Divalent Palladium Catalyzed Stereoselective Synthesis of α-(Z)-(Halomethylene)-γ-butyrolactone Derivatives and Its Mechanism

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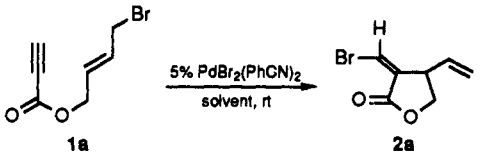
α-Methylene-γ-butyrolactone rings have been constructed by bis(benzonitrile)palladium dihalide or Pd(OAc)$_2$–LiX catalyzed cyclization reaction of haloallylic 2-alkynoates. A mechanism involving a trans halopalladation, followed by intramolecular insertion of a carbon–carbon double bond to a carbon–palladium bond and subsequent dehalopalladation, is briefly discussed.

Introduction

Recently, much attention has been focused on transition metal(0) catalyzed ring construction.[1-4] However, the transition metal(0) catalyzed cyclization of α,β-unsaturated acid allylic esters that would lead to lactones has not been studied, probably due to the possibility of allylic carbon–oxygen bond cleavage by the low-valent transition metal catalysts.[5]

The α-methylene-γ-butyrolactone ring is an integral building block of many natural products, especially the sesquiterpene lactones in which the conjugated exocyclic double bond is considered to be responsible for their interesting biological properties.[6] Since the discovery of several naturally occurring cytotoxic or antitumor agents (e.g., eupurotin, elephantin, vernolepin, etc.) that possess the α-methylene lactone ring, much interest has been shown in this class of compounds. Several reviews dealing with the synthesis of α-methylene lactones have been published.[7] Generally, the α-methylene lactones are synthesized by α-methylenation of preformed lactones, by oxidation of α-methylenecyclobutanone and β-methylene tetrahydrofuran, or from functionalized acyclic precursors. This lactone ring can also be built up by radical cyclization, albeit in poor yield.[8] There are reports in the literature of palladium-catalyzed cyclocarbonylation of hydroxy-substituted vinyl halides,[9] cyclization of homoallylic carbonochloridates,[10] and the reaction of alkynyl alcohols with nickel carbonyl to construct the α-methylene-γ-butyrolactones.[11] Thus, it is of interest to study the transition metal catalyzed cyclization of allylic 2-alkynoates to the α-methylene-γ-butyrolactone ring. In this approach, the lactone ring is constructed by a carbon–carbon bond formation reaction of an acyclic ester and would provide a new methodology for the formation of the α-methylene lactone ring (eq 1).

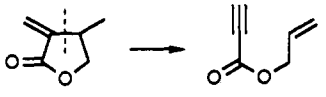
Table I. Bis(benzonitrile)palladium Dibromide Catalyzed Cyclization of 4′-Bromo-2′(E)-butenyl 2-Propynoate (1a) in Different Solvents[a]



1a 2a

entry	solvent	reaction time (h)	isolated yield (%)
1	benzene	96	10[b]
2	EtOH	24	40
3	CH_3CN	24	55
4	CH_3NO_2	24	30
5	THF	24	50
6	DMF	18	60
7	HOAc	1	70

[a] The reaction was monitored by TLC on silica gel. [b] 50% of 1a was recovered.



(1)

Generation of a low-valent metal complex that would lead to the allylic carbon–oxygen bond cleavage of the allylic ester[5] must be avoided. In the literature, where a divalent palladium complex is the catalytically active species, zero-valent palladium is usually formed during the reaction and is reoxidized by oxidants to complete the catalytic cycle.[12] In some cases, the divalent palladium complex is used in stoichiometric amount.[13] Kaneda et al. reported the bis(benzonitrile)palladium dihalide catalyzed codimerization of alkynes and allylic halides in which

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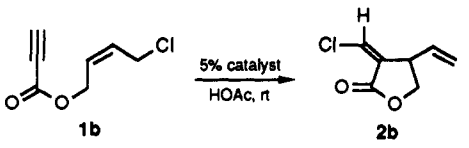
Table II. Cyclization of 4′-Chloro-2′(Z)-butenyl 2-Propynoate (1b) with Different Catalysts in Acetic Acid



1b 2b

entry	catalyst	reaction time[a] (h)	isolated yield (%)
1	$PdCl_2(PhCN)_2$	1	81
2	$PdCl_2$	96	86
3	$PdCl_2$–5LiCl	8.5	93
4	$PdCl_2(PPh_3)_2$	144	–[b]
5	$Pd(OAc)_2$	24	64
6	$Pd(dba)_2$	35	43

[a] The reaction was monitored by TLC on silica gel. [b] 1b was completely recovered.

the divalent palladium was regenerated by dehalopalladation.[14] Thus, it occurred to us that it might be possible to form α-methylene-γ-butyrolactones from molecules that incorporate both a carbon–carbon triple bond and an allylic halide. In a preliminary communication, we have reported the bis(benzonitrile)palladium dihalide catalyzed cyclization of 4′-halo-2′-alkenyl 2-alkynoates to form α-(Z)-(halomethylene)-γ-butyrolactone derivatives stereoselectively.[15] In this paper, we describe this reaction in detail and report a more efficient procedure than the original one.

Results and Discussion

Effect of Solvent. Table I shows the results of cyclization of 4′-bromo-2′(E)-butenyl 2-propynoate (1a) under the catalysis of bis(benzonitrile)palladium dibromide in different solvents. The most suitable solvent is acetic acid in which this reaction finished within 1 h to give α-(bromomethylene)-β-vinyl-γ-butyrolactone (2a) in good yield. GC–MS analysis showed two peaks with the same molecular ionic peak, indicating that 2a was a mixture of two geometrical isomers referred to the exocyclic double bond. The ^1H NMR spectra showed signals at δ 7.60 and 6.80 ppm with a ratio of 3:97. The configuration of the exocyclic double bond in the main isomer was determined to be Z on the basis of the literature data that higher field chemical shift was assigned for the Z isomer.[16]

Effect of Catalysts. Several palladium complexes were tried for the cyclization of 4′-chloro-2′(E)-butenyl 2-propynoate (1b) (Table II). Palladium dichloride catalyzed this reaction slowly (Table II, entry 2), probably due to its low solubility in acetic acid. However, when 25% of lithium chloride was added, the reaction was faster (Table II, entry 3). Strangely, bis(triphenylphosphine)-palladium dichloride did not catalyze this conversion (Table II, entry 4).

