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Michael Addition−Elimination Mechanism for Nucleophilic Substitution Reaction of Cycloalkenyl Iodonium Salts and Selectivity of 1,2-Hydrogen Shift in Cycloalkylidene Intermediate

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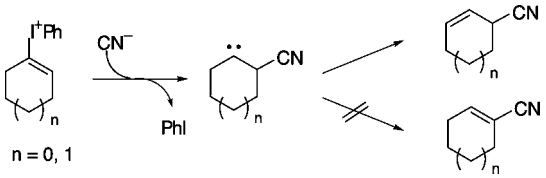

Reactions of cyclohexenyl and cyclopentenyl iodonium salts with cyanide ion in chloroform give cyanide substitution products of allylic and vinylic forms. Deuterium-labeling experiments show that the allylic product is formed via the Michael addition of cyanide to the vinylic iodonium salt, followed by elimination of the iodonio group and 1,2-hydrogen shift in the 2-cyanocycloalkylidene intermediate. The hydrogen shift preferentially occurs from the methylene rather than the methine β-position of the carbene, and the selectivity is rationalized by the DFT calculations. The Michael reaction was also observed in the reaction of cyclopentenyliodonium salt with acetate ion in chloroform. The vinylic substitution products are ascribed to the ligand-coupling (via λ^3-iodane) and elimination−addition (via cyclohexyne) pathways.

Introduction

Alkenyl(phenyl)iodonium salts[1] are highly electron-deficient vinyl compounds with a positively charged iodonio group, which is highly nucleofugal[2] and responsible for the high reactivity.[1] Simple alk-1-enyl salts undergo very facile α-elimination[3,4] and S_N2-type substitution[5−7] at the α position, but possible reactions at the β position are not readily observed due to the higher reactivity at the α position. The cycloalkenyl structure of the substrate excludes the possibility of α-elimination and in-plane S_N2 substitution ($S_NV\sigma$)[1m] and may enable observation of reactions at the β position. Thus, β-elimination was observed with cyclohex-1-enyl iodonium salts under mild basic conditions:[8] the resulting cyclohexyne readily undergoes nucleophilic attack, leading to overall nucleophilic substitution via an elimination−addition

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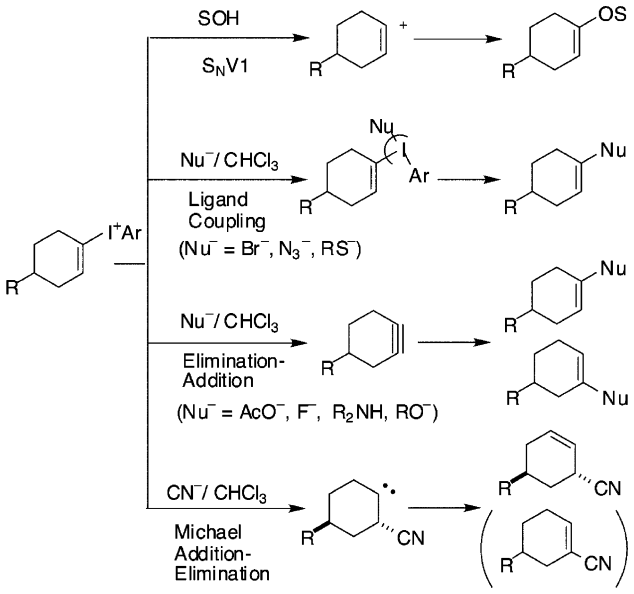
SCHEME 1. Mechanisms for Reactions of Cyclohexenyl Iodonium Salt with Nucleophiles



(EA) mechanism. Another possible reaction of nucleophile at the β position is the Michael addition, but it has not been observed probably due to the remaining competition at the α position, out-of-plane substitution ($S_NV\pi$),[1m] or the ligand coupling[9−11] via a hypervalent iodine(III) adduct (λ^3-iodane).[1] S_N1-type solvolysis is also possible for this secondary vinylic iodonium salt.[2] In further examinations we have now found and will present in this paper that the Michael addition−elimination (AE) does take place during the reaction of cyclohexenyl and cyclopentenyl iodonium salts with cyanide ion in chloroform.[12] Possible reaction pathways for the nucleophilic/basic reactions of cyclohexenyliodonium salt are summarized in Scheme 1 showing typical reaction conditions.

The Michael addition is followed by elimination of the iodonio group to give a substituted cycloalkylidene intermediate in the last reaction. Small ring cycloalkylidene is known to be a singlet carbene and undergoes 1,2-hydrogen shift to give cycloalkene.[13] Ease of the hydrogen shift in a singlet carbene is controlled by the orientation of the ground-state orbital concerned and the bonding orbital of the migrating hydrogen[14,15] and is also affected by electronic[16] and steric effects of adjacent groups. These factors determine the migration origin if there are two possibilities. In the Michael AE reaction of the iodonium salts, the selectivity of the hydrogen migration of the 2-substituted cycloalkylidene intermediate determines the product selectivity.

The Michael addition to vinylic compounds activated with a positively charged onium group takes place to give ylides.[17,18] For vinyl iodonium salts, the Michael reaction of 2-haloalk-1-enyliodonium salts with sulfinate is followed by elimination of the halide to give the 2-sulfonylalk-1-enyl iodonium salt.[18] The Michael reactions are more often observed for alkynyliodonium salts, which lead to alkylidenecarbene intermediates by ensuing loss of the iodonio group from incipient ylides.[19] The intramolecular insertion or migration of the carbene intermediate results in cyclopentenylation or alkynylation.[19] A similar reaction was observed with alkynylbismuthonium salts,[20] but the Michael reaction of alkynylselenonium salts resulted in formation of ylides.[21]

Results

Reactions of cyclohex-1-enyl(phenyl)iodonium tetrafluoroborates (**1a**) and 4-*tert*-butyl derivative **1b** with tet-

