Journal of Organometallic Chemistry, 473 (1994) 63–70

Diversity in the reaction modes of anionic and cationic stannyl reagents: γ-chloro allylstannanes as a vinyl carbene equivalent, and its application for (±)-bakuchiol synthesis

Jun Fujiwara and Tadashi Sato

Department of Applied Chemistry, Faculty of Science and Engineering, Waseda University, Ookubo 3, Shinjuku-ku, Tokyo 169 (Japan)

(Received December 1, 1993; in revised form January 19, 1994)

Abstract

Diversity in the reaction modes of anionic stannyl reagents is demonstrated by synthon representation. A new cationic stannyl reagent, γ-chloro allylstannane, has been developed as a vinyl carbene equivalent, and its utility is demonstrated by (±)-bakuchiol synthesis.

Key words: Allyltin; Vinyl carbene; Monoterpene; Lewis acid; Bifunctional reagent; Organic synthesis

1. Introduction

Tributyltin hydride is the most widely used organotin reagent. The typical reaction mode of this reagent is homolytic, and the reagent has usually been used as a generator of radical species. However, organotin compounds used as delivery reagents of tin atom into organic substrates are generally ionic. We can classify the ionic tin reagents into two categories: anionic reagents which deliver the tin-containing moieties as nucleophiles, and cationic reagents which deliver the tin-containing group as electrophiles. Typical examples of the former category are lithium-containing tin reagents like **1**, while tin reagents containing leaving groups such as halides or triflate belong to the latter category.

We have so far developed several reactions using two anionic stannyl reagents, trimethylstannyllithium **1a** and trimethylstannylmethyllithium **1b** [1]. In view of the carbanionic nature of the tin-bearing carbon, the lithium reagents **1** behave as double anion equivalents **2**, and undergo consecutive reaction with two different electrophiles, first as an explicit anion provided by lithium, and then as a latent anion provided by tin. In this context, the reagents can be classified as bifunctional reagents. Due to the diverse reactivities of the carbon–tin bond towards the electrophilic centers, the reagents undergo several types of novel reactions. Since the novelty of the reaction modes can be demonstrated more clearly by synthon representation, we first give a brief overview of the reaction patterns of the anionic stannyl reagents observed so far, and then a novel reaction type induced by a new cationic stannyl reagent is discussed.

2. Results and discussion

2.1. Synthon representation of bifunctional reagents

Reagents containing multiple functionalities are important in organic synthesis. Diazomethane (**3**), in which both nucleophilic and electrophilic centers coexist in one molecule, is a classical example. As exemplified by its reaction with ketones (Demjanov reaction), the two step reaction leads to the formal insertion of a methylene group into a C–C bond. Apparently the reagent can be viewed as a methylene cation/anion equivalent **6**, and the reaction can be depicted as eqn. (1) by synthon representation. Ylides **4** and **5** are other examples of bifunctional reagents undergoing the two-stage reaction, and we can similarly scheme two reactions, oxirane formation from ketone by sulfur

Correspondence to: Professor T. Sato.

0022-328X/84/$7.00
SSDI 0022-328X(94)24476-Y

$Me_3Sn\text{-}(CH_2)_n\text{-}Li\ (Mg) \equiv (CH_2)_n^{=}$

1 2

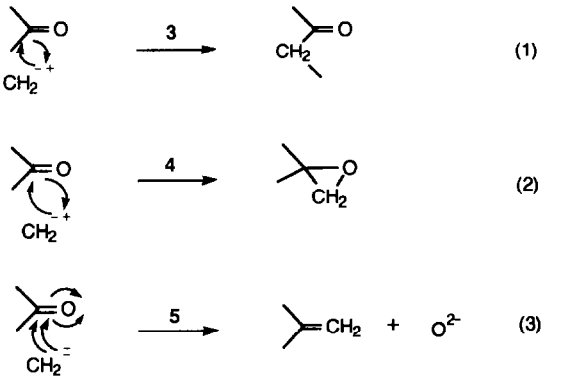
a: n = 0; b: n = 1; c: n = 3

ylide **4**, and the Wittig methylenation reaction by phosphorus ylide **5**, as shown by eqns. (2) and (3), respectively. Evidently, sulfur ylide reacts as an equivalent to **6**, while phosphorus ylide reacts as a methylene double anion equivalent **7**. The reversal of the polarity of the phosphorus ylide is apparently caused by the increase in the valence of phosphorus from P^{III} to P^{V} during the reaction.

The characteristic feature of these reagents is that the two functionalities are integrated into the reagent molecules as a "one-set", inducing simultaneous two-step reactions.

We can specify another type of bifunctional reagent under a second category, in which two functionalities work independently. A typical example is dithiane **8**, which serves as a conjunctive reagent connecting two electrophiles with the carbonyl group. Although the reagent functions as a carbonyl dianion equivalent, the reaction can be schemed as a simple cumulation of two independent reactions, without being influenced by each other or by the other functional groups. Several other examples have been listed in the literature [2].

