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A New, Efficient Method for Direct α-Alkenylation of β-Dicarbonyl Compounds and Phenols Using Alkenyltriarylbismuthonium Salts

Yoshihiro Matano* and Hiroshi Imahori

Department of Molecular Engineering, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan

matano@scl.kyoto-u.ac.jp

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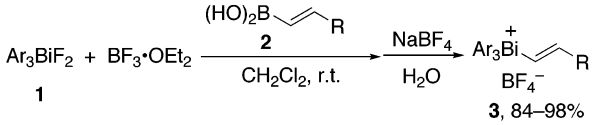
Abstract: Direct α-alkenylation of β-keto esters, β-diketone, and phenols with alkenyltriarylbismuthonium salts proceeded smoothly in the presence of 1,1,3,3-tetramethylguanidine to afford the corresponding α-alkenylated carbonyl compounds (β,γ-unsaturated carbonyl compounds) in good yields. The high leaving ability of the triarylbismuthonio group is a key driving force to achieve the C−C bond formation at the vinylic carbon under mild conditions.

α-Alkenylation of enolizable compounds with alkenyl cation equivalents is a reliable method for the synthesis of β,γ-unsaturated ketones and esters, which are useful building blocks in organic synthesis. However, it is known that nucleophilic substitution at a vinylic carbon is difficult,[1] and only a few methods are available for the direct α-alkenylation of enolates with simple haloalkenes.[2,3] One of the promising ways to enhance the nucleofugality of the vinylic *ipso* carbon is replacement of the halogen atom by a good leaving group. On the basis of this concept, alkenyllead triactetates[4] and alkenylphenyliodonium salts[5] have been developed as the alkenyl cation equivalents, both of which undergo α-alkenylation of enolizable substrates to give β,γ-unsaturated carbonyl compounds, accompanied by the formation of lead(II) acetate and iodobenzene, respectively.

Like lead(IV) and iodine(III) compounds, organobismuth(V) compounds possess high nucleofugality derived from the facile Bi(V)/Bi(III) redox process.[6] Taking advantage of this property of bismuth, Barton and coworkers developed a general method for the α-phenylation of enolizable substrates using phenylbismuth(V) compounds of the types Ph_4BiX and Ph_3BiX_2,[7] where α-phenylated products are obtained under neutral or basic conditions together with phenylbismuth(III) compounds. Quite recently, Ooi, Goto, and Maruoka reported a high-yield synthesis of β,γ-unsaturated ketones using fluoro(styryl)tris(4-methylphenyl)bismuth(V) and silyl enolates.[8] These results suggested to us that the α-alkenylation of enolizable substrates would be also developed using alkenylbismuth(V) compounds as the alkenyl cation equivalents. We report herein a new efficient method for the synthesis of β,γ-unsaturated carbonyl compounds via direct α-alkenylation of β-dicarbonyl compounds and phenols using alkenyltriarylbismuthonium salts.

SCHEME 1



3a: R = *n*-Bu, Ar = *p*-MeC_6H_4 **3g:** R = *n*-C_6H_{13}, Ar = *p*-MeC_6H_4
3b: R = *n*-Bu, Ar = Ph **3h:** R = *n*-C_6H_{13}, Ar = *p*-$MeOC_6H_4$
3c: R = *n*-Bu, Ar = *p*-$MeOC_6H_4$ **3i:** R = *n*-C_6H_{13}, Ar = *p*-*t*-BuC_6H_4
3d: R = *n*-Bu, Ar = *p*-*t*-BuC_6H_4 **3j:** R = Ph, Ar = *p*-MeC_6H_4
3e: R = *n*-Bu, Ar = *o*-$MeOC_6H_4$ **3k:** R = Ph, Ar = *o*-$MeOC_6H_4$
3f: R = *t*-Bu, Ar = *p*-MeC_6H_4 **3l:** R = Me, Ar = *p*-MeC_6H_4

