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DOI: 10.1039/D0CC03986A

COMMUNICATION

Cyclization of 5-Alkynylketones with Chromium Alkylidene Equivalents Generated *in situ* from *gem*-Dichromiomethanes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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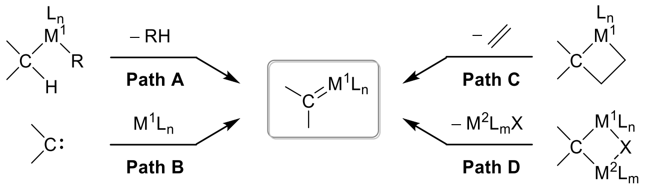
A rare example of cyclization with alkynylketones, which possess non-polar alkynyl and less electrophilic polar keto carbonyl groups, was demonstrated. The key to promoting carbene/alkyne metathesis followed by alkylidenation with pendant C=O double bonds was the Schrock-type nucleophilic reactivity of the generated chromium carbene equivalents from readily available diiodomethanes and $CrCl_2$ by simple heating.

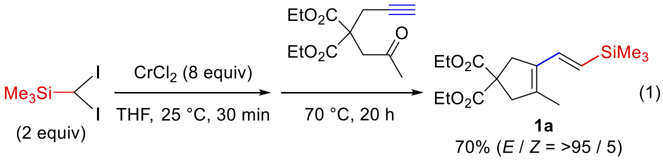
Metal carbenes are well-established reagents in modern organic synthesis.[1] Strategies, including α-hydrogen abstraction of dialkylmetal species (Figure 1, Path A), complexation of metal species with carbene equivalents, such as diazoalkanes (Path B), and elimination of ethylene *via* ring-cleavage of metallacyclobutanes (Path C), have been reported for the reliable generation protocols of metal carbene species.[2] Another approach involves conversion of *gem*-metalloalkanes ($M^1{-}CR_2{-}M^2$), possessing two metal atoms on the alkylene carbon (Path D).[3,4] Although Grubbs *et al*. realized the possibility of the route by the generation of titanium carbene species from the Tebbe reagent ($Ti{-}CH_2{-}Al$) upon treatment with 4-(dimethylamino)pyridine in 1982,[4] few studies expanding on this method have been reported. In the current study, a *gem*-dichromiomethane species ($Cr{-}CR_2{-}Cr$), which can be readily prepared from $CrCl_2$ and dihalomethanes, was chosen as a readily available and stable metal carbene generator *via* Path D, and was used as a precursor for the facile *in situ* generation of Schrock-type carbene equivalents.[5,6] The group 6 metal carbene species stabilized by heteroatom or aryl group substitution at the α-carbon, represented by chromium Fischer-type carbenes, $[R^1R^2C{=}M(CO)_5]$ (*e