Referring to these reaction patterns, we can characterize the typical points observed in the reactions of the anionic stannyl reagents **1** as follows. (1) Because of the low reactivity of the carbon–tin bond towards electrophiles, no obvious interference of the stannyl group is exerted during the first-stage reaction of the explicit anionic center, thus allowing a variety of electrophilic centers to be introduced into the stannyl compounds. (2) The stannyl compounds thus prepared are usually isolable, and therefore we can manipulate the second-stage reaction in various ways by changing the nature of the electrophilic centers, reaction conditions, and activation methods. (3) Albeit less reactive than the carbon–lithium bond, the carbon–tin bond is far more reactive than the other carbon–hetero atom bonds, such as the carbon–silicon bond; thus various types of reactions become feasible. (4) The further modification of the reaction pattern in the second-stage reaction can be realized by introducing an auxiliary functional group into the substrate.

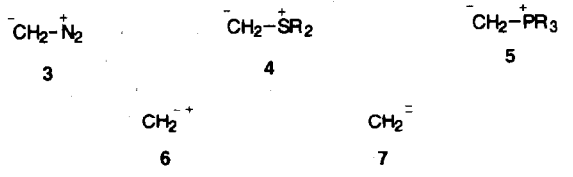


The following examples exhibiting these characteristics are shown in eqns. (4)–(8) as listed in Table 1 with synthon representations.

(a) *Example 1.* The conjugate addition of **1a** to α,β-enones and the succeeding aldol reaction afford β-stannyl-β'-hydroxy ketones **9** [3]. Treatment of **9** with Lewis acid affords β,γ-enones **12** (path a), while treatment with mesyl chloride or PCl_3 affords cyclopropyl ketones **13** (path b) [4]. Using the double electron synthon **2a**, the reactions can be represented by eqn. (4).

(b) *Example 2.* The reaction of **1b** with ketones affords 1-olefins **14** (eqn. (5)). Although the reaction proceeds in the same pattern as Wittig and Peterson reactions, the novelty of the stannyl compounds emerges in the reaction with functionalized ketones, such as α-chloro or α,α-epoxy ketones [5]. The formal insertion of a methylene group between the carbonyl and oxirane moieties of α,β-epoxy ketone **15** proceeds as shown in eqn. (6). This type of reaction cannot be achieved with the corresponding silyl reagent. This is an example of the reaction with a carbonyl group being influenced by the second functional group, in this case, the oxirane ring.

Cleavage of a double bond by **1b** is an another example. γ-Stannyl ketones **10**, obtained from **1b** and α,β-enones [6], undergo a bond cleavage to afford **17** as shown in eqn. (7) [7]. A similar type of bond cleav-



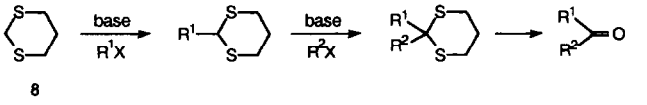
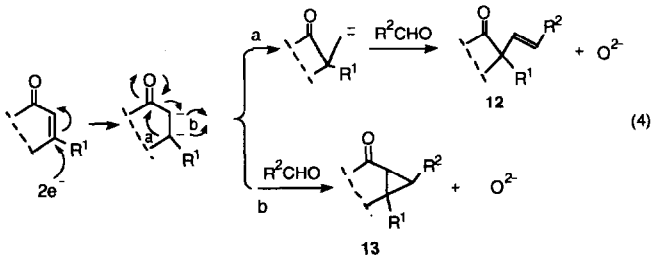
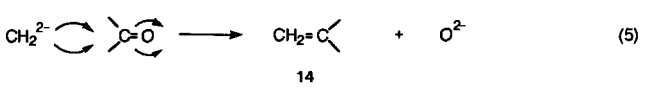


TABLE 1. Synthon represenation of reactions induced by anioc stannyl reagents

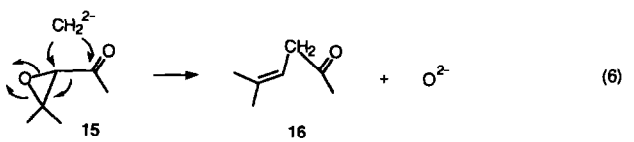
Example	Synthon representation



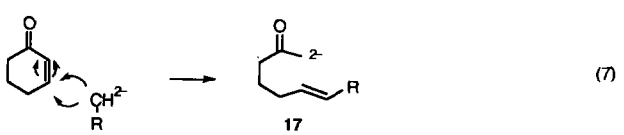
(4)



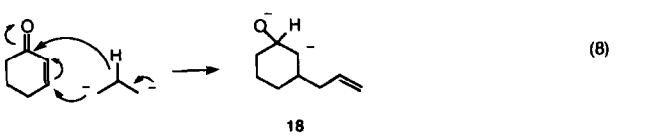
(5)



(6)



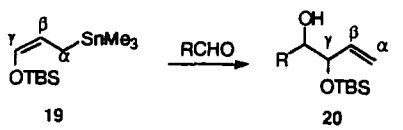
(7)



(8)

age has been known only in strained-ring systems in the case of the corresponding silyl compounds [8].

(c) *Example 3.* Conjugate addition of **1c** to α,β-enones affords stannyl ketones **11**, which undergo a stereospecific 1,5-hydride shift to give **18** [9]. This is an example of the original 1,3-propadiyl dianion reacting



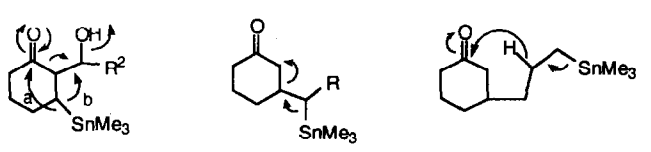
as a composite of allyl anion and hydride, as shown in eqn. (8).