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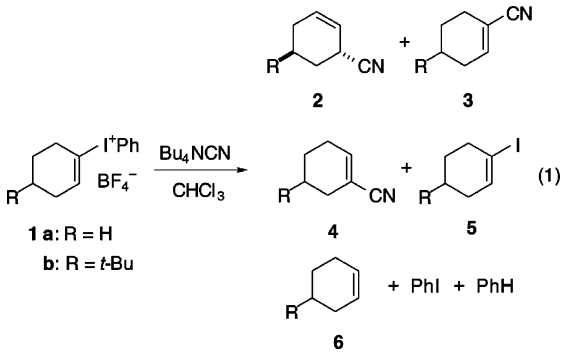
TABLE 1. Reaction of 1 with Bu_4NCN in Chloroform[a]

			yield (%)							
subst.	$[CN^-]$ (M)	[MeOH] (M)	**2**	**3**	**4**	**5**	**6**	ArI	ArH	ArCN
1a	0.01	0	12	18	*b*	25	*c*	64	*c*	<1
1a	0.10	0	15	16	*b*	33	*c*	62	*c*	<1
1a	0.01[d]	0	17	25	*b*	17	*c*	75	*c*	<1
1a	0.01	0.08	9	54	*b*	4	*c*	80	*c*	<1
1a	0.01	0.16	5	65	*b*	3	*c*	90	*c*	<1
1a	0.01	0.25	3	64	*b*	2	*c*	85	*c*	<1
1a	0.01	0.82	<1	73	*b*	<1	*c*	89	*c*	<1
1b	0.01	0	18	5	12	25	6	64	19[e]	<1
1b	0.10	0	14	3	7	36	7	49	*c*	<1
1b	0.01[d]	0	25	8	18	19	4	70	*c*	<1
1b	0.01	0.04	19	10	30	6	2	75	*c*	<1
1b	0.01	0.08	19	10	30	5	2	70	*c*	<1
1b	0.01	0.12	10	12	37	4	1	75	*c*	<1
1b	0.01	0.16	9	13	37	3	3	68	*c*	<1
1b	0.01	0.25	8	17	49	3	1	91	*c*	<1
1b	0.01	0.82	2	19	49	2	<1	83	*c*	<1
1b	0.01	2.47	<1	24	51	<1	2	81	*c*	<1
1b′	0.01	0	17	*f*	16	20	10	*f*	14	*c*

[a] [**1**] = 3 mM, at 60 °C for 1 h. [b] **4a** is identical with **3a**. [c] The yield was not determined by GC because of high volatility or for other reasons. [d] A neutral salt Bu_4NBF_4 (0.09 M) was added. [e] Determined by ^1H NMR in $CDCl_3$. [f] GC peaks of **3** and ArI are overlapped.

rabutylammonium cyanide were carried out in chloroform at 60 °C. The products include three cyanocyclohexenes **2**−**4** (**3a** and **4a** are identical where R = H), iodocyclohexene **5**, iodobenzene, benzene, and a small amount of cyclohexene **6** (eq 1). The reaction products



are fully characterized by NMR and mass spectroscopy and/or identified by comparison with authentic samples. The trans configuration of **2b** was confirmed by the coupling constants and NOE observed in ^1H NMR (Experimental Section). The product yields were usually determined by gas chromatographic analyses and are summarized in Table 1. Formation of benzene was confirmed by the ^1H NMR spectrum of the reaction mixture. 4-*tert*-Butylcyclohex-1-enyl(mesityl)iodonium tetrafluoroborate (**1b′**) was also examined, and the results are similar to those obtained with **1b**. Mesitylene was determined by gas chromatography (Table 1).

Similar results were obtained using sodium and potassium cyanide in the presence of crown ethers (Table 2). In the absence of a crown ether, the sodium or potassium salt is not very soluble in chloroform, and the reaction of **1** gave only a trace amount of cyanide-substitution products.

The cyanide reaction was also examined with 2,6,6-trideuterated cyclohex-1-enyl iodonium salts **1**-d_3. The deuterated substrates were prepared at ca. 90% D purity from 2,2,6,6-tetradeuterated cyclohexanone, which was obtained by H/D exchange. Product yields are given in

TABLE 2. Reaction of 1 with Cyanide in Chloroform Containing Crown Ether[a]

			yield (%)					
subst.	cyanide[b]	crown ether[c]	**2**	**3**	**4**	**5**	**6**	PhI
1a	Bu_4NCN	A(0.05)	13	19	*d*	13	*e*	62
1a	NaCN	A(0.08)	22	32	*d*	11	*e*	81
1a	KCN	A(0.10)	24	30	*d*	18	*e*	82
1a	NaCN	B(0.08)	22	32	*d*	11	*e*	81
1b	Bu_4NCN	A(0.04)	26	5	14	27	6	69
1b	Bu_4NCN	A(0.09)	26	7	18	22	6	72
1b	NaCN	A(0.04)	25	6	13	15	3	79
1b	KCN	A(0.08)	32	6	15	24	6	73
1b	KCN	A(0.14)	29	6	16	24	6	72

[a] [**1**] = 3 mM, at 60 °C for 1 h. Benzene was not detected by GC because of the high volatility. Yield of benzonitrile is less than 1%. [b] Sodium and potassium salts were saturated in solution, while the concentration of tetrabutylammonium salt was 0.01 M. [c] A: 18-crown-6, B: 15-crown-5. The values in parentheses are concentrations of the crown ether in M. [d] **4a** is identical with **3a**. [e] Not determined.

TABLE 3. Reaction of 1-d_3 with Bu_4NCN in Chloroform[a]

		yield (%)						
subst.	[MeOH] (M)	**2**	**3**	**4**	**5**	**6**	PhI	PhCN
1a-d_3	0	15	7		18	*b*	47	<1
1a-d_3	0.04	22	21		6	*b*	66	<1
1a-d_3	0.08	19	27		6	*b*	69	<1
1a-d_3	0.25	13	40		4	*b*	68	<1
1a-d_3	0.82	3	45		2	*b*	67	<1
1b-d_3	0	16	2	5	19	4	52	<1
1b-d_3	0.08	19	5	19	7	2	66	<1
1b-d_3	0.16	15	6	22	6	2	67	<1
1b-d_3	0.25	12	6	24	7	3	67	<1
1b-d_3	0.82	5	10	31	6	2	72	<1

[a] [**1**] = 3 mM, $[CN^-]$ = 0.01 M, at 60 °C for 1 h. [b] Not determined.

