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Synthesis of Adamantane Derivatives by Bridgehead Radical Addition to Electron-Deficient Unsaturated Bonds

Masatomi Ohno, Kenichi Ishizaki, and Shoji Eguchi*

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464, Japan

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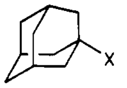
Introduction of β-functional alkyl and alkenyl groups to the adamantane bridgehead was carried out by radical-mediated reactions of 1-adamantyl bromide and iodide (**1a** and **1b**) with alkenes and alkynes containing electron-withdrawing groups in the presence of tributyltin hydride and AIBN. As expected, the reactions of polybromoadamantanes **7–9** with acrylonitrile gave 1,3-, 1,3,5-, and 1,3,5,7-polycyanoethyl-substituted derivatives; yield decreased with increasing substitution. Notably, by this method, α-hydroxy ester and monohydrazine derivatives were obtained by using the silyl enol ether of pyruvate ester and diethyl azodicarboxylate as a radical acceptor, respectively. The course of reaction is rationalized as a radical chain cycle, and the reactivity pattern of alkenes indicates that the radical addition process is governed by a SOMO–LUMO interaction of a radical and an alkene. A recently reported reaction of an alkyl halide with a zinc–copper couple in aqueous ethanol is complementary to the above tin method. Thus, **1b** reacted with α,β-unsaturated carbonyl compounds in the presence of a zinc–copper couple; in some cases the yield was improved greatly.

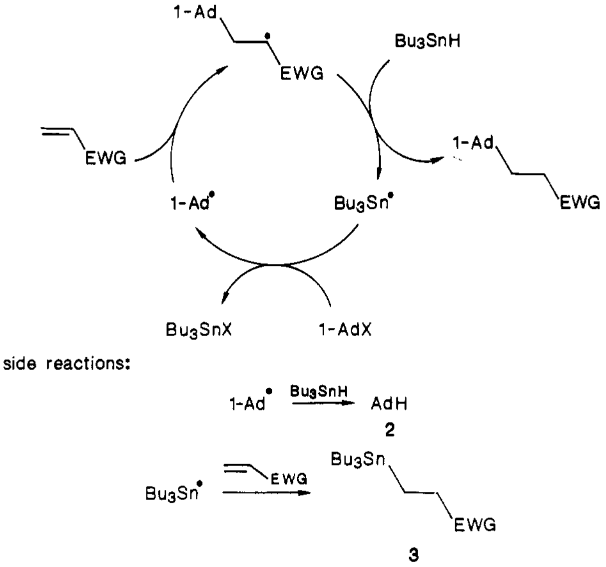
The unique structure of adamantane is attractive from the physical and pharmacological viewpoints, and a variety of adamantane derivatives have been synthesized.[1] The straightforward way of obtaining such adamantane derivatives is a substitution reaction at its bridgehead. Until now, most of the methods for this purpose rely on polar S_N1 substitution reaction under electrophilic conditions,[2] since the bridgehead cation is relatively stable and easily generated by wide variety of methods. Less attention has been paid to the radical-mediated substitution reaction.[3] However, radicals manifest high utility in carbon–carbon bond formation, for which an advanced review appeared recently.[4] Adamantane chemistry is not exceptional, and several works on the bridgehead substitution of adamantane have been published.[5] In a series of synthetic studies on adamantane derivatives,[2c] we have employed the radical addition of 1-adamantyl halides **1a,b** to a number of electron-deficient olefins and acetylenes. The tributyltin hydride (donor)–azobis(isobutyronitrile) (AIBN, initiator) method[4,6] or a zinc–copper (ethanol/water) system[7] was used to bring about reaction. Results of these reactions demonstrate a useful way of preparing bridgehead-substituted adamantane derivatives.