2.2. Reactions with cationic stannyl reagents

In addition to the novel reaction types observed with the anionic stannyl reagents **1**, we have now found an interesting reaction mode with cationic stannyl reagents [10]. It has been known that γ-(t-butyldimethylsilyloxy) allylstannane **19** reacts with aldehydes at the γ-position, and the reaction has been used widely as a methodology for the synthesis of stereochemically defined 1,2-diols **20** [11]. In our paper on the reaction of **9**, we reported that the $TiCl_4$-induced reaction of γ-(trimethylsilyloxy) allylstannanes **21** with aldehydes gave the same β,γ-enones **23** as those from **9** [3]. Referring to eqn. (4), the reaction proceeds in the manner depicted in Scheme 1. Obviously the reaction site in **21** is in the β-position, in contrast to the γ-position as generally observed.

In view of these observations, we investigated the reaction of trifluoromethanesulfonates (triflates) **24**, obtainable by the conjugate addition of Me_3SnLi upon α, β-enones, followed by quenching with $PhNTf_2$ [12]. When the triflates were reacted with aldehydes **26** in the presence of BF_3–etherate in CH_2Cl_2 at room temperature to reflux temperature, the corresponding **28–30** were obtained (Table 2, runs 1–4). We schemed the reaction as involving a nucleophilic attack of the allylstannanes on aldehydes at the γ-position to produce **27**, followed by a directed pinacol-pinacolone type rearrangement with 1,2-migration of either R^3 (Type I) or H (Type II) [13] (Scheme 2). These reactions are formal insertions of allylic carbons into the C–R^3 or C–H bonds of the aldehydes, respectively, and it is evident that the triflate group functions as a leaving group. We can therefore represent the triflate reagents as a cation/anion reagent **31** or as a vinyl carbene equivalent **32**, and scheme the reaction as in .

The Type I reaction is particularly attractive from



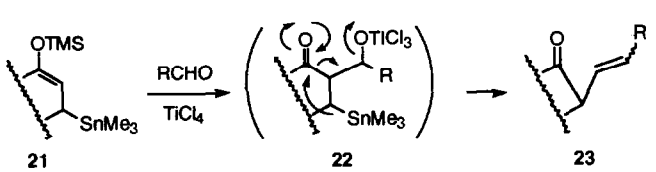
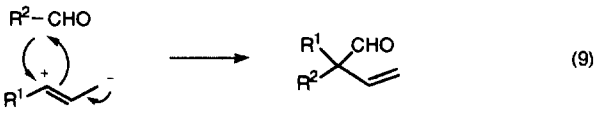


TABLE 2. Reactionof γ-substituted allylstannanes with aldehydres

Run	Allylstannane	Aldehyde	Products and yield (%) [a]		
			28	29	30
1	**24a**	**26k**	48	0	0
2	**24a**	**26l**	23	0	0
3	**24b**	**26k**	0	0	63
4	**24a**	**26m**	0	0	13
5	**25a**	**26k**	45 (34) [b]	6 (34)	0 (0)
6	**25a**	**26l**	61 (81)	0 (0)	0 (0)
7	**25a**	**26n**	53 (59)	0 (18)	0 (0)
8	**25a**	**26o**	0 (68)	0 (0)	0 (0)
9	l25a	**26p**	41 (59)	0 (0)	0 (0)
10	**25a**	**26p**	tr (tr)	53 (52)	0 (0)

[a] Catalyzed by BF_3–etherate. [b] Values in parentheses are the yields by $ZnBr_2$ catalyst.

the synthetic viewpoint since it affords compounds having quaternary carbons substituted by vinyl and formyl groups, which are potential functional groups for further manipulation. However, the yields were only moderate or poor, and several attempts at improving the yields were unsuccessful. We attributed the low yields to the sluggish reactivity at the γ-position due to the presence of the strong electron-withdrawing group (OTf), thus preventing the effective generation of a carbanionic character, and inducing side reactions. Actually large amount of the self aldol condensation product was obtained in the case of propanal (Table 2, run 4). We expected that the yields could be improved by changing the triflate group to a less electron-withdrawing substituent retaining the good leaving ability. Actually better yields were obtained with γ-chloro

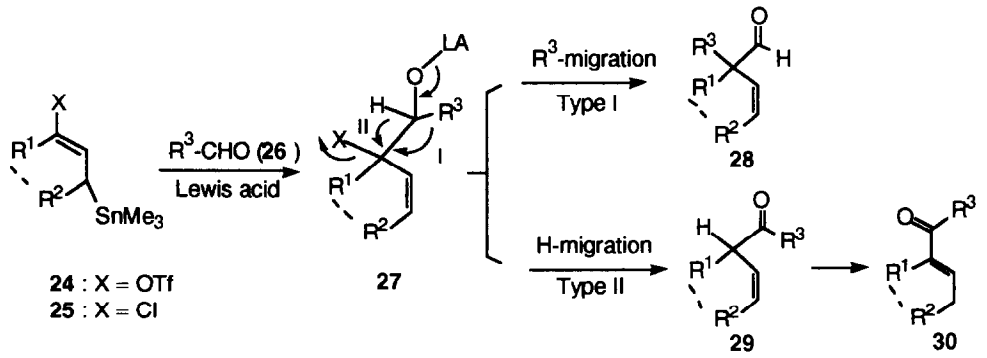


(9)

allylstannane **25a** (runs 5–10), easily available from 1,3-dichloro-2-butene and Me_3SnLi. Generally, $ZnBr_2$ and BF_3–etherate (except in runs 4 and 8) induced clean reactions, while other Lewis acids such as $TiCl_4$, TMSOTf, and $AlCl_3$ gave only complex mixtures.