Cyclization of 4′-Halo-2′-alkenyl 2-Alkynoates (1). The results of the cyclization reaction using bis(benzonitrile)palladium dihalide as the catalyst (method A) are shown in Table III. 4′-Halo-2′-butenyl 2-propynoates gave the α-(Z)-(halomethylene)-β-vinyl-γ-butyrolactones stereoselectively, while with substituted 2-alkynoates the reaction was slower with poor stereoselectivity.

In the case of 4′-iodo-2′(E)-butenyl 2-propynoate (1d), 1 equiv of lithium iodide was added to dissolve the insoluble palladium diiodide, and the reaction was carried out at 20–60 °C. In addition to lactone 2d, another product characterized as 4′-iodo-2′-butenyl 3(Z)-iodopropenoate (3) was isolated. In the absence of PdI_2, the reaction of lithium iodide with 1d in acetic acid at 60 °C afforded 4′-acetoxy-2′-butenyl 3(Z)-iodopropenoate (4) exclusively in 67% yield,[17] indicating that 3 might be formed by the nucleophilic addition of lithium iodide to the electron-deficient carbon–carbon triple bond in 1d.[18]

Using method A, it can be seen that with different halogen atom in the allylic moiety in 2-alkynoates (1), different palladium dihalides were desired. Thus, it occurred to us that it would be more convenient to use the same palladium(II) complex in combination with different halide salts as the catalysts. Since it has been found that the reaction of 1b catalyzed by $Pd(OAc)_2$ afforded 2b in 64% yield in 24 h, without any α-(acetoxymethylene)-β-vinyl-γ-butyrolactone (5) being detected (Table II, entry 5), $Pd(OAc)_2$ was chosen to meet this requirement. Addition of the less soluble sodium chloride as the halogen source catalyzed 1b to 2b in 86% yield in 10 h, while when lithium chloride was added, the reaction became homogeneous immediately and finished within 1 h with quantitative yield. The results using $Pd(OAc)_2$–LiX as the catalyst are shown in Table III (method B). Comparison of the results of methods A and B in Table III shows that both the reaction rate and yield of cyclization are greatly improved by using method B.

From Table III, it can also be seen that the configuration of the allylic double bond does not influence the reaction (compare entries 2 and 3). With the tetrasubstituted allylic double bond in 1e, both methods A and B gave the cyclized product in poor yield.

Stereoselectivity. The exocyclic double bonds were formed highly stereoselectively with the unsubstituted 2-alkynoates (1), while with substituents on the carbon–carbon triple bond, both methods A and B afforded 2 with low stereoselectivity. When more lithium halide was added, the stereoselectivity improved (compare methods A and B of entry 6 in Table III). The effect of lithium halide on the stereoselectivity was demonstrated by the cyclization of 1g as shown in Table IV. The reaction occurred highly stereoselectively in the presence of 4 equiv of lithium bromide. This may be due to the fact that addition of lithium halide favors the trans halopalladation.[14,19]

Mechanism. The present reaction might occur through a mechanism similar to that of the codimerization of acetylenes and allylic halides proposed by Kaneda et al.[14] This would involve an intramolecular insertion of the allylic carbon–carbon double bond into the carbon–palladium bond in the vinylpalladium intermediate formed by the halopalladation of the carbon–carbon triple bond, followed by dehalopalladation to yield α-methylene-γ-butyrolactone derivatives 2 and the catalytically active divalent palladium species (Scheme I).

Using 5 mol % of $PdCl_2(PhCN)_2$ as the catalyst, the cyclization of 1a afforded 2a in 70% yield while when 50 mol % of $PdCl_2(PhCN)_2$ was used, both 2a and 2b were isolated in 35% and 19% yields, respectively. This fact illustrates that the bromine atom comes from the allylic bromine atom in 1a, i.e., as soon as the reaction is initiated, the palladium bromide species formed during the reaction plays the main role and enters the catalytic cycle together

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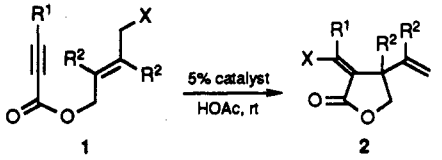
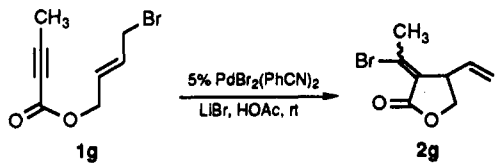
Table III. Cyclization of 4'-Halo-2'-butenyl 2-Alkynoates (1)



	1[a]				method A[b]			method B[c]		
entry	R^1	R^2	X	2	time	yield (%)	Z/E[d]	time	yield (%)	Z/E[d]
1	H	H	Br (1a)	2a	3 h	86	97/3	1 h	98	97/3
2	H	H	Cl (1b[e])	2b	1 h	81	>97/3	1 h	100	>97/3
3	H	H	Cl (1c)	2c = 2b	1 h	75	>97/3	1 h	100	>97/3
4	H	H	I (1d)	2d	6 d	53	88/12[e]	6 d	24	97/3[f]
5	H	Me	Br (1e)	2e	6 d	<5		9 d	<5	
6	n-C_5H_{11}	H	Br (1f)	2f	24 h	71	55/45	1 h	88	87/13[g]
7	Me	H	Br (1g)	2g	30 h	56	56/44[h]	24 h	75	58/42
8	Ph	H	Br (1h)	2h	9 d	36	40/60[i]	23 h	86	67/33[j]

[a] The allylic double bonds in 1 are in the E configuration except in 1b, which is in the Z configuration. [b] Method A: $PdX_2(PhCN)_2$(5%), HOAc (0.2 M), rt. [c] Method B: $Pd(OAc)_2$ (5%), LiX (25%), HOAc (0.2 M), rt. [d] The ratios of Z/E isomer referred to the exo double bond determined by 90-MHz ^1H NMR spectra, except in 2f, 2g, and 2h, in which the two isomers were isolated by preparative TLC on silica gel. [e] Besides 2d, 3 was isolated in 31% yield. [f] PdI_2 + LiI was added as catalyst; 64% of 1d was recovered. [g] One equivalent of LiBr was added. [h] 12% of 1g was recovered. [i] 50% of 1h was recovered. [j] Four equivalents of LiBr was added.

