JOC Note

Reversal Phenomenon of Reaction Velocity in a Mixed Reaction System: Silylations between Simple Alcohols and α- or β-Hydroxyketones Using Anilinosilanes and Catalytic TBAF Agent

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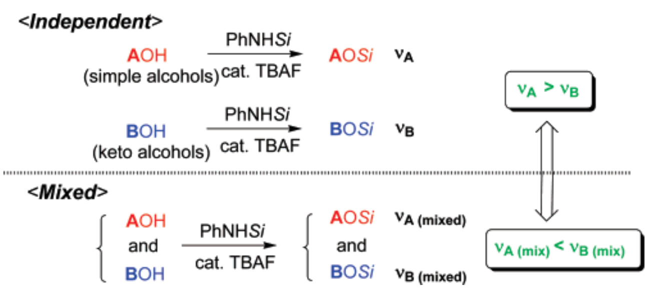
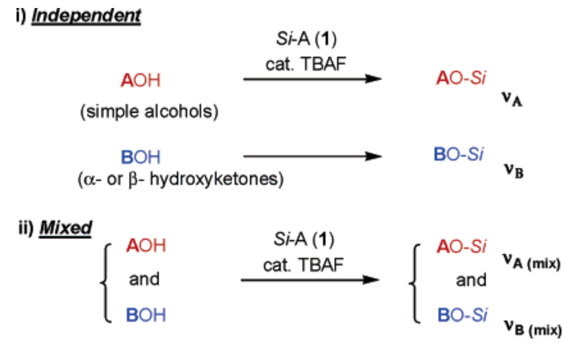


We encountered a unique phenomenon of reaction velocity reversal during the silylation between mixed simple alcohols (**A**; AOH) and α- or β-hydroxyketones (**B**; BOH). The present reaction system using anilinosilanes **1a** [PhNH(TMS)] (TMS-A) and **1b** [PhNH(TES)] (TES-A) with the catalytic TBAF (0.02 equiv) reagent showed that the order of silylation−velocity between the independent system and the mixed system was distinctively reversed [$\nu_A > \nu_B \approx \nu_{B(mix)} > \nu_{A(mix)}$]. A total of seven examples indicate its high generality: AOH = linalool, 3-octanol; BOH = valeroin, benzoin, 5-hydroxy-4-methyl-3-undecanone. Time-dependent IR spectroscopy analysis rationally supported this speculation.

It is the usual behavior of chemical reactions that when an equimolar mixture of comparable substrates **A** and **B** (assuming that **A** is more reactive than **B**) is subjected to a particular chemical reaction **A** is preferentially transformed more rapidly than **B**. On the basis of this assumption, competitive experiments are frequently performed to compare the reactivity of **A** and **B**. In our studies of practical silylations and a desilylation,[1] we encountered a unique phenomenon of reaction velocity reversal during the silylation between mixed simple alcohols (**A**; AOH) and α- or β-hydroxyketones (**B**; BOH).

Silazanes and catalytic TBAF (tetrabutylammonium fluoride) are efficient silylation agents.[1a,2,3] Extensive screening of silazanes reveals that anilinosilanes **1** [abbreviated TMS-A (**1a**) or TES-A (**1b**)] are powerful reagents for sterically crowded alcohols.[2e] A striking aspect of **1** and cat TBAF reagent lies in its substrate specificity between simple alcohols and α- or β-hydroxyketones (Scheme 1). The order of silylation−velocity between the independent system and the mixed system was distinctively reversed [$\nu_A > \nu_B \approx \nu_{B(mix)} > \nu_{A(mix)}$].

SCHEME 1. Reversal Phenomenon of Reaction Velocities between Independent and Mixed Reaction Systems



Initial examination was guided by the silylation of linalool (**2**) and valeroin (**3**) using TMS-A (**1a**) and cat TBAF. As shown in Figure 1, for an independent reaction, linalool (**2**) was trimethylsilylated to give TMS ether **2′** in 100% conversion yield within 1 min (●), whereas the conversion of valeroin (**3**) to TMS ether **3′** required 60 min for completion despite being a more reactive secondary alcohol (○). The competitive reaction using equimolar mixtures of **2** and **3** under otherwise identical conditions, however, produced an entirely opposite result; **3** was trimethylsilyl-