Alkenyltriarylbismuthonium salts (**3**) were prepared in 84−98% yield by the BF_3•OEt_2-promoted metathesis reaction of triarylbismuth difluorides (**1**) with alkenylboronic acids (**2**) according to a previously reported procedure (Scheme 1).[9]

In contrast to alkenyllead triacetates, the alkenylbismuthonium salts **3** are thermally and air stable and easy to handle. They are soluble in CH_2Cl_2 and $CHCl_3$, slightly soluble in toluene, and hardly soluble in ether. In the ^1H NMR spectra of **3**, the α-vinyl protons were observed as broad signals at around δ 7.8 for the β-alkyl derivatives and at δ 8.3−8.6 for the β-phenyl derivatives. In the ^{13}C NMR of **3**, the α-vinyl carbons were observed at δ 151−161. In the FABMS spectra, the $[RCH{=}CHBiAr_3]^+$ ion was observed as a parent peak.

With alkenyltriarylbismuthonium salts **3** in hand, we first examined the direct α-alkenylation of β-dicarbonyl compounds under basic conditions. Treatment of **3a** with ethyl 2-oxocyclohexanecarboxylate (**4**) in the presence of 1,1,3,3-tetramethylguanidine (TMG) in toluene afforded ethyl 1-((*E*)-hex-1-enyl)-2-oxocyclohexanecarboxylate (**5a**)

(1) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; pp 295−304.

(2) Transition metal-catalyzed direct α-alkenylation with haloalkenes, see: (a) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833. (b) Chieffi, A.; Kamikawa, K.; Ahman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897. (c) Hamada, T.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 999.

(3) Photoinduced direct α-alkenylation with haloalkenes, see: Bunnett, J. F.; Creary, X.; Sundberg, J. E. *J. Org. Chem.* **1976**, *41*, 1707.

(4) (a) Moloney, M. G.; Pinhey, J. T. *J. Chem. Soc., Chem. Commun.* **1984**, 965. (b) Moloney, M. G.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2847. (c) Pinhey, J. T. *Aust. J. Chem.* **1991**, *44*, 1353. (d) Parkinson, C. J.; Pinhey, J. T.; Stoermer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1911. (e) Hambley, T. W.; Holmes, R. J.; Parkinson, C. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1917. (f) Hashimoto, S.; Shinoda, T.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1988**, 1137. (g) Chen, C.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 10784.

(5) (a) Beringer, F. M.; Galton, S. A. *J. Org. Chem.* **1965**, *30*, 1930. (b) Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095. (c) Ochiai, M.; Shu, T.; Nagaoka, T.; Kitagawa, Y. *J. Org. Chem.* **1997**, *62*, 2130. In some cases, the competing α-phenylation becomes predominant.

(6) The leaving ability of the triphenylbismuthonio group is higher than that of triflate ion. See: Matano, Y. *Organometallics* **2000**, *19*, 2258.

(7) (a) Barton, D. H. R.; Blazejewski, J.-C.; Charpiot, B.; Finet, J.-P.; Motherwell, W. B.; Papoula, M. T. B.; Stanforth, S. P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2667. (b) Barton, D. H. R.; Bhatnagar, N. Y.; Finet, J.-P.; Motherwell, W. B. *Tetrahedron* **1986**, *42*, 3111. (c) Abramovitch, R. A.; Barton, D. H. R.; Finet, J.-P. *Tetrahedron* **1988**, *44*, 3039.

(8) Ooi, T.; Goto, R.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 10494.

(9) Matano, Y.; Begum, S. A.; Miyamatsu, T.; Suzuki, H. *Organometallics* **1998**, *17*, 4332.