(1-Ad)

1a, X = Br
b, X = I
c, X = Cl

Scheme I. Radical Chain Reaction of 1 with an Alkene



Results and Discussion

The reaction course is depicted as well-known cyclic radical chain process (Scheme I).[6] Possible side reactions are reduction of **1** to adamantane (**2**) and competitive addition of tin radical to an olefin leading to tin adduct **3**.

The adamantyl radical is nucleophilic,[5c] and accordingly an electrophilic unsaturated bond is favored.[6] Therefore, for a standard run, we selected a cyano group substituted alkene and alkyne as a radical acceptor. The first experiment was carried out under the typical conditions by refluxing in toluene containing 1.2 equiv of Bu_3SnH and 5 mol % of AIBN together with **1** and 1.2 equiv of acrylonitrile. As for *tert*-butyl halide,[6] 1-adamantyl chloride (**1c**) did not show any reactivity but resulted in 84% recovery of **1c**. 1-Adamantyl bromide (**1a**) and iodide (**1b**), however, gave the desired **4** in 74% and 77% yields, respectively, along with byproducts **2** (21%) and **3** (EWG = CN, 15% based on Bu_3SnH). When 2 equiv of acrylo-

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[1] (a) Fort, R. C., Jr. *Adamantanes*; Marcel Dekker: New York, 1976. (b) Bingham, R. C.; Schleyer, P. v. R. *Topics in Current Chemistry*; Springer-Verlag: New York, 1971.

[2] (a) Reference 1, Chapters 3 and 4. (b) Reference 1b, p 52. (c) Reactions with unsaturated organosilanes: Sasaki, T.; Nakanishi, A.; Ohno, M. *J. Org. Chem.* **1982**, *47*, 3219. Sasaki, T.; Usuki, A.; Ohno, M. *Ibid.* **1980**, *45*, 3559.

[3] (a) Reference 1, Chapter 5. (b) Reference 2, p 65.

[4] Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986.

[5] (a) Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339. (b) Barton, D. H. R.; Garcia, B.; Togo, H.; Zard, S. Z. *Tetrahedron Lett.* **1986**, *27*, 1327. (c) Testaferri, L.; Tiecco, M.; Tingoli, M.; Fiorentino, M.; Troisi, L. *J. Chem. Soc., Chem. Commun.* **1978**, 93. (d) Cross-coupling reaction of **1** with Grignard reagents via a radical mechanism: Ohno, M.; Shimizu, K.; Ishizaki, K.; Sasaki, T.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 729.

[6] (a) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 753; (b) **1985**, *24*, 553.

[7] Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149.

Scheme II. Radical vs Ionic Disubstitution of 1,3-Dihaloadamantane

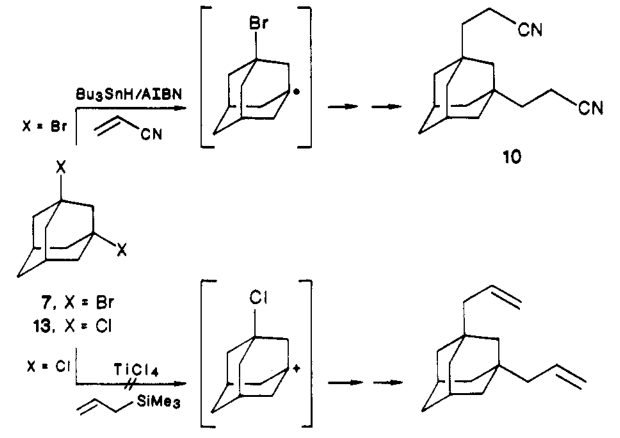
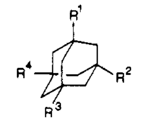
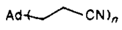
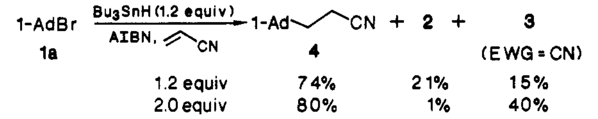
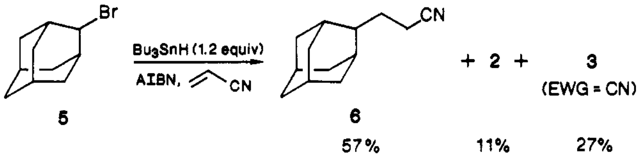