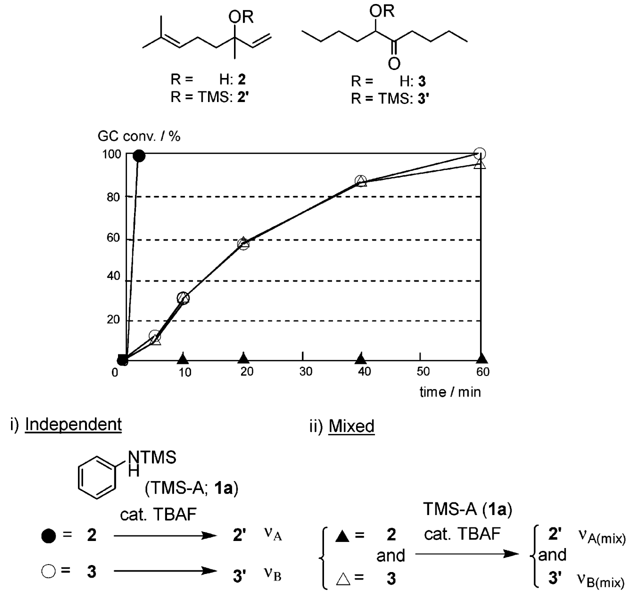


FIGURE 1. Reversal phenomenon of trimethylsilylation using **2** and **3**/**1a**/catalytic TBAF.

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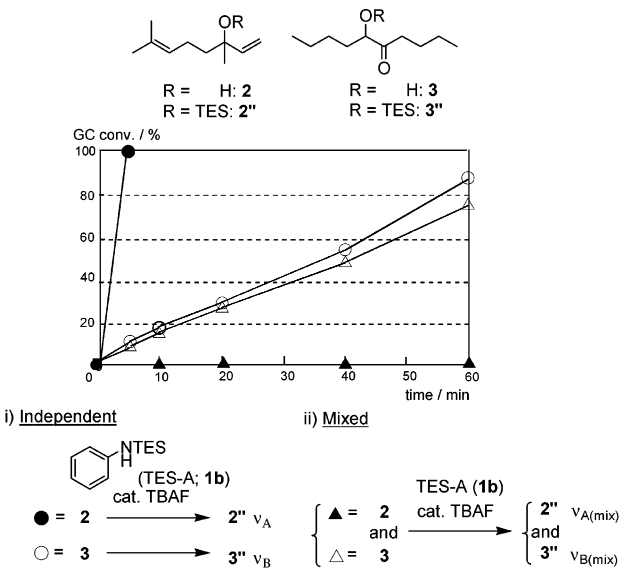


FIGURE 2. Reversal phenomenon of triethylsilylation using **2** and **3**/**1b**/catalytic TBAF.

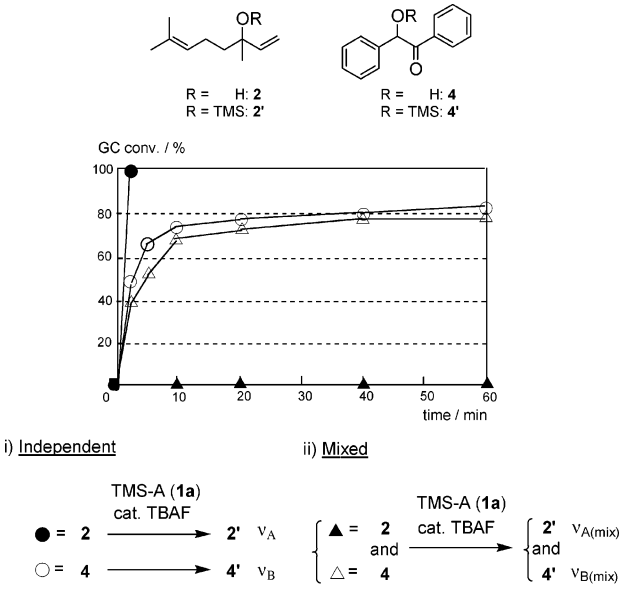


FIGURE 3. Reversal phenomenon of trimethylsilylation using **2** and **4**/**1a**/catalytic TBAF.

ated in 100% conversion yield during 60 min (△), with almost quantitative recovery of **2** (▲). It is apparent that the order of velocity was reversed: $\nu_{\mathrm{A}} > \nu_{\mathrm{B}} \approx \nu_{\mathrm{B(mix)}} > \nu_{\mathrm{A(mix)}}$. Independent and mixed triethylsilylations of **2** and **3** using TES-A (**1b**) and cat TBAF also produced quite a similar reversal phenomenon (Figure 2).