The balance between the Type I and Type II reactions seems to be controlled by the migratory aptitudes of R^3 and H in **27**; the Type I reaction predominated with aryl or alkenyl aldehydes, while aliphatic saturated aldehydes preferred the Type II reaction. The only exception was the case of cyclic system, run 3, where H-migration overcame the phenyl migration. The selectivity between Types I and II also depended upon the Lewis acids employed. As a general trend, $ZnBr_2$ gave better yields but showed less selectivity of **28** compared with BF_3–etherate. In the particular case of run 8, BF_3–etherate was totally ineffective, probably because of the complexation of BF_3 with the methoxy oxygen.

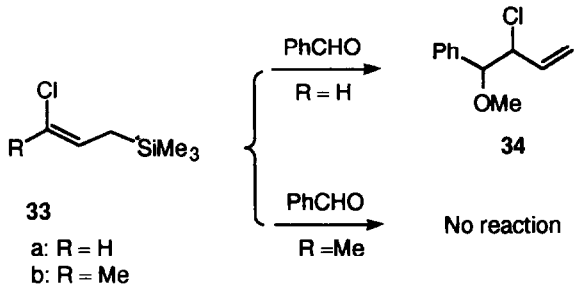
A comparison with the corresponding γ-chloro allylsilanes **33** is noteworthy. It has been reported that the reaction of **33a** with aldehydes affords unexpected



	R^1	R^2
a	Me	H
b	-$(CH_2)_3$-	

	R^3
k	Ph
l	PhCH=CH-
m	Et
n	*p*-tol

	R^3
o	*p*-$MeOC_6H_4CH$=CH-
p	MeCH=CH-
q	*n*-C_6H_{13}



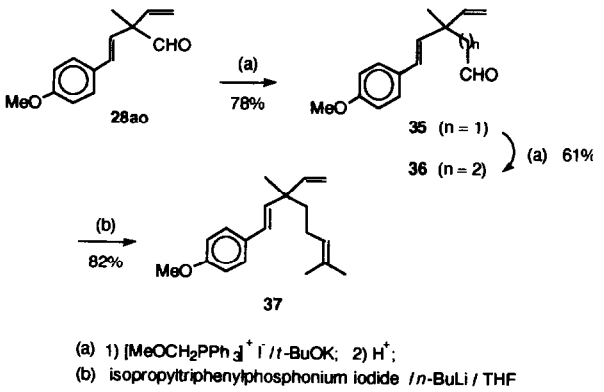
methyl ether **34**, and no further reaction from **34** has been observed [14]. It has also been reported that the introduction of a chlorine atom retards the reactivity of the allylsilane by the electronic and steric effects. Here we examined the Lewis acid-induced reaction of **33b**, a silyl counterpart of **25a**, with benzaldehyde, but no reaction proceeded, resulting in a quantitative recovery of the aldehyde.

2.3. Synthetic application

With the yields now fairly improved, we intended to apply the present reaction for synthetic purposes, and chose (±)-bakuchiol methyl ether **37** as a target. (+)-Bakuchiol is a phenolic monoterpene found in the seeds of *Psoralea corylifolia* Linn. [15,16]. As shown in Scheme 3, double homologation of **28ao**, obtained in 68% yield from **25a** and **26o** (run 8), and the succeeding Wittig reaction with isopropylidenephosphorane gave **37**. The demethylation to bakuchiol has been published [15].

3. Conclusion

In this paper, several reaction types induced by anionic and cationic stannyl reagents are demonstrated by synthon representation. The characteristic feature of these reagents is that diverse types of reactions can be realized, and the diversity can be ascribed to the medium reactivity of the carbon–tin bond as a carbanionic species. The lower reactivity than that of the ordinary explicit carbanions allows us to prepare stannyl compounds having electrophilic centers within the same molecule as stable intermediates. The higher reactivity of the carbon–tin bond than that of the carbon–silicon bond, for instance, allows us to stimulate the latent carbanionic nature to be reactive enough towards the electrophilic centers. As evident from the comparison of the reactivities of **25a** and **33b**, the nucleophilic ability of the allylstannanes is still retained even with the electron-withdrawing effect of the chlorine atom, in contrast to the case of the corresponding silyl compounds, in which the depressing effect by the chlorine atom totally deprives the allylsilane of nucleophilic ability.