Table I. Consecutive Substitution at Adamantane Bridgeheads

polybromoadamantane 					yield (%) 			
	R^1	R^2	R^3	R^4	**4** $n = 1$ (1)	**10** $n = 2$ (1,3)	**11** $n = 3$ (1,3,5)	**12** $n = 4$ (1,3,5,7)
7	H	H	Br	Br	19	51		
8	H	Br	Br	Br	7	46	32	
9	Br	Br	Br	Br	10	29	24	6

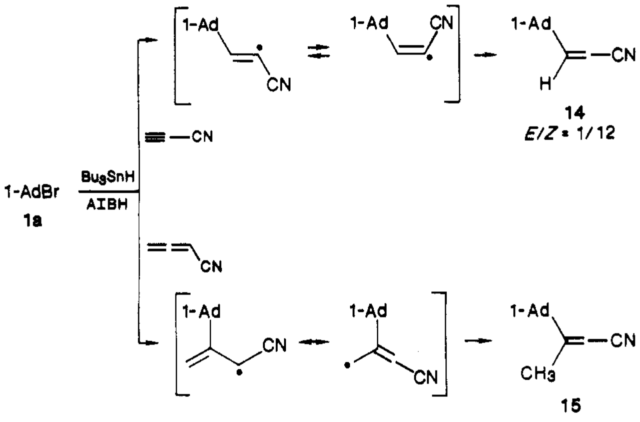
nitrile were used,[8] formation of **2** was greatly reduced. The yield of **4** was raised slightly and **3** increased in yield. Isomeric 2-adamantyl bromide (**5**) was less reactive than **1a** but gave adduct **6** in 57% yield.



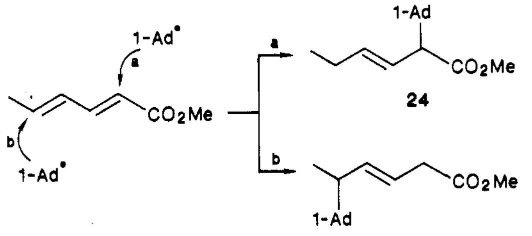


Reactions of polybromoadamantanes **7–9** lead to the formation of polysubstituted adamantane derivatives. A twofold excess of the reagents with 1,3-dibromoadamantane (**7**) gave 2:1 adduct **10** in 51% yield, accompanied by the 1:1 adduct **4** (19%), probably from interference with reduction at the second stage. It is noteworthy that 1,3-dichloroadamantane (**13**) does not undergo such a double substitution reaction via a cationic intermediate;[2c] $TiCl_4$-catalyzed electrophilic reaction with allylsilane fails as the result of hyperconjugative destabilization of the 3-substituted intermediate carbonium ion.[9] By contrast, the radical intermediate involved here is not negatively influenced by this 1,3-interaction; accordingly, difunctionalization is allowed (Scheme II). Consecutive radical addition at each of four bridgeheads afforded tri- and tetrasubstituted adamantane derivatives **11** and **12**, as summarized in Table I; however, the more substituted, the lower the yield of adduct. Thus **12** was produced in only 6% yield.

Scheme III. Reaction of 1a with Cyanoacetylene and -allene

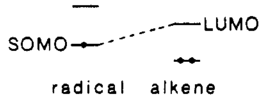


Scheme IV. Addition of 1-Adamantyl Radical to Methyl Sorbate

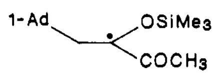


1-Adamantyl bromide (**1a**) also reacted with acetylenic and allenic analogues (Scheme III). Products **14** from cyanoacetylene consisted of *E*/*Z* isomers separable by preparative TLC, in which the *Z* isomer predominated ($E/Z = 1/12$). The intermediate vinyl radical which was formed after the addition of the bridgehead radical to the triple bond abstracted hydrogen predominantly at the less hindered side to give thermodynamically less favored *Z* isomer. In the allenic case, α,β- rather than β,γ-unsaturated nitrile **15** was produced as the result of hydrogen donation to once formed allylic radical at the less hindered γ-position.

