β-Functionalized and α,β-Difunctionalized Ketones from 1-Arylallylic Alcohols via Dipotassio α,β-Dianion Intermediates

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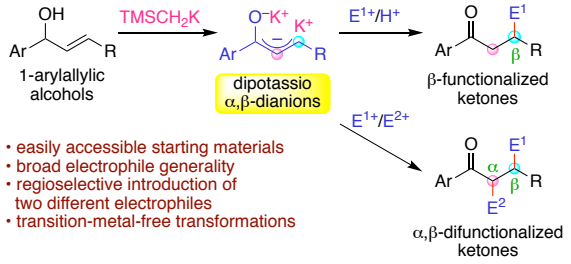
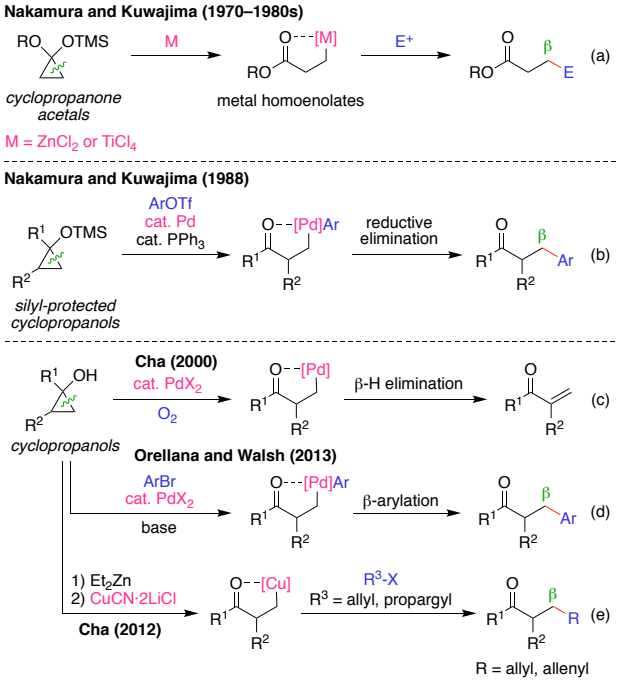
ABSTRACT: This study reports the synthesis of diverse β-functionalized ketones from readily available 1-arylallylic alcohols in the presence of (trimethylsilyl)methylpotassium ($TMSCH_2K$). The reaction proceeded via the formation of the highly nucleophilic dipotassio α,β-dianion as the key intermediate, which served as a metal homoenolate equivalent. This protocol also allowed the one-pot synthesis of α,β-difunctionalized ketones using two different electrophiles, thus demonstrating its synthetic advantages over other protocols involving metal homoenolates.