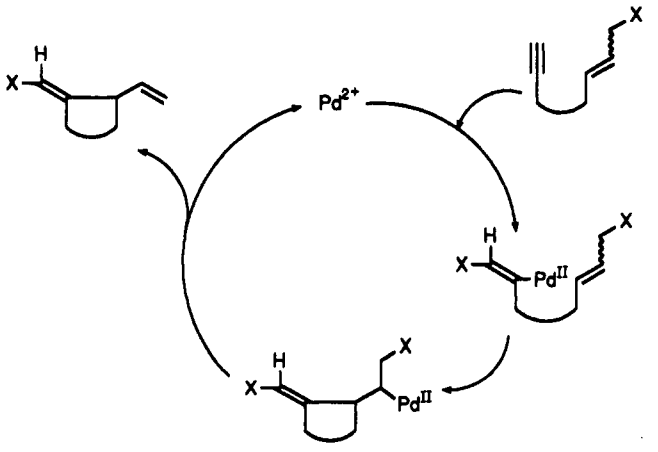
Table IV. Effect of the Amount of Lithium Halide on the Stereoselectivity of the Exocyclic Carbon–Carbon Double Bond in 2g



entry	lithium bromide added[a] (equiv)	reaction time (h)	yield (%)	Z/E
1	0.5	6	68	78/22
2	2	2	82	89/11
3	4	1	82	>95/5

[a] Based on 1g.

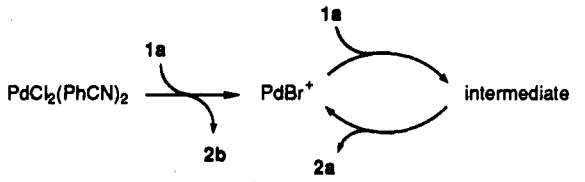
Scheme I



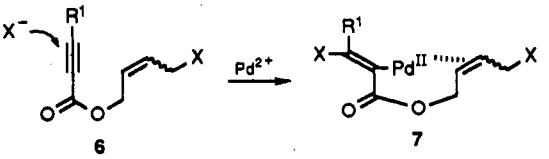
with the minute amount of the orginally added palladium dichloride to complete the catalytic process. When only 5% of $PdCl_2(PhCN)_2$ was used, no 2b could be isolated (Scheme II).

Halopalladation of unsaturated carbon–carbon bonds has been extensively studied.[19] The addition of lithium halide and use of polar solvents usually favor trans halopalladation,[14,19] which is in accordance with the results shown in Tables III and IV. But in our case, even the sluggish reaction in benzene afforded the trans halopalladation product 2a stereoselectively (Table I, entry 1), indicating that the high stereoselectivity might also be attributed to another factor. Thus, coordination of palladium with the carbon–carbon multiple bonds in 1 to form a palladium–enyne complex is suggested. Similar complexes such as palladium–diynes or –dienes appear in several publications.[20] The formation of a palladium–enyne complex favors the attack of halide anion from outside of the coordination sphere, which would be expected to give trans halopalladation.[19,21] The fact that bis(triphenylphosphine)palladium dichloride failed to catalyze this cyclization (Table II, entry 4) is probably due to the stronger coordination ability of triphenylphosphine compared to that of benzonitrile. Thus, the formation of a palladium–enyne complex is crucial to this reaction.

Scheme II



The stereochemistry of the exocyclic carbon–carbon double bond and the formation of the five-membered ring 2 as the sole product showed that the halopalladation process is both highly stereo- (trans) and regioselective. The ester group directed the palladium to the α-carbon of the alkynoates,[14] which led to the five-membered ring instead of a six-membered ring (eq 2).



(2)

Regioselective exo intramolecular insertion of the allylic carbon–carbon double bond to the carbon–palladium bond in 7 formed a new palladium intermediate 8, which afforded 2 through dehalopalladation. The possibility of

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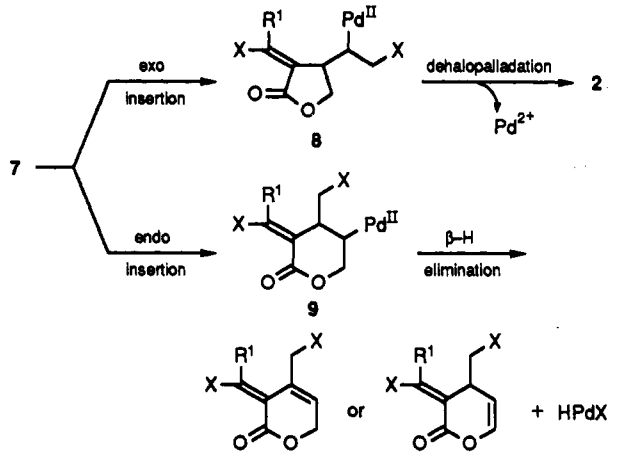
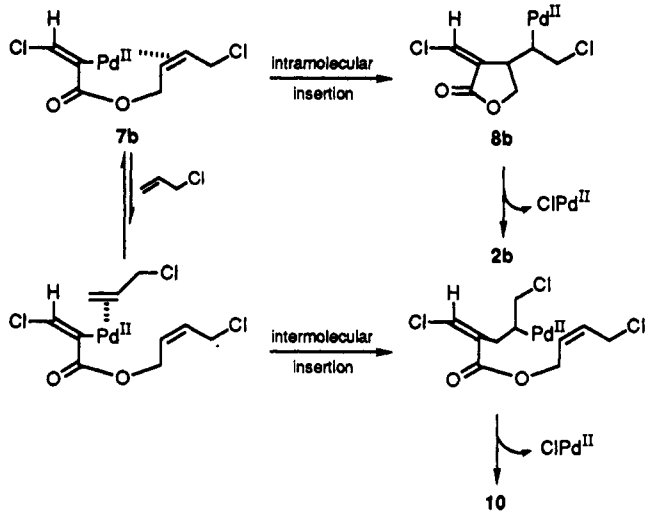
Scheme III