With these results in mind, we tried the addition reactions of **1** with a variety of alkenes and alkynes substituted with electron-withdrawing groups; these are summarized in Table II. In entries 2–5 are listed α,β-unsaturated ketones. The reactions, typically, with methyl vinyl ketone and 2-cyclohexenone afforded the expected adducts **16** and **17** in modest yields, but, not unexpectedly, those with mesityl oxide and benzalacetone resulted in only the formation of **2** because of the essential steric sensitiveness of this radical chain reaction.[6] The interesting comparison is made between the reactions with methyl vinyl ketone and with 3-siloxy-3-buten-2-one (entries 2 and 5); the yield was much lowered in the latter case. This fact indicates that the radical addition process is governed by the SOMO–LUMO interaction[6] of a radical and an olefin [A]



[A]



[B]

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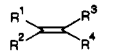
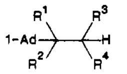
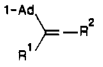
[8] In most reactions of radicals with electrophilic olefins, a massive excess (10–15 equiv) of olefins may be required to obtain a reasonable yield. However, this is not the case for **1a,b**, because they seem to be more favored than *tert*-butyl halides to react with such olefins in both electronic and steric effects; 1-adamantyl radical is more nucleophilic (i.e., higher SOMO level) because of the so-called "cage" effect, and furthermore, it is less hindered around the radical center because of its pyramidal geometry (vs planar one for *tert*-butyl radical); see ref 3a.

[9] Olah, G. A.; Parakash, G. K. S.; Shih, J. G.; Krishnamurthy, V. V.; Mateescu, G. D.; Liang, G.; Sipos, G.; Buss, V.; Gund, T. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1985**, *107*, 2764.

Table II. Bridgehead Radical Addition Reactions of 1 with Alkenes and Alkynes

entry	alkene (alkyne) R^1	alkene (alkyne) R^2	alkene (alkyne) R^3	alkene (alkyne) R^4	product	yield (%) Bu$_3$SnH method[a]	yield (%) Zn–Cu method[b]
							
1	H	H	H	CN	**4**[c]	80	
2	H	H	H	$COCH_3$	**16**	43	
3	H	H	$-(CH_2)_3CO-$		**17**	33	91 (23)
4	CH_3	CH_3	H	$COCH_3$	**18**	0	12
5	H	H	$OSi(CH_3)_3$	$COCH_3$	**19**	14	
6	H	H	H	$COOCH_3$	**20**[d]	70	
7	H	$COOC_2H_5$	H	$COOC_2H_5$	**21**	60	
8	H	H	$OSi(CH_3)_3$	$COOC_2H_5$	**22**	42 (54)	
9	$CH_3CH{=}CH$	H	H	$COOCH_3$	**24** + **25**[e]	41	
10	H	H	H	SOPh	**26**	35	41
11	H	H	H	Ph	**27**[f]	31	
12	H	H	Cl	Cl	**28**	40 (58)	
13	H	H	Cl	CN	**29**	29 (76)	
14	H	H	CN	$COOCH_3$	**30**	0 (36)	
15	$CH_2{=}$		H	CN	**15**[e]	26 (37)	
	$R^1-\equiv-R^2$						
16	H	CN			**14** [E/Z = 1/12]	66	
17	H	$COOCH_3$			**31** [E/Z = 2/3]	0 (40)	33 [E/Z = 2/3]
18	H	Ph			**32**[f] [Z only]	0 (15)	17 [Z only]
19	Cl	CN			**33**[g] [E/Z = 3/2]	0 (27)	
20	$COOCH_3$	$COOCH_3$			**34**	0 (0)	42 [E/Z = 3/7]

