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Synthesis of α-Alkenyl α,β-Unsaturated Ketones via Dehydrogermylation of Oxagermacycles with Regeneration of the Germanium(II) Species

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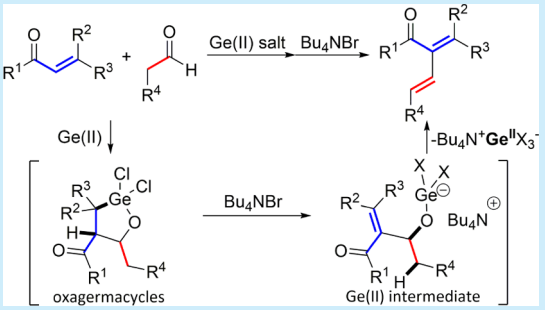
Supporting Information

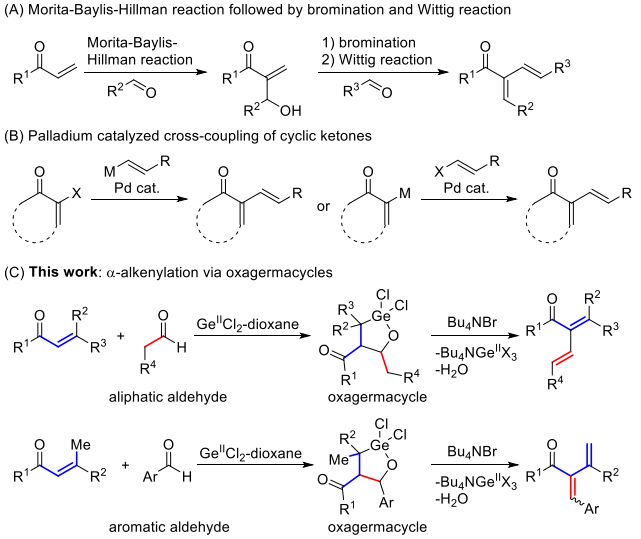
ABSTRACT: The synthesis of α-alkenyl α,β-unsaturated ketones using germanium(II) salts is reported. Oxagermacycles derived from α,β-unsaturated ketones with germanium(II) salts and aldehydes can be transformed into α-alkenyl α,β-unsaturated ketones. Ammonium salts promoted the elimination of Ge(II) species to afford the two classes of α-alkenyl α,β-unsaturated ketones in good yields. The α-alkenyl α,β-unsaturated ketones are precursors for multisubstituted heterocycles.



In the field of organic synthesis, multisubstituted α,β-unsaturated ketones are important building blocks that are successfully employed in the syntheses of bioactive compounds.[1−3] The bifunctionality inherent in α,β-unsaturated carbonyl and 1,3-diene moieties endows α-alkenyl α,β-unsaturated carbonyls with synthetic values that make them capable precursors for highly functionalized organic molecules. The synthesis of α-alkenyl α,β-unsaturated carbonyls has been accomplished via several methods.[4−8] The synthesis of α-alkenyl α,β-unsaturated carbonyls with strong electron-withdrawing groups,[9] such as esters[10] and nitriles,[11] has been established using a combination of the Morita−Baylis−Hillman and Wittig reactions to construct the diene structure (Scheme 1A). Transition-metal-catalyzed cross-coupling reactions,[12] as well as the direct α-alkenylation of heterocyclic α,β-unsaturated ketones,[13−17] have attained modest success in the synthesis of cyclic α-alkenyl α,β-unsaturated ketones (Scheme 1B). The α-alkenylation of acyclic α,β-unsaturated ketones remains undeveloped, however, and this has hampered the flexible and broad-ranging utilization of α-alkenyl α,β-unsaturated carbonyls.

Metallacyclic compounds are important intermediates in stoichiometric and/or catalytic carbon−carbon bond formations,[18,19] metathesis reactions,[20,21] and polymerizations.[22] Oxidative cyclization of low-valent transition metals is one of the well-developed methods for the formation of metallacycles.[23−30] A low-valent group of 14 species, each with an oxidation state of +2, are used to perform oxidative cyclization with unsaturated organic molecules to give the metallacycles that are incorporated in this group of 14 metals (along with the oxidation state changed into +4).[31−36] Divalent silicons,[37] germaniums,[38,39] and tins[39] readily react with α,β-unsaturated carbonyls or 1,3-dienes to afford the corresponding five-membered metallacycles. However, the high or inert reactivity of divalent silicon and tin salts, respectively, interferes with the synthetic applications of the metallacycles based on these metals. For example, $SiCl_2$ is a highly reactive intermediate, and

