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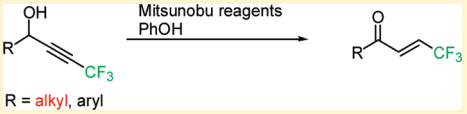
Application of Mitsunobu Reagents to Redox Isomerization of CF_3-Containing Propargylic Alcohols to (*E*)-α,β-Enones

Yohsuke Watanabe and Takashi Yamazaki*

Division of Applied Chemistry, Institute of Engineering, Tokyo University of Agriculture and Technology, 2-24-16 Nakacho, Koganei 184-8588, Japan

Supporting Information

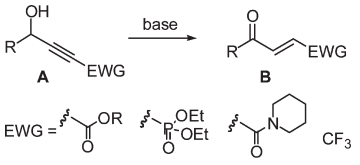
ABSTRACT: Isomerization of CF_3-containing secondary propargylic alcohols proceeds with excellent *E* selectivity by treatment with Mitsunobu reagents, tris(*p*-methoxyphenyl)phosphine (TMPP), and 1,1′-(azodicarbonyl)dipiperidine (ADDP) in the presence of phenol.



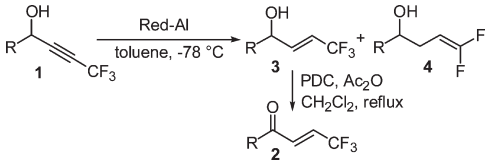
Trifluoromethylated compounds have recently attracted significant interest in various fields such as medicine, pharmaceuticals, and functional materials due to such unique properties of the trifluoromethyl group as high electronegativity, electron density, and hydrophobicity.[1] Highly electrophilic β-trifluoromethyl α,β-enones **2**, as a result of the lower LUMO energy levels than the corresponding nonfluorinated counterparts,[2b] have been utilized as quite important building units for a wide variety of reactions including Diels−Alder cycloadditions[2] and Michael-type additions.[2a,3]

In 1949, the first example of redox isomerization of the γ-hydroxy-α,β-alkynyl ester **A** to the γ-oxo-α,β-alkenyl ester **B** in the presence of Et_3N was reported by Nineham and Raphael for the single substrate of EWG = CO_2Me, R = Ph (Scheme 1).[4] Koide and Sonye clarified that this isomerization was widely applicable to materials possessing not only ester functionality but also phosphate and amide moieties as EWGs in **A** whose conversions were promoted by DABCO or $NaHCO_3$.[5b−e] In recent years, we have also reported that propargylic alcohols with a trifluoromethyl (CF_3) group at the distal position of the triple bond (EWG) could be converted to enones by treatment with Et_3N in THF.[5f] These base-mediated reactions were found to be limited to only substrates with aryl substituents as R, and the isomerization of primary and alkyl-substituted secondary propargylic alcohols usually requires high-cost transition-metal catalysts.[6] We have previously disclosed the synthetic pathway to ketones **2** by successive Red-Al reduction of **1a**, followed by PDC oxidation (Scheme 2). However, the first step, conversion of propargylic alcohols **1** to the corresponding allylic counterparts **3**, sometimes suffered from overreduction of the desired **3** to the difluorinated homoallylic alcohols **4**, and separation of these two compounds was a quite troublesome task.[7] While our above-mentioned process shown in Scheme 1 (EWG = CF_3) is recognized as the alternative protocol to **2**, quite unfortunately, this technique is applicable to only the case for R = Ar as mentioned above. Herein, we report the first example of the redox isomerization of secondary propargylic alcohols **1** to α,β-enones **2** by treatment with Mitsunobu reagents,[8] which is effective for substrates with not only an aromatic moiety but also an alkyl group as R without using any transition-metal catalysts.

Scheme 1. Base-Mediated Redox Isomerization



Scheme 2. Synthetic Route to α,β-Enones 2



In our initial investigation, we found that the reaction of the model CF_3-containing propargylic alcohol **1a** with triphenylphosphine, diisopropyl azodicarboxylate (DIAD), and phenol in Et_2O at room temperature afforded α,β-enone **2a** in good yield (*Z*/*E* = 75:25, Table 1, entry 1). THF also worked as a solvent but in a less efficient manner, furnishing **2a** in 41% yield (*Z*/*E* = 42:58, entry 2). Among the reagent combinations examined, formation of a number of byproducts was noticed under the PPh_3-DIAD conditions probably by nucleophilic attack of the