Table 3. Protium contents at the vinylic and allylic positions of products **2**−**5** (eq 2) were determined by ^1H NMR spectroscopy and are summarized in Table 4. The allylic products **2** contain deuterium atoms distributed at positions 1, 2, and 3. The vinylic hydrogen of the vinylic products **3** and **4** becomes mostly protium. Pro-

TABLE 4. Protium Contents (%) of Products Obtained from 1-d_3[a]

	2			3a			3b	4b	5		
[MeOH] (M)	H-1	H-2	H-3	H-2	H-6	H-3	H-2	H-2	H-2	H-6	H-3
					(a) products from **1a**-d_3						
δ (ppm)[b]	5.92	5.62	3.22	6.59	2.18	2.13			6.31	2.47	2.06
0[c]	6	7	<5	91	54	62			<5	16	d
0.04	6	9	<5	100	77	44			*e*	e	*e*
0.25[c]	6	16	5	100	72	42			<5	13	100
0.82	5	12	8	100	62	48			*e*	*e*	*e*
					(b) products from **1b**-d_3						
δ (ppm)[b]	5.95	5.61	3.29				6.61	6.59	6.28	2.51	2.06
0	12	13	9				69	97	10	*d*	*d*
0[c]	9	10	9				85	100	11	10	100
0.08	12	13	*d*				81	98	6	*d*	*d*
0.16	14	17	*d*				100	100	7	*d*	*d*
0.25	13	21	*d*				100	100	6	*d*	*d*
0.25[c]	8	16	6				100	100	4	12	100
0.82	9	19	13				100	100	8	*d*	*d*

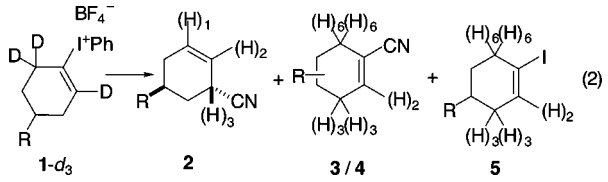
[a] The experimental errors for protium content are within ±10%. Product yields are summarized in Table 3. [b] Chemical shifts of the protons concerned. [c] Protium content was determined after purification by column chromatography. [d] The ^{1}H NMR signal was overlapped with other signals. [e] Cannot be determined due to a low yield of **5**.

TABLE 5. Reaction of Cyclopentenyliodonium Salt 7 with Nucleophiles in Chloroform[a]

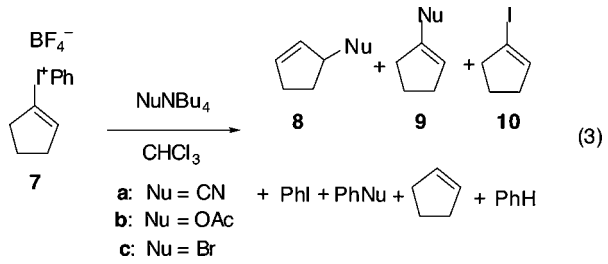
			yield (%)						
subst.	nucleophile (concentration, M)	time (h)	**8**	**9**	**10**	PhI	PhNu	C_5H_8	C_6H_6
7	CN^- (0.10)	22	15	<2	64	30	<2	2	40
7	AcO^- (0.01)	84	18	27	26	70	12	<2	<2
7	AcO^- (0.10)	27	18	25	29	60	8	<2	<2
7-d_3	AcO^- (0.10)	22	19	24	10	82	9	<2	<2
7	Br^- (0.01)	24	<2	58	17	64	20	<2	<2

[a] [**7**] = 8 mM, at 60 °C.

tium is not incorporated at either the vinylic or allylic position of iodocyclohexene **5**.

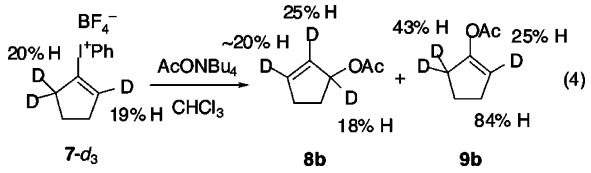


Reactions of cyclopent-1-enyl(phenyl)iodonium tetrafluoroborate (**7**) with cyanide as well as acetate and bromide were carried out in chloroform at 60 °C. The cyclopentenyl derivative **7** is much less reactive than the cyclohexenyl substrates **1**. Products were determined in the same way as cyclohexenyl derivatives. Observed products are shown in eq 3, and yields are given in Table 5.



Although the main product of the cyanide reaction was 1-iodocyclopentene (**10**), the allylic cyano product **8a** was also obtained. The acetate reaction gave both allylic and vinylic products **8b** and **9b**, while the reaction with bromide gave only the vinylic product **9c** but no allylic bromide **8c**.

2,5,5-Trideuterated cyclopent-1-enyl iodonium salt **7**-d_3 (ca. 80% D) was employed for the acetate reaction. Products **8b** and **9b** maintain most of the deuterium label of the starting iodonium salt **7**-d_3 as shown in eq 4. The allylic product **8b** contains the deuterium labels at positions 1, 2, and 3, as observed similarly for 3-cyanocyclohexene **2**. The vinylic deuterium in the vinylic product **9b** was also retained, but it is noteworthy that the deuterium label is distributed partially at position 3 of **9b** (84% H content) at the expense of deuterium at position 5.



Rates for the reactions of cyclopentenyliodonium salt **7** and its deuterated analogue **7**-d_3 were determined 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 pseudo-first-order rate constants are given in Table 6 as averages of at least three runs within ±5%. The reaction with acetate is about 3−4 times faster than the bromide reaction. The observed rate constants are not very dependent on concentrations of the nucleophile. Kinetic

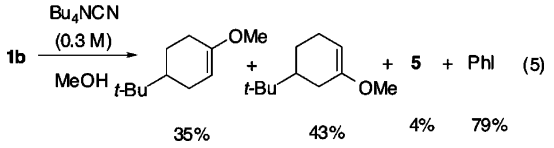
TABLE 6. Pseudo-First-Order Rate Constants (k_H and k_D) for the Reactions of Iodonium Salts 7 and 7-d_3 with Tetrabutylammonium Bromide or Acetate in Chloroform at 60 °C

[Bu_4NNu] (M)	10^5k_H (s^{-1})	10^5k_D (s^{-1})	k_H/k_D
	Nu = Br		
0.001	1.45	1.10	1.3
0.005	1.46	1.07	1.4
0.025	1.52	1.04	1.5
0.075	1.57	1.08	1.5
	Nu = OAc		
0.001	6.89	5.90	1.2
0.005	6.98	5.83	1.2
0.025	7.35	6.79	1.1
0.050	7.22	5.68	1.3
0.10	8.24	7.29	1.1

isotope effects are small for both the acetate ($k_H/k_D = 1.1-1.3$) and the bromide reactions ($k_H/k_D = 1.3-1.5$).