Scheme 1. Synthesis of α-Alkenyl α,β-Unsaturated Ketones via (A) Combination of the Morita−Baylis−Hillman and Wittig Reactions, (B) Palladium-Catalyzed Cross-Coupling, and (C) Olefination of Oxagermacycles Used in This Work



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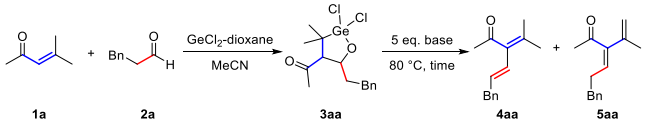
$SnCl_2$ is a bench-stable reductant in organic synthesis. On the other hand, divalent germanium salts with moderate stability and enough reduction capacity can provide the synthetic utility of a low-valent metal. The allylations[40] or aldol-type reactions[41−45] of carbonyl compounds have been accomplished using low-valent germanium.[46] Recently, we reported the diastereoselective synthesis of oxagermacycles via the aldol reactions of aldehydes with C,*O*-chelated germyl enolates derived from Ge(II) salts and α,β-unsaturated ketones. The oxagermacycles were transformed into triols bearing four stereocenters with perfect disatereoselectivity.[47] Further transformation of the oxagermacycles is a promising strategy that could be used to construct highly functionalized molecules in short steps. Herein, we report the synthesis of α-alkenyl α,β-unsaturated ketones via dehydrogermylation of oxagermacycles (Scheme 1C). The addition of ammonium salts promoted the initial dehydrogermylation and the subsequent elimination of a Ge−O moiety. The obtained α-alkenyl α,β-unsaturated ketones are applicable as a synthon for functionalized heterocyclic compounds.

In an initial study, in order to activate a germanium center of **3** via coordination of a ligand, tetrabutylammonium salts were utilized. The treatment of oxagermacycle **3aa**, which is derived from the Ge(II)-mediated aldol reaction[47] of 4-methyl-3-penten-2-one **1a** and 3-phenylpropanal **2a**, with Bu_4NBr gave the α-alkenyl α,β-unsaturated ketones **4aa**/**5aa** in 76% yield (90:10 selectivity) (entry 1 in Table 1). Those results prompted

Table 1. Optimization of the Reaction Conditions



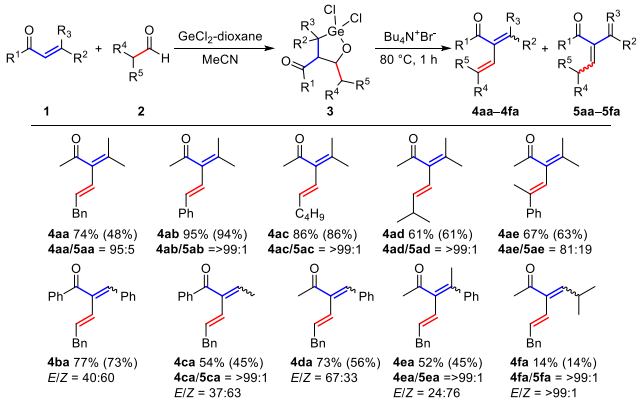
entry	base	time (h)	yield (%)[b]	4aa/5aa[c]
1	$Bu_4N^+Br^-$	24	76	90:10
2	$Bu_4N^+Cl^-$	24	69	91:9
3	$Bu_4N^+I^-$	24	54	81:19
4	$Bu_4N^+HSO_3^-$	24	58	88:12
5	KOAc	24	29	>99:1
6	Cs_2CO_3	24	0	-
7	Et_3N	24	0	-
8	pyridine	24	0	-
9[a]	$Bu_4N^+Br^-$	1	74 (48)	95:5
10[d]	$Bu_4N^+Br^-$	24	69	86:14

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), $GeCl_2$-dioxane (0.6 mmol), base (2.5 mmol), MeCN (2 mL), 80 °C. [b]Yields were determined by ^{1}H NMR measurement using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yield is in parentheses. [c]The ratio of **4aa**/**5aa** was determined by ^{1}H NMR measurement of the crude reaction mixture. [d]$GeBr_2$-dioxane was used instead of $GeCl_2$-dioxane.

us to further optimize the reaction conditions for the synthesis of diene **4**. Bu_4NCl, Bu_4NI, Bu_4NHSO_3, and KOAc were also productive, but the yields of the product were insufficient (entries 2−5). The size of halide was crucial, either smaller or larger than bromide is not suitable (entries 2 and 3). Other typical bases such as Cs_2CO_3, Et_3N, and pyridine promoted the dissociation of **3aa** to **1a** and **2a** (entries 6−8). An improvement in the selectivity of **4aa**/**5aa** was afforded when the reaction time was shortened from 24 to 1 h (entry 9). Instead of $GeCl_2$-dioxane, $GeBr_2$-dioxane worked to give slightly lower yield (entry 10).

