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The Regioselective 1,4-Addition Reaction of Alkenylboronic Acids to $\alpha,\beta,\alpha',\beta'$-Unsaturated Ketones

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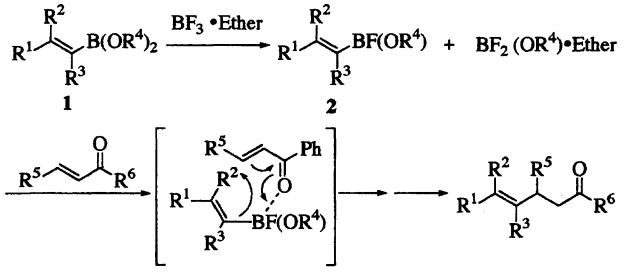
The effect of substituents on the double bond of α,β-unsaturated ketones for the 1,4-addition reaction rate of alkenylboronic acids induced by cyanuric fluoride was studied in detail. When the steric hindrance around the β-carbon of the unsaturated ketones increased, the 1,4-addition reaction rate significantly decreased. An alkyl substituent on the α-carbon was also found to significantly affect the 1,4-addition reaction. From these results, unsymmetric $\alpha,\beta,\alpha',\beta'$-unsaturated ketones (**10a—f**) were designed for the regioselective 1,4-addition reaction with alkenylboronic acids (**4a—j**). Since they have substituents to disturb the 1,4-addition reaction on only one double bond, the alkenylboronic acids reacted with them from only one side to selectively provide $\gamma,\delta,\alpha',\beta'$-unsaturated ketones (**11a—q**). Further transformations of the resulting $\gamma,\delta,\alpha',\beta'$-unsaturated ketones were also performed.

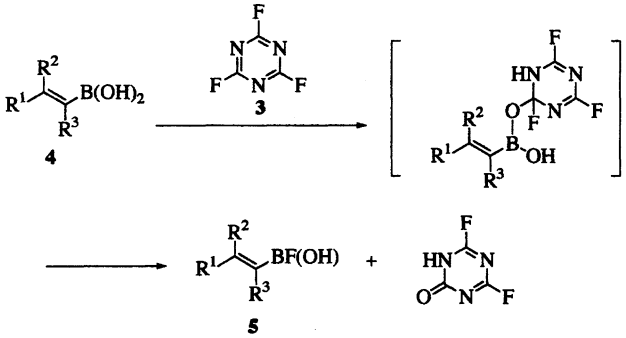
The 1,4-addition reaction of organometallic reagents to α,β-unsaturated carbonyl compounds is an effective method for carbon–carbon bond extension with the introduction of functional groups, and many organometallic reagents have been developed for this purpose.[1] Among them, organoboranes have an advantage over other organometallic reagents because they can be directly prepared from alkynes or alkenes by hydroboration or haloboration reactions.[2] Previously, we reported[3] that the 1,4-addition reaction of alkenyldialkoxyboranes (**1**) to α,β-unsaturated ketones could be induced by diethyl ether-boron trifluoride and the reactive specie of the reaction was alkenylfluoroalkoxyboranes (**2**) generated by disproportionation with diethyl ether–boron trifluoride. The fluorine substitution increased the Lewis acidity of the boron atom, and the 1,4-addition reaction proceeded through the coordination of the boron atom to the carbonyl oxygen (Scheme 1).

Though the diethyl ether–boron trifluoride could effectively activate the alkenyldialkoxyboranes **1**, its strong acidity could cause undesired side reactions. For the synthesis of the γ,δ-unsaturated ketones having acid sensitive functional groups, the introduction of the new reagent, which can activate the alkenylboronic acid derivatives as effectively as diethyl ether–boron trifluoride and under milder conditions, was necessary. Cyanuric fluoride (**3**) was known to convert the carboxylic acids to the corresponding acid fluorides under mild conditions.[4] However, the application of **3** for the activation of **1** was unsuccessful, and in the presence of **3** the 1,4-addition reaction of **1** to α,β-unsaturated ketones scarcely took place. On the other hand, the 1,4-addition reaction of the alkenylboronic acids (**4**) to α,β-unsaturated ketones was efficiently induced by **3**. Through the reactive species could not be isolated, the fluorination on boron of **4** might take place, since **3** converted the carboxylic acids to the acid fluorides and the generated reactive species (**5**) reacted with α,β-unsaturated ketones through the coordination of boron to the carbonyl oxygen (Scheme 2).

Since the cyanuric fluoride-induced 1,4-addition reaction proceeds under mild conditions, the introduction of functional groups onto the alkenylboranes and unsaturated ketones was possible; consequently, polyfunctionalized γ,δ-



Scheme 1.