INTRODUCTION

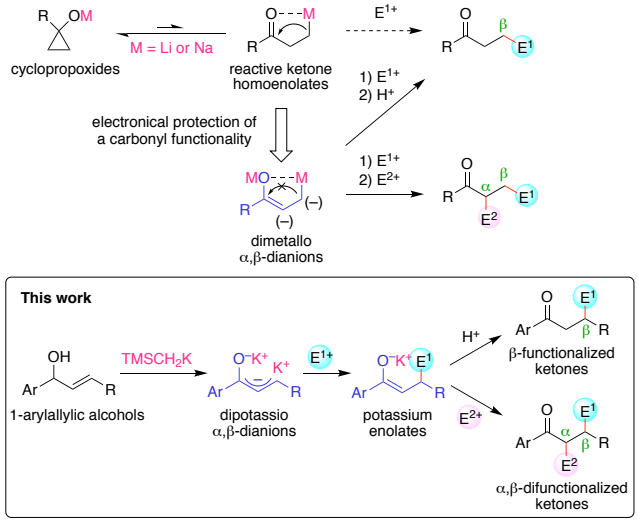
Metal homoenolates, one-carbon homologues of metal enolates, are useful nucleophiles that have been employed in the synthesis of β-functionalized carbonyl compounds.[1] Unfortunately, owing to their complicated preparation methods, their use in organic synthesis has been limited. Although various homoenolate precursors have been reported, only a limited number of preparation methods are reliable, with the metal-promoted carbon–carbon bond cleavage of cyclopropane rings being considered as the most promising strategy. In the 1970–1980s, Nakamura and Kuwajima demonstrated that cyclopropanone acetals are widely used homoenolate precursors, particularly for generating Ti[2] and Zn[3] homoenolates. They also showed that trapping such metal homoenolates by a variety of electrophiles can result in β-functionalized esters (Scheme 1a). Cyclopropanol derivatives have been also employed as useful homoenolate precursors. In 1988, Nakamura and Kuwajima reported the formation of β-aryl ketones via the Pd-catalyzed cross-coupling reaction of silyl-protected cyclopropanols with aryl triflates (Scheme 1b).[4] Despite this major finding and the discovery of the Kulinkovich reaction,[5] the chemistry of unprotected cyclopropanols[6] remained largely unexplored until the study by Cha et al. in 2000,[7] which reported the Pd-catalyzed transformation of cyclopropanols into enones via Pd homoenolates (Scheme 1c). In 2013, Orellana[8] and Walsh[9] independently developed a Pd-catalyzed intermolecular cross-coupling of cyclopropanols with aryl bromides, which provided β-aryl ketones instead of β-hydride elimination products (Scheme 1d). Since these reports, a wide variety of Pd-catalyzed carbon–carbon bond formations using cyclopropanols have been developed via arylation,[10] alkenylation,[11] allenylation,[12] dienylation,[13] benzylation,[14] and acylation.[15] In 2012, Cha et al. were the first to report the Cu-promoted S_N2' β-allylation/allenylation[16] using cyclopropanols with Et_2Zn (Scheme 1e), which inspired the development of Cu-promoted β-functionalizations, such as trifluoromethylation/trifluoromethylthiolation,[17] alkylation,[18] alkynylation,[19] amination/amidation,[20] cyanation,[21] and sulfonylation.[22] Metals, such as Rh,[23] Co,[24] Ni,[25] Ag,[26] Mn,[27] and Zn,[28] have been also employed in β-functionalization of cyclopropanols.

Scheme 1. Representative Reactions of Metal Homoenolates via Cyclopropane Ring Opening



Despite such recent progress in cyclopropanol-derived metal homoenolates of ketones, several drawbacks still exist. The first drawback is related to regioselectivity. When a 1,2-disubstituted cyclopropanol is converted into the corresponding metal homoenolate, ring opening occurs at the least substituted carbon–carbon bond, thus generating the less nucleophilic metal homoenolate. Accordingly, with this method, the introduction of an electrophile into the most substituted β-carbon is difficult unless β-keto radicals are involved instead of metal homoenolates. The second drawback is that ketone homoenolates are less reactive than ester homoenolates, thus limiting their synthetic utility. To the best of our knowledge, the reaction of cyclopropanol-derived ketone homoenolates with aldehydes, which are highly reactive electrophiles, has not been reported. The production of more nucleophilic ketone homoenolates (M = Li or Na) from cyclopropanols has been unsuccessful due to their tendency to undergo rapid cyclization into the metal cyclopropoxides (Scheme 2).[29] Consequently, an alternative strategy involving dimetallo α,β-dianions was investigated.[30] This method can transiently mask a carbonyl moiety and prevent the cyclization without a protection/deprotection sequence, and thus, can generate ketone homoenolate equivalents with highly reactive metals. Furthermore, these species possess two nucleophilic sites, thus offering an easy access to α,β-difunctionalized ketones. In 1976, Dimmel et al. reported the generation of a ketone dilithio α,β-dianion via the reaction of α-vinylbenzyl alcohol with *n*-butyllithium (*n*BuLi).[31] Unfortunately, upon quenching the dianion with methyl iodide, a mixture of regioisomers was obtained, which limited the applicability of the reaction. In 1977, Trost et al. generated a dilithio α,β-dianion of 6-methoxy-1-indanone, but the substrate scope was very limited, and only alkyl iodides were used as electrophiles.[32] Sonoda, Ryu, and coworkers were the first to develop a practical method for the generation of dilithio α,β-dianions from β-stannyl ketones and investigated their reactions with electrophiles.[33] Unfortunately, this system has several disadvantages because the starting materials are prepared in multiple steps, in addition to the high toxicity of organotin compounds and the narrow scope of electrophiles. Therefore, a new system, in which highly nucleophilic dimetallo α,β-dianion of ketones can be generated from simple starting materials, is highly desirable. In this paper, a general method for the preparation of ketone dipotassio α,β-dianions from 1-arylallylic alcohols and their reactions with electrophiles is described.