Discussion

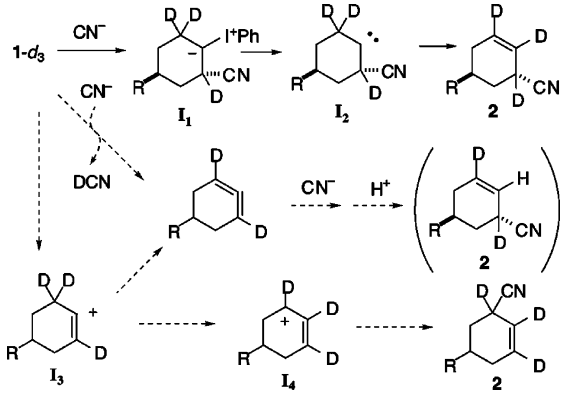
Reaction of Cyclohexenyliodonoium Salt 1 with Cyanide. The cyanide reaction of **1** gave allylic cyanide **2** as well as *ipso*- and *cine*-substitution products, **3** and **4**. This product pattern of substitution is completely different from those observed previously for the reactions of **1** (Scheme 1). Allylic products have never been observed. When methanol was employed as a solvent, the cyanide reaction of **1b** gave rise to quite different results:[8b] the major reaction was the base-promoted β-elimination−addition (EA) to give *ipso*- and *cine*-substitution products, and no allylic product was formed. Moreover, the nucleophile was methoxide (or methanol), but cyanide products were less than a few percent (eq 5).[8b]



The effects of added methanol on the cyanide reaction in chloroform are in fact large (Table 1). Yields of the vinylic cyanides, **3** and **4**, increase with increasing methanol, whereas those of allylic cyanide **2** and iodocyclohexene **5** decrease. Concentrations of tetrabutylammonium cyanide and added tetrabutylammonium tetrafluoroborate slightly affect the product yields, but the effects are much weaker than those of methanol. The vinylic *ipso* and *cine* cyanide products may be mainly derived from the EA mechanism, but how is the allylic product formed?

Mechanism for Formation of Allylic Product. A characteristic product observed in the cyanide reaction of **1** and **7** as well as in the acetate reaction of **7** is the allylic substitution product, **2** or **8**. The cyano group of these products is located at the *cine* position next to the original position of the leaving group. Possible mechanisms for formation of the allylic product **2** are summarized in Scheme 2 for the reaction of deuterated substrate **1**-d_3. We first considered the elimination−addition (EA) mechanism via cyclohexa-1,2-diene as an extension of the EA mechanism via cyclohexyne to give the *ipso* and *cine* products (**3** and **4**). If **2** was formed via

SCHEME 2. Possible Pathways of Formation of Allylic Product



the 1,2-diene, an external proton should have been incorporated into position 2 of product **2** and should have been detected when the reaction was started with deuterated substrate **1**-d_3. This mechanism is excluded since position 2 was not protonated but the original three deuterium atoms of **1**-d_3 were maintained at positions 1, 2, and 3 of **2.** The results show that the original deuterium atom should migrate to position 2 of **2**.

The most reasonable route compatible with the isotope incorporation experiments involves the initial Michael addition of highly nucleophilic cyanide to give iodonium ylide ($\mathbf{I_1}$), followed by elimination of the iodonio group to yield a carbene intermediate ($\mathbf{I_2}$), which undergoes 1,2-hydrogen (deuterium) migration to result in **2**. The iodonium ylide formation followed by elimination to give carbene has been reported in the Michael reaction of alkynyliodonium salts.[19] Hydrogen has a high migratory aptitude in the 1,2-rearrangement of singlet carbenes.[13] There are two possible migration origins of hydrogen, but the migration from >CHCN to give one of the vinylic products **4** is less favorable, as shown by the isotope incorporation experiments (Table 4, see the discussion in the next section). Theoretical calculations support this selectivity (see below).

Alternatively, an allylic cation intermediate $\mathbf{I_4}$ may not be impossible to form via 1,2-hydrogen rearrangement of the initial vinylic cation $\mathbf{I_3}$ if generated. This cationic route can lead to **2** without loss of deuterium, but this is less likely; the reaction medium is rather basic, and furthermore, no allylic substitution product was obtained during the solvolysis of **1**, where the vinylic cation was confirmed as a major intermediate.[2]

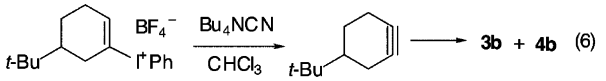
The allylic cyanide **2b** is solely in the trans form. The configuration indicates that the cyanide attack occurs from the axial direction of cyclohexenyl ring of **1b**. The tendency of axial attack has been observed generally in electrophilic additions to cyclohexanone enolates to avoid an unstable twist−boat conformation during the bond-formation step,[22,23] and the stereochemical situation for the present reaction is similar to the reaction of the enolate. Formation of the allylic product **8** from cyclopentenyliodonium salt **7** can also be explained by a

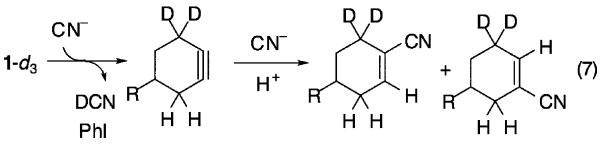
(22) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 1.

(23) Fraser, R. R.; Banville, J.; Dhawan, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7999−8001. Kuehne, M. E. *J. Org. Chem.* **1970**, *35*, 171−175.

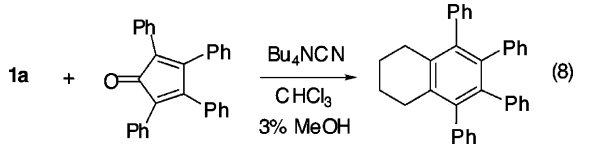
similar mechanism involving the Michael addition−elimination followed by 1,2-hydrogen shift.

Mechanism for Formation of Vinylic Cyanides 3 and 4. As mentioned above, vinylic products **3** and **4** may be derived from the EA mechanism via the intermediate cyclohexyne. In this mechanism the vinylic hydrogen should come from the external proton source, and it should be completely protium if the reaction is carried out with a deuterated substrate **1**-d_3 in a normal solvent. This is the case for the products in the presence of methanol (Table 4). Under these conditions, **3** and **4** are major products, and about 3-fold preference of **4b** over **3b** was observed, in good agreement with the regioselectivity of nucleophilic addition to 4-*tert*-butylcyclohexyne.[8] Actually a similar product ratio (**4b/3b** = 7/3) was obtained during the reaction of 5-*tert*-butycyclohex-1-enyliodonium salt **11** with cyanide (0.05 M) in the presence of 1% (0.25 M) methanol (eq 6). The regioisomeric iodonium salt **11** can yield 4-*tert*-butylcyclohexyne as a common intermediate to the reaction of **1b**. Although **3** and **4** are identical (as **3a**) in the reaction of **1a**, deuterium is distributed at both of the two allylic positions (C-3 and C-6) of **3a** in the reaction of deuterated substrate **1a**-d_3. The observation is consistent with the EA mechanism (eq 7).