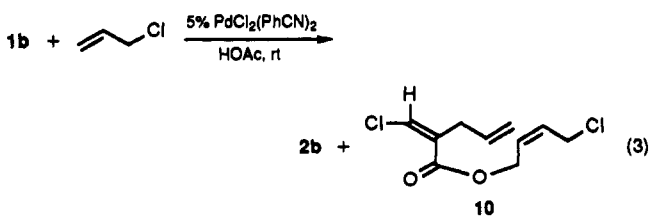


Scheme IV



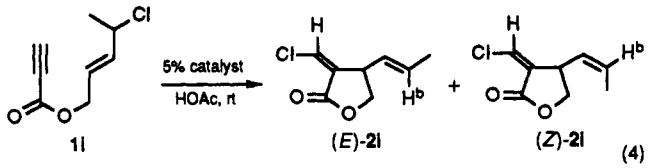
dehalopalladation might also be one of the factors controlling the direction of insertion. The endo insertion would form a six-membered intermediate **9**, including a carbon–palladium bond incapable of dehalopalladation (Scheme III), thus, a catalytic cycle could not be formed.

When the $PdCl_2(PhCN)_2$-catalyzed cyclization of **1b** was carried out in the presence of 1.2 equiv of allylic chloride, **2b** was still isolated as the sole product, indicating that the regioselective intramolecular insertion of the allylic carbon–carbon double bond into the carbon–palladium bond in **7b** is favored due to the entropy effect (Scheme IV). Only when 14 or 24 equiv of allyl chloride were added, the intermolecular insertion product **10** was isolated (19 and 37%, respectively) along with the main product **2b** (eq 3).



(3)

The stereochemistry of dehalopalladation was studied by the cyclization of 4′-chloro-2′(*E*)-pentenyl 2-propynoate (**1i**). Irradition of the signal at δ 1.75 ppm (methyl protons) of the product **2i** led to the observation of two groups of H^b with coupling constants of 10.0 and 14.0 Hz, respectively, implying that the product **2i** was a mixture of two geometrical isomers referred to the propenyl carbon–carbon double bond, the ratio of which was determined by 200-MHz ^1H NMR spectra (eq 4). The results indicate that the dehalopalladation is nonstereospecific and tends to favor the formation of a carbon–carbon double bond in the *E* configuration.



(4)

catalyst	yield (%)	*E*/*Z* ratio
$PdCl_2(PhCN)_2$	42	78:22
$Pd(OAc)_2$-5LiCl	95	67:33

Experimental Section

GC–MS spectra were taken on a 5% XE-60 column (3 m × 0.3 mm, 100–200 °C (5 °C/min)).

Materials. The catalysts $PdCl_2(PhCN)_2$,[22] $PdBr_2$,[23] $PdBr_2(PhCN)_2$,[22] PdI_2,[24] $PdCl_2(PPh_3)_2$,[25] $Pd(OAc)_2$,[26] and $Pd(dba)_2$[27] were prepared according to the literature methods. (*E*)-2-Butenyl 1,4-dibromide,[28] (*E*)- or (*Z*)-2-butenyl 1,4-dichloride,[29] 2,3-dimethyl-2-butenyl dibromide,[30] 2-propynoic acid,[31] 2-butynoic acid,[32] phenyl 2-propynoic acid, and 2-octynoic acid[33] were also prepared from the literature methods.

Synthesis of 2-Alkynoates. Typical Procedure: 4′-Bromo-2′(*E*)-butenyl 2-Propynoate (1a). To a solution of 2-propynoic acid (3.50 g, 50 mmol) in DMF (25 mL) was added in portions powdered $NaHCO_3$ (8.40 g, 100 mmol). After an additional stirring at rt for 0.5 h, 2(*E*)-butenyl 1,4-dibromide (16.00 g, 75 mmol) was added. The reaction was stirred at rt for 24 h. Water (25 mL) was then added, and the mixture was extracted with ether (3 × 25 mL). The extracts were dried over $MgSO_4$, and the product **1a** was purified by chromatography on silca gel using petroleum ether/ethyl acetate (10:1) as the eluent; yield 4.0 g (39%). The analytic sample was further purified by Kugelrohr distillation at ot 86–88 °C (2 mmHg): IR (neat) 3300, 2100, 1710, 1210, 985 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5.90 (m, 2 H), 4.60 (d, J = 4.4 Hz, 2 H), 3.85 (d, J = 6.0 Hz, 2 H), 2.80 (s, 1 H); MS *m*/*e* (%) 135 ($M^+(^{81}Br)$ – C_3HO_2, 5.82), 133 ($M^+(^{79}Br)$ – C_3HO_2, 5.76), 123 (M^+ – Br, 100.0). Anal. Calcd for $C_7H_7BrO_2$: C, 41.41; H, 3.47. Found: C, 40.87; H, 3.40.

The following compounds were prepared similarly. Unless otherwise stated, the solvent used was DMF.

4′-Chloro-2′(*Z*)-butenyl 2-propynoate (1b): yield 3.76 g (47%); ot 74–76 °C (1.8 mmHg); IR (neat) 3300, 2100, 1710, 1210 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 5.83 (m, 2 H), 4.77 (d, J = 4.7 Hz, 2 H), 4.10 (d, J = 7.2 Hz, 2 H), 2.93 (s, 1 H); MS *m*/*e* (%) 161 ($M^+(^{37}Cl)$ + 1, 0.18), 159 ($M^+(^{35}Cl)$ + 1, 0.57), 158 ($M^+(^{35}Cl)$, 0.01), 123 (M^+ – Cl, 36.79), 54 ($C_3H_2O^+$, 100.00). Anal. Calcd for $C_7H_7ClO_2$: C, 53.02; H, 4.45. Found: C, 52.51; H, 4.35.