The present reversal phenomenon of trimethylsilylation was also observed in independent and mixed reactions between linalool **2** (as an AOH) and benzoin **4** (as a BOH) (Figure 3).

The present phenomenon is general enough because four additional examples were performed (Figures 4–6, S8). Figure 4 depicts independent and mixed trimethylsilylations between 3-octanol **5** instead of linalool **2** and valeroin **3**. Due to the higher reactivity of **5** than **2**, **5** was slightly trimethylsilylated (25% yield) in a mixed system, but a significant reversal phenomenon was performed (**3** was trimethylsilylated in 70%).

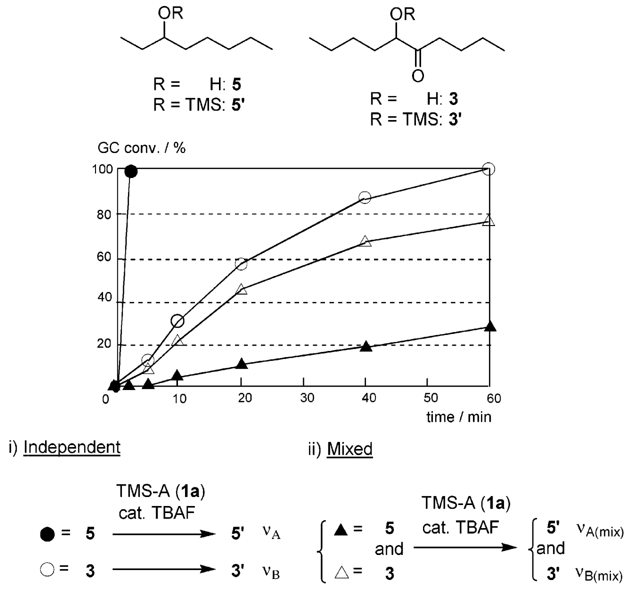


FIGURE 4. Reversal phenomenon of trimethylsilylation using **5** and **3**/**1a**/catalytic TBAF.

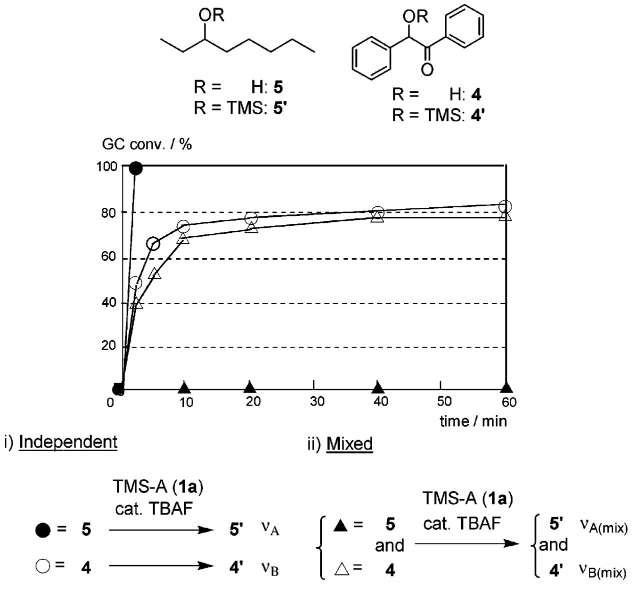


FIGURE 5. Reversal phenomenon of trimethylsilylation using **5** and **4**/**1a**/catalytic TBAF.

Similar result was obtained by the reaction between **5** and benzoin **4**, as shown in Figure 5.

Figure 6 shows a trimethylsilylation using **1a** between **2** and β-hydroxyketone (aldol) **6**, which also served as a suitable substrate for the present reaction system. The reversal phenomenon using *N*-methyl-*N*-TMS-acetamide (**7**), a good silylation agent, was observed with TBAF catalyst[1a,e] (Figure S8 in Supporting Information).

As shown in Scheme 2, a cross-over experiment eliminated one plausible explanation (i.e., that **2** is initially silylated to give **2′** and the TMS group in **2′** is then transferred to **3** during the course of the mixed reaction); there was no substantial TMS transfer (no reaction) when using equimolar mixtures of **2′** and **3** under identical conditions [in either the presence or absence of TMS-A (**1a**)].