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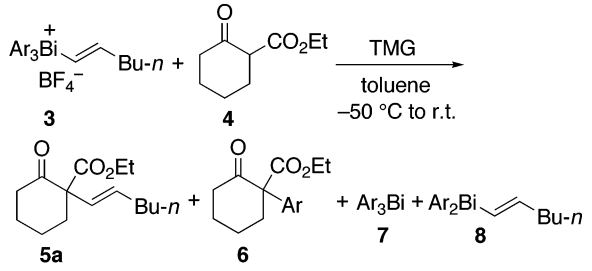
TABLE 1. Reaction of 3a−e with 4



entry	3	products (yield/%)[a]
1	**3a**	**5a** (89), **6a** (4), **7a** (85), **8a** (5)
2	**3b**	**5a** (73), **6b** (14), **7b** (80), **8b** (15)
3[b]	**3c**	**5a** (90), **6c** (trace)
4[b]	**3d**	**5a** (91)
5	**3e**	no C−C coupling

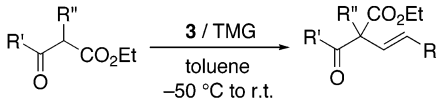
[a] **6**−**8**: **a** = *p*-MeC$_6$H$_4$; **b** = Ph; **c** = *p*-MeOC$_6$H$_4$. [b] Yields of other products were not determined.

and tris(4-methylphenyl)bismuthane (**7a**) as major products (Table 1, entry 1). No reaction took place in the absence of a base, suggesting that an enolate, generated from **4** and TMG, is the active nucleophile for the α-alkenylation (vide infra). Careful inspection of the reaction mixture by ^{1}H NMR showed the presence of small amounts (<5%) of ethyl 2-oxo-1-(4-methylphenyl)-cyclohexanecarboxylate (**6a**) and ((*E*)-hex-1-enyl)bis(4-methylphenyl)bismuthane (**8a**). This finding implies that the transfer of the 1-hexenyl group is preferable to that of the 4-methylphenyl group. The bismuthanes **7a** and **8a** precipitated out from the reaction mixture by adding a small amount of MeOH and were recovered by filtration. Concentration of the MeOH filtrate gave an oily residue, which was purified by column chromatography on silica gel to afford **5a** in 89% isolated yield.

To examine the effect of the aryl ligands attached to the bismuth, similar reactions were carried out using other bismuthonium salts **3b**−**e** bearing phenyl or substituted aryl groups (Table 1, entries 2−5). Among the para- and nonsubstituted compounds **3a**−**d**, the alkenyl transfer was predominant in all cases and the alkenyl/aryl selectivity slightly increased by introducing an electron-donating substituent. On the other hand, introduction of the *o*-methoxy group dramatically retarded the reactivity: neither alkenylation nor arylation occurred between **3e** and **4**.

Both cyclic and acyclic β-keto esters were α-alkenylated by **3** under the same reaction conditions to give the corresponding β,γ-unsaturated carbonyl compounds with retention of the stereochemistry of the vinyl moiety (Table 2). In the presence of TMG, **3g**,**j** reacted with **4** to afford **5b**,**c** in good yields (entries 1 and 2). Similarly, **3j** reacted with ethyl 2-oxocyclopentanecarboxylate (**9**) to yield **10** (entry 3). When ethyl 3-oxobutanoate (**11**) was treated with 1 equiv of **3j** in the presence of 1 equiv of TMG, α,α-dialkenyl-β-keto ester **12** was obtained in 48% yield based on **11** (96% yield based on **3j**) (entry 4). The monoalkenylated ketone **13** that would be formed as an initial product was not obtained at all, suggesting that the second alkenylation of **13** proceeded much more rapidly than the first alkenylation of **11**. This is probably because of the higher acidity of the allylic methine proton of **13** as compared to the methylene protons of **11**. When