4. Experimental details

4.1. General

GLC experiments were carried out on a 2.5 m × 3 mm stainless steel column packed with Silicone SE-30 on silanized Chromosorb W, and a 25 m × 0.25 mm capillary column (SE-30). Preparative TLC was carried out on DC-Fertigplatten, Kieselgel 60 F254 (thickness 0.5 mm, 20 × 20 cm, Merck, Art. 5744), using solvents as indicated. Column chromatography was carried out on Kieselgel 60, Art. 7734 (70–230 mesh ASTM) using solvents as indicated. ^{1}H NMR (60 MHz) spectra were recorded on a Jeol PMX 60 SI spectrometer. ^{1}H NMR (90 MHz) and ^{13}C NMR (22.5 MHz) spectra were measured on a Hitachi R-90H spectrometer, ^{13}C NMR (67.5 MHz) spectra on a Jeol EX-270 spectrometer, and ^{1}H NMR (400 MHz) spectra on a Jeol GSX400 spectrometer. GC-MS spectra were taken on a Shimadzu QP-1000 mass spectrometer and high resolution mass spectra on a Jeol-DX-300 mass spectrometer. IR spectra were recorded on a Perkin-Elmer 1640 type FT-IR spectrometer. Unless otherwise stated, all the spectroscopic data were determined on pure samples obtained by either distillation or column chromatography. The mass spectra were obtained by EI method at 70 eV or 20 eV. The ^{1}H NMR data on the 60 MHz machines were obtained with CCl_4 solutions, the ^{1}H NMR (400 MHz) and ^{13}C NMR (67.5 MHz) data with $CDCl_3$ solutions, and IR spectra with neat samples.

All of the ^{1}H NMR signals of the methyl group on tin atom at $\delta = \sim 0$ ppm accompanied splitting signals by ^{117}Sn (7.54% abundance, $J = 51$ Hz) and ^{119}Sn (8.62% abundance, $J = 53$ Hz). Mass spectrum peaks of the tin-containing fragments showed an isotope pattern typical of the tin atom, but only values corresponding to ^{120}Sn were shown.

4.2. General procedure for the preparation of trifluoromethanesulfonyloxy allylstannanes ***24a*** *and* ***24b***

A THF solution of the corresponding α,β-enones (0.3 M, 1 equiv.) was dropped into a THF solution of Me_3SnLi (0.3 M, 6.5–12.0 mmol, prepared as described previously [3]) over 1 h at −78°C. After the addition, the solution was stirred for 30 min and *N*-phenyltrifluoromethanesulfonimide (Tf_2NPh, equimolar to Me_3SnLi) was added into the solution in one portion. After the addition, the solution was warmed up to room temperature and stirred for 4.5 h. The solution was quenched with saturated aqueous NH_4Cl and extracted with ether. The ether extracts, after dried over $MgSO_4$, were concentrated *in vacuo*. Column chromatography (silica gel, hexane/ether, 10:1) gave pure materials.

4.2.1. 2-Trifluoromethanesulfonyloxy-4-trimethylstannyl-2-butene ***24a***

The product was obtained in 50% yield (1.84 g, 2:1 *E/Z* isomer mixture from GLC analysis) from methyl vinyl ketone (0.70 g, 10.0 mmol), Me_3SnLi solution (12.0 mmol, prepared from 2.39 g of Me_3SnCl) and Tf_2NPh (4.28 g, 12.0 mmol). ^1H NMR (*E/Z* mixture, 400 MHz): main isomer: δ 0.16 (s, 9H); 1.59 (d, 2H, $J = 9.9$ Hz); 2.00 (s, 3H); 5.72 (t, 1H, $J = 9.9$ Hz); minor isomer: δ 0.15 (s, 9H); 1.75 (dd, 2H, $J = 1.1$, 9.5 Hz); 2.05 (broad s, 3H); 5.38 (dt, 1H, $J = 0.8$, 9.5 Hz). MS (20 eV, *m/z*): 161,162, 163,164,165 (base), 351, 352, 353, 354.

4.2.2. 1-Trifluoromethanesulfonyloxy-3-trimethylstannyl-1-cyclohexene ***24b***

The product was obtained in 75% yield (1.75 g) from 2-cyclohexen-1-one (0.57 g, 5.93 mmol), Me_3SnLi solution (6.52 mmol, prepared from 1.30 g of Me_3SnCl) and Tf_2NPh (2.33 g, 6.52 mmol). ^1H NMR (90 MHz): δ 0.14 (s, 9H); 1.45–2.60 (m, 7H); 5.85 (broad d, 1H, $J = 4.4$ Hz). MS (20 eV, *m/z*): 68, 79, 95, 145, 161, 162, 163, 164, 165 (base), 166, 167, 169, 225, 227, 229, 258, 259, 260, 261, 262.

4.3. 2-Chloro-4-trimethylstannyl-2-butene ***25a***

A THF solution of Me_3SnLi (20 ml, 13.0 mmol, prepared from 2.60 g of Me_3SnCl) was added into a THF solution (15 ml) of 1,3-dichloro-2-butene (0.9 g, 7.20 mmol) at 0°C. The solution was gradually warmed up to room temperature and stirred for 30 min. The solution was quenched with saturated aqueous NH_4Cl and extracted with ether. The ether extract, dried over $MgSO_4$, was concentrated *in vacuo*. Column chromatography (hexane) gave **24b** in 50% yield (0.92 g). ^1H NMR (90 MHz): δ 0.12 (s, 9H); 1.77 (dd, 2H, $J = 1$, 9 Hz); 2.08 (d, 3H, $J = 1$ Hz); 5.62 (dd, 1H, $J = 1$, 9 Hz). MS (20 eV, *m/z*): 161, 162,163,164, 165 (base), 167,169, 181,182,183,184, 185, 187, 189, 251, 252, 253, 254 (M), 256.