Scheme 2.

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unsaturated ketones could be prepared by this method.[5] During the course of our study, we found that the 1,4-addition reaction rate of alkenylboronic acids to α,β-unsaturated ketones largely depends on the substituents on the unsaturated ketones. We now report on the effect of substituents on the 1,4-addition reaction of alkenylboronic acids to α,β-unsaturated ketones and the regioselective 1,4-addition reaction of alkenylboronic acids to unsymmetric $\alpha,\beta,\alpha',\beta'$-unsaturated ketones.

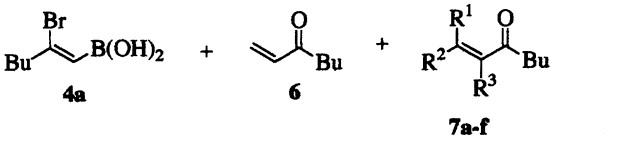
Results and Discussion

Crossover Reactions of Unsubstituted α,β-Unsaturated Ketone and Substituted α,β-Unsaturated Ketones with Alkenylboronic Acid. The crossover reactions of 1-hepten-3-one (**6**) and α,β-unsaturated ketones having substituents on the double bond (**7a—f**) with (Z)-(2-bromo-1-hexenyl)boronic acid (**4a**) were examined (Eq. 1). In the presence of cyanuric fluoride **3**, the reaction of **4a** with a mixture of **6** and 2-octen-4-one (**7a**) gave 1,4-addition products (**8** and **9a**) in the ratio of 63 : 37 (Entry 1 in Table 1). The products from **7** decreased in the reaction mixture as the steric hindrance around the β-carbon increased. When a *t*-butyl group (**7c**) or two methyl groups were attached on the β-carbon (**7d**), **8** could be exclusively obtained (Entries 3 and 4). The introduction of a substituent at the α-carbon is more effective in disturbing the 1,4-addition reaction and in the crossover reactions of **6** and **7f**, which have a methyl substituent at the α-carbon; therefore, **8** could be selectively obtained (Entry 6).

Table 1. Crossover Reaction of Unsaturated Ketones **6** and **7** with Alkenylboronic Acid **4a** Induced by Cyanuric Fluoride **3**

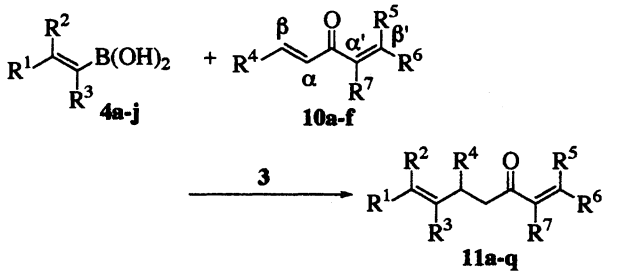
Entry	7	9	8	9[a]	Total yield/%[b]
1	**7a**	**9a**	63	37	81
2	**7b**	**9b**	88	12	76
3	**7c**	**9c**	100	0	73
4	**7d**	**9d**	100	0	79
5	**7e**	**9e**	77	23	82
6	**7f**	**9f**	95	5	77

a) Determined by GC. b) Isolated yield based on borane **4a**.



(1)