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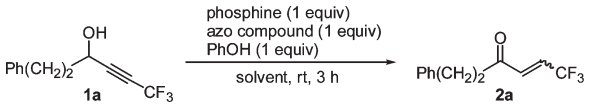
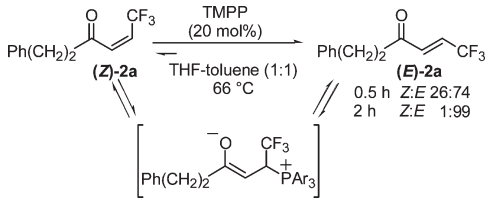
Table 1. Screening of Reagents for Isomerization of the Propargylic Alcohol 1a[a]



entry	azo compd	phosphine	solvent	yield[b] (%)	Z/E[b]
1	DIAD	PPh_3	Et_2O	68	75:25
2	DIAD	PPh_3	THF	41	42:58
3	ADDP	PPh_3	THF	12	42:58
4	ADDP	2-pyridyl-PPh_2	THF	14	58:42
5	ADDP	4-$MeOC_6H_4$-PPh_2	THF	40	48:52
6	ADDP	$(4\text{-}MeOC_6H_4)_3P$	THF	60	44:56
7	ADDP	$(4\text{-}MeOC_6H_4)_3P$	toluene	71	39:61
8	ADDP	$(4\text{-}MeOC_6H_4)_3P$	CH_2Cl_2	60	38:62
9	ADDP	$(4\text{-}MeOC_6H_4)_3P$	MeCN	N.R.[c]	
10	ADDP	$(4\text{-}MeOC_6H_4)_3P$	DMF	0	
11	ADDP	$(4\text{-}MeOC_6H_4)_3P$	THF−H_2O (5:1)	N.R.[c]	
12	ADDP	$(4\text{-}MeOC_6H_4)_3P$	THF−toluene (1:1)	51	48:52
13	ADDP	$(4\text{-}MeOC_6H_4)_3P$ (1.2 equiv)	THF−toluene (1:1)	80	12:88
14[d]	ADDP	$(4\text{-}MeOC_6H_4)_3P$ (1.2 equiv)	THF−toluene (1:1)	98	<1:>99

[a] The reactions were carried out in a 0.6 mmol scale with 6 mL of a solvent. [b] Yields and ratios were determined by integration of the ^{19}F NMR peaks of crude products using $PhCF_3$ as an internal standard. [c] No reaction. [d] This reaction was carried out at 66 °C.

Scheme 3. TMPP-Catalyzed Isomerization Experiments

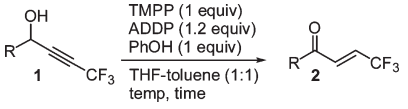


Huisgen zwitterion to the carbonyl compound **2a** formed (entries 1 and 2).[9,10] This is the major reason why we selected tris(*p*-methoxyphenyl)phosphine (TMPP) and 1,1′-(azodicarbonyl)dipiperidine (ADDP) as the most effective reagent system.[11] A THF−toluene mixed solvent promoted the reaction well, affording the least number of byproducts (entry 12). The best result was eventually obtained by using TMPP (1.2 equiv), ADDP (1.0 equiv), and PhOH (1.0 equiv) at 66 °C in this solvent system, which provided the desired α,β-enone **2a** in 98% yield with complete *E* selectivity (entry 14).

Perfect interconversion of (*Z*)-**2a** to the corresponding (*E*)-isomer proceeded with a small excess amount of TMPP which was proved by independent subjection of (*Z*)-**2a** to a solution containing 20 mol % of this phosphine (Scheme 3). The role of TMPP here seemed to be closely related to the one of Et_3N in our previous report.[5f]

The reaction condition determined above was found to be generally applicable to a variety of CF_3-containing propargylic alcohols **1**, furnishing products **2** in good to excellent yields as well as with high (*E*)-selectivity (Table 2). On the other hand, nonfluorinated materials with a $Ph(CH_2)_2$ group as R, and *n*-Bu (**1i**) or CO_2Et (**1j**) moieties instead of a CF_3 group failed to follow this transformation (entries 9 and 10) probably due to the insufficient activation of the propargylic proton and the side reaction via nucleophilic 1,4-addition of TMPP or the TMPP−ADDP zwitterion to the alkyne moiety in the latter case.