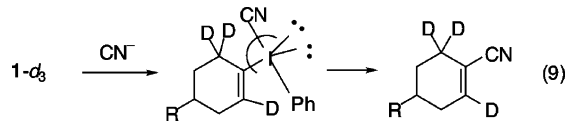




Data in Table 3 show that deuterium-labeled iodonium salts **1**-d_3 generally give lower yields of **3** and **4** than normal **1** (Table 1) in the reaction with cyanide. These results conform to the EA mechanism via cyclohexyne, where deprotonation is rate determining and the primary isotope effects are operative. The cyclohexyne intermediate could be trapped by tetraphenylcyclopentadienone under the reaction conditions to give tetrahydronaphthalene in 37% yield (eq 8).

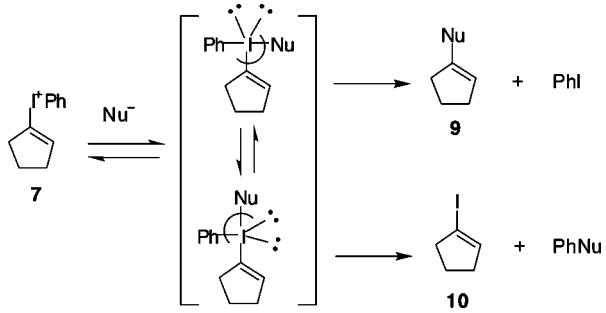


In the absence of methanol, yields of the vinylic cyanides decrease and the relative amount of the *ipso* product **3b** increases (**4b/3b** = ca. 2/1). Under these conditions some deuterium is retained at the vinylic position of the *ipso* substitution product **3** but not in the other vinylic product **4**. Thus, some additional reaction pathway other than the EA mechanism must be at work to give the *ipso* vinylic cyanide **3** without loss of the vinylic deuterium in the absence of effects of methanol. Ligand coupling within the cyanide-coordinated hypervalent iodine complex (λ^3-iodane) is the most probable pathway to give the additional **3** (eq 9). On the other hand, the possibility is excluded that **4** is formed via the Michael AE and 1,2-hydrogen shift from the methylene of the cyclohexylidene.



Mechanism for Vinylic Substitution of Cyclopentenyl Iodonium Salt 7. Reaction of **7** with bromide ion gave the vinylic bromide **9c** and bromobenzene accompanied by the formation of the counterpart iodobenzene and 1-iodocyclopentene (**10**) (Table 5). The nucleophilic substitutions both at the vinylic and phenyl groups of vinyl(phenyl)iodonium salt are observed during the ligand-coupling mechanism in λ^3- iodane[9] (Scheme 3). The observed rate constants are not very dependent on the concentration of bromide, and this will be explained by a mechanism involving the initial equilibrium formation of λ^3-iodane, which is an equilibrium of the two conformational isomers due to pseudorotation and leads to two pairs of ligand-coupling products.[9] Small kinetic isotope effects observed (k_H/k_D = 1.3−1.5) are not incompatible with this mechanism. Some unidentified side reactions may be partially responsible for the observed isotope effects. The ligand-coupling mechanism has been proposed for reactions of some vinylic iodonium salts with halide ions and other nucleophiles.[9]

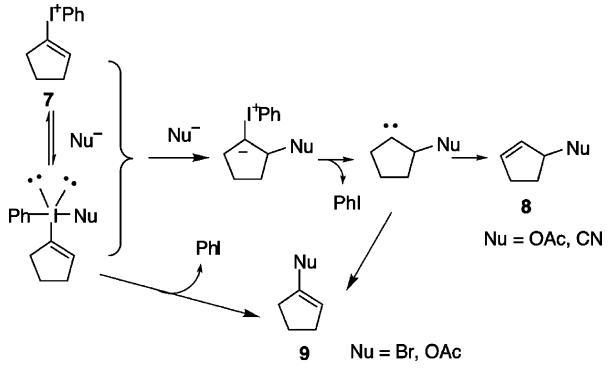
SCHEME 3. Ligand Coupling Mechanism



Acetate substitution reaction of **7** also gave both vinylic acetate **9b** and phenyl acetate in addition to allylic acetate **8b**. The deuterium label essentially remains at the vinylic position of the product **9b** in the reaction of **7**-d_3 (eq 4). These results are consistent with the ligand-coupling mechanism for the formation of **9b** and phenyl acetate. Allylic acetate **8b** must be formed via the Michael AE mechanism as discussed above. Thus, the acetate reaction of **7** proceeds through both the Michael AE and ligand-coupling pathways. Small kinetic isotope effects (k_H/k_D = 1.1−1.3) were observed for the acetate reaction (Table 6), and the deuterium labeling in **7**-d_3 did not affect the product ratio of **8b/9b**. These results are compatible with the competing ligand-coupling and Michael AE pathways, both of which exert no primary deuterium isotope effects in the rate-determining or product-determining step.

The concentration of acetate ion does not affect product distribution or yields in the range of [AcO^-] = 0.01−0.1 M (Table 5) nor affect the observed rate constant (Table 6). These results suggest that both the ligand-coupling and the Michael reaction pathways proceed via λ^3-iodane.

SCHEME 4. Mechanism for Nucleohilic Substitution Reactions of 7



The Michael reaction yields a cyclopentylidene intermediate, which leads to allylic product **8** and possibly to vinylic product **9**. The vinylic deuterium label of **9b** is essentially retained, but the allylic labels are distributed at the two allylic positions of **9b**. The distribution of allylic labels of **9b** can be rationalized if **9b** is formed both via ligand-coupling and Michael AE mechanisms (Scheme 4). In the latter mechanism, the hydrogen at >CHOAc of 2-acetoxycyclpentylidene may migrate preferentially (see the theoretical discussion below).

On the other hand, the cyanide reaction of **7** gave only **8a** but no **9a**, the former of which may be derived via the Michael AE followed by 1,2-hydrogen shift from $>CH_2$ of the carbene intermediate. That is, the hydrogen shift occurs from $>CH_2$ rather than >CH(CN) of 2-cyanocyclpentylidene in a manner similar to 2-cyanocyclohexylidene. The migration ability of hydrogen of substituted cycloalkylidenes will be theoretically discussed below.