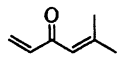
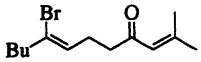
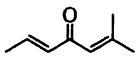
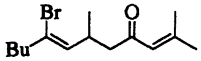
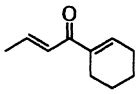
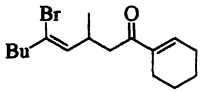
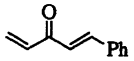
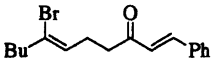
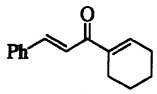
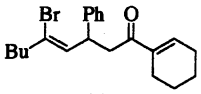
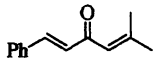
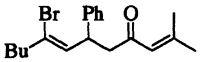
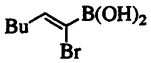
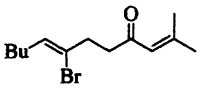
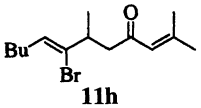
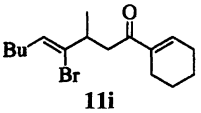
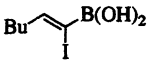
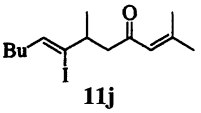
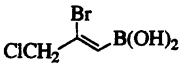
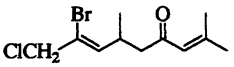
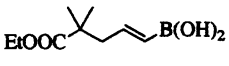
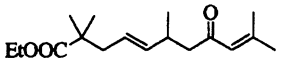
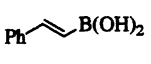
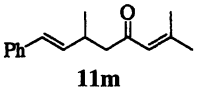
Regioselective 1,4-Addition Reaction of Alkenylboronic Acids to $\alpha,\beta,\alpha',\beta'$-Unsaturated Ketones. From the preceding results, unsymmetrically substituted $\alpha,\beta,\alpha',\beta'$-unsaturated ketones (**10a—f**) were designed for the regioselective 1,4-addition reaction with alkenylboronic acids. They have a hindered substituent or two methyl groups at the β' carbon or a substituent at the α' carbon to disturb the attack of alkenylboronic acids from the β'-position. There is no substituent at the α carbon and no substituent, or a relatively small substituent, at the β carbon of **10**, which does not disturb the 1,4-addition from the β-position. As expected, they selectively reacted with alkenylboronic acids (**4a—j**) at the β-position to give only one kind of 1,4-addition product (**11a—q**) (Eq. 2). Since the 1,4-addition reaction of alkenylboronic acids proceeds under mild conditions, the introduction of a variety of functional groups into the alkenylboronic acids and, consequently, the introduction of functionalized alkenyl groups at the β-position of $\alpha,\beta,\alpha',\beta'$-unsaturated ketones becomes possible (Table 2).



(2)

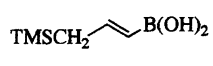
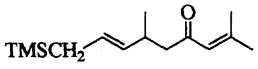
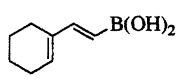
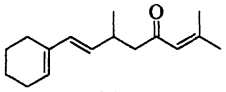
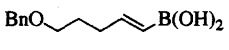
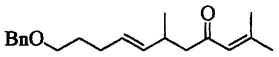
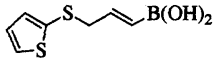
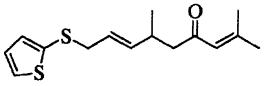
The Introduction of Nucleophiles at the β'-Position of $\gamma,\delta,\alpha',\beta'$-Unsaturated ketones. After the regioselective 1,4-addition reaction of **4** to $\alpha,\beta,\alpha',\beta'$-unsaturated ketones **10**, there remains an active α',β'-unsaturated carbonyl function in the products (**11a—q**), which can be used for further transformation by the 1,4-addition reaction with strong nucleophiles. For instance, the introduction of a cyano group at the β'-position of **11c** could be achieved by the Et_3Al-mediated 1,4-addition reaction of Me_3SiCN to give the β'-cyano-γ,δ-unsaturated ketone (**12**).[6] An alkynyl group was also introduced by the diethyl ether–boron trifluoride-mediated 1,4-addition reaction of 1-hexynyldiisopropoxyborane

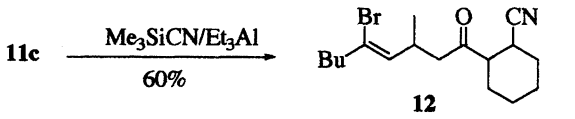
Table 2. Reaction of Alkenylboronic Acids with $\alpha,\beta,\alpha',\beta'$-Unsaturated Ketones[a)]

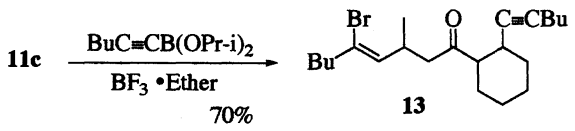
Boronic acids **4**	Ketone **10**	Products **11**	Reaction conditions	Yield/%[b)]
4a	 **10a**	 **11a**	40 °C 16 h	93
4a	 **10b**	 **11b**	40 °C 16 h	86
4a	 **10c**	 **11c**	40 °C 2 d	86
4a	 **10d**	 **11d**	40 °C 16 h	92
4a	 **10e**	 **11e**	40 °C 3 d	86
4a	 **10f**	 **11f**	40 °C 3 d	92
 **4b**	**10a**	 **11g**	40 °C 16 h	87
4b	**10b**	 **11h**	40 °C 2 d	85
4b	**10c**	 **11i**	40 °C 4 d	50
 **4c**	**10b**	 **11j**	40 °C 3 d	85
 **4d**	**10b**	 **11k**	40 °C 16 h	91
 **4e**	**10b**	 **11l**	40 °C 6 d	65
 **4f**	**10b**	 **11m**	40 °C 16 h	92

a) The reaction was carried out as described in text. b) Isolated yields based on **10** used.