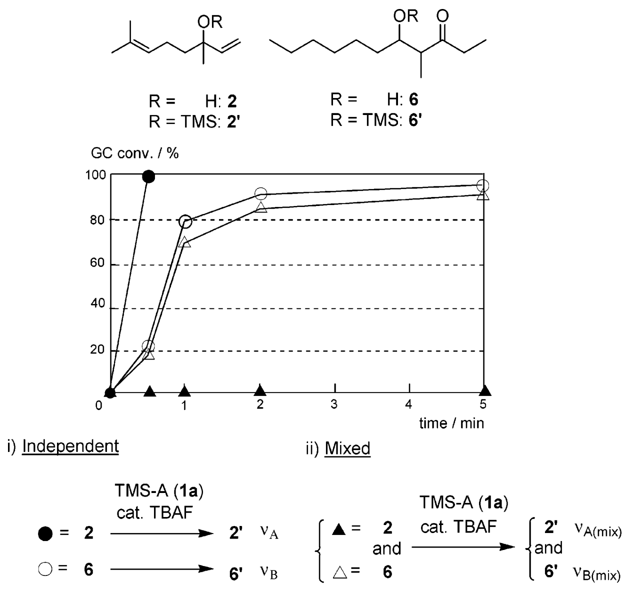
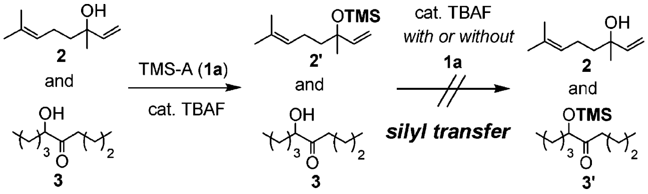
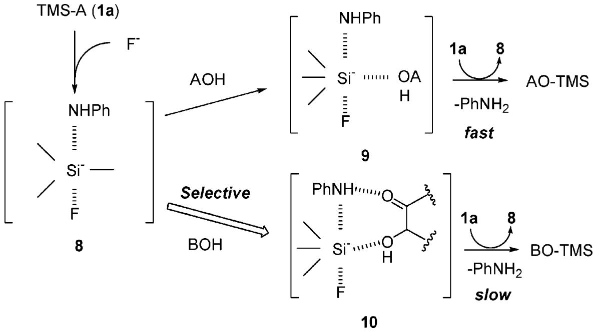


FIGURE 6. Reversal phenomenon of trimethylsilylation using **2** and **6**/**1a**/catalytic TBAF.

SCHEME 2



SCHEME 3. Proposed Mechanism



We propose the following mechanism for this unique phenomenon (Scheme 3). TMS-A (**1a**) initially traps catalytic F^- to form reactive hypervalent silicate **8**,[4] which coordinates exclusively toward an acyloin (BOH) over a coexistent simple alcohol (AOH) to form a stable chelate intermediate **10**. **10** slowly changes into BO-TMS, whereas the nonchelate intermediate **9** produced in an independent reaction rapidly transforms into AO-TMS.

This speculation is supported by the following experimental finding, that is, the existence of the C═O⋯HN interaction based on time-dependent IR spectroscopy analysis between **3** and TMS-A (**1a**), as depicted in Figure 7. The band shift of both the C═O group of **3** and the NH group of **1a** was monitored during the reaction.[5] Figure 7a shows the spectra of **3** and **3′** without TBAF catalyst (no reaction). **1a** was added to the mixture of **3** and TBAF (0.02 equiv) to generate TMS ether **3′** and aniline at 20−25 °C for 3 min. The temporal change of the spectra in the 1680−1750 cm^{-1} region is shown in Figure 7b. The C═O stretching band of **3** at 1713 cm^{-1} first shifted, then eventually the spectra became almost identical to that of **3′**. Figure 7c shows the temporal change of the top peak position. The C═O stretching band at 1713 cm^{-1} (**3**) shifted toward a lower wavenumber by ca. 1 cm^{-1} just after the addition of **1a**, then gradually shifted again to a higher wavenumber at 1715 cm^{-1} (**3′**) (○). In general, interaction of the XH (X = O and N) group with the lone pairs of the C═O oxygen atom causes the lower wavenumber change of the stretching band.[6,7]

These wavenumber shifts of **3**, therefore, strongly suggest a C═O⋯HN interaction. Figure 7c affords additional information under two other conditions: (i) no wavenumber shift (▲) was observed using **3** and **1a** (no reaction); and (ii) a lower wavenumber band shift (×) was observed using **3**, **1a**, and TBAF with coexistence of linalool **2**. These results indicate that the interaction between **3** and **1a** holds over in the presence of **2** and supports the selective transformation of **3**.