Any sign of the EA mechanism was not found for the cyclopentenyliodonium salt **7**. This is not unexpected because of a high ring strain of cyclopentyne. The Michael reaction of acetate with **7** (but not with **1**) may take place for this reason.

Reaction of iodonium salt **1** or **7** with cyanide ion involves an appreciable side reaction, giving iodocycloalkene **5** or **10** with accompanying benzene (mesitylene from **1b′**). The ligand-coupling pathway can yield iodocycloalkene, but the counterpart product, benzonitrile, was not observed. The observed counterpart product was benzene, and the pair of iodocycloalkene and benzene must be produced by one-electron reduction of iodonium ion, followed by homolysis to iodocycloalkene and phenyl radical.[9b,24,25] This reaction is particularly obvious for the cyclopentenyl derivative **7** (Table 5), reflecting the slower nucleophilic reaction in competition.

Hydrogen Shift in Substituted Cycloalkylidenes. The Michael reaction pathway takes place during the reaction of **1** with cyanide and the reaction of **7** with acetate and cyanide ions to give 2-cyanocyclohexylidene, 2-acetoxycyclopentylidene, and 2-cyanocyclopentylidene,

SCHEME 5. 1,2-Hydrogen Shift in 2-Substituted Cycloalkylidene

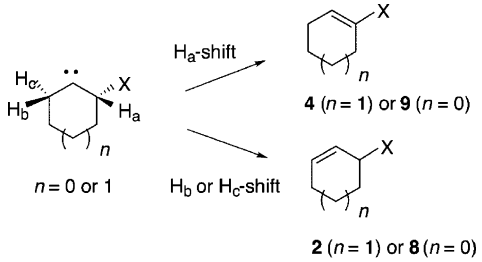


CHART 1

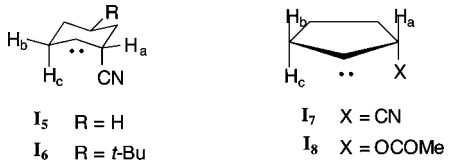


TABLE 7. Activation Energies for 1,2-Hydrogen Shift in Substituted Cycloalkylidenes Calculated by B3LYP/6-31G(d)

	$\Delta G^{\ddagger}$ ($\Delta E^{\ddagger}$)[a]/kcal mol^{-1}		
carbene	H_a	H_b	H_c
I_5	4.6(7.3)	3.8(6.2)	3.0(5.4)
I_6	4.1(6.4)	3.0(5.4)	2.4(4.7)
I_7	6.1(7.3)	5.7(6.7)	4.2(5.3)
I_8	4.6(5.6)	7.8(9.2)	5.1(6.2)

[a] Gibbs free energies $\Delta G^{\ddagger}$ are calculated at 298.15 K and 1.00 atm.

respectively. Theoretical calculations were carried out on the transition states for 1,2-hydrogen shift in these carbenes at the level of B3LYP/6-31G(d). 2-Substituted cycloalkylidene contains three different hydrogens, H_a, H_b, and H_c, which can participate in the 1,2-hydrogen shift (Scheme 5), and the intramolecular competition of hydrogen shift determines the destination of intermediate carbene to vinylic or allylic product.

Calculations were carried out on cycloalkylidenes **I_5**−**I_8** (Chart 1). Activation energies calculated for the hydrogen shift are summarized in Table 7.[26] For 2-cyanocyclohexylidene, the axial conformer **I_5** is slightly more stable than the equatorial conformer (by 0.27 kcal mol^{-1}). Both conformers give similar results regarding energy barriers for the hydrogen shift, and the results for the latter conformation are not recorded here. For the 4-*tert*-butyl derivative, the trans isomer **I_6** was employed for calculations, since the allylic product **2b** is in the trans configuration. For cyanocycloalkylidenes **I_5**−**I_7**, the shift of H_c from the methylene has a lower barrier and is more favorable than that of H_a from the methine, thus preferentially leading to the allylic cyanide. This is compatible with the product distribution in cyanide reactions of **1** and **7**. In contrast, acetoxycyclopentylidene **I_8** has a lower barrier for the shift of H_a than that of H_b or H_c.[27] The migration origin of hydrogen shift in carbene is controlled by substitution at the β-position of carbene. Methoxy, phenyl, and alkyl substituents facilitate the

(24) (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) Chen, D.-W.; Ochiai, M. *J. Org. Chem.* **1999**, *64*, 6804−6814.

(25) The possibility of the reduction product formation via benzyne intermediate can be eliminated: similar reduction was observed in both cases of **1b** and **1b′**, although **1b′** cannot give the benzyne-type intermediate.

(26) A small difference between $\Delta G^{\ddagger}$ for the shift of the axial H_c and equatorial H_b agrees well with the previous calculations of cycloalkylidenes.[15]

migration of the hydrogen on the same carbon (H_a).[13] The effect of the acetoxy group in $\mathbf{I_8}$ is similar to these groups, but the cyano group exerts adverse effects. The electron-withdrawing ability of the cyano group may be responsible for this tendency. When the C−H bond is partially cleaved in the transition state for 1,2-hydrogen shift in carbene, a positive charge develops at the carbon,[16] which is stabilized by electron-donating groups including the acetoxy group but destabilized by the cyano group.

In summary, reactions of cycloalkenyl iodonium salts **1** and **7** with cyanide ion involve a new type of reaction pathway of vinyliodonium salts, Michael addition−elimination. The Michael reaction leads to a cycloalkylidene intermediate, and the reactivity of the carbene affects the product distribution. 2-Cyanocycloalkylidenes undergo a shift of the methine hydrogen preferentially to give the allylic cyanide product, in contrast to phenyl-, alkyl-, methoxy-, and acetoxy-substituted cycloalkylidenes.

Experimental Section

Preparation of Deuterium-Labeled Iodonium Salts. Cyclic ketones were treated with D_2O in THF containing K_2CO_3 to yield the deuterium-incorporated ketones. The deuterium-labeled iodonium salt **1**-d_3 was prepared from the labeled ketone according to the literature procedures.[8b,11a] The isotopic purity was determined by comparison of ^{1}H NMR peak areas due to the vinylic and allylic protons with that for the aromatic protons. Selected data for **1a**-d_3: Deuterium contents at C-2 (δ = 7.0 ppm) and C-6 (δ = 2.56 ppm) are 96 and 91 atom %, respectively. HRMS (ESI) calcd for $C_{12}H_{11}D_3I$ (M − BF_4) 288.0329, found 288.0291. Selected data for **1b**-d_3: Deuterium contents at C-2 (δ = 7.0 ppm) and C-6 (δ = 2.66 ppm) are 91 and 93 atom %, respectively. HRMS (ESI) calcd for $C_{16}H_{19}D_3I$ (M − BF_4) 344.0955, found 344.0935. Selected data for **7**-d_3: Deuterium contents at C-2 (δ = 6.93 ppm) and C-5 (δ = 2.7 ppm) are 81 and 80 atom %, respectively. HRMS (ESI) calcd for $C_{11}H_9D_3I$ (M − BF_4) 274.0172, found 274.0128.