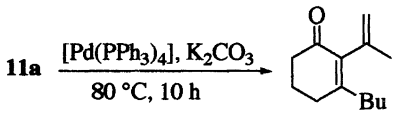
Table 2. (Continued)

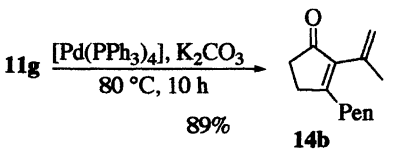
Boronic acids **4**	Ketone **10**	Products **11**	Reaction conditions	Yield/%[b]
 **4g**	**10b**	 **11n**	40 °C 2 d	68
 **4h**	**10b**	 **11o**	40 °C 2 d	89
 **4i**	**10b**	 **11p**	40 °C 5 d	58
 **4j**	**10b**	 **11q**	40 °C 6 d	87





Scheme 3.





Scheme 4.

to selectively give the β'-(1-hexynyl)-γ,δ-unsaturated ketone (**13**)[7] (Scheme 3). Now, the stepwise introductions of different nucleophiles into the β and β' positions of the $\alpha,\beta,\alpha',\beta'$-unsaturated ketones are possible.

Cyclization of $\gamma,\delta,\alpha',\beta'$-Unsaturated Ketones. (*Z*)-(2-Bromo-1-hexenyl)boronic acid (**4a**) and (*Z*)-(1-bromo-1-hexenyl)boronic acid (**4b**), prepared by the haloboration reaction of 1-hexyne and the hydroboration reaction of 1-bromo-1-hexyne, provided δ-bromo-$\gamma,\delta,\alpha',\beta'$-unsaturated ketones (**11a**) and γ-bromo-$\gamma,\delta,\alpha',\beta'$-unsaturated ketones (**11g**) by the reaction with **10a**, respectively. They cyclized under the internal Heck reaction conditions[8] to selectively give the cyclohexenone derivative (**14a**) and cyclopentenone derivative (**14b**) (Scheme 4).

Experimental

General: IR spectra were recorded on a Hitachi 260-30 Infrared Spectrometer in the form of a film. ^{1}H NMR spectra were obtained using a Hitachi R-90H FT spectrometer (90 MHz) or measured at the NMR Laboratory, Faculty of Engineering, Hokkaido University, using a Bruker NSL-400 Spectrometer (400 MHz) in $CDCl_3$ employing TMS as the internal standard. FAB- and EI-High-resolution mass spectra were measured on JEOL JMS-HX110 and JMS-DX303 respectively. Elemental micro analyses were taken by a Yanagimoto CHN Corder MT-5. GC analyses were performed on a Shimadzu Gas Chromatograph GC-14A equipped on a 25 m Silicon OV-1 capillary silica column. Cyanuric fluoride was supplied by Tohkem Products Co., Ltd. and used without purification. Since cyanuric fluoride is a highly toxic liquid (bp 74 °C), it should be used in a bench hood and kept in a refrigerator. Alkenylboronic acids **4a**—**j** were prepared from the corresponding alkynes using previously reported procedures.[3,9] α,β-Unsaturated ketones **6**, **7a**, **7d**, **7e**, and **7f** were prepared by the treatment of acrylaldehyde, crotonaldehyde, 3-methyl-2-butenal, cinnamaldehyde, or 2-methylpropenal with butyllithium, followed by oxidation of the resulting alcohols with PCC. Unsaturated ketones **7b**,**c** were prepared by aldol condensation of 2-hexanone with 2-methylpropanal or 2,2-dimethylpropanal, followed by dehydration of the resulting aldol products with methanesulfonyl chloride and Et_3N.[10] Unsaturated keton **10a** was prepared from mesityl oxide and trioxane using a previously reported procedure.[11] Unsaturated ketones **10b**,**f** were prepared by the aldol condensation of mesityl oxide with acetaldehyde or benzaldehyde, respectively,[10] **10c**,**e** were prepared from 1-acetylcyclohexene and acetaldehyde or benzaldehyde,[10] and **10d** was prepared from 3-buten-2-one and benzaldehyde.[10]

Crossover Reactions of Unsubstituted α,β-Unsaturated Ketone and Substituted α,β-Unsaturated Ketones with Alkenylboronic Acid. The crossover reaction of 1-hepten-3-one (**6**) and 2-octen-4-one (**7a**) with (*Z*)-(2-bromo-1-hexenyl)boronic acid (**4a**) is representative. A CH_2Cl_2 solution (10 ml) of **4a** (207 mg, 1 mmol), **6** (112 mg, 1 mmol), **7a** (126 mg, 1mmol), and cyanuric fluoride **3** (203 mg, 1.5 mmol) was stirred under reflux conditions.