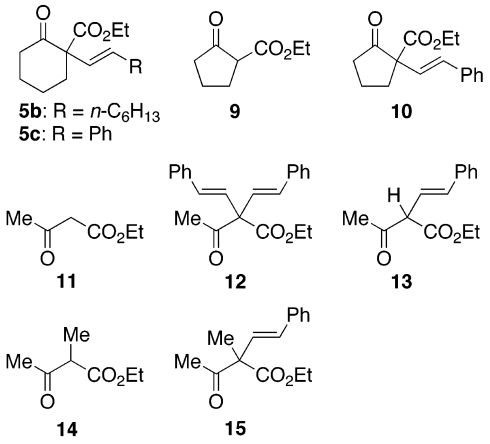
TABLE 2. α-Alkenylation of β-Keto Esters with 3



entry	β-keto ester	3	product (yield/%)
1	**4**	**3g**	**5b** (86)
2	**4**	**3j**	**5c** (88)
3	**9**	**3j**	**10** (90)
4	**11**	**3j**	**12** (48)
5	**11**	**3j**[a]	**12** (96)
6	**14**	**3j**	**15** (90)

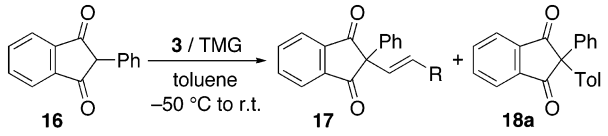
[a] 2 equiv of **3j**/TMG was used.

2 equiv of **3j** and TMG were used, **12** was obtained in 96% yield based on **11** (entry 5). The α-methine carbon of ethyl 2-methyl-3-oxobutanoate (**14**) was smoothly alkenylated to give **15** in 90% yield (entry 6). In contrast, the alkenyl group of **3** could not be transferred efficiently to simple monoketones such as acetophenone and cyclohexanone, which possess less acidic α-protons than the above substrates. In these reactions alkynes and bismuthanes **7** were formed as major products, indicating that the α-proton abstraction from **3** occurred predominantly (vide infra).



Treatment of the β-monosubstituted alkenylbismuthonium salts **3a**,**f**,**g**,**j**,**l** with 2-phenylindan-1,3-dione (**16**) in the presence of TMG afforded the corresponding 2-alkenyl-2-phenylindan-1,3-diones (**17a**−**e**) in 73−92% yields (Table 3, entries 1−5). In the reaction of **3l′** (an

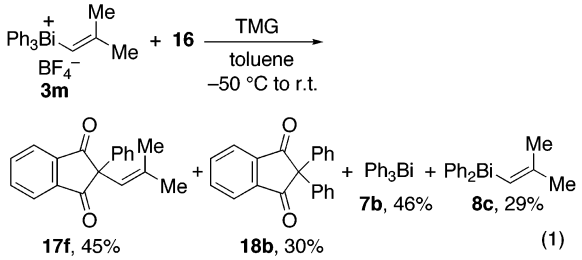
TABLE 3. Reaction of 3 with 16



entry	3	products (yield/%)
1	**3a**	**17a** (R = *n*-Bu, 89), **18a** (5)
2	**3f**	**17b** (R = *t*-Bu, 92), **18a** (trace)
3	**3g**	**17c** (R = *n*-C$_6$H$_{13}$, 86),**18a** (2)
4	**3j**	**17d** (R = Ph, 82), **18a** (3)
5	**3l**	**17e** (R = Me, 73), **18a** (13)
6	**3l′**[a]	**17e′**[b] (R = Me, 72), **18a** (9)

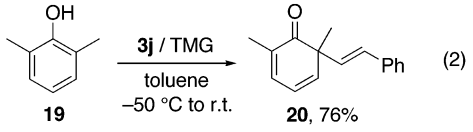
[a] *E*/*Z* = 30/70. [b] *E*/*Z* = 34/66.

E/*Z* mixture: *E*/*Z* = 30/70) with **16**, the stereochemistry of the vinyl moiety is mostly retained, affording **17e′** with an *E*/*Z* ratio of 34/66 (entry 6). On the other hand, the *β*,*β*-dimethyl derivative **3m** reacted with **16** to afford α-alkenyl and α-phenyl ketones **17f** and **18b** in 45% and 30% yield, respectively, together with **7b** and **8c** (eq 1). Thus, the selectivity of the alkenyl vs aryl transfer (**17** vs **18**) strongly depended on the *β*-substituents of the vinyl moiety, which was found to be in the order *β*-alkyl, *β*-phenyl > *β*-methyl > *β*,*β*-dimethyl.