Reaction of 1 with Nucleophile. The tetrafluoroborate salt of **1** (4 mg) was dissolved in 3 mL of chloroform containing tetrabutylammonium cyanide and kept at 60 °C. After addition of an ether solution containing tetradecane (5 μmol), the products were extracted with ether and washed with water. The yields of the products were determined by gas chromatography with tetradecane as an internal standard. The retention times of **2a**, **3a**, and **5a** were 8.5, 10.6, and 13.3 min, respectively, at a column temperature of 50 °C (DB-1). In the GC analysis of the reaction mixture from **1b**, products **6b**, **2b**, **4b**, **3b**, and **5b** were detected at retention times of 2.1, 8.3, 10.8, 11.2, and 12.5 min, respectively, when the temperature of the column (DB-1) was maintained at 100 °C during the initial 10 min and then raised at the rate of 10 °C min^{-1}.

Authentic samples of **2a**,[28] **3b**,[11a] and **5a,b**[11a] were prepared according to the literature methods. Selected data for **2a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.62 (m, 1H), 3.22 (m, 1H), 1.94−1.91 (m, 2H), 1.85−1.54 (m, 4H); MS (EI) *m/z* (relative intensity, %) 107 (36, M$^+$), 92 (58), 79 (100). The data agree well with the reported values: ^{1}H NMR (CCl_4) δ 5.9 (m, 1H), 5.6 (m, 1H), 3.15 (m, 1H), 2.2−1.6 (m, 6H).[29] Selected data for **3b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.61 (m, 1H), 2.32−2.28 (m, 1H), 2.25−2.16 (m, 2H), 1.92−1.86 (m, 2H), 1.29−1.23 (m, 1H), 1.21−1.11 (m, 1H), 0.85 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.67, 119.75, 112.10, 42.55, 32.14, 28.02, 27.57, 26.95, 22.97; MS (EI) *m/z* (relative intensity, %) 163 (10, M$^+$), 148 (10), 107 (50), 57 (100). The data agree well with the reported values: ^{1}H NMR (CCl_4) δ 6.7−6.4 (m, 1H), 2.5−1.0 (m, 7H), 0.89 (s, 9H); MS (EI) *m/z* (relative intensity, %) 163 (69, M$^+$), 148 (63), 107 (100), 57 (84).[30]

Authentic samples of **3a** and **4b** were also prepared from reaction of $KCu(CN)_2$ with **1a** and 5-*tert*-butylcyclohex-1-enyl(phenyl)iodonium tetrafluoroborate (**11**), respectively. Selected data for **3a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.59 (m, 1H), 2.20−2.16 (m, 2H), 2.15−2.10 (m, 2H), 1.67−1.62 (m, 2H), 1.61−1.58 (m, 2H); MS (EI) 107 (59, M$^+$), 92 (96), 79 (100), 67 (33), 52 (45). The data agree well with the reported values: ^{1}H NMR ($CDCl_3$) δ 6.72−6.44 (m, 1H), 2.36 (br, 4H), 1.86−1.46 (m, 4H).[31] Selected data for **4b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.59 (m, 1H), 2.30 (dq, J = 19.9, 2.4 Hz, 1H), 2.22 (m, 1H), 2.13 (m, 1H), 1.98 (m, 1H), 1.83 (m, 1H), 1.29 (tdd, J = 12.4, 5.5, 2.7 Hz, 1H), 1.12 (qd, J = 12.4, 5.5 Hz, 1H), 0.87 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 144.84, 119.90, 112.68, 42.20, 32.23, 28.41, 27.18, 26.97, 22.27; MS (EI) 163 (6, M$^+$), 148 (5), 107 (57), 57 (100); HRMS (ESI) calcd for $C_{11}H_{17}NNa$ (M + Na) 186.1259, found 186.1269.

***trans*-5-*tert*-Butyl-3-cyanocyclohexene (2b).**[32] Reaction of **1b** (109 mg, 0.25 mmol) with Bu_4NCN (101 mg, 0.38 mmol) was carried out in chloroform (20 mL) at room temperature for 1 h to give **2b**, which was purified (3.2 mg, 8% yield) by preparative GC. The NMR peaks are assigned using ^{1}H−^{1}H and ^{13}C−^{1}H COSY. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.95 (ddt, $J_{1,2}$ = 9.6 Hz, $J_{1,6eq}$ = 5.5 Hz, $J_{1,6ax}$ = 2 Hz, J = 2 Hz, 1H, H-1), 5.61 (ddt, $J_{1,2}$ = 9.6 Hz, $J_{2,3}$ = 5 Hz, J = 2 Hz, 1H, H-2), 3.29 (tq, $J_{3,4ax}$ = $J_{2,3}$ = 5 Hz, $J_{3,4eq}$ = 2 Hz, J = 2 Hz, 1H, H-3), 2.14 (dddt, $J_{6eq,6ax}$ = 17.9 Hz, $J_{1,6eq}$ = 5.5 Hz, $J_{5,6eq}$ = 4.8 Hz, J = 2 Hz, 1H, H-6$_{eq}$), 2.08 (d quint, $J_{4eq,4ax}$ = 13.1 Hz, $J_{4eq,5}$ = $J_{3,4eq}$ = 2 Hz, J = 2 Hz, 1H, H-4$_{eq}$), 1.81 (ddq, $J_{6eq,6ax}$ = 17.9 Hz, $J_{5,6ax}$ = 11.7 Hz, $J_{1,6ax}$ = 2 Hz, J = 2 Hz, 1H, H-6$_{ax}$), 1.62 (dddd, $J_{4ax,5}$ = 12 Hz, $J_{5,6ax}$ = 11.7 Hz, $J_{5,6eq}$ = 4.8 Hz, $J_{4eq,5}$ = 2 Hz, 1H, H-5), 1.40 (ddd, $J_{4eq,4ax}$ = 13.1 Hz, $J_{4ax,5}$ = 12 Hz, $J_{3,4ax}$ = 5 Hz, 1H, H-4$_{ax}$), 0.88 (s, 9H, *t*-Bu); ^{13}C NMR (150 MHz, $CDCl_3$) δ 132.94 (C-1), 121.12 (CN), 120.05 (C-2), 40.35 (C-5), 32.03 (*t*-Bu), 27.49 (C-3), 27.32 (C-4), 26.95 (*t*-Bu), 26.44 (C-6); MS (EI) *m/z* (relative intensity, %) 163 (2, M$^+$), 148 (5), 121 (6), 107 (22), 79 (20), 57 (100); HRMS (ESI) calcd for $C_{11}H_{17}NNa$ (M + Na) 186.1259, found 186.1267; NOE between H-5 (δ = 1.62 ppm) and H-3 (δ = 3.29 ppm) was not observed, and NOE between H-4$_{ax}$ (δ = 1.40 ppm) and H-6$_{ax}$ (δ = 1.81 ppm) and that between H-4$_{ax}$ (δ = 1.40 ppm) and H-3 (δ = 3.29 ppm) were detected with 2% and 4%, respectively.