With the optimized conditions in hand, a variety of α,β-unsaturated ketones and aliphatic aldehydes was applied in the reaction to give the corresponding α-alkenyl α,β-unsaturated ketones **4** (Scheme 2). The reaction with the linear aldehydes

Scheme 2. Substrate Scope of α,β-Unsaturated Ketones and Aliphatic Aldehydes[a]

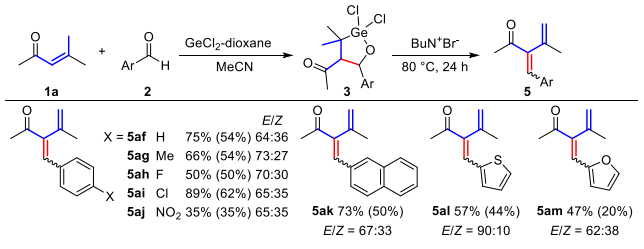


[a]Yields were determined via ^{1}H NMR measurement with 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are in parentheses. Due to the adsorption of the products on silica gel, the isolated yields decreased. Ratios of **4**/**5** for the *E*/*Z* mixtures were determined by ^{1}H NMR measurement of the crude reaction mixture.

2a−**2d** selectively afforded the products **4aa**−**4ad** with an internal butadiene framework in good yields. The employment of an α-branched aldehyde **2e** also gave the diene **4ae** as the main product, but the generation of **5ae** with a terminal butadiene framework was slightly increased. Several unsaturated ketones (**1b**−**1f**) were applicable to the reaction. Products **4ba**−**4fa** were generated as *E*/*Z* mixtures with respect to the carbon−carbon double bond adjacent to the carbonyl group. Presumably, the observed ratios depend on the thermodynamic stability between the two isomers. A perfect *E*-selectivity for the carbon−carbon double bond derived from aldehyde was found in **4**. This result suggests that the E2-type mechanism involves the formation of the carbon−carbon double bond.

Next, we examined the reaction of **1a** with aromatic aldehydes **2f**−**2m** (Scheme 3). For aromatic aldehydes, the obtained butadienes **5af**−**5am** proved to be the terminal versions as *E*/*Z* mixtures. In these cases, prolonged reaction times resulted in sufficient yields. The benzaldehyde derivatives bearing electron-donating (**2g**) and electron-withdrawing (**2h**, **2i**, **2j**) groups and

Scheme 3. Substrate Scope of Aromatic Aldehydes[a]



[a]Yields were determined by ^{1}H NMR measurement using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are in parentheses. Due to the adsorption of the products on silica gel, the isolated yields decreased. The *E*/*Z* ratio was determined by ^{1}H NMR measurement of the crude reaction mixture.

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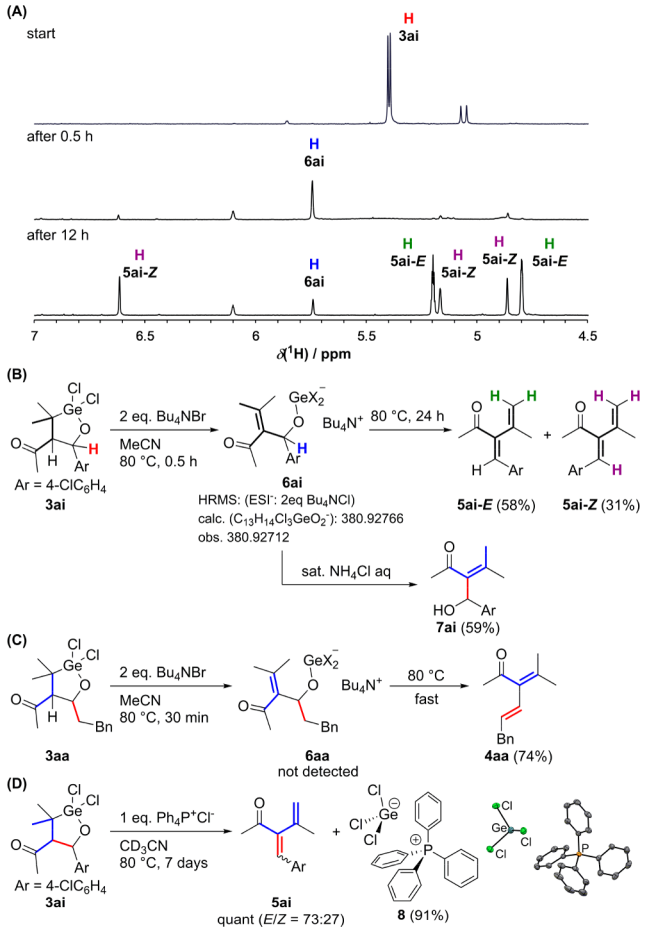
2-naphthaldehyde (**2k**) were applicable to the reaction, but **2j** possessed a strong electron-withdrawing nitro group that suppressed the yield. The ratio between *E*- and *Z*-isomers remained relatively constant among products **5af**–**5ak**. Heteroaromatic aldehydes (**2l**, **2m**) were utilized in this reaction. For the diene **5al** from 2-thiophenecarboxaldehyde **2l**, the ratio of the *E*-isomer was slightly increased presumably because of the electrostatic repulsion between the carbonyl group and the sulfur atom.