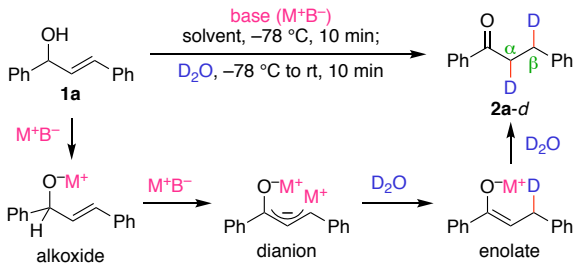
Scheme 2. Preparation of Ketone Dimetallo α,β-Dianions and Their Reactions with Electrophiles



RESULTS AND DISCUSSION

Initially, the appropriate base and reaction conditions for the smooth transformation of allylic alcohols into the corresponding dimetallo α,β-dianions were investigated. Allylic alcohol **1a** was treated with a base in tetrahydrofuran (THF) at –78 °C for 10 min, and the reaction was then quenched with deuterium oxide (D_2O). The deuterium content at the α- and β-positions of the resulting ketone was analyzed (Table 1). With 2 equiv of Schlosser's base, a 57% yield of ketone **2a**-*d* was obtained with excellent deuterium content both at the α- and β-positions, thus supporting the intermediacy of the expected dipotassio α,β-dianion (entry 1). Due to the recovery of a considerable amount of **1a**, the amount of Schlosser's base was increased; nevertheless, **1a** was not fully consumed even in the presence of 4 equiv of Schlosser's base (entries 2 and 3), and thus an alternative potassium base capable of promoting this transformation more effectively was investigated. It turned out that (trimethylsilyl)methylpotassium ($TMSCH_2K$),[34] an isolable alkylpotassium reagent which has been recently employed in some strong base-catalyzed reactions,[35] allowed the complete conversion of **1a**, providing **2a**-*d* in an improved yield of 86% (entry 4). Solvent effects were also studied. While the reactions in cyclopentyl methyl ether (CPME) and diethyl ether (Et_2O) led to slightly lower yields of **2a**-*d*, less coordinating ethers, such as *tert*-butyl methyl ether (*t*BuOMe) and diisopropyl ether ($^iPr_2O$), resulted in poor conversions (entries 5–8). In the presence of other representative strong bases, including *n*BuLi, *tert*-butyllithium (*t*BuLi), and potassium hexamethyldisilazide (KHMDS), conversions were not observed (entries 9–11). It was thus concluded that potassium carbanions were indispensable for the generation of a dianion from **1a**.

Table 1. Optimization of the Reaction Conditions[a]