Reaction of 7 with Nucleophile. Iodonium salt **7** (1.5 mg) was dissolved in chloroform-*d* (0.5 mL) containing tetrabutylammonium salt of nucleophile. The NMR tube containing the solution was sealed and kept at 60 °C. Product yields were determined by ^{1}H NMR using the residual $CHCl_3$ as an internal standard. Authentic samples of **8b**[33] and **9b**[34] were prepared according to the reported methods. 1-Iodocyclopentene (**10**) was prepared by the reaction of **7** with tetrabutyl-

(27) The barrier in Table 7 is for the most stable conformer of $\mathbf{I_8}$ among some torsional conformers due to the rotation of acetoxy group. An acetoxy-bridged structure is by 2.4 kcal mol^{-1} more stable than the most stable conformation of $\mathbf{I_8}$ and gives the acetoxy migration product with a low energy barrier ($\Delta G^{\ddagger}$ = 0.5 kcal mol^{-1}). However, the free-energy barrier from $\mathbf{I_8}$ to the bridged form is 12.1 kcal mol^{-1} and much higher than $\Delta G^{\ddagger}$ for the 1,2-hydrogen shift shown in Table 7. The energy diagram for the acetoxy shift in $\mathbf{I_8}$ is shown in Scheme S1 (Supporting Information). That is, the possibility of acetoxy migration in $\mathbf{I_8}$ is excluded from the reaction pathway to **9b**.

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ammonium iodide, and the ^{1}H NMR and MS spectra agree well with those reported.[35] The products **8a**,[36] **9a**,[37] and **9c**[35] were assigned by ^{1}H NMR in comparison with the reported data.

Determination of Protium Contents of Products from Labeled Iodonium Salts. The reaction mixture obtained from **1**-d_3 was analyzed by both GC and ^{1}H NMR. GC analysis reveals the ratio of products, **2a**, **3a**, **5a**, and iodobenzene. The ^{1}H NMR measurements provide the relative peak areas due to respective protons. Protium contents were calculated from the GC and ^{1}H NMR analysis by using iodobenzene as an internal standard. Assignments of the vinylic and allylic protons for **3a** and **5** were undertaken by comparison with authentic samples of deuterated **3a** and **5**. The selectively deuterated samples of **3a** and **5** were prepared by the reaction of **1**-d_3 with $KCu(CN)_2$ and iodide salt, respectively. Signals due to **2** were assigned using the ^{1}H−^{1}H COSY NMR measurements described above. The chemical shifts of the protons concerned are given in Table 4.

Direct ^{1}H NMR determination of protium contents without GC analysis was also carried out for **2b** isolated from the reaction mixture of **1b**-d_3 by preparative GC. The protium content of **2b** was determined using the peak area due to *t*-Bu (0.88 ppm) as a reference: Protium contents at H-1, H-2, and H-3 of **2b** are 12%, 16%, and 7%, respectively (Supporting Information). The results agree well with those in Table 4, which are determined by combination of ^{1}H NMR and GC peak areas.

The reaction of **7**-d_3 (16 mM, 19 mg) with Bu_4NOAc (0.1 M) was carried out in $CHCl_3$ (3 mL), and the reaction mixture extracted with pentane was analyzed by GC and ^{1}H NMR in $CDCl_3$. The molar ratio of **8b**:**9b**:**10b**:PhI determined by GC is 0.3:0.3:0.15:1.0. The ratio agrees well with the product yields determined in an independent run of reaction of **7**-d_3, which gave **8b**, **9b**, **10b**, and PhI in 19%, 24%, 10%, and 82% yield, respectively. Chemical shifts for H-1, H-2, and H-3 of 3-acetoxycyclopentene (**8b**) were assigned to be 6.08, 5.81, and 5.68 ppm, respectively.[38] ^{1}H NMR peaks due to 1-acetoxycyclopentene (**9b**) were assigned by comparison with the normal product from **7** and the selectively deuterated sample prepared by reaction of **7**-d_3 with cupric acetate in acetic acid. Chemical shifts for H-2, H-3, and H-5 of 1-acetoxycyclopentene (**9b**) are 5.38, 2.35, and 2.42 ppm, respectively. Protium contents at these positions are calculated from the peak areas in reference to that for the acetoxy group, which is independently observed at 2.11 and 2.01 ppm for **8b** and **9b**, respectively. The protium contents are shown in eq 4. The peak at 6.08 ppm for H-1 of **8b** overlaps with that for the vinylic proton of **10**. The ratio of the peak area at 6.08 ppm and that for the acetyl group at 2.11 ppm is 0.36:3, indicating that the protium content at C-1 of **8b** is less than 36%, probably about 20%.

Trapping of Cyclohexyne with Tetraphenylcyclopentadienone. A solution containing **1a** (36.3 mg, 0.098 mmol), tetrabutylammonium cyanide (70 mg, 0.26 mmol), tetraphenylcyclopentadienone (85.5 mg, 0.22 mmol), and methanol (0.6 mL) in chloroform (20 mL) was stirred at 60 °C for 1 h. The mixture was purified by chromatography (SiO_2, eluent: 40% $CHCl_3$ in hexane) to give 5,6,7,8-tetraphenyl-1,2,3,4-tetrahydronaphthalene[8b] (15.6 mg, 0.036 mmol, 37% yield).

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Supporting Information Available: General experimental procedures, computational details, and additional data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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