[a] The reaction was carried out using 2 equiv of alkene or alkyne in the presence of 5 mol % of AIBN with **1a** or **1b** (in parentheses) in refluxing toluene for 2 h. The yield was based on 1. [b] The reaction was carried out using an alkene or alkyne with 1.5 equiv of **1b** or **1a** (in parentheses) in 9/1 ethanol/water (in entry 20, methanol was used insteadly) under sonication at ambient temperature for 2 h (entry 3), 5 h (entries 4 and 10), and 9 h (entries 17, 18, and 20). The yield was based on the alkene or alkyne, and the excess halide 1 was recovered. [c] Reference 19. [d] Reference 20. [e] The product structure is expressed by the formula in the text not in the table. [f] The structure was determined by comparison with the sample in our hand (ref 2c and 5d). [g] Reference 21.

rather than the relative stability of a formed radical after addition to an olefin [B]. If no so, the latter (captodative olefin in which a radical is stabilized[10]) would give the better result. The reaction with acrolein resulted in the recovery of nearly half of **1a**, presumably because of the prevailing reactivity of aldehydic hydrogen. In entries 6–9 are shown the reactions with α,β-unsaturated esters, affording the adducts **20–25** in fair to good yield. Here α-hydroxy ester **22** could be obtained by using the silyl enol ether of ethyl pyruvate as a radical acceptor (entry 8), and the product was further hydrolyzed to 1-adamantyllactic acid (**23**). This reaction constitutes a method for preparing lactic acid derivatives from a halide and pyruvate ester. In the reaction with methyl sorbate (Scheme IV), many products were produced, from which major two isomeric unsaturated esters were isolated in a 2/1 ratio after preparative TLC. In ^{1}H NMR spectra, coupling patterns due to the terminal methyl protons and protons α to the ester group were utilized to determine the structures, which were assigned to methyl 2-(1-adamantyl)-3-hexenoate (**24**, major isomer) and methyl 5-(1-adamantyl)-3-hexenoate (**25**, minor isomer), respectively. Both isomer arose from 1,4-addition directed each by the propenyl and methoxycarbonyl groups, although appreciable regiochemical selectivity was not attained.

Phenyl vinyl sulfoxide was also found to act modestly as a radical acceptor (entry 10), while it has been utilized more efficiently as a Michael acceptor in carbanion chemistry.[11] Further, for a diene conjugated system, the reaction with styrene gave the adduct **27** fairly effectively (entry 11) in contrast to that with isoprene which only resulted in the formation of **2**. In addition to these monosubstituted alkenes, 1,1-disubstituted alkenes such as vinylidene chloride, α-chloroacrylonitrile, and methyl α-cyanoacrylate underwent the similar addition reactions to give β,β-bifunctionalized 1-ethyladamantanes **28–30** (entries 12–14). It is noted, however, that a more reactive alkene is not necessarily a good candidate as a radical acceptor; under the employed conditions methyl α-cyanoacrylate predominately polymerized without involvement of the bromide **1a**, and even the iodide **1b** reacted at best in 36% yield. On the basis of behavior of cyclopropane which resembles that of olefin in some respects,[12] diethyl cyclopropane-1,1-dicarboxylate was tried in the present reaction; however, no adduct could be isolated. Alkynes with an electron-withdrawing group should behave similarly to cyanoacetylene (vide supra). However, reaction of **1a** with other alkynes such as methyl propiolate, phenylacetylene, and chlorocyanoacetylene resulted in the recovery of **1a**, because undesired tin radical addition became a major reaction course. Nevertheless, when more reactive **1b** was employed, β-(1-adamantyl)alkenes **31–33** were produced in modest yields, usually with predominant cis configuration (adamtyl to functional group). However,

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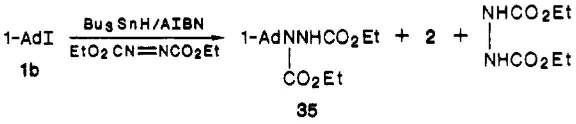
(10) Hoecke, M.; Borghese, A.; Penelle, J.; Merenyi, R.; Viehe, H. G. *Tetrahedron Lett.* **1986**, *27*, 4569 and references cited therein.