4.4. General procedure for the $BF_3 \cdot OEt_2$-induced reaction of ***24a*** *and* ***24b*** *with aldehydes (runs 1–4)*

A CH_2Cl_2 solution (5 ml) of allylstannane **24a** or **24b** (0.3–0.6 mmol) and aldehydes (0.3–0.5 mmol) were treated under N_2 with a CH_2Cl_2 solution (2 ml) of BF_3–OEt_2 (0.3–0.5 mmol, equimolar to the corresponding aldehydes) under the conditions cited below. The mixture was quenched with saturated $NaHCO_3$, and extracted with CH_2Cl_2. After drying over $MgSO_4$, the solvent was removed *in vacuo*, and the crude material was purified by column chromatography (silica gel, hexane/ether, 5:1) to give the products.

4.4.1. Reaction of ***24a*** *with* ***26k*** *(run 1)*

The reaction of **24a** (0.22 g, 0.59 mmol) and **26k** (0.05 g, 0.47 mmol) at room temperature for 11 h gave **28ak** in 48% yield (36.2 mg). ^1H NMR (60 MHz): δ 1.44 (s, 3H); 5.02 (dd, 1H, $J = 2$, 18 Hz); 5.25 (dd, 1H, $J = 2$, 10 Hz); 6.07 (dd, 1H, $J = 10$, 18 Hz); 7.10 (broad s, 5H); 9.27(s, 1H). MS (20 eV, *m/z*): 91, 115, 116, 117, 129, 131 (base), 132,160 (M). HRMS: $C_{11}H_{12}O$ calcd. (M): 160.0888, Found: 160.0899.

4.4.2. Reaction of ***24a*** *with* ***26l*** *(run 2)*

The reaction of **24a** (0.20 g, 0.55 mmol) and **26l** (0.06 g, 0.45 mmol) under reflux for 4 h gave **28al** in 23% yield (18.8 mg). ^1H NMR (90 MHz): δ 1.40 (s, 3H); 5.19 (distort d, 1H, $J = 1$, 7.5 Hz); 5.35 (distort d, 1H, $J = 1$, 10 Hz); 6.00 (dd, 1H, $J = 7.5$, 10 Hz); 6.20 (d, 1H, $J = 16$ Hz); 6.49 (d, 1H, $J = 16$ Hz); 7.20–7.40 (m, 5H); 9.45 (s, 1H). ^{13}C NMR (22.5 MHz): δ 199.1, 138.0, 136.6, 132.1, 129.1, 128.5, 127.8, 126.3, 117.1, 55.6, 19.3. IR (neat): 2978, 2810, 2712, 1726, 1694, 1631, 1610, 1493, 1450, 969, 912, 746, 693 cm^{-1}. MS (20 eV, *m/z*): 79, 91, 115, 128, 129, 130, 141, 142, 143, 157 (base), 158, 186 (M). HRMS: $C_{13}H_{14}O$ calcd. (M): 186.1045, Found: 186.1041.

4.4.3. Reaction of ***24b*** *with* ***26k*** *(run 3)*

The reaction of **24b** (0.21 g, 0.55 mmol) and **26k** (0.05 g, 0.47 mmol) at room temperature for 13 h gave **30bk** in 65% yield (52.5 mg). The NMR spectrum coincided with the reported data [17].

4.4.4. Reaction of ***24a*** *with* ***26m*** *(run 4)*

The reaction of **24a** (0.14 g, 0.39 mmol) and **26m** (0.02 g, 0.37 mmol) at room temperature for 6.5 h gave **30am** in 13% yield (4.5 mg). The NMR spectrum coincided with the reported data [18].

4.5. General procedure for the $ZnBr_2$-induced reaction of 25a with aldehydes (runs 5–10)

A CH_2Cl_2 solution of **25a** (1–4 mmol, 1 equiv., 0.25 M) and aldehydes (0.8 equiv.) was poured into a suspension of $ZnBr_2$ (0.8–3.2 mmol, 0.8 equiv.) in CH_2Cl_2 (6 ml per 1 mmol of $ZnBr_2$) with a cannula tube at room temperature under N_2. After the addition, the mixture was refluxed for 4 h and quenched with saturated aqueous $NaHCO_3$ (10 ml). The mixture was passed through a celite column to remove the solid materials and extracted with CH_2Cl_2. After drying over $MgSO_4$, the solvent was removed *in vacuo*, and the crude material was purified by column chromatography (silica gel, hexane/ether, 5:1) to give the products.

4.5.1. Reaction with 26k (run 5)

The reaction of **25a** (0.54 g, 2.12 mmol) and **26k** (0.18 g, 1.70 mmol) gave **28ak** (92.0 mg, 34%) and **29ak** (92.1 mg, 34%). The former product was identical with the product obtained in Section 4.4.1, and the NMR spectrum of the latter product coincided with the reported data [19].