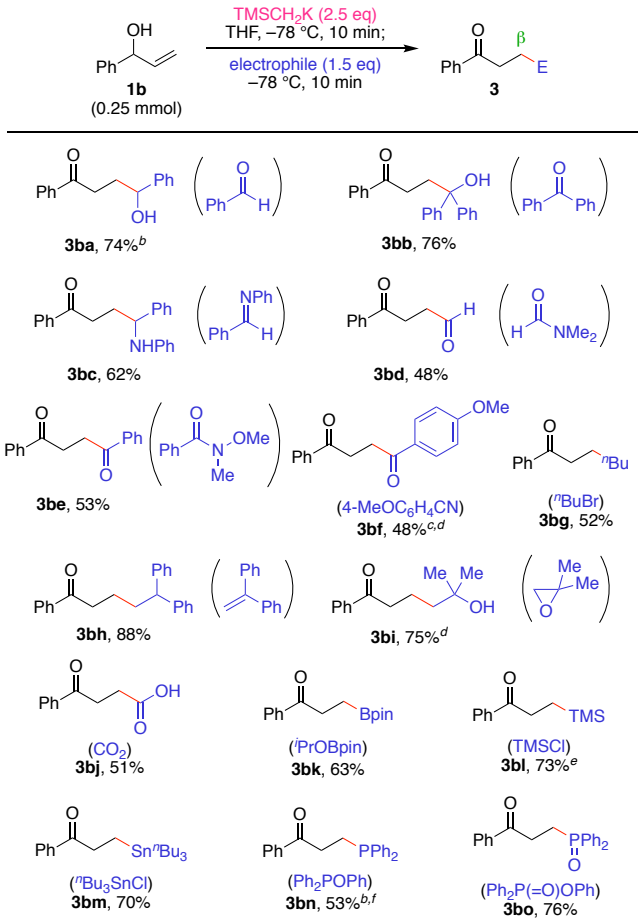


run	base (eq)	solvent	yield (%)[b]		D content (%)[b]	
			1a	**2a**-*d*	α	β
1	^{n}BuLi/KO^{t}Bu (2)	THF	38	57	100	102
2	^{n}BuLi/KO^{t}Bu (3)	THF	28	67	99	103
3	^{n}BuLi/KO^{t}Bu (4)	THF	22	67	99	103
4	$TMSCH_2K$ (2.5)	THF	0	86	100	86
5	$TMSCH_2K$ (2.5)	CPME	6	77	83	83
6	$TMSCH_2K$ (2.5)	Et_2O	8	68	88	97
7	$TMSCH_2K$ (2.5)	^{t}BuOMe	91	7	73	69
8	$TMSCH_2K$ (2.5)	^{i}Pr$_2$O	>99	0	–	–
9	^{n}BuLi (2.5)	THF	>99	0	–	–
10	^{t}BuLi (2.5)	THF	>99	0	–	–
11	KHMDS (2.5)	THF	>99	0	–	–

[a]Conditions: **1a** (52.6 mg, 0.25 mmol) and base in solvent (3 mL) at –78 °C for 10 min followed by D_2O (1 mL) at –78 °C to rt for 10 min. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture.

The scope of electrophiles was investigated under the optimal conditions (Scheme 3). Various electrophiles, including those that could not be used in previously reported systems, were trapped by the dipotassio dianions to provide the corresponding β-functionalized ketones in good-to-excellent yields. Allylic alcohol **1b** was reacted with carbonyl compounds and their derivatives, including aldehyde, ketone, imine, *N*,*N*-dimethylformamide, and Weinreb amide with the aid of $TMSCH_2K$, producing **3ba**–**3be** in yields of 48–76%. The reaction with anisonitrile followed by hydrolysis resulted in 1,4-diketone **3bf** with a 48% yield. *n*-Butyl bromide also turned out to be a suitable electrophile (**3bg**). The dianion from **1b** was smoothly added to the double bond of 1,1-diphenylethylene to give **3bh** in an excellent yield of 88%. Raising the reaction temperature from –78 °C to room temperature enabled the use of isobutylene oxide in this transformation (**3bi**). Upon performing the reaction under a balloon pressure of CO_2, γ-keto acid **3bj** was obtained in 51% yield. In addition to carbon–carbon bond formation, carbon–heteroatom bonds could also be constructed at the β-position of the resulting ketones. With 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (^{i}PrOBpin), a 63% yield of β-boryl ketone **3bk** was formed. The reaction with trimethylsilyl chloride (TMSCl) followed by desilylation of the silyl enol ether moiety gave β-silyl ketone **3bl** in 73% yield. Tri-*n*-butyltin chloride (^{n}Bu$_3$SnCl) could also be used in this reaction, affording a 70% yield of β-stannyl ketone **3bm**. With Ph_2POPh, the desired ketone **3bn** was isolated in 53% yield; however, a 17% yield of **3bo** via oxidation was observed in the crude reaction mixture. The use of $Ph_2P(=O)OPh$ produced β-phosphoryl ketone **3bo** with a high yield of 76%.

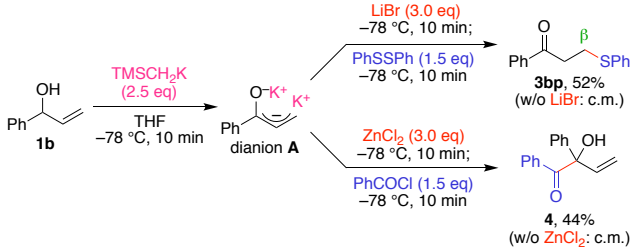
Scheme 3. Scope of Electrophiles[a]