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4'-Chloro-2'(*E*)-butenyl 2-propynoate (1c): yield 1.00 g (44%); ot 76–78 °C (1.8 mmHg); IR (neat) 3300, 2100, 1710, 1210, 985 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5.90 (m, 2 H), 4.65 (m, 2 H), 4.00 (d, J = 5.0 Hz, 2 H), 2.80 (s, 1 H); MS m/e (%) 161 ($M^+(^{37}Cl)$ + 1, 0.32), 160 ($M^+(^{37}Cl)$, 0.14), 159 ($M^+(^{35}Cl)$ + 1, 0.37), 158 ($M^+(^{35}Cl)$, 0.10), 123 (M^+ – Cl, 100.00). Anal. Calcd for $C_7H_7ClO_2$: C, 53.02; H, 4.45. Found: C, 52.61; H, 4.40.

4'-Bromo-2',3'-dimethyl-2'-butenyl 2-propynoate (1e): yield 1.46 g (44%); ot 85–87 °C (2 mmHg); IR (neat) 3300, 2100, 1710, 1210 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 4.60 (m, 2 H), 3.95 (d, J = 6.6 Hz, 2 H), 2.73 (s, 1 H), 1.80 (s, 6 H); MS m/e (%) 233 ($M^+(^{81}Br)$ + 1, 0.49), 231 ($M^+(^{79}Br)$ + 1, 0.61), 163 ($M^+(^{81}Br)$ – C_3HO_2, 4.34), 161 ($M^+(^{79}Br)$ – C_3HO_2, 4.62), 152 (M^+ + 1 – Br, 3.88), 151 (M^+ – Br, 46.52), 53 (C_3HO^+, 100.00). Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80. Found: C, 46.49; H, 4.74.

4'-Bromo-2'(*E*)-butenyl 2-octynoate (1f): yield 1.55 g (40%); ot 138–140 °C (0.50 mmHg); IR (neat) 2200, 1705, 1220, 1090, 985 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5.90 (m, 2 H), 4.55 (d, J = 4.0 Hz, 2 H), 3.85 (d, J = 6.0 Hz, 2 H), 2.25 (m, 2 H), 1.40 (m, 6 H), 0.90 (t, 3 H); MS m/e (%) 135 ($M^+(^{81}Br)$ – $C_8H_{11}O_2$, 13.81), 133 ($M^+(^{79}Br)$ – $C_8H_{11}O_2$, 9.31), 123 (M^+ + 1 – Br – C_5H_{11}, 13.81), 53 (C_3HO^+, 100.00). Anal. Calcd for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27. Found: C, 52.32; H, 6.28.

4'-Bromo-2'(*E*)-butenyl 2-butynoate (1g): yield 2.95 g (56%); ot 88–90 °C (1 mmHg); IR (neat) 2225, 1705, 1250, 1090, 985 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5.93 (m, 2 H), 4.60 (m, 2 H), 3.93 (m, 2 H), 2.00 (s, 3 H); MS m/e (%) 219 ($M^+(^{81}Br)$ + 1, 6.46), 217 ($M^+(^{79}Br)$ + 1, 5.96), 151 (M^+ – C_4H_3O, 8.44), 138 (58.28), 137 (11.53), 135 (0.07), 133 (9.60), 68 ($C_4H_4O^+$, 100.00). Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18. Found: C, 44.30; H, 4.36.

4'-Bromo-2'(*E*)-butenyl 3-phenyl-2-propynoate (1h): solvent HMPA; yield 1.50 g (39%); ot 146–148 °C (3 mmHg); IR (neat) 2200, 1705, 1290, 1190, 985, 780 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.40 (m, 5 H), 5.93 (m, 2 H), 4.66 (m, 2 H), 3.90 (m, 2 H); MS m/e (%) 281 ($M^+(^{81}Br)$ + 1, 2.99), 280 ($M^+(^{81}Br)$, 0.49), 279 ($M^+(^{79}Br)$ + 1, 3.36), 278 ($M^+(^{79}Br)$, 0.23), 200 (M^+ + 1 – Br, 72.72), 199 (M^+ – Br, 24.10), 131 (22.05), 130 (M^+ + 1 – OC_4H_6Br, 100.00), 101 (M^+ – C_4H_6Br – CO_2, 6.59). Anal. Calcd for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97. Found: C, 55.81; H, 3.93.

4'-Chloro-2'(*E*)-pentenyl 2-propynoate (1i): solvent HMPA; yield 0.37 g (10%); ot 80–82 °C (4 mmHg); IR (neat) 3300, 2100, 1705, 1150, 985 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5.80 (m, 2 H), 4.65 (m, 2 H), 4.50 (m, 1 H), 2.80 (m, 1 H), 1.27 (d, 3 H); MS m/e (%) 175 ($M^+(^{37}Cl)$ + 1, 1.37), 174 ($M^+(^{37}Cl)$, 0.71), 173 ($M^+(^{35}Cl)$ + 1, 3.50), 172 ($M^+(^{35}Cl)$, 1.09), 53 (100.00). Anal. Calcd for $C_8H_9ClO_2$: C, 55.67; H, 5.26. Found: C, 55.05; H, 5.41.

4'-Iodo-2'(*E*)-butenyl 2-Propynoate (1d). A mixture of 4'-chloro-2'(*E*)-butenyl 2-propynoate (1c) (300 mg, 1.89 mmol) anhydrous $ZnCl_2$ (100 mg, 0.74 mmol), and anhydrous NaI (570 mg, 3.80 mmol) in CS_2 (2 mL) was stirred at rt for 11 h. After filtration and removal of the solvent, the pure product **1d** was obtained via chromatography on silica gel and distillation: yield 0.42 g (89%); ot 117–120 °C (1.5 mmHg); IR (neat) 3300, 2100, 1710, 1210, 980 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5.80 (m, 2 H), 4.75 (d, J = 5.2 Hz, 2 H), 4.10 (d, J = 7.0 Hz, 2 H), 2.85 (s, 1 H); MS m/e (%) 251 (M^+ + 1, 91.00), 250 (M^+, 5.46), 181 (M^+ – C_3HO_2, 100.00). Anal. Calcd for $C_7H_7IO_2$: C, 33.63; H, 2.82. Found: C, 33.00; H, 2.58.

