from **7b**. [e] The product ratio of **8b**/**9b** obtained from **10d**.

Regioselectivity of Nucleophilic Addition to Cyclohexyne. The regioselectivity of the acetate reaction in the formation of *ipso* and *cine* substitution products should primarily reflect the regioselectivity of nucleophilic addition to the intermediate cyclohexyne. The conformity of the product ratios obtained from the regioisomeric iodonium substrates **1** and **2**, which should provide a common cyclohexyne, is in fact satisfactory. This convergency of regioisomeric products becomes loose due to the accompanying reactions at the *ipso* position, the S_N1-type reaction and ligand coupling. Although contributions from the *ipso* reactions seem to be greater in the reactions of piperidine, methoxide, and bromide than in the acetate reaction, the similarity of observed product ratios with different nucleophiles substantiates that the intrinsic regioselectivity of cyclohexyne toward nucleophiles can be assessed from the acetate reaction. The regioselectivities for various substituted cyclohexynes are mainly derived from the data given in Table 1 and are summarized in Table 8. The magnitudes of **3**/**4** range from 0.3 to 4 for 4-alkyl, phenyl, and cyano substitutions.

The regioselectivity of nucleophilic addition to substituted benzynes has been extensively studied, and the inductive effect of the substituent is considered to be responsible for the selectivity.[13a,35] The selectivity, log(**4**/**3**), is plotted against the inductive substituent constant σ_I[48] in Figure 1. Points for 4-CN, 4-Ph, H, and 4-Me seem to conform to the electronic effects, but those for 4-Et and 4-*t*-Bu greatly deviate upward from the correlation. The alkyl groups have similar electronic effects σ_I, and the position of substitution is separated by two bonds from the reaction site. Moreover, a bulky *tert*-butyl group prefers a nucleophilic attack at the closer carbon of the triple bond to

(47) (a) The iodonium substrate is in a fast equilibrium with the λ^3-iodane in the presence of nucleophile. Although the reactivity of the vinylic group is greater in the iodonium form than the iodane form, the latter is often the main reactive species, and thus the apparent substrate reactivity varies with the concentration and the identity of the nucleophile. The Michael addition of cyanide to **1** has recently been discovered as an additional reaction pathway to lead to the carbene intermediate, which undergoes 1,2-hydrogen shift to give allylic cyanide.[47b] (b) Fujita, M.; Kim, W. H.; Okuyama, T. *Chem. Lett.* **2003**, *32*, 382−383.

(48) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; John Wiley & Sons: New York, 1975; Chapter 3.

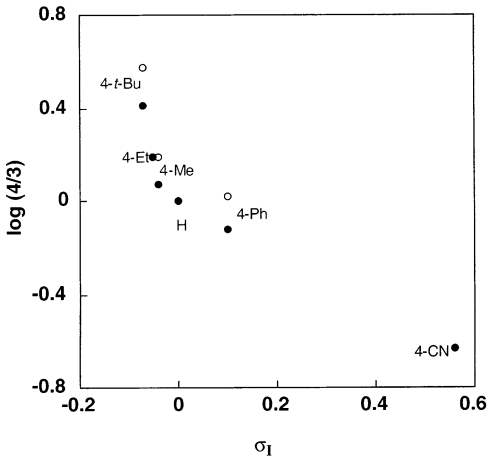


Figure 1. Plot of logarithms of ratios of the acetate products **4**/**3** obtained from **1** (filled circle) and **2** (open circle) against the inductive parameter σ_I.