The NH stretching band of **1a** at 3383 cm^{-1} also shows a wavenumber shift ca. 4 cm^{-1} after the addition of **1a** due to the interaction between the NH (**1a**) and C═O (**3**) group (Figure S9 in Supporting Information).

These show a clear band shift toward lower wavenumbers of both the C═O and NH band. All of these time-dependent IR spectroscopy measurements reveal the existence of intermediate **10** in Scheme 3. The second derivatives of the spectra in Figures 7b and S9b are described in the Supporting Information. These show a clear band shift toward lower wavenumber of both the C═O and NH band.

We disclosed a unique reversal phenomenon of reaction velocity in a mixed reaction system. There was a distinctive switching mode of reaction velocity between the independent system and the mixed system [$\nu_A > \nu_B \approx \nu_{B(mix)} > \nu_{A(mix)}$] during the silylation of simple alcohols (**A**; AOH) and α- or β-hydroxyketones (**B**; BOH) promoted by anilinosilanes **1a** and **1b**. A total of seven examples using two simple alcohols and three α- or β-hydroxyketones indicate its high generality. Time-dependent IR spectroscopy analysis rationally supported this speculation.

Experimental Section

General. All reactions were carried out in oven-dried glassware under an argon atmosphere. *N*,*N*-Dimethylformamide (DMF) was distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. TLC analysis was performed on 0.25 mm silica gel Merck 60 F_{254} plates. NMR spectra were recorded on a JEOL DELTA 300 spectrometer, operating at 300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR. Chemical shifts (δ, ppm) in $CDCl_3$ were reported downfield from TMS (=0) for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. Flash column chromatography was performed with silica gel Merck 60 (230−400 mesh ASTM) according to the method of Still.[8] GC data were

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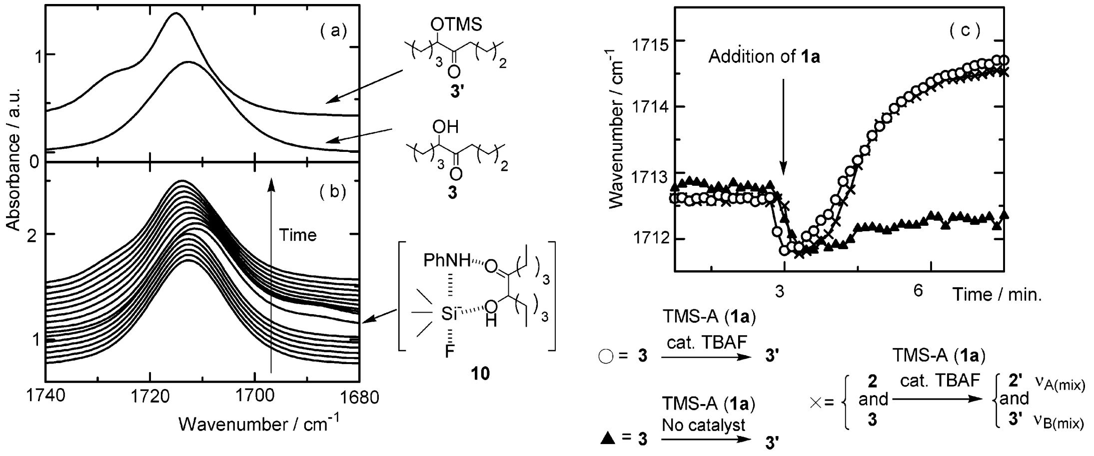

FIGURE 7. (a) IR spectra of **3** and **3′**/THF in the 1680−1740 cm^{-1} region. (b) Temporal change of IR spectra is continuously measured every 9 s during the reaction, where **1a** is added to the mixture of **3** and TBAF/THF to generate **3′** and aniline. (c) Temporal changes of the peak top position of the 1680−1740 cm^{-1} region. **1a** was added to the mixture of **3** + TBAF (○), **3** (▲), and **2** + **3** + TBAF (×), respectively. These top peak positions were determined by zero crossing points of the first derivative of the raw spectra as shown in (b) with data interpolation.

obtained on a SIMAZU GC-17A [column, Widebore DB-1701; Ø 0.53 mm × 30 m; oven temp = 50−250 °C (20 °C/min); injection/detection (FID) temp = 250 °C; carrier gas, N_2]. IR spectra were recorded on a FT/IR-5300 spectrophotometer. Mass spectra were measured on a T100LC spectrometer.