[a]Conditions: **1b** (33.6 mg, 0.25 mmol) and $TMSCH_2K$ (78.9 mg, 0.625 mmol) in THF (3 mL) at –78 °C for 10 min followed by an electrophile (0.375 mmol) at –78 °C for 10 min. Yields of isolated products are shown. [b]With 3.0 equiv of $TMSCH_2K$. CPME was employed as solvent. [c]Hydrolysis of imine was performed with 3 M HCl (2 mL) at rt for 1 h. [d]The reaction temperature was raised to rt and stirred for 30 min. [e]With 2.2 equiv of TMSCl. Desilylation of Si–O bond was performed with 1 M HCl (0.5 mL) in Et_2O/THF (4 mL, 1:1) at rt for 30 min. [f]A 17% yield of **3bo** was observed in the crude reaction mixture.

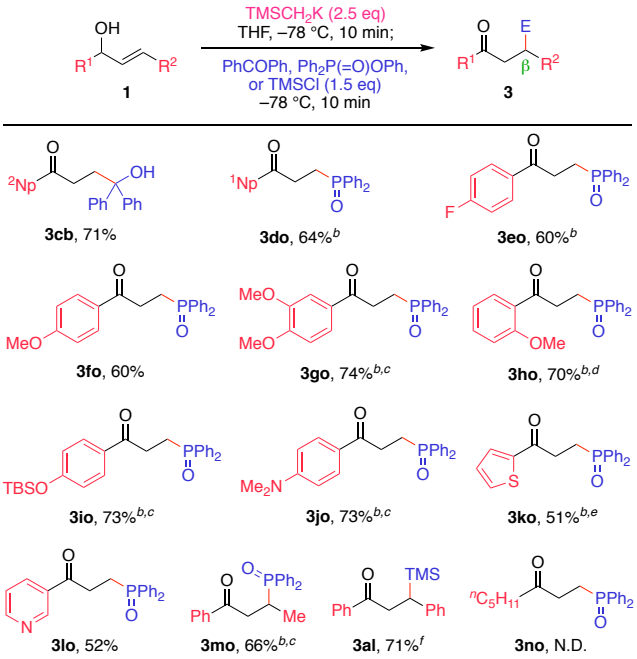
Unlike cyclopropanol-derived metal homoenolates, dipotassio dianions are highly nucleophilic, and consequently, a wide range of electrophiles can be introduced at the β-position, rendering this method synthetically more attractive. However, highly reactive electrophiles were not tolerated under the current reaction conditions due to the fierce reactivity of dipotassio dianions. To further expand the scope of electrophiles, the reactivity of dianions was tuned by metal counterion exchange (Scheme 4). For example, although the reaction of diphenyl disulfide with the dipotassio dianion **A** resulted in a complex mixture, the addition of LiBr produced a 52% yield of β-phenylsulfanyl ketone **3bp**. Furthermore, the reaction with benzoyl chloride in the presence of $ZnCl_2$ exhibited almost exclusive branch-selectivity, providing the benzoin derivative **4** in 44% yield. Recently, Yoshikai et al. reported similar selectivity in the reactions of dizincio α,β-dianions with aldehydes.[36]

Scheme 4. Tuning of the Nucleophilicity of Dianions by Metal Counterion Exchange



The scope of allylic alcohols **1** was then investigated using benzophenone, $Ph_2P(=O)OPh$, and TMSCl as the electrophiles (Scheme 5). Various 1-arylallylic alcohols reacted well to afford β-functionalized ketones **3cb** and **3do**–**3jo** in yields of 60–74%, regardless of the electronic properties of the aryl groups. Heteroaromatic substrates **1k** and **1l** were also employed in this transformation. Alcohol **1m** bearing a methyl group at the 3-position participated in the reaction to provide **3mo**, which would not be prepared from a metal homoenolate derived from 2-methyl-1-phenylcyclopropanol. 3-Phenyl-substituted substrate **1a** also provided β-silyl ketone **3al** in 71% yield. Unfortunately, no reaction was observed with **1n** bearing an alkyl substituent at C1, owing to the lack of anion-stabilizing ability.