The reaction mixture was monitored by ^{1}H NMR spectroscopy to investigate the reaction mechanism. The NMR measurement of the reaction of **3ai** with Bu_4NBr in acetonitrile-d_3 showed that a singlet signal appeared at 5.74 ppm after being mixed for 0.5 h at 80 °C (Scheme 4A). The observed singlet signal should be assigned to the benzylic proton. Quenching the reaction in 30 min with saturated aqueous NH_4Cl gave the benzylic alcohol **7ai** in 59% yield, which strongly suggests that the observed singlet signals at 5.74 ppm should be from an intermediate, **6ai** (Scheme 4B). Actually, the ESI-MS measurement directly detected a molecular ion for **6ai** in the reaction mixture (Figures S4 and S5). The isolated alcohol **7ai** was quantitatively transformed into the diene **5ai** in the presence of both a Lewis acid and Bu_4NBr (entry 1 in Table S1). The absence of either Bu_4NBr or Ge(II) salts gave none of product **5ai** (entries 2 and 3 in Table S1). Because the combination of either $GeCl_4$ or BF_3–Et_2O with Bu_4NBr also succeeded (entries 4 and 5, respectively), the utility of Lewis acids and Bu_4NBr was expected to promote the elimination of the Ge–O moiety. We also attempted to observe the germanium alkoxide intermediate **6aa** or trap the alcohol **7aa** derived from the aliphatic aldehyde **2a**, but the fast olefination of **3aa** into **4aa** under the same conditions hampered these trials (Scheme 4C). We postulated that the alkoxygermanium intermediate **6** was formed as a key intermediate in the initial step of the reaction, which was followed by the elimination of the Ge–O moiety to give α-alkenyl α,β-unsaturated ketones **4** and **5**.

After the completion of the reaction, we examined the structure of the germanium species. When tetraphenylphosphonium salt was utilized instead of Bu_4NBr, the highly crystalline nature of the Ph_4P^+ ions facilitated the isolation of germanium salts after the reaction. The treatment of the oxagermacycle **3ai** with an equimolar amount of tetraphenylphosphonium chloride quantitatively gave **5ai** with $Ph_4P^+[GeCl_3]^-$ **8**. The structure of $Ph_4P^+[GeCl_3]^-$ **8** was confirmed by X-ray crystallographic analysis (Scheme 4D). The regeneration of the germanium(II) species suggested that the intermediate **6ai** was formed not via direct β-hydride elimination, but rather by the base-promoted 1,2-elimination of the germanium moiety. The base-promoted 1,2-elimination can be found in the reaction of a β-stannyl ketone.[48] Although regeneration of the germanium(II) species might be unusual, the bistability of the two oxidation states of germanium (Ge(II)/Ge(IV)) enabled the dissociation of the Ge–C bond. The stepwise change in the oxidative state of the germanium center may have led to a catalytic reaction. The regenerated germanium(II) species **8** did not show catalytic activity due to the formation of an inert tricoordinated germanate(II) complex. Further investigation of the catalytic condition of Ge(II) salt is ongoing in our group.