The reaction was monitored by GC and continued until the reaction stopped (10—25 h). The mixture was then extracted with ether, dried over $MgSO_4$, and concentrated under reduced pressure. The products were purified by column chromatography (silica gel/hexane : ether = 95 : 5) and isolated as a mixture of **8** and **9a**. The ratio of the products was determined by GC.

(*Z*)-9-Bromo-8-tridecen-5-one (8): Colorless oil; IR (neat) 1720 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.90 (6H, t, J = 6.4 Hz), 1.10—1.72 (8H, m), 2.32—2.47(8H, m), 5.65 (1H, t, J = 5.8 Hz). Found: C, 56.62; H, 8.26%. Calcd for $C_{13}H_{23}BrO$: C, 56.73; H, 8.42%.

(*Z*)-9-Bromo-7-methyl-8-tridecen-5-one (9a): Colorless oil; IR (neat) 1720 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.76—1.11 (9H, m), 1.06—1.60 (8H, m), 2.31—2.41 (6H, m), 2.86—3.29 (1H, m), 5.16 (1H, d, J = 9 Hz). Found: C, 57.93; H, 8.71%. Calcd for $C_{14}H_{25}BrO$: C, 58.13; H, 8.71%.

(*Z*)-9-Bromo-7-isopropyl-8-tridecen-5-one (9b): Colorless oil; IR (neat) 1720 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.84—1.03 (12H, m), 1.10—1.83 (9H, m), 2.16—2.64 (6H, m), 2.74—3.00 (1H, m), 5.42 (1H, d, J = 9.2 Hz). HRMS (FAB), Calcd for $C_{16}H_{29}BrO$; (M^++H), 317.1472. Found: *m/z* 317.1483.

(*Z*)-9-Bromo-7-phenyl-8-tridecen-5-one (9e): Colorless oil; IR (neat) 1715 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.75—0.94 (6H, m), 1.05—1.66 (m, 8H), 2.27—2.48 (4H, m), 2.50—3.00 (2H, m), 4.18—4.44 (1H, m), 5.79 (1H, d, J = 11.3 Hz), 7.25 (5H, s). Found: C, 64.88; H, 7.79%. Calcd for $C_{19}H_{27}BrO$: C, 64.96; H, 7.75%.

(*Z*)-9-Bromo-6-methyl-8-tridecen-5-one (9f): Colorless oil; IR (neat) 1720 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.89 (6H, t, J = 6.4 Hz), 1.09 (3H, d, J = 7.7 Hz), 1.10—1.72 (8H, m), 2.14—2.76 (7H, m) 5.59 (1H, t, J = 6.4 Hz). Found: C, 57.93; H, 8.71%. Calcd for $C_{14}H_{25}BrO$: C, 58.13; H, 8.71%.

Regioselective 1,4-Addition Reaction of Alkenylboronic Acids to $\alpha,\beta,\alpha',\beta'$-Unsaturated Ketones. The reaction of **4a** with 5-methyl-1,4-hexadien-3-one (**10a**) is representative. A mixture of **10a** (110 mg, 1 mmol), **4a** (311 mg, 1.5 mmol), and **3** (203 mg, 1.5 mmol) in CH_2Cl_2 (10 ml) was stirred under reflux for 16 h. The product was extracted three times with ether, and the combined organic layers were washed with aqueous $NaHCO_3$. The mixture was dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (silica gel/hexane : ether = 10 : 1) to provide (*Z*)-8-bromo-2-methyl-2,7-dodecadien-4-one (**11a**) in 93% yield.

(*Z*)-8-Bromo-2-methyl-2,7-dodecadien-4-one (11a): Colorless oil; IR (neat) 1695 (C=O), 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.89 (3H, t, J = 6.4 Hz), 1.10—1.68 (4H, m), 1.90 (3H, s), 2.17 (3H, s), 2.32—2.58 (6H, m), 5.68 (1H, t, J = 6.4 Hz), 6.07 (1H, s). HRMS (EI), Calcd for $C_{13}H_{21}BrO$: M, 274.0755. Found: *m/z* 274.0772.

(*Z*)-8-Bromo-2,6-dimethyl-2,7-dodecadien-4-one (11b): Colorless oil; IR (neat) 1690 (C=O), 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.81—1.05 (6H, m), 1.18—1.59 (4H, m), 1.98 (3H, s), 2.12 (3H, s), 2.30—2.43 (4H, m), 2.48—3.31 (1H, m), 5.47 (1H, d, J = 11.6 Hz), 6.09 (1H, s). HRMS (EI), Calcd for $C_{14}H_{23}BrO$: M, 288.0912. Found: *m/z* 288.0887.