Effect of Solvent. General Procedure. To a solution of $PdBr_2(PhCN)_2$ (6 mg, 0.0125 mmol) in a solvent (0.5 mL) was added **1a** (0.25 mmol) dropwise at room temperature with monitoring by TLC on silca gel. After the reaction was over, the reaction mixture was submitted to preparative TLC on silca gel (eluent: petroleum ether/ethyl acetate, 10:1) to give the product **2a** (Table I).

Effect of Catalyst. General Procedure. To a solution of **1b** (0.5 mmol) in HOAc (2.5 mL), LiCl or NaCl (if needed) and the catalyst (0.025 mmol) were added subsequently. After the reaction was over, ether (30 mL) was added. The mixture was then washed with water (3 × 5 mL), saturated $NaHCO_3$ (3 × 5 mL) solution, and saturated NaCl (5 mL) solution and dried ($MgSO_4$). Preparative TLC on silica gel (eluent: petroleum ether/ethyl acetate, 10:1) afforded the product **2b** in pure form (Table II).

Cyclization of 4'-Halo-2'-butenyl 2-Alkynoates (1). Typical Procedure: Method A. To a solution of **1a** (100 mg, 0.50 mmol) in HOAc (2.5 mL) was added bis(benzonitrile)palladium dibromide (13 mg, 0.025 mmol) with stirring. After the reaction was carried out at rt for 3 h as monitored by TLC, ether (30 mL) was added. The mixture was then washed with water (3 × 5 mL), saturated $NaHCO_3$ (3 × 5 mL) solution, and saturated NaCl (5 mL) solution subsequently and dried ($MgSO_4$). Preparative TLC on silca gel (eluent: petroleum ether/ethyl acetate, 10:1) afforded the product **2a** in pure form.

Method B. To a solution of **1a** (100 mg, 0.50 mmol) in HOAc (2.5 mL) and LiBr (10 mg, 0.13 mmol) was added $Pd(OAc)_2$ (5 mg, 0.025 mmol) with stirring. The reaction was carried out at rt for 1 h (monitored by TLC). Similar workup as in method A gave product **2a**.

The following compounds were prepared using both methods (Table III). The spectra data of compounds **2a**, **2b**, **2d**, and **2f** were recorded in ref 15.

α-(Bromomethylene)-β-vinyl-γ-butyrolactone (2a): ot 132–134 °C (2 mmHg). Anal. Calcd for $C_7H_7BrO_2$: C, 41.41; H, 3.47. Found: C, 41.55; H, 3.41.

α-(Chloromethylene)-β-vinyl-γ-butyrolactone (2b): ot 96–98 °C (3 mmHg). Anal. Calcd for $C_7H_7ClO_2$: C, 53.02; H, 4.45. Found: C, 52.88; H, 4.71.

α-(Iodomethylene)-β-vinyl-γ-butyrolactone (2d): HRMS calcd for $C_7H_7IO_2$ 249.9489, found 249.9486.

4'-Iodo-2'-butenyl (*Z*)-3-iodopropenoate (3): ot 160–165 °C (6 mmHg); IR (neat) 1710, 1600, 1190, 1160, 980 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 7.55 (d, J = 8.6 Hz, 1 H), 6.90 (d, J = 8.6 Hz, 1 H), 5.90 (m, 2 H), 4.75 (m, 2 H), 4.10 (m, 2 H); MS m/e (%) 378 (M^+, 0.54), 377 (M^+ – 1, 0.51), 376 (11.56), 306 (M^+ – $C_3H_4O_2$, 12.35), 252 (M^+ + 1 – I, 4.12), 251 (M^+ – I, 72.74), 181 (M^+ – I – $C_3H_2O_2$, 100.00). Anal. Calcd for $C_7H_8I_2O_2$: C, 22.25; H, 2.13. Found: C, 23.75; H, 2.17 (this compound is readily decomposed).

α-(1'-Bromohexylidene)-β-vinyl-γ-butyrolactone (2f). *Z* isomer: ot 170–172 °C (0.5 mmHg); HRMS calcd 272.0412 (^{79}Br), 274.0392 (^{81}Br), found 272.0441 (^{79}Br), 274.0392 (^{81}Br). Anal. Calcd for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27. Found: C, 53.28; H, 7.00.

E isomer: ot 140–142 °C (1 mmHg). Anal. Calcd for $C_{12}H_{17}BrO_2$: C, 52.76; H, 6.27. Found: C, 52.59; H, 5.92.

α-(1'-Bromoethylidene)-β-vinyl-γ-butyrolactone (2g). *Z* isomer: ot 154–156 °C (3.5 mmHg); IR (neat) 1760, 1640, 1210, 1130 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.00–5.60 (m, 1 H, =CH), 5.26–5.00 (m, 2 H, $=CH_2$), 4.34 (dd, J = 7.6 Hz, J = 7.7 Hz, 1 H, OCH), 4.02 (dd, J = 7.6 Hz, J = 2.6 Hz, 1 H, OCH), 3.78 (m, J = 7.7 Hz, 1 H, OCCH), 2.48 (d, 3 H, CH_3); MS m/e (%) 220 (8.62), 219 ($M^+(^{81}Br)$ + 1, 70.92), 218 ($M^+(^{81}Br)$, 18.09), 217 ($M^+(^{79}Br)$ + 1, 70.99), 216 ($M^+(^{79}Br)$, 11.52), 200 (10.32), 198 (10.05), 137 (M^+ – Br, 20.43), 107 (M^+ – Br – OCH_2, 49.72), 93 (20.32), 91 (24.04), 79 (100.00), 77 (47.16); HRMS calcd 215.9786 (^{79}Br), 217.9766 (^{81}Br), found 215.9778 (^{79}Br), 217.9779 (^{81}Br). Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18. Found: C, 44.76; H, 4.27.