Table 2. Scope of Isomerization of Propargylic Alcohols 1 with Mitsunobu Reagents[a]



entry	1	R	temp (°C)	time (h)	2	yield[b] (%)
1	**1a**	$Ph(CH_2)_2$	66	3.0	**2a**	98
2	**1b**	Ph	rt	3.0	**2b**	89
3	**1c**	*n*-C_6H_{13}	66	3.0	**2c**	94
4	**1d**	$BnO(CH_2)_2$	66	3.0	**2d**	51
5[c]	**1e**	*c*-C_6H_{11}	111	2.0	**2e**	70
6[c]	**1f**	Ph(MOMO)CH	111	3.0	**2f**	71
7[d]	**1g**	(*E*)-$C_3H_7CH{=}CH$	rt	4.0	**2g**	60
8	**1h**	*t*-Bu$C{\equiv}C$	rt	0.5	**2h**	63
9[e]	**1i**	$Ph(CH_2)_2$	66	1.0	**2i**	0
10[f]	**1j**	$Ph(CH_2)_2$	66	1.0	**2j**	0

[a] The reaction was carried out in a 0.6 mmol scale with 3 mL each of both solvents, and the products were obtained in an (*E*)-exclusive manner unless otherwise noted. [b] Isolated yield. [c] The reaction was conducted in 6 mL of toluene. [d] *Z*/*E* selectivity of the products was 6:94. [e] **1i** possessed a *n*-Bu group instead of a CF_3 group and was recovered in 99% yield. [f] **1j** possessed a CO_2Et group instead of a CF_3 group.

To gain mechanistic insight into this reaction, deuterium-labeling experiments were conducted. Deuterium from the propargylic position of the alcohol **1b**-*d* was incorporated into the β-position (77% D) of the α,β-enone **2b**-*d*, not the α-position (0% D) as determined by ^1H NMR (Scheme 4,

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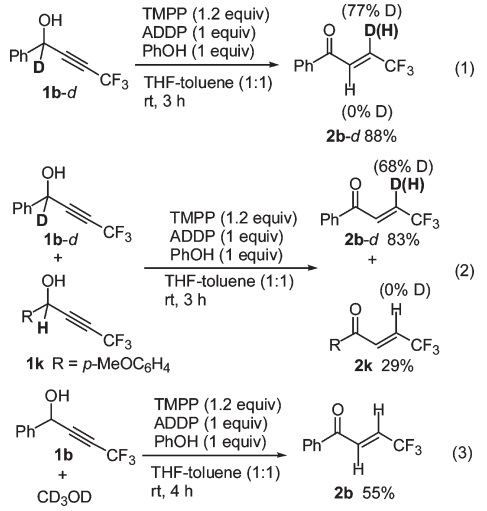
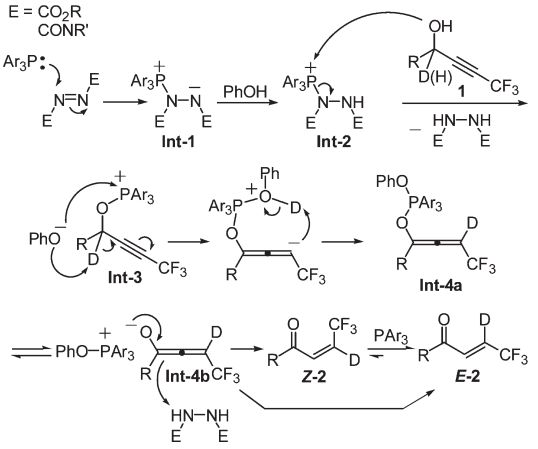
Scheme 4. Deuterium-Labeling Experiments



Scheme 5. Plausible Mechanism for Isomerization of Propargylic Alcohols



eq 1). Moreover, to address a mode of proton migration, an equimolar mixture of **1b**-*d* and **1k** was treated under the same conditions to exclusively furnish deuterated **2b**-*d* and nondeuterated **2k** (Scheme 4, eq 2). Furthermore, treatment of a 1:1 mixture of propargylic alcohol **1b** and methanol-d_4 under the standard protocol afforded nondeuterated **2b** (eq 3) as the sole product. These results clearly demonstrated the intramolecular migration of deuterium at the propargylic position of **1b**-*d* to the β-position of the ketone **2b**-*d* regiospecifically. This phenomenon led to expectation that the propargylic or the allenyl anions would form a tight ion pair with a proton source after abstraction of D(H).