(11) Paquette, L. A.; Carr, R. V. C. *Org. Synth.* **1985**, *64*, 157.

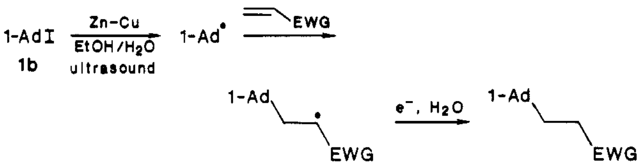
(12) Pete, J.-P. *Bull. Soc. Chim. Fr.* **1967**, 357.

dimethyl acetylenedicarboxylate did not react even with **1b** (entry 20).

The above reaction was extended to hetero-unsaturated bonds, for which diethyl azodicarboxylate, ethyl cyanoformate, phenyl and trimethylsilyl isocyanates, and acetophenone were examined. Among them, only the azo compound led to carbon–nitrogen bond formation; reaction of **1b** with excess diethyl azodicarboxylate gave 1-adamantylhydrazine **35** in 26% yield, together with reduction products **2** (41%) and bis(ethoxycarbonyl)hydrazine (48%).



Very recently, new conjugate addition reactions of alkyl halides to α,β-unsaturated carbonyl compounds have been reported,[7] for which a radical pathway was proposed as a likely mechanism. This procedure is applicable to **1** and is complementary to the present method; in fact, yields were improved, in some cases, considerably. Iodide **1b** was found to be much better than bromide **1a** (see entry 3), and thus, the reaction was conducted using **1b** with Zn–Cu suspension in 9/1 ethanol/water. Products were separated by column chromatography after the conventional workup. Results are summarized in Table II (Zn–Cu method). As is seen from the table, the yield of **17** was increased from 33% to 91%, and the adducts with dimethyl acetylenedicarboxylate and with mesityl oxide (more hindered ketone) were obtained in 42% and 12% yields, respectively. In addition reactions to alkynes, the stereochemistry of this reaction parallelled that of the tin-initiated reaction.



All of the compounds obtained above were characterized by elemental and spectral analyses; in ^{1}H NMR spectra, the products derived from alkenes possessed characteristic signals due to an A_2B_2 or an ABX pattern at the appropriate region, together with signals due to adamantane ring protons. The product derived from alkynes possessed olefinic protons with the coupling constants 16 Hz for the *E* isomer and 12–13 Hz for the *Z* isomer. For the trisubstituted olefinic products,[13] the stereochemistry of **33** and **34** was estimated by the reported additivity rule.[14]

In conclusion, 1-adamantyl bromide (**1a**) and iodide (**1b**) were converted to a variety of β-functionalized alkyl- and alkenyladamantanes in fair to good yield by either a tributyltin hydride or zinc–copper method. Among them, some pharmacologically interesting compounds (e.g. **17** and **23**)[15] were synthesized. Through these experiments, new methods for preparing an α-hydroxy ester and a monoalkylhydrazine were developed.

Experimental Section

Infrared spectra were determined on a JASCO A-100 spectrophotometer. NMR spectra were determined at 60 MHz with a JEOL 60-HL spectrometer, and chemical shifts were recorded in δ with tetramethylsilane as an internal standard. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. The chromatographic separation was carried out on a silica gel column (Fuji-Davison BW-300) or preparative TLC (Merck silica gel 60 F-254) eluted with the solvent noted. Toluene used as a reaction solvent was dried over Na. Except for commercially available reagents, 1,3-, 1,3,5-, and 1,3,5,7-polybromoadamantanes,[16] cyanoallene,[17] 3-(trimethylsiloxy)-3-buten-2-one,[18] and ethyl 2-(trimethylsiloxy)-2-propenoate[18] were prepared according to the reported methods. Methyl α-cyanoacrylate, cyanoacetylene, and chlorocyanoacetylene were gifts from TOAGOSEI Chemical Ltd. and TAKEDA Chemical Industries Ltd.