E isomer: ot 140–142 °C (3.5 mmHg); IR (neat) 1750, 1620, 1215, 1135 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.00–5.60 (m, 1 H, =CH), 5.30–5.00 (m, 2 H, $=CH_2$), 4.38 (dd, J = 7.6 Hz, J = 7.7 Hz, 1 H, OCH), 4.12 (dd, J = 7.6 Hz, J = 2.6 Hz, 1 H, OCH), 3.79 (m, J = 7.6 Hz, 1 H, OCCH), 2.86 (d, 3 H, CH_3); MS m/e (%) 220 (1.05), 219 ($M^+(^{81}Br)$ + 1, 10.78), 218 ($M^+(^{81}Br)$, 10.45), 217 ($M^+(^{79}Br)$ + 1, 11.58), 216 ($M^+(^{79}Br)$, 10.58), 200 (14.42), 198 (15.31), 137 (M^+ – Br, 69.95), 107 (M^+ – Br – OCH_2, 38.25), 93 (21.23), 92 (10.50), 91 (64.57), 79 (100.00), 77 (96.19). Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18. Found: C, 44.53; H, 4.20.

α-(1'-Bromobenzylidene)-β-vinyl-γ-butyrolactone (2h). *Z* isomer: mp 78–80 °C; IR (KCl) 1760, 1645, 1200, 1100 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.37 (s, 5 H, Ph), 5.86–5.44 (m, 1 H, =CH), 5.04–4.68 (m, 2 H, $=CH_2$), 4.34 (dd, J = 7.6 Hz, J = 7.7 Hz, 1 H, OCH), 4.02 (dd, J = 7.6 Hz, J = 2.6 Hz, 1 H, OCH), 3.74 (m, J = 7.6 Hz, 1 H, OCCH); MS m/e (%) 282 (7.58), 281 ($M^+(^{81}Br)$ + 1, 49.83), 280 ($M^+(^{81}Br)$, 23.48), 279 ($M^+(^{79}Br)$ + 1, 58.43), 278 ($M^+(^{79}Br)$, 17.43), 276 ($M^+(^{79}Br)$ – 2, 8.23), 263 ($M^+(^{81}Br)$ – OH, 2.77), 261 ($M^+(^{79}Br)$ – OH, 2.75), 250 ($M^+(^{81}Br)$ – OCH_2, 2.47), 248 ($M^+(^{79}Br)$ – OCH_2, 4.42), 247 (3.23), 199 (M^+ – Br, 21.61), 155 (M^+ – Br – CO_2, 100.00), 154 (39.52), 153 (32.22), 152 (13.07), 142 (18.30), 141 (M^+ – Br – CO_2 – CH_2, 87.57), 129 (M^+ – Br – CO_2 – C_2H_2, 19.65), 128 (M^+ – Br – CO_2 – C_2H_3, 23.87), 127 (12.00), 115 (M^+ – Br – CO_2 – C_3H_4, 72.78); HRMS calcd

277.9942 (^{79}Br), 279.9922 (^{81}Br), found 277.9918 (^{79}Br), 279.9886 (^{81}Br). Anal. Calcd for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97. Found: C, 55.32; H, 3.77.

E isomer: mp 70–72 °C; IR (KCl) 1760, 1640, 1220, 1200, 1100 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.37 (m, 5 H, Ph), 6.16–5.72 (m, 1 H, =CH), 5.44–5.20 (m, 2 H, =CH_2), 4.50 (dd, J = 7.6 Hz, J = 7.7 Hz, 1 H, OCH), 4.20 (d, J = 7.6 Hz, J = 2.6 Hz, 1 H, OCH), 3.96 (m, J = 7.6 Hz, 1 H, OCCH); MS *m/e* (%) 282 (1.10), 281 (M^+(^{81}Br) + 1, 11.44), 280 (M^+(^{81}Br), 53.35), 279 (M^+(^{79}Br) + 1, 17.88), 278 (M^+(^{79}Br), 53.35), 277 (M^+(^{79}Br) − 1, 7.88), 199 (M^+ − Br, 19.60), 155 (M^+ − Br − CO_2, 100.00), 141 (M^+ − Br − CO_2 − CH_2, 95.91), 129 (M^+ − Br − CO_2 − C_2H_2, 21.27), 128 (22.32), 127 (16.40), 115 (M^+ − Br − CO_2 − C_3H_4, 76.77). Anal. Calcd for $C_{13}H_{11}BrO_2$: C, 55.94; H, 3.97. Found: C, 55.52; H, 3.78.

α-(Chloromethylene)-β-(1′-propenyl)-γ-butyrolactone (2i): ot 120–122 °C (8 mmHg); IR (neat) 1760, 1620, 1090 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.55, 6.49 (d, J = 2.8 Hz, 1 H, =CHCl), 5.94–5.60 (m, 1 H, =CH), 5.34 (m, 1 H, =CH), 4.45 (t, J = 8.0 Hz, 1 H, OCH), 4.18, 3.80 (m, J = 8.0 Hz, J = 2.8 Hz, 1 H, OCCH), 3.95 (t, J = 8.0 Hz, 1 H, OCH), 1.75 (m, 3 H, CH_3); MS *m/e* (%) 176 (3.16), 175 (M^+(^{37}Cl) + 1, 27.39), 174 (M^+(^{37}Cl), 4.05), 173 (M^+(^{35}Cl) + 1, 73.79), 172 (M^+(^{35}Cl), 8.85), 157 (M^+(^{37}Cl) − OH, 3.56), 156 (1.19), 155 (M^+(^{35}Cl) − OH, 10.55), 145 (4.20), 144 (M^+(^{37}Cl) − OCH_2, 17.53), 143 (9.63), 142 (M^+(^{35}Cl) − OCH_2, 45.86), 137 (M^+ − Cl, 22.29), 131 (M^+(^{37}Cl) + 1 − CO_2, 1.36), 130 (M^+(^{37}Cl) − CO_2, 2.95), 129 (M^+(^{37}Cl) − 1 − CO_2, 5.87), 128 (M^+(^{35}Cl) − CO_2, 7.75), 127 (M^+(^{35}Cl) − 1 − CO_2, 14.72), 116 (M^+(^{37}Cl) − CO_2 − CH_2, 7.77), 115 (6.19), 114 (M^+(^{35}Cl) − CO_2 − CH_2, 20.86), 79 (100.00). Anal. Calcd for $C_5H_5ClO_2$: C, 55.67; H, 5.26. Found: C, 55.27; H, 5.40.