The following rationalization would be advanced to explain the product formation (Scheme 5). It is highly possible that phosphines would first react with azo compounds to form Huisgen zwitterions **Int-1** which were protonated by phenol and then accepted the attack by propargylic alcohols **1** to furnish **Int-3**. Intermediates **Int-3** would be further isomerized to allenyl intermediates **Int-4** by quick elimination of D(H) with the aid of phenoxide. Spontaneous coordination of the resultant PhOD to the phosphonium cation, followed by recapture of D(H) at the CF_3-attached carbon atom would realize the intramolecular deuterium migration. While dialkoxytrialkylphosphoranes are generally and readily transformed into the corresponding phosphine oxides,[12] this would not be the case for **Int-4a** due to the stronger two $C_{sp2}-O$ bonds making such conversion difficult. Instead, **Int-4a** would experience cleavage of a P−O bond to give **Int-4b**, which would be further converted to a mixture of β-trifluoromethylated α,β-unsaturated ketones (*E*)- and (*Z*)-**2**, usually the latter preferred as the kinetically controlled products due to favorable $\pi^*_{CF3}-\pi_{C=O}$ orbital interaction. This initial *Z*-preference would be also explained by orthogonal orientation of the both π systems, leading to selective protonation of **Int-4a** from the less hindered enolate face, *syn* to D.[13] Reversible 1,4-addition of TMPP to (*Z*)-**2** as exemplified in Scheme 3 would allow free rotation around the $C_\alpha-C_\beta$ axis of the carbonyl group and would eventually furnish thermodynamically more stable (*E*)-**2** as the sole products. Effectiveness of the combination of TMPP and ADDP over the usual PPh_3 and DIAD pair would stem from the easier formation of **Int-1** by the more nucleophilic former phosphine and the harder nature of the corresponding anion by attachment of the less anion-stabilizing amide group as E for TMPP, reducing the likelihood of Michael addition **2**, rather than the case of DIAD with a more electron-withdrawing ester moiety as E.

In conclusion, we have discovered the novel isomerization of CF_3-containing secondary propargylic alcohols **1** to the corresponding (*E*)-α,β-unsaturated ketones **2** by treatment with a combination of tris(*p*-methoxyphenyl)phosphine, 1,1′-(azodicarbonyl)dipiperidine, and phenol. Thus, in connection with our previous method dealing with the same isomerization reaction limited to the substrates with aromatic substituents at the propargylic position, the present process successfully solved such problems, rendering the transformation of **1** to **2** much more useful and applicable to a wide variety of CF3-containing propargylic alcohols **1**.

EXPERIMENTAL SECTION

Substrates **1a**,**b**,[14] **1c**,[7] **1d**,**e**,[14] **1f**,[15] and **1k**[16] were prepared as described in the literature.

(*E*)-1,1,1-Trifluoronon-5-en-2-yn-4-ol (1g). To a solution of LDA (66 mmol) in THF (100 mL) was added dropwise 2-bromo-3,3,3-trifuluoropropene (3.0 mL, 30 mmol) at −80 °C. After the mixture was stirred for 5 min at that temperature, crotonaldehyde (2.17 g, 31 mmol) in THF (3 mL) was added, and stirring was continued for 1.5 h at −80 °C. Usual workup and chromatography (*n*-hexane/AcOEt, 15:1) afforded **1g** (4.61 g, 24 mmol, 80%): colorless oil, R_f = 0.52 (*n*-hexane/EtOAc, 4:1); ^{1}H NMR 0.93 (t, *J* = 7.2 Hz, 3H), 1.44 (sex, *J* = 7.2 Hz, 2H), 1.95 (d, *J* = 6.6 Hz, 1H), 2.08 (q, *J* = 7.2 Hz, 2H), 4.94 (m, 1H), 5.60 (ddt, *J* = 15.3, 6.6, 1.5 Hz, 1H), 5.93 (dtd, *J* = 15.0, 6.6, 0.9 Hz, 1H); ^{13}C NMR 13.6, 21.8, 34.0, 62.3 (q, *J* = 1.3 Hz), 72.8 (q, *J* = 52.0 Hz), 86.3 (q, *J* = 6.2 Hz), 114.1 (q, *J* = 256.8 Hz), 126.5 (q, *J* = 1.3 Hz), 136.1; ^{19}F NMR −51.94 (s); IR (neat) 607, 632, 742, 919, 966, 1031, 1145, 1216, 1276, 1459, 1669, 2271, 2877, 2935, 2965, 3320 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_9H_{12}F_3O$ $[M + H]^+$ 193.0840, found 193.0862.

1,1,1-Trifluorooct-7,7-dimethyl-2,5-octa-2,5-diyn-4-ol (1h): 45% yield; brown oil; R_f = 0.52 (*n*-hexane/EtOAc, 4:1); ^{1}H NMR 1.24 (s, 9H), 2.40 (s, br, 1H), 5.20 (q, *J* = 3.0 Hz, 1H); ^{13}C NMR 22.8, 30.5, 51.7 (q, *J* = 1.2 Hz), 70.4 (q, *J* = 53.3 Hz), 73.8 (q, *J* = 1.9 Hz), 84.7 (q, *J* = 6.9 Hz), 95.5 (q, *J* = 1.2 Hz), 114.1 (q, *J* = 257.4 Hz); ^{19}F NMR −52.15 (d, *J* = 4.8 Hz); IR (neat): 622, 837, 880, 949, 1038, 1082, 1149, 1209, 1277, 1340, 1365, 1458, 1634, 1672, 1716, 2251, 2873, 2932, 2973, 3380 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{10}H_{12}F_3O$ $[M + H]^+$ 205.0840, found 205.0849.