Table 9. LUMO Populations[a] and Bond Angles[b] at the Acetylenic Carbons of Substituted Cyclohexynes Optimized by B3LYP/6-31G(d)

substituent	f_1	f_2	$f_2 - f_1$	θ_1 (deg)	θ_2 (deg)	$\theta_2 - \theta_1$ (deg)
H	0.40037	0.40037	0.00000	131.7	131.7	0.0
4-Me	0.39413	0.40146	0.00733	130.9	132.0	1.1
4-Et	0.39426	0.40301	0.00875	130.6	132.2	1.6
4-*t*-Bu	0.38741	0.40724	0.01983	129.5	133.5	4.0
4-Ph	0.37927	0.37332	−0.00595	131.2	132.1	0.9
4-CN	0.40728	0.37523	−0.03205	133.4	130.9	−2.5
3-Me	0.39543	0.39884	0.00341	131.6	132.3	0.7
H(4-*t*-Bu)[c]	0.39100	0.40950	0.01850	129.5	133.5	4.0

[a] f_1 and f_2 are the LUMO populations at C1 and C2 of the substituted cyclohexyne, respectively. [b] θ_1 and θ_2 are the bond angles at C1 and C2 of the substituted cyclohexyne, respectively. [c] A model calculation on the optimized cyclohexyne ring for 4-*tert*-butylcyclohexyne, but the *tert*-butyl group is replaced with hydrogen.

give **4d**. What controls the regioselectivity of nucleophilic addition to the substituted cyclohexynes?

Theoretical calculations were carried out on various substituted cyclohexynes at the level of B3LYP/6-31G(d). The calculations on the parent cyclohexyne show that the bond angles of acetylenic carbons are strongly deformed to about 130° in accord with previous calculations,[19h] and the LUMO is considerably lowered and mainly located at the acetylenic carbons developing in the plane of cyclohexyne ring. The consequence is a facile reactivity of cyclohexyne toward a nucleophile. The electronic populations of LUMO at the acetylenic carbons calculated are summarized in Table 9. All the 4-alkylcyclohexynes have a higher LUMO population at C2 (f_2) than at C1 (f_1), and the *tert*-butyl derivative has the largest difference ($f_2 - f_1$) among those calculated. This conforms to the product distribution of nucleophilic addition to the cyclohexyne in favor of the attack at C2 (formation of **4**). The differences between the LUMO populations at C2 and C1 ($f_2 - f_1$) are correlated with the logarithms of the product ratios **4**/**3** for 4-substituted cyclohexynes and the equivalent values for the 3-methyl derivative in Figure 2.[49] It shows a good correlation between the regioselectivity and the LUMO populations. This correlation can be extended to the 4-phenyl and 4-cyano derivatives.

If the inductive electronic effect of alkyl groups is not solely responsible for the change in LUMO populations, what controls

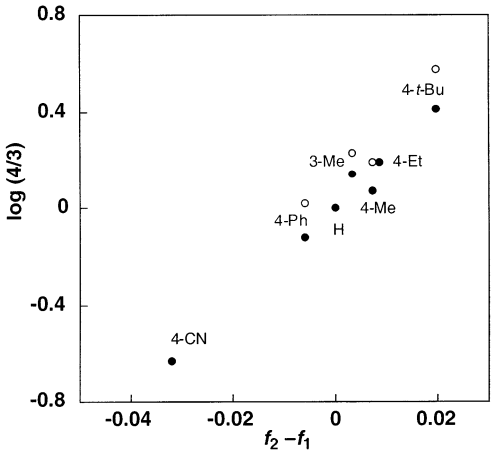


Figure 2. Plot of logarithms of ratios of the acetate products **4**/**3** obtained from **1** (filled circle) and **2** (open circle) against the differences in LUMO populations, $f_2 - f_1$. In the case of 3-methylcyclohexyne (3-Me), the starting substrate were **7b** and **10b** in place of **1b** and **2b**, respectively, and the product ratio of **9b**/**8b** is employed for **4b**/**3b**.