General Procedure For Silylations of Alcohols Using Anilinosilanes [PhNH(TMS)] (TMS-A) 1a and [PhNH(TES)] (TES-A) 1b. TMS-A **1a** (1.5 mmol) or TES-A **1b** (1.5 mmol) was added to a stirred solution of alcohol (1.0 mmol) and TBAF (1 M THF solution, 0.02 mL, 0.02 mmol) in DMF (2.0 mL) at 20−25 °C under an Ar atmosphere. After stirring at the same temperature for 5−60 min, the mixture was quenched with water (5.0 mL), which was extracted with ether. The combined organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane) to give a desired silylether.

3,7-Dimethyl-3-(trimethylsiloxy)-1,6-octadiene (**2′**),[9] 3-(triethylsiloxy)-3,7-dimethyl-1,6-octadiene (**2″**),[10] 6-(trimethylsiloxy)-5-decanone (**3′**),[11] 2-(trimethylsiloxy)-1,2-diphenylethanone (**4′**),[12] 3-(trimethylsiloxy)octanone (**5′**),[13] and 5-hydroxy-4-methyl-3-undecanone (**6**)[14] were known compounds.

Reversal Phenomenon of Figure 1 (Independent System): TMS-A (**1a**, 74 mg, 0.45 mmol) was added to a stirred solution of linalool (**2**, 44 mg, 0.30 mmol) *or* valeroin (**3**, 52 mg, 0.30 mmol) and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere. **Mixed system: 1a** (74 mg, 0.45 mmol) was added to a stirred solution of a mixture of **2** (44 mg, 0.30 mmol), **3** (52 mg, 0.30 mmol), and 1 M TBAF (THF solution, 0.6 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere.

Figure 2 (Independent System): TES-A (**1b**, 93 mg, 0.45 mmol) was added to a stirred solution of **2** (44 mg, 0.30 mmol) *or* **3** (52 mg, 0.30 mmol) and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere. **Mixed system: 1b** (93 mg, 0.45 mmol) was added to a stirred solution of a mixture of **2** (44 mg, 0.30 mmol), **3** (52 mg, 0.30 mmol), and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere.

Figure 3 (Independent System): 1a (74 mg, 0.45 mmol) was added to a stirred solution of **2** (44 mg, 0.30 mmol) *or* benzoin (**4**, 64 mg, 0.30 mmol) and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere. **Mixed system: 1a** (74 mg, 0.45 mmol) was added to a stirred solution of a mixture of **2** (44 mg, 0.30 mmol), **4** (64 mg, 0.30 mmol), and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere.

Figure 4 (Independent System): 1a (74 mg, 0.45 mmol) was added to a stirred solution of 3-octanol (**5**, 39 mg, 0.30 mmol) *or* **3** (52 mg, 0.30 mmol) and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere. **Mixed system: 1a** (74 mg, 0.45 mmol) was added to a stirred solution of a mixture of **5** (39 mg, 0.30 mmol) and **3** (52 mg, 0.30 mmol) and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere.

Figure 5 (Independent System): 1a (74 mg, 0.45 mmol) was added to a stirred solution of **5** (39 mg, 0.30 mmol) *or* **4** (64 mg, 0.30 mmol) and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere. **Mixed system: 1a** (74 mg, 0.45 mmol) was added to a stirred solution of a mixture of **5** (39 mg, 0.30 mmol), **4** (64 mg, 0.30 mmol), and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at 0−5 °C under an Ar atmosphere.

Figure 6 (Independent System): 1a (74 mg, 0.45 mmol) was added to a stirred solution of **2** (44 mg, 0.30 mmol) *or* 5-hydroxy-4-methyl-3-undecanone (**6**, 60 mg, 0.30 mmol) and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at −45 to −50 °C under an Ar atmosphere. **Mixed system: 1a** (74 mg, 0.45 mmol) was added to a stirred solution of a mixture of **2** (44 mg, 0.30 mmol), **6** (60 mg, 0.30 mmol), and 1 M TBAF (THF solution, 6.0 μL, 6.0 μmol) in DMF (0.60 mL) at −45 to −50 °C under an Ar atmosphere.

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Supporting Information Available: ^{1}H and/or ^{13}C NMR spectral chart for compounds **3″** and **7′**. Figures S8 and S9. This material is available free of charge via the Internet at http://pubs.acs.org.

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