(*Z*)-1-(1-Cyclohexenyl)-5-bromo-3-methyl-4-nonen-1-one (11c): Colorless oil; IR (neat) 1675 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.82—1.11 (6H, m), 1.18—1.69 (8H, m), 2.18—2.47 (6H, m), 2.51—2.74 (2H, m), 2.89—3.27 (1H, m) 5.50 (1H, d, J = 9.0 Hz), 6.90 (1H, s). HRMS (EI), Calcd for $C_{19}H_{25}BrO$: M, 314.1067. Found: *m/z* 314.1091.

(1*E*, 6*Z*)-7-Bromo-1-phenyl-1,6-undecadien-3-one (11d): Colorless oil; IR (neat) 1690 (C=O), 1630 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ = 0.88 (3H, t, J = 6.4 Hz), 1.10—1.69 (4H, m), 2.16—2.88 (6H, m), 5.72 (1H, t, J = 6.4 Hz), 6.72 (1H, d, J = 15.4 Hz), 7.37—7.67 (6H, m). HRMS (EI), Calcd for $C_{17}H_{21}BrO$: M, 322.0755. Found: *m/z* 322.0784.

(*Z*)-1-(1-Cyclohexenyl)-5-bromo-3-phenyl-4-nonen-1-one (11e): Colorless oil; IR (neat) 1675 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.88 (3H, t, J = 6.4 Hz), 1.06—1.66 (8H, m), 2.15—2.25 (4H, m), 2.40 (2H, t, J = 7 Hz), 2.80—3.30 (2H, m), 4.21—4.58 (1H, m), 5.80 (1H, d, J = 10.3 Hz), 6.86 (1H, s), 7.24 (5H, s). HRMS (EI), Calcd for $C_{21}H_{27}BrO$: M, 374.1245. Found: *m/z* 374.1237.

(*Z*)-8-Bromo-2-methyl-6-phenyl-2,7-dodecadien-4-one (11f): Colorless oil; IR (neat) 1700 (C=O), 1630 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.87 (3H, t, J = 6.4 Hz), 1.07—1.59 (4H, m), 1.87 (3H, s), 2.05 (3H, s), 2.40 (2H, t, J = 5.8 Hz), 2.60—3.05 (2H, m), 4.21—4.45 (1H, m), 5.79 (1H, d, J = 10 Hz), 6.07 (1H, brt), 7.27 (5H, s). Found: C, 65.53; H, 7.29%. Calcd for $C_{19}H_{25}BrO$: C, 65.33; H, 7.21%. HRMS (EI), Calcd for $C_{19}H_{25}BrO$: M, 350.1050. Found: *m/z* 350.1048.

(*Z*)-7-Bromo-2-methyl-2,7-dodecadien-4-one (11g): Colorless oil; IR (neat) 1690 (C=O), 1620 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ = 0.91 (3H, t, J = 6.4 Hz), 1.10—1.49 (4H, m), 1.88 (3H, s), 1.97—2.26 (2H, m), 2.08 (3H, s), 2.69 (4H, s), 5.66 (1H, t, J = 7.1 Hz), 5.99—6.09 (1H, m). HRMS (EI), Calcd for $C_{13}H_{21}BrO$: M, 274.0755. Found: *m/z* 274.0750.

(*Z*)-7-Bromo-2,6-dimethyl-2,7-dodecadien-4-one (11h): Colorless oil; IR (neat) 1700 (C=O), 1630 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ = 0.89 (3H, t, J = 6.4 Hz), 1.11 (3H, d, J = 7.7 Hz), 1.20—1.61 (4H, m), 1.88 (3H, s), 2.01—3.19 (5H, m), 2.10 (3H, s), 5.76 (1H, t, J = 7.7 Hz), 6.07 (1H, s). HRMS (EI), Calcd for $C_{14}H_{24}BrO$: (M^++H), 287.1010. Found: *m/z* 287.1038. Found: C, 58.89; H, 8.35%. Calcd for $C_{14}H_{23}BrO$: C, 58.54; H, 8.07%.

(*Z*)-1-(1-Cyclohexenyl)-4-bromo-3-methyl-4-nonen-1-one (11i): Colorless oil; IR (neat) 1680 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.88 (3H, t, J = 6.4 Hz), 1.10 (3H, d, J = 6.4 Hz), 1.19—1.74 (8H, m), 2.01—2.38 (6H, m), 2.47—3.23 (3H, m), 5.72 (1H, t, J = 6.4 Hz), 6.93 (1H, s). HRMS (EI), Calcd for $C_{16}H_{25}BrO$: M, 312.1089. Found: *m/z* 312.1112.