Cyclization of 4′-Chloro-2′(*E*)-butenyl 2-Propynoate (1b) in the Presence of Allyl Chloride. A mixture of **1b** (80 mg, 0.50 mmol), allyl chloride, and $PdCl_2(PhCN)_2$ (10 mg, 0.025 mmol) in acetic acid (2.5 mL) was stirred at room temperature. Workup as above afforded the products **2b** and **10** in pure form. Allyl chloride added, reaction time, and yields of **2b** and **10**, respectively, are as follows: 0.6 mmol, 3 h, 57%, 0%; 7 mmol, 21 h, 57%, 19%; 12 mmol, 24 h, 41%, 37% (22% of **1b** was recovered).

4′-Chloro-2′-butenyl 2-allyl-3-chloropropenoate (10): ot 95–97 °C (1.5 mmHg); IR (neat) 3080, 1710, 1620, 1600, 1200, 1110, 1100 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.42 (t, J = 1.4 Hz, 1 H), 5.82 (m, 3 H), 5.18 (m, 1 H), 5.10 (m, 1 H), 4.83 (d, J = 6.0 Hz, 2 H), 4.19 (d, J = 7.2 Hz, 2 H), 3.10 (m, J = 6.6 Hz, J = 1.4 Hz, 2 H); MS *m/e* (%) 235 (M^+(^{35}Cl) + 1, 0.06), 202 (M^+(^{37}Cl) + 1 − Cl, 2.59), 201 (M^+(^{37}Cl) − Cl, 21.92), 200 (M^+(^{35}Cl) − HCl, 10.33), 199 (M^+(^{35}Cl) − 2 − Cl, 79.32), 131 (M^+(^{37}Cl) − Cl − OC_4H_6, 28.84), 130 (7.99), 129 (M^+(^{35}Cl) − Cl − OC_4H_6, 95.26), 103 (M^+(^{37}Cl) − Cl − CO_2 − C_4H_6, 4.80), 102 (3.20), 101 (M^+(^{35}Cl) − Cl − CO_2 − C_4H_6, 10.27), 100 (3.96), 66 ($C_5H_6^+$, 27.23), 65 ($C_5H_5^+$, 100.00), 53 ($C_4H_5^+$, 85.20). Anal. Calcd for $C_{10}H_{12}Cl_2O_2$: C, 51.09; H, 5.14. Found: C, 51.67; H, 5.07.

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Registry No. **1a**, 129178-04-7; **1b**, 129178-00-3; **1c**, 129178-03-6; **1d**, 129178-05-8; **1e**, 129178-07-0; **1f**, 129178-06-9; **1g**, 134078-80-1; **1h**, 134078-81-2; **1i**, 134078-82-3; (*Z*)-**2a**, 129178-02-5; (*E*)-**2b**, 134078-83-4; (*Z*)-**2b**, 129178-01-4; (*E*)-**2d**, 129178-10-5; (*Z*)-**2d**, 129178-08-1; (*E*)-**2f**, 129178-11-6; (*Z*)-**2f**, 129178-09-2; (*E*)-**2g**, 134078-85-6; (*Z*)-**2g**, 134078-84-5; (*E*)-**2h**, 134078-87-8; (*F*)-**2h**, 134078-86-7; (*Z,E*)-**2i**, 134078-88-9; (*Z,Z*)-**2i**, 134078-89-0; **3**, 129178-13-8; **10**, 134078-90-3; $PdBr_2(PhCN)_2$, 15003-43-7; $PdCl_2(PhCN)_2$, 14220-64-5; $PdCl_2$, 7647-10-1; $PdCl_2(PPh_3)_2$, 13965-03-2; $Pd(OAc)_2$, 3375-31-3; $PdI_2(PhCN)_2$, 36234-35-2; PdI_2, 7790-38-7; 2-propynoic acid, 471-25-0; 2-octynoic acid, 5663-96-7; 2-butynoic acid, 590-93-2; 3-phenyl-2-propynoic acid, 637-44-5; (*E*)-1,4-dibromo-2-butene, 821-06-7; (*Z*)-1,4-dichloro-2-butene, 1476-11-5; (*E*)-1,4-dichloro-2-butene, 110-57-6; (*E*)-1,4-dibromo-2,3-dimethyl-2-butene, 6044-73-1; bis(dibenzylideneacetone)-palladium, 32005-36-0; (*E*)-1,4-dichloro-2-pentene, 53920-96-0.

Supplementary Material Available: ^{1}H NMR spectra for compounds **1a,b,d,i**, **2d**, **2f** (*Z* isomer), **2g** (*Z* isomer), **2h** (*Z* isomer), **3**, and **10** (10 pages). Ordering information is given on any current masthead page.

A New Approach to α,α-Difluoro-Functionalized Esters

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The addition reaction of iododifluoroacetates to alkenes is initiated by copper powder (10–20 mol %) at 50–60 °C. Both terminal and internal alkenes give good yields of adducts. The reaction is also applicable to alkenes containing a variety of functional groups, such as epoxy, hydroxy, ketone, ester, and phosphonate moieties. This reaction can be carried out either neat or in solvents such as hexane, benzene, acetonitrile, DMF, DMSO, and HMPA and is suppressed by *p*-dinitrobenzene and di-*tert*-butyl nitroxide. A single electron transfer initiated radical mechanism is proposed. In the presence of nickel dichloride hexahydrate, reduction of the adducts with zinc in moist THF provides the corresponding α,α-difluoro esters in good yields.

Introduction

The introduction of fluorine into an organic molecule causes dramatic change in biological activities.[1] The change is mainly due to the high electronegativity of fluorine, the strong carbon–fluorine bond, and increased lipid solubility. In recent years, fluorinated ketones have been widely employed as enzyme inhibitors.[2] Therefore, the synthesis of compounds containing a difluoromethylene group adjacent to a carbonyl group has attracted much attention.

The most widely utilized method for the introduction of such types of functionality has been the Reformatsky reaction using halodifluoroacetates[3] and halodifluoromethyl ketones.[4] More recently, difluoroketene silyl

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