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Tris(*p*-methoxyphenyl)phosphine (TMPP).[17] *n*-BuLi (1.6 *M* in *n*-hexane, 20.6 mL, 33 mmol) was added to a THF solution (50 mL) of *p*-bromoanisole (6.2 g, 33 mmol) at −50 °C. After 30 min of stirring at the same temperature, phosphorus trichloride (0.87 mL, 10 mmol) was added at −50 °C, and the mixture was stirred for 3 h at −10 °C. The mixture was quenched with saturated aq NH_4Cl, and usual workup followed by recrystallization from EtOH yielded the desired phosphine TMPP (1.93 g, 5.5 mmol, 55%): white solid, R_f = 0.61; mp 132−134 °C (*n*-hexane/EtOAc, 4:1); ^{1}H NMR 3.79 (s, 9H), 6.84−6.89 (m, 6H), 7.19−7.26 (m, 6H).

General Procedure for Isomerization of Propargylic Alcohols 1 to α,β-Enones 2d with PhOH in the Presence of Mitsunobu Reagents. To a THF−toluene (1:1) solution (2 mL) of the alcohol **1d** (0.158 g, 0.60 mmol) were added TMPP (0.256 g, 0.72 mmol), phenol (0.057 g, 0.60 mmol), and 1,1′-(azodicarbonyl)-dipiperidine (ADDP) (0.153 g, 0.60 mmol) at room temperature, and the mixture was stirred for 3 h at 66 °C. After being cooled to room temperature, the reaction mixture was passed through a short silica gel chromatography column (*n*-hexane/AcOEt, 6:1). The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (*n*-hexane/AcOEt, 30:1) to afford **2d** (0.0805 g, 0.306 mmol, 51%): colorless oil; R_f = 0.55 (*n*-hexane/EtOAc, 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) 2.90 (t, *J* = 6.0 Hz, 2H), 3.80 (t, *J* = 6.0 Hz, 2H), 4.52 (s, 2H), 6.61 (dq, *J* = 16.2, 6.3 Hz, 1H), 6.75 (dq, *J* = 15.9, 1.8 Hz, 1H), 7.26−7.38 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 42.0, 64.9, 73.4, 122.5 (q, *J* = 269.8 Hz), 127.7, 127.8, 128.5 128.9 (q, *J* = 35.4 Hz), 134.3 (q, *J* = 5.6 Hz), 137.9, 196.5; ^{19}F NMR (283 MHz, $CDCl_3$) −66.55 (d, *J* = 6.8 Hz); IR (neat) 630, 699, 741, 972, 1029, 1135, 1181, 1276, 1304, 1368, 1455, 1662, 1714, 2869 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{14}F_3O_2$ $[M + H]^+$ 259.0946, found 259.0934.

(*E*)-5,5,5-Trifluoro-1-(methoxymethoxy)-1-phenylpent-3-en-2-one (2f): 71% yield; colorless oil; R_f = 0.57 (*n*-hexane/EtOAc, 4:1, v/v); ^{1}H NMR 3.37 (s, 3H), 4.72 (d, *J* = 6.9 Hz, 1H), 4.75 (d, *J* = 6.9 Hz, 1H), 5.25 (s, 1H), 6.71 (dq, *J* = 15.6, 6.6 Hz, 1H), 6.75 (dq, *J* = 15.6, 2.1 Hz, 1H), 7.32−7.41 (m, 5H); ^{13}C NMR 56.3, 83.2, 95.5, 122.4 (q, *J* = 267.3 Hz), 127.3, 129.1, 129.2, 129.9 (q, *J* = 35.3 Hz), 130.1 (q, *J* = 5.6 Hz), 134.3, 194.5; ^{19}F NMR −66.57 (d, *J* = 6.8 Hz); IR (neat) 617, 701, 748, 920, 974, 1039, 1135, 1215, 1275, 1307, 1454, 1496, 1656, 1715, 2896, 2954 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{14}F_3O_3$ $[M + H]^+$ 275.0895, found 275.0860.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data for all new prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: tyamazak@cc.tuat.ac.jp.

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