(*Z*)-7-Iodo-2,6-dimethyl-2,7-dodecadien-4-one (11j): Colorless oil; IR (neat) 1710 (C=O), 1640 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.82—1.07 (6H, m), 1.19—1.42 (4H, m), 1.89 (3H, s), 1.99—2.78 (5H, m), 2.11 (3H, s), 5.65 (1H, t, J = 6.4 Hz), 6.04 (1H, s). HRMS (EI), Calcd for $C_{14}H_{23}IO$: (M^++H), 335.0871. Found: *m/z* 335.0849.

(*Z*)-8-Bromo-9-chloro-2,6-dimethyl-2,7-nonadien-4-one (11k): Colorless oil; IR (neat) 1690 (C=O), 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 1.06 (3H, d, J = 7.2 Hz), 1.91 (3H, s), 2.14 (3H, s), 2.41—2.51 (2H, m), 2.95—3.28 (1H, m), 4.26 (2H, s), 5.95—6.06 (2H, m). HRMS (EI), Calcd for $C_{11}H_{16}BrClO$: M, 278.0074. Found: *m/z* 278.0052.

Ethyl (*E*)-2,2,6,10-Tetramethyl-8-oxo-4,9-undecadienoate (11l): Colorless oil; IR (neat) 1730 (C=O), 1690 (C=O), 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.97 (3H, d, J = 6.4 Hz), 1.11 (6H, s), 1.23 (3H, t, J = 7.3 Hz) 1.86 (3H, s), 2.11 (3H, s), 2.15—2.43 (4H, m), 2.50—2.83 (1H, m), 4.09 (2H, q, J = 7.3 Hz), 5.06—5.57 (2H, m), 6.03 (1H, s). HRMS (EI), Calcd for $C_{17}H_{28}O_3$: M, 280.2039. Found: *m/z* 280.2029.

(*E*)-2,6-Dimethyl-8-phenyl-2,7-octadien-4-one (11m): Colorless oil; IR (neat) 1700 (C=O), 1630 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 1.12 (3H, d, J = 6.6 Hz), 1.86 (3H, s), 2.12 (3H, s), 2.42—2.53 (2H, m), 2.60—3.09 (1H, m), 6.00—6.49 (3H, m),

7.01—7.34 (5H, m). HRMS (EI), Calcd for $C_{16}H_{20}O$: M, 228.1514. Found: *m/z* 228.1521.

(*E*)-2,6-Dimethyl-9-(trimethylsilyl)-2,7-nonadien-4-one (11n): Colorless oil; IR (neat) 1690 (C=O), 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = −0.01 (9H, s), 0.96 (3H, d, J = 7.7 Hz), 1.36 (2H, d, J = 5.9 Hz), 1.88 (3H, s), 2.11 (3H, s), 2.22—2.45 (2H, m), 2.48—2.88 (1H, m), 4.96—5.59 (2H, m), 6.05 (1H, s). HRMS (EI), Calcd for $C_{14}H_{26}OSi$: M, 238.175. Found: *m/z* 238.1730.

(*E*)-8-(1-Cyclohexenyl)-2,6-dimethyl-2,7-octadien-4-one (11o): Colorless oil; IR (neat) 1695 (C=O), 1625 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 1.03 (3H, d, J = 6.4 Hz), 1.60—2.22 (8H, m), 1.87 (3H, s), 2.12 (3H, s), 2.33—2.44 (2H, m), 2.53—2.89 (1H, m), 5.34—5.65 (2H, m), 5.93—6.11 (2H, m). HRMS (EI), Calcd for $C_{16}H_{24}O$: M, 232.1827. Found: *m/z* 232.1826. Found: C, 82.72; H, 10.28%. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.28%.

(*E*)-11-Benzyloxy-2,6-dimethyl-2,7-undecadien-4-one (11p): Colorless oil; IR (neat) 1695 (C=O), 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.98 (3H, d, J = 7.7 Hz), 1.57—2.85 (7H, m), 1.86 (3H, s), 2.11 (3H, s), 3.45 (2H, t, J = 6.5 Hz), 4.48 (2H, s), 5.32—5.41 (2H, m), 6.03 (1H, brt), 7.32 (5H, s). HRMS (EI), Calcd for $C_{20}H_{28}O_2$: M, 300.2090. Found: *m/z* 300.2086.