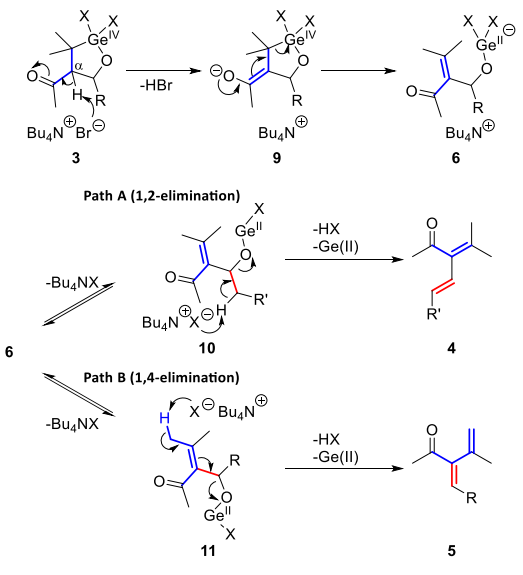
Although details of the reaction mechanism remain uncertain, we believe that Scheme 5 offers a plausible mechanism for the transformation of the oxagermacycle **3** into dienes. Initially, the treatment of an oxagermacycle intermediate **3** with Bu_4NBr

Scheme 4. Mechanistic Studies[a]



[a]Conditions: (A) ^{1}H NMR spectra (400 MHz, acetonitrile-d_3) showing the progress of the transformation of **3ai** to **5ai** via **6ai** at 80 °C by Bu_4NBr; (B) transformation of **3ai** to **5ai** via **6ai** and protonation of the reaction intermediate; (C) transformation of **3aa** to **4aa** via **6aa**; and (D) determination of the germanium species after the completion of the reaction.

Scheme 5. Plausible Reaction Mechanism



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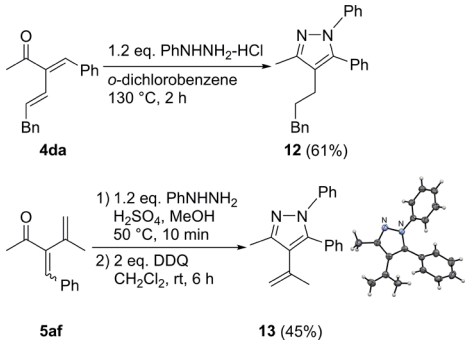
triggered the deprotonation of an α-proton of the carbonyl group. The generated enolate **9** cleaved the Ge−C bond to afford the alkoxygermanium species **6** in situ. For the aliphatic aldehydes (path A), the deprotonation at the β position of **6** led to elimination of the Ge−O moiety of **10** to primarily give diene **4**. When the main product was **4** rather than **5**, this suggested that the 1,2-elimination of the Ge−O moiety would proceed via an E2-type mechanism. In contrast, for the aromatic aldehyde (path B), the 1,4-elimination of the Ge−O moiety of **11** selectively gave the *E*-isomer of **5** as a kinetically controlled product. A gradual isomerization was observed to afford an *E*/*Z* mixture (see Figure S3). Because the 1,4-elimination was slower than the 1,2-elimination, intermediate **6ai** was observed by NMR spectroscopy.

The obtained α-alkenyl α,β-unsaturated ketones were applied to the synthesis of 1,5-diphenyl-3-methylpyrazole derivatives **12** and **13** (Scheme 6). The analogues of 1,5-diphenyl-3-methylpyrazole have shown potential for use as HIV-1 reverse transcriptase inhibitors.[49,50] The treatment of **4da** with phenylhydrazine hydrochloride afforded the 1,5-diphenyl-3-methylpyrazole derivative **12** in 61% yield.[51] The 1,5-diphenyl-3-methylpyrazole derivative **13** was synthesized from **5af** via the treatment of phenylhydrazine followed by oxidation with DDQ.[52] The formation of **13** was confirmed by X-ray crystallographic analysis.

Scheme 6. Synthesis of 1,5-Diphenyl-3-methylpyrazole Derivatives



In conclusion, we have developed a method for the synthesis of α-alkenyl α,β-unsaturated ketones from α,β-unsaturated ketones with aldehydes using germanium(II) salts. Highly substituted α,β-unsaturated ketones were successfully synthesized. Various aldehydes, such as aromatic, heteroaromatic, and alkyl versions, are applicable to the reaction. The internal butadienes were obtained from aliphatic aldehydes. On the other hand, the terminal butadienes were formed from aromatic aldehydes. From a mechanistic perspective, tetrabutylammonium bromide worked as a base, which promoted dehydrogermylation to give a germanium alkoxide intermediate with the regeneration of divalent germanium species. The intermediate was transformed to α-alkenyl α,β-unsaturated ketones in the presence of germanium salts and tetrabutylammonium salts. The internal dienes **4** and the terminal dienes **5** were formed via the 1,2-elimination and the 1,4-elimination of the Ge−O moiety, respectively. The 2-acyl-1,3-butadiene derivatives **4** and **5** could be transformed into highly substituted pyrazoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03454.

Experimental procedures, characterization of products, and spectroscopic data (PDF)

Accession Codes

CCDC 1953429−1953430 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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