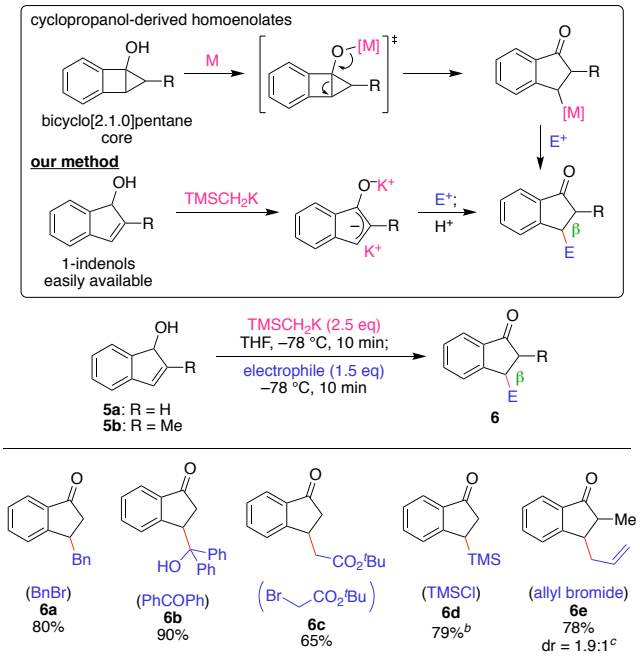
Scheme 5. Scope of Allylic Alcohols[a]



[a]For general reaction conditions, see Scheme 3. [b]With 3.0 equiv of $TMSCH_2K$. [c]The reaction of **1** with $TMSCH_2K$ was conducted at –60 °C. [d]The reaction of **1h** with $TMSCH_2K$ was conducted at –20 °C. [e]CPME was employed as solvent. [f]With 2.5 equiv of TMSCl. Desilylation of Si–O bond was performed with 1 M HCl (1 mL) in THF at rt for 30 min.

The current system was then applied to the synthesis of β-functionalized 1-indanones because such products are difficult to prepare using the ring-opening strategy, which requires cyclopropanols having bicyclo[2.1.0]pentane cores as the starting materials. As a result, various β-functionalized 1-indanones **6a**–**6e** were obtained in high yields from the easily accessible 1-indenols **5** (Scheme 6).

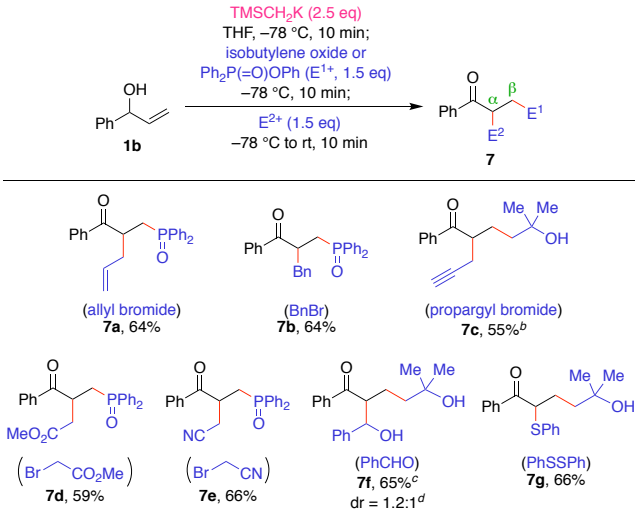
Scheme 6. Synthesis of β-Functionalized 1-Indanones from 1-Indenols[a]



[a]For general reaction conditions, see Scheme 3. [b]With 2.5 equiv of TMSCl. Desilylation of Si–O bond was performed with 1 M HCl (1 mL) in THF at rt for 1 h. [c]Determined by ^1H NMR analysis of the crude reaction mixture.

To further demonstrate the synthetic utility of this method, the one-pot synthesis of α,β-difunctionalized ketones from allylic alcohol **1b** was explored (Scheme 7). It was hypothesized that the reaction of a dianion with the first electrophile (E^{1+}) occurred at the β-position to yield a potassium enolate, which captured the second electrophile (E^{2+}) at the α-position. In fact, two different electrophiles could be sequentially installed at the β- and α-positions to provide structurally diverse ketones **7**, thus highlighting the synthetic advantages of this system.