(*E*)-2,6-Dimethyl-9-(2-thienylthio)-2,7-nonadien-4-one (11q): Colorless oil; IR (neat) 1700 (C=O), 1630 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.94 (3H, d, J = 6.5 Hz), 1.88 (3H, s), 2.13 (3H, s), 2.24—2.33 (2H, m), 2.48—2.84 (1H, m), 3.32 (2H, d, J = 5.8 Hz), 5.15—5.65 (2H, m), 6.01 (1H, s), 6.94—7.09 (2H, m), 7.28—7.34 (1H, m). HRMS (EI), Calcd for $C_{15}H_{20}OS_2$: M, 280.0956. Found: *m/z* 280.0955.

Synthesis of (*Z*)-1-(2-Cyanocyclohexyl)-5-bromo-3-methyl-4-nonen-1-one (12) by the Reaction of 11c with Cyanotrimethylsilane. To a mixture of Me_3SiCN (2 mmol, 198 mg) and **11c** (1 mmol, 315 mg) in dry THF (5 ml) was added Et_3Al (2 mmol, 1.75 ml of 1.14 M hexane solution, 1 M = 1 mol dm^{-3}) at room temperature; the resulting mixture was stirred under reflux. After 2 h, the consumption of **11c** could be confirmed by GC, and aqueous NH_4Cl was added. The mixture was extracted three times with ether and the combined organic layers were dried over $MgSO_4$. Purification by preparative TLC (silica gel/benzene) provided **12** in 60% yield and a GC analysis showed that product was a mixture of isomers: Colorless oil; IR (neat) 2250 (CN), 1720 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.90 (3H, t, J = 7.0 Hz), 1.03—1.05 (3H, m), 1.25—2.17 (12H, m), 2.37—2.52 (5H, m), 3.09—3.19 (2H, m), 5.46—5.50 (1H, m). HRMS (FAB), Calcd for $C_{17}H_{26}BrNO$: (M^++H), 340.1275. Found: *m/z* 340.1283.

Synthesis of (*Z*)-[2-(1-Hexynyl)cyclohexyl]-5-bromo-3-methyl-4-nonen-1-one (13) by the 1,4-Addition of (1-Hexynyl)-diisopropoxyborane to 11c. To a mixture of (1-hexynyl)-diisopropoxyborane (2 mmol, 418 mg) and **11c** (1 mmol, 315 mg) in CH_2Cl_2 (5 ml) was added $Et_2O{\cdot}BF_3$ (2 mmol, 0.246 ml) at room temperature and the resulting mixture was stirred under reflux. After 18 h, the consumption of **11c** could be confirmed by GC, and the mixture was extracted three times with ether. The combined organic layers were dried over $MgSO_4$ and purification by preparative TLC (silica gel/benzene) provided **13** in 70% yield and GC analysis showed that product was a mixture of isomers: Colorless oil; IR (neat) 1720 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.87—0.92 (6H, m), 1.00—1.03 (3H, m) 1.23—2.14 (16H, m), 2.29—2.61 (7H, m), 3.08—3.18 (2H, m), 5.47—5.53 (1H, m). HRMS (FAB), Calcd for $C_{22}H_{35}BrO$: (M^++H), 395.1949. Found: *m/z* 395.1936.

Intramolecular Heck Cyclization. The synthesis of 2-isopropenyl-3-butyl-2-cyclohexenone (**14a**) is representative. A mixture of **11a** (1.0 mmol, 274 mg), K_2CO_3 (2.0 mmol, 288 mg), and $(PPh_3)_4Pd$ (0.05 mmol, 58 mg) in CH_3CN (10 ml) was stirred at 80 °C for 10 h. The consumption of **11a** was confirmed by GC, and the mixture was extracted with ether. Purification of the reaction mixture by column chromatography (silica gel/CH_2Cl_2) provided **14a** in 87% yield; colorless oil; IR (neat) 1670 (C=O), 1620 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ = 0.82—1.03 (3H, m), 1.13—1.65 (4H, m), 1.81—2.50 (11H, m), 4.66 (1H, s), 5.18 (1H, s). HRMS (EI), Calcd for $C_{13}H_{20}O$: M, 192.1515. Found: *m/z* 192.1523.

2-Isopropenyl-3-pentyl-2-cyclopentenone (14b). Colorless oil; IR (neat) 1710 (C=O), 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 0.90 (3H, t, J = 6.8 Hz), 1.26—1.38 (4H, m), 1.50—1.57 (2H, m), 1.91 (3H, s), 2.39—2.56 (6H, m), 4.77 (1H, s), 5.18 (1H, s). HRMS (EI), Calcd for $C_{13}H_{20}O$: M, 192.1514. Found: *m/z* 192.1512. Found: C, 80.99; H, 10.45%. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48%.

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