General Procedure for the Reaction of 1 with Alkenes and Alkynes: Bu_3SnH Method. A solution of **1** (1 mmol), Bu_3SnH (1.2 mmol), alkene or alkyne (2.0 mmol), and AIBN (8 mg; 5 mol %) in toluene (3 mL) was stirred at reflux temperature for 2 h. Then, the reaction mixture was treated with aqueous KF solution (0.2 M, 10 mL) at room temperature overnight, or otherwise, it was washed with ammonia water (0.2 M, 10 mL). After the products were extracted with ether, the organic layer was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on a silica gel column; the first elution with hexane removed **2**, and the second elution with 5% hexane–ethyl acetate (20% and 30% hexane–ethyl acetate for **26** and **35**, respectively) gave the products after the fraction of tin adducts **3**. For the separations of the products from styrene and methyl sorbate, preparative TLC was employed with hexane and 2% hexane–ethyl acetate, respectively. The *E*/*Z* isomers from alkynes were also separated on preparative TLC after the isolation of the crude adducts on a column. See Tables I and II for the yields.

The adduct **22** was converted to **23** by stirring in 1 N NaOH in ethanol overnight at room temperature followed by treatment with excess 1 N HCl for 30 min, 58% yield: mp 110.9–111.7 °C; IR (KBr) 1730, 3360 cm^{-1}; ^{1}H NMR (DMSO-d_6) 1.07–2.23 (m, 16 H), 1.22 (dd, 1 H, J = 7.5 and 13 Hz), 4.06 (dd, 1 H, J = 4.5 and 7.5 Hz), 7.0 (br s, 2 H). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.91; H, 8.99. Found: C, 69.61; H, 9.09.

General Procedure for the Reaction of 1b with Alkenes and Alkynes: Zn–Cu Method. A suspension of Zn powder (150 mg, 2.4 mmol) and CuI (90 mg, 0.5 mmol) in 9/1 ethanol (methanol only for **34**)/water (4 mL) was sonicated with Branson P-220 (125 W) for 3 min, and to this was added **1b** (394 mg, 1.5 mmol) and alkene or alkyne (1 mmol). The mixture was further sonicated for a specified period, and then aqueous saturated NaCl (10 mL) and ether (10 mL) were added to the reaction mixture. After the solids were filtered off, the organic layer was separated, washed with water, and dried over Na_2SO_4. The products were separated by the chromatography as described above.

The compounds obtained as above had the following melting points: compound, mp (°C): **4**, 49.1–49.6; **6**, 30.0; **10**, 47.6–48.4; **11**, 110.0–111.8; **12**, 155.0–158.5; **14**(*E*), 39.5–42.0; **14**(*Z*), 47.5–49.3; **15**, 47.6–49.4; **17**, 60.2–61.6; **18**, 38.5–40.0; **21**, 52.6–53.1; **26**, 79.5–81.0; **30**, 31.6–32.1. All the others were obtained as oils.

Acceptable microanalytical data were obtained for the new compoounds **6**, **10**, **11**, **12**, **14**(*E* and *Z*), **15**, **16**, **17**, **18**, **19**, **21**, **24**, **25**, **26**, **28**, **29**, **30**, **31**(*E* and *Z*), **34**(*E* and *Z*), and **35**.

Supplementary Material Available: IR and NMR data for the compounds listed in Tables I and II (3 pages). Ordering information is given on any current masthead page.

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[13] At present the stereochemistry of **15** was not confirmed, although the thermodynamically more favored *E* configuration may be assumed from the mechanistic consideration.

[14] Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; p 184.

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