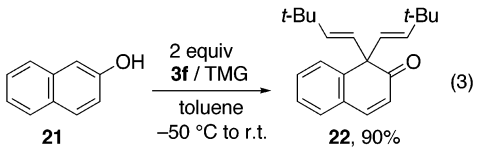


(1)

Phenols were also alkenylated at the α-position (ortho-position) using alkenylbismuthonium salts **3**. Thus, **3j** reacted with 2,6-dimethylphenol (**19**) in the presence of TMG to give 2,6-dimethyl-6-styrylcyclohexa-2,4-dienone (**20**) in 76% yield (eq 2). When 2-naphthol (**21**) was used as the substrate, α,α-dialkenyl ketone **22** was obtained in a good conversion yield (eq 3). As was observed for the reaction of **11**, monoalkenylated ketone was not formed at all.



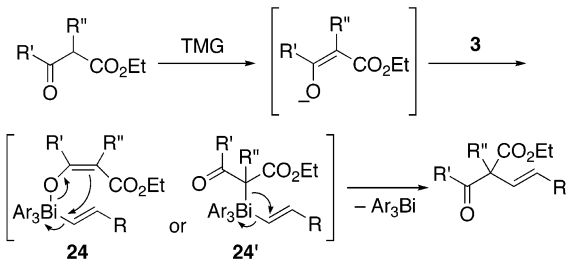
(2)



(3)

There are several conceivable mechanisms for the present α-alkenylation: S_N2 reaction, S_N1 reaction, C−H insertion via an alkylidene carbene, addition−elimination, and ligand exchange−ligand coupling.[10] Among them, the S_N2 and S_N1 mechanisms can be discarded because they cannot explain the retention of the stereochemistry.[11] Furthermore, the generation of a vinylic cation in toluene seems to be unlikely.[12] The alkylidene carbene, generated by the α-proton abstraction from **3**, is a possible intermediate.[13] In fact, terminal acetylenes **23** were formed exclusively from **3** and TMG (eq 4), which is the main side reaction in the present system. However, the free carbene mechanism cannot explain the stereochemical outcome of the α-alkenylation with **3l** and **3l′**:

SCHEME 2



the *E*/*Z* ratio of **17e** differs considerably from that of **17e′**.[14] The addition−elimination mechanism, proposed for the nucleophilic substitution of alkenyliodonium salts bearing an electron-withdrawing substituent at the *β*-position,[15] explains the retention of the stereochemistry. In compounds **3**, however, the vinylic *β*-carbon bears no electron-withdrawing group that is necessary for stabilizing a betain intermediate. In contrast to the above pathways, the ligand exchange-ligand coupling[16] mechanism well explains not only the stereochemical outcome but also the substituent effects on the reactivity and selectivity. Thus, the enolate attacks the bismuth center to generate pentacoordinate species **24** or **24′**, followed by ligand coupling to give the products (Scheme 2).[17] A key driving force of the last step is the high leaving ability of the triarylbismuthonio group. The low reactivity recognized for **3e** might be due to the coordination of the three *o*-methoxy oxygen atoms to the cationic bismuth center,[18] which prevents the nucleophilic attack of the enolate to the bismuth both electronically and sterically. When the α-proton of enolizable substrates is less acidic than the α-vinyl proton of **3**, however, the α-proton abstraction from **3** becomes a main pathway.