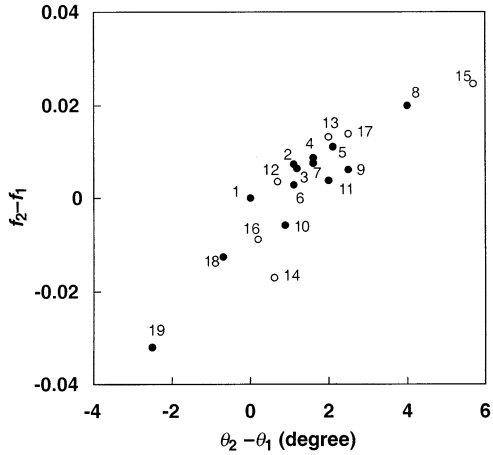


Figure 3. Plot of the LUMO populations ($f_2 - f_1$) vs the bond angles ($\theta_2 - \theta_1$) for 4-substituted (filled circle) and 3-substituted cyclohexynes (open circle). The numbering refers to Tables S3 and S5.

the LUMO? The bond angles at the acetylenic carbons of the optimized structure are given in the last columns of Table 9. The difference in LUMO populations ($f_2 - f_1$) can be noticed to conform to the difference between the bond angles at C2 and C1 ($\theta_2 - \theta_1$), as plotted in Figure 3. The points in Figure 3 include not only those for the optimized structures but also those for local minimum structures given in Table S5. The difference in LUMO populations does increase as that in bond angles increases. The acetylenic carbon of the larger bond angle has a higher LUMO population than that of the smaller bond angle. That is, the LUMO population is strongly correlated with the ring structure represented by the bond angles at the acetylenic carbons. This can be further confirmed by a model calculation on the deformed cyclohexyne ring, which has the same structure of the ring of the optimized 4-*tert*-butylcyclo-

(49) Theoretical calculations also indicate the presence of other local minimum structure(s) of a substituted cyclohexyne as well as the optimized structure where the substituent is equatorial. The LUMO populations can be modified by the contribution from other conformations in equilibrium at the reaction temperature (60 °C). The modified values are given in Table S2 of Supporting Information, but they are not much different from the unmodified values for the optimized structures. Thus, the simple, original LUMO population is satisfactory in representing the regioselectivity of nucleophilic addition to substituted cyclohexynes.

hexyne but the *tert*-butyl group is replaced with hydrogen (the last entry of Table 9).

When an electron-withdrawing group such as CN or CF_3 is introduced at C4 of the cyclohexyne ring, both values of $\theta_2 - \theta_1$ and $f_2 - f_1$ become negative. This inverse effect of the electron-withdrawing group compared with alkyl substituents must be attributed to the electronic effect. In contrast, the relatively large values of $\theta_2 - \theta_1$ and $f_2 - f_1$ for *tert*-butyl-substituted cyclohexyne compared with those for other alkyl derivatives cannot be explained only by their electronic effects. Steric effects of the alkyl group may be responsible for the deformation of the cyclohexyne ring, and the resulting bond angles control the LUMO population and in turn the regioselectivity of nucleophilic addition.

The more deformed of the two acetylenic carbons has the lower LUMO population. When the acetylenic carbon is deformed from the linear structure, the π orbital in the plane of the cyclohexyne ring begins to have some s character. The increase in s character of the π orbital results in the increase in electron density in occupied MO and conversely the decrease in the LUMO population. The atomic charge at the acetylenic carbon actually changes with the bond angles (Figure S1). The more deformed of the two acetylenic carbons has the more negative atomic charge, but the correlation between the atomic charge and the product distribution is relatively poor (Figure S2). The LUMO population best represents the regioselectivity of nucleophilic addition to substituted cyclohexynes (Figure 2).

In conclusion, the elimination−addition mechanism for nucleophilic substitution at the vinylic carbon is established, and the reaction can be employed as a mild method for generation of cyclohexynes. The regioselectivity of nucleophilic addition to the substituted cyclohexynes is explored for the first time and is rationalized from the angle strain and the LUMO population at the acetylenic carbons.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas (Reaction Control of Dynamic Complexes, No. 15036260) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental and computational details and additional data (CIF and PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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