4.5.2. Reaction with 26l (run 6)

The reaction of **25a** (0.58 g, 2.28 mmol) and **26l** (0.24 g, 1.82 mmol) gave **28al** in 81% yield (276 mg), identified with the product obtained in Section 4.4.2.

4.5.3. Reaction with 26n (run 7)

The reaction of **25a** (0.65 g, 2.56 mmol) and **26n** (0.25 g, 2.08 mmol) gave **28an** (210 mg, 59%) and **29an** (18%, 65 mg).

28an: ^{1}H NMR (90 MHz): δ 1.52 (s, 3H); 2.34 (s, 3H); 5.15 (dd, 1H, J = 1, 18 Hz); 5.38 (dd, 1H, J = 1, 11 Hz); 6.22 (dd, 1H, J = 11, 18 Hz); 7.15 (s, 4H); 9.55 (s, 1H). ^{13}C NMR (67.5 MHz): δ 199.4, 138.5, 137.2, 136.9, 129.6, 127.4, 117.1, 57.5, 20.9, 20.1. IR (neat): 3088, 2981, 2925, 2871, 2812, 2712, 1727, 1632, 1513, 1453, 1413, 1019, 921, 814 cm^{-1}. MS (20 eV, m/z): 53, 91,105, 115, 117, 129, 130,131,143,145 (base), 146, 159, 174 (M). HRMS: $C_{12}H_{14}O$ calcd. (M): 174.1045, Found: 174.1038.

29an: ^{1}H NMR (400 MHz): δ 1.32 (d, 3H, J = 7.0 Hz); 2.41 (s, 3H); 4.15 (quintet, 1H, J = 7.0 Hz); 5.12 (dd, 1H, J = 1, 10 Hz); 5.17 (dd, 1H, J = 1, 17 Hz); 5.99 (ddd, 1H, J = 7.0, 10, 17 Hz); 7.25 (dd, 2H, J = 1.7, 8.4 Hz); 7.88 (d, 2H, J = 8.4 Hz). ^{13}C NMR (67.5 MHz): δ 200.8, 143.7, 138.3, 133.8, 129.2, 128.7, 116.3, 45.4, 21.6, 17.1. IR (neat): 3076, 2976, 1680, 1607, 1453, 1223, 994, 963, 916, 831, 768, 733 cm^{-1}. MS (20 eV, m/z): 91, 119 (base), 120, 174 (M). HRMS: $C_{12}H_{14}O$ calcd. (M): 174.1045. Found: 174.1004.

4.5.4. Reaction with 26o (run 8)

The reaction of **25a** (1.00 g, 3.92 mmol) and **26o** (0.51 g, 3.14 mmol) gave **28ao** in 68% yield (462 mg). ^{1}H NMR (60 MHz): δ 1.29 (s, 3H); 3.61 (s, 3H); 4.97 (dd, 1H, J = 2, 16 Hz); 5.11 (dd, 1H, J = 2, 10 Hz); 5.81 (dd, 1H, J = 10, 16 Hz); 5.79 (d, 1H, J = 16 Hz); 6.18 (d, 1H, J = 16 Hz); 6.51 (d, 2H, J = 8.5 Hz); 7.01 (d, 2H, J = 8.5 Hz); 9.06 (s, 1H). MS (70 eV, m/z): 77, 78, 79, 91, 115, 121, 128, 129, 135, 144, 145, 157, 158, 159, 172, 173, 187 (base), 188, 216 (M). HRMS: $C_{14}H_{16}O_2$ calcd. (M): 216.1150. Found: 216.1201.

4.5.5. Reaction with 26p (run 9)

The reaction of **25a** (0.72 g, 2.83 mmol) and **26p** (0.16 g, 2.28 mmol) gave **28ap** in 59% yield (165 mg). ^{1}H NMR (60 MHz): δ 1.27 (s, 3H), 1.75 (dd, 3H, J = 2, 4.4 Hz), 5.20 (dd, 1H, J = 1, 16 Hz); 5.30 (dd, 1H, J = 1, 10 Hz); 5.50–5.80 (m, 2H); 6.00 (dd, 1H, J = 10, 16 Hz); 9.05 (s, 1H). ^{13}C NMR (22.5 MHz): δ 199.7, 138.5, 130.5, 128.2, 116.4, 55.4, 19.2, 18.4. IR (neat): 3087, 2976, 2935, 2858, 2808, 2710, 1729, 1629, 1451, 1413, 1379, 1368, 970, 923, 734 cm^{-1}. MS (20 eV, m/z): 41, 43, 53, 55, 65, 67, 79, 81, 93, 95 (base), 96, 124 (M). HRMS: C_8H_{12O} calcd. (M): 124.0888. Found: 124.0856.