(4)

We developed a new efficient method for the synthesis of *β*,*γ*-unsaturated ketones and esters by the TMG-promoted reaction of alkenyltriarylbismuthonium salts with *β*-dicarbonyl compounds and phenols. It should be noted here that a quaternary, allylic α-carbon center is readily constructed from the active methylene or methine compounds under mild conditions. Although the enolizable substrates are limited to those having relatively

(10) For reviews on the nucleophilic vinylic substitutions, see: (a) Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474. (b) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (c) Modena, G. *Acc. Chem. Res.* **1971**, *4*, 73.

(11) If the alkenylation proceeds through an S_N2 or S_N1 mechanism, the stereochemistry of the vinylic moiety is inverted or lost significantly.

(12) Richey, H. G., Jr. In *The Chemistry of Alkenes*; Zabicky, J. Ed.; Wiley: London, 1970; Vol. 2, Chapter 2, pp 39−114.

(13) For a review, see: Stang, P. J. *Chem. Rev.* **1978**, *78*, 383.

(14) If the reaction proceeds via the C−H insertion of a free alkylidene carbene, the *E*/*Z* ratio of **17e** should be the same as that of **17e′**.

(15) For example, see: (a) Ochiai, M.; Oshima, K.; Masaki, Y. *Tetrahedron Lett.* **1991**, *32*, 7711. (b) Ochiai, M.; Oshima, K.; Masaki, Y. Kunishima, M.; Tani, S. *Tetrahedron Lett.* **1993**, *34*, 4829. (c) Zefirov, N. S.; Koz'min, A. S.; Kasumov, T.; Potekhin, K. A.; Sorokin, V. D.; Brel, V. K.; Abramkin, E. V.; Struchkov, Y. T.; Zhdankin, V. V.; Stang, P. J. *J. Org. Chem.* **1992**, *57*, 2433.

(16) (a) Oae, S.; Uchida, Y. *Acc. Chem. Res.* **1991**, *24*, 202. (b) Finet, J.-P. *Ligand Coupling Reactions with Heteroatomic Compounds*; Elsevier: London, 1998, and references therein.

(17) A similar ligand coupling mechanism was proposed by Barton and co-workers for the α-phenylation of enolizable substrates with tetraphenylbismuthonium salts. See ref 7.

(18) X-ray crystallographic analyses of bismuthonium salts bearing *o*-anisyl groups disclosed the intramolecular coordination between the *o*-methoxy oxygens and the bismuth center. Suzuki, H.; Ikegami, T.; Azuma, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1609. See also ref 6.

acidic α-protons, the present method qualifies as a reliable addition to the existing methods for the direct α-alkenylation of carbonyl compounds.

Experimental Section

Reaction of 3 with Carbonyl Compounds in the Presence of TMG. General Procedure. To a mixture of **3** (0.50 mmol), carbonyl compound (0.50 mmol), and toluene (5 mL) was added TMG (65 μL, 0.50 mmol) at −50 °C. The resulting mixture was allowed to warm to room temperature with vigorous stirring. Water (5 mL) and Et_2O (5 mL) were added to the mixture, and the organic phase was washed with water (2 mL × 3), dried over $MgSO_4$, and concentrated under reduced pressure. Adding a suitable amount of MeOH (5−10 mL) to the residue caused precipitation of the bismuthane as a colorless solid. After removal of the bismuthane by filtration, the filtrate was concentrated in vacuo to give an oily residue, which was chromatographed on silica gel using hexane/ethyl acetate as eluents to afford β,γ-unsaturated carbonyl compounds.

Reaction of 3 with TMG. To a $CDCl_3$ solution (ca. 0.5 mL) of **3a**,**f**,**j** (0.02 mmol) was added TMG (0.02 mmol), and the resulting mixture was monitored at room temperature by ^1H NMR spectroscopy. In all cases examined, bismuthane **7a** and acetylene **23** were formed in good yields.

Acknowledgment. This work was partially supported by a Grant-in-Aid (No. 14540494) from the Ministry of Education, Science, Sports and Culture of Japan and a Toray Award in Synthetic Organic Chemistry, Japan.

Supporting Information Available: Experimental details and characterization data for **3** and the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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