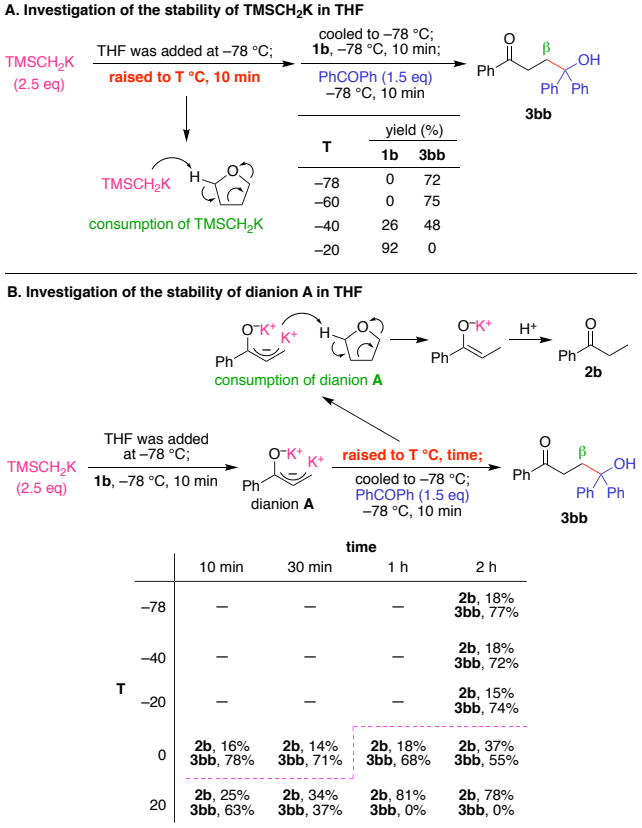
Scheme 7. One-pot Synthesis of α,β-Difunctionalized Ketones 7 from Allylic Alcohol 1b Using Two Different Electrophiles[a]



[a]Conditions: **1b** (33.6 mg, 0.25 mmol) and $TMSCH_2K$ (78.9 mg, 0.625 mmol) in THF (3 mL) at –78 °C for 10 min followed by an electrophile (0.375 mmol) at –78 °C for 10 min. Then, another electrophile (0.375 mmol) was added at –78 °C and stirred at rt for 10 min. Yields of isolated products are shown. [b]The reaction with propargyl bromide was conducted at –78 °C. [c]The reaction with benzaldehyde was conducted at –78 °C for 30 min. [d]Determined by ^1H NMR analysis of the crude reaction mixture.

Organometallic bases represented by alkyllithiums are known to be unstable and gradually decompose in ethereal solvents via the abstraction of the C–H bond adjacent to the oxygen atom. Thus, the thermal stabilities of $TMSCH_2K$ and dipotassio dianion **A** prepared from **1b** in THF were investigated (Scheme 8). Initially, the stability of $TMSCH_2K$ was investigated. To a vial containing $TMSCH_2K$, cold THF was added at –78 °C, and the solution was warmed to various temperatures (–60 to –20 °C) for 10 min and allylic alcohol **1b** was then added. The prepared dianion was then trapped by benzophenone. Below –60 °C, β-functionalized product **3bb** was obtained in high yields with complete consumption of **1b**. However, at –40 °C, the yield of **3bb** decreased to 48%, and 26% of **1b** was detected. At –20 °C, **3bb** was not detected, and **1b** was recovered with a nearly quantitative yield. These results indicated that $TMSCH_2K$ gradually decomposed even at –40 °C and was fully consumed by THF at –20 °C within 10 min. The stability of dianion **A** was then investigated. **1b** was added to a solution of $TMSCH_2K$ in THF at –78 °C and stirred for 10 min. The mixture was then warmed to various temperatures (–40 to 20 °C) and stirred for different durations (10 min to 2 h). The mixture was then re-cooled to –78 °C and reacted with benzophenone for 10 min. **3bb** was obtained in yields above 70% below –20 °C after 2 h and even at 0 °C within 30 min, thus indicating the relative stability of dianion **A** in THF.[37]

Scheme 8. Investigation of the Thermal Stabilities of $TMSCH_2K$ and Dianion A in THF



The lowest-energy structure of dipotassio dianion **A** (Figure 1) was obtained with the aid of the artificial force induced reaction (AFIR) algorithm[38] (see the Supporting Information for details). The structure was calculated by M06-2X+GD3[39]/6-311+G(d,p) level of density functional theory (DFT) calculation. The THF solvent effects were included by the integral equation formalism variant (IEFPCM) method.[40] The lowest-energy structure had a potassium cation on each side of the dianion. This conformer was clearly more stable than other conformers, in which two potassium cations were located on one side of dianion.