4.5.6. Reaction with 26q (run 10)

The reaction of **25a** (0.31 g, 1.22 mmol) and **26q** (0.11 g, 0.96 mmol) gave **29aq** in 52% yield (85.7 mg). ^{1}H NMR (90 MHz): δ 0.7–1.0 (broad t, 3H, J = 6.3 Hz); 1.16 (d, 3H, J = 7 Hz); 1.20–1.35 (m, 6H); 1.5–1.6 (m, 2H); 2.46 (dt, 2H, J = 1, 7.5 Hz); 3.20 (quintet, 1H, J = 7 Hz); 5.13 (dd, 1H, J = 1, 10 Hz); 5.16 (dd, 1H, J = 1, 17 Hz); 5.83 (ddd, 1H, J = 7, 10, 17 Hz). ^{13}C NMR (67.5 MHz): δ 211.7, 137.7, 116.6, 51.3, 40.7, 31.6, 28.9, 23.6, 22.5, 15.8, 14.0. IR (neat): 3081, 2930, 2858, 1839, 1787, 1714, 1668, 1634, 1455, 1411, 1372, 1129, 1028, 995, 918 cm^{-1}. MS (20 eV, m/z): 41, 43, 44, 55, 57, 69, 83, 85, 95, 111, 113 (base), 114, 168 (M). HRMS: $C_{11}H_{20}O$ calcd. (M): 168.1514. Found: 168.1483.

4.6. General procedure for the $BF_3 \cdot OEt_2$-induced reaction of 25a

The reaction was carried out using a solution of BF_3–OEt_2 in CH_2Cl_2 (0.3 M, equimolar to aldehydes), instead of $ZnBr_2$ at room temperature (30 min 2 h, by monitoring the disappearance of **25a** on TLC) under the otherwise same conditions as described in Section 4.5. The results shown in Table 2 were obtained. Only in the case of run 8 did the reaction did not proceed because insoluble material was formed by the reaction of $BF_3 \cdot OEt_2$ and the aldehyde.

4.7. Total synthesis of (±)-bakuchiol methyl ether (37)

4.7.1. Synthesis of 35

(Methoxymethyl)triphenylphosphonium chloride (1.23 g, 3.59 mmol) was added to a dry dioxane solution (25 ml) of ^{t}BuOK (0.41 g, 3.65 mmol) at room temperature under N_2, and the reddish solution was stirred for 3 h. Into this solution was added a dry dioxane solution (10 ml) of **28ao** (0.52 g, 2.41 mmol) and the mixture was stirred for another 1 h. The mixture was quenched with saturated aqueous NH_4Cl, extracted with ether, and concentrated up to 10 ml *in vacuo*. After water (10 ml) and *p*-toluensulfonic acid (0.1 g) were added into the solution, the mixture was refluxed for 1.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. After drying over $MgSO_4$, the solvent was removed *in vacuo*. The crude material was purified by column chromatography (silica gel, hexane/ether, 2:1) to give **35** in 78% yield (0.43 g). ^{1}H NMR (60 MHz): δ 1.27 (s, 3H); 2.38 (d, 2H, J = 3 Hz); 3.64 (s, 3H); 4.90 (dd, 1H, J = 2, 18 Hz); 4.98 (dd, 1H, J = 2, 9 Hz); 5.82 (dd, 1H, J = 9, 18 Hz); 5.80 (d, 1H, J = 16 Hz); 6.13 (d, 1H, J = 16 Hz); 6.53 (d, 2H, J = 9 Hz); 7.00 (d, 2H, J = 9 Hz); 9.39 (t, 1H, J = 3 Hz). MS (70 eV, m/z) 77, 79, 91, 105, 121, 128, 129, 134, 135, 144, 158, 159, 172, 187 (base), 188, 230 (M). HRMS: $C_{15}H_{18}O_2$ calcd. (M): 230.1307. Found: 230.1339.

4.7.2. Synthesis of 36

The aldehyde **36** was obtained from **35** (0.22 g, 0.96 mmol) in 61% yield (0.14 g) by the same operation as mentioned above. ^{1}H NMR (60 MHz): δ 1.15 (s, 3H); 1.76 (dt, 2H, J = 2, 9 Hz); 2.33 (dt, 2H, J = 2, 9 Hz); 3.65 (s, 3H); 4.90 (dd, 1H, J = 2, 18 Hz); 4.97 (dd, 1H, J = 2, 9 Hz); 5.73 (dd, 1H, J = 9, 18 Hz); 5.76 (d, 1H, J = 16 Hz); 5.88 (d, 1H, J = 16 Hz); 6.60 (d, 2H, J = 9 Hz); 7.04 (d, 2H, J = 9 Hz); 9.49 (broad d, 1H, J = 2 Hz).

4.7.3. Synthesis of (±)-bakuchiol methyl ether (37)

To a dry THF solution (1 ml) of isopropyltriphenylphosponium iodide (0.38 g, 0.88 mmol) was added n-butyllithium (hexane solution, 1.69 M, 0.88 mmol) at room temperature under N_2, and the reddish solution was stirred for another 1 h. A dry THF solution (1 ml) of **36** (0.14 g, 0.57 mmol) was added, and the solution was stirred for 8 h at room temperature. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. After drying over $MgSO_4$, the solvent was removed *in vacuo*. The crude material was purified by preparative TLC (thickness 0.5 mm, hexane) to give (±)-bakuchiol methyl ether **37** in 82% yield (0.13 g). The NMR and IR spectra coincided with the reported data [15].

Acknowledgement

Financial support from the Grant-in-Aid for Scientific Research Nos. 0345033 and 05236235 from the Ministry of Education, Science and Culture is greatly acknowledged.

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