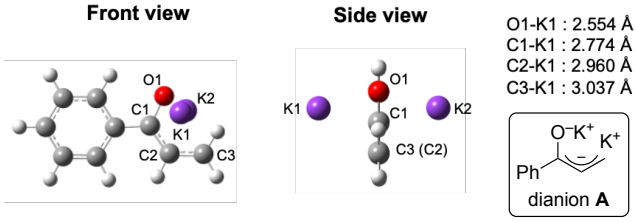
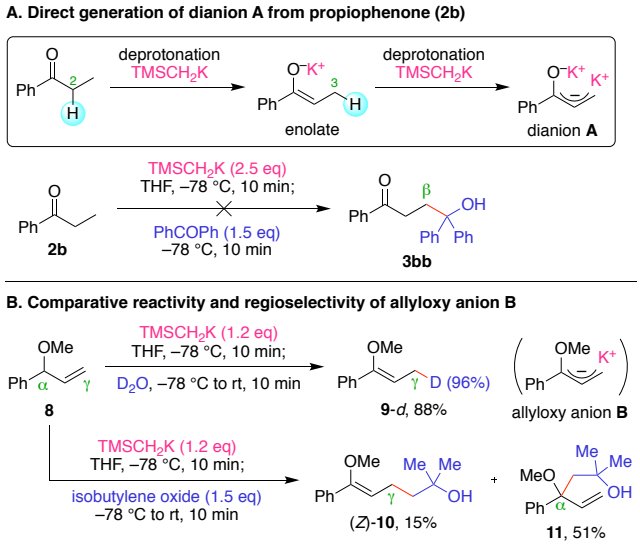


Figure 1. The lowest-energy conformer of dianion **A** obtained by M06-2X+GD3/6-311+(d,p) level of calculation.

To investigate the feasibility of the direct generation of dianion **A** from propiophenone (**2b**) via sequential abstraction of two protons at C2 and C3 by $TMSCH_2K$, **2b** was reacted with $TMSCH_2K$ and subsequently trapped by benzophenone. **3bb** was not observed in this case,[41] thus indicating that dianion **A** was not accessible from **2b**, likely due to the high energy barrier for the deprotonation at C3 of the enolate.[42] To investigate the influence of the potassium alkoxide on the reactivity and regioselectivity of the allylic anion moiety in dianion **A**, substrate **8**, which is a methyl ether derivative of **1b**, was synthesized. The reaction of **8** with $TMSCH_2K$ followed by quenching with

D_2O provided **9**-*d*, thus demonstrating the in situ-generation of allyloxy anion **B**. In sharp contrast to dianion **A**, which led to the linear product **3bi**, the reaction of allyloxy anion **B** with isobutylene oxide resulted in the linear product (*Z*)-**10**[43] with a 15% yield only, while the branched **11** was the major product. These results indicated the significant influence of the potassium alkoxide moiety of the dianion on the regioselectivity and its contribution to the formation of linear products.[44]

Scheme 9. Control Experiments



CONCLUSION

In summary, the $TMSCH_2K$-promoted synthesis of β-functionalized ketones from simple and readily available 1-arylallylic alcohols is reported. The reactions proceeded via the formation of highly nucleophilic ketone dipotassio α,β-dianions. Consequently, various electrophiles that could not be employed in previously reported systems were successfully regioselectively introduced. Dipotassio α,β-dianions possess two nucleophilic sites; thus, two different electrophiles were sequentially introduced at the β- and α-positions, leading to structurally diverse α,β-difunctionalized ketones. The thermal stabilities of $TMSCH_2K$ and the dipotassio α,β-dianion derived from **1b** in THF were also reported. Currently, further studies are being conducted to expand the substrate scope and explore asymmetric transformations.

ASSOCIATED CONTENT

General information, experimental procedures, characterization data, computational study, and NMR spectra.

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Notes

The authors declare no competing financial interest.

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(43) The configuration of **10** was confirmed by NOESY.

(44) While the exact reason for such a difference in regioselectivity between dianion **A** and allyloxy anion **B** remains unclear, we think that the formation of the conjugated enolate after the reaction at the γ-position would be energetically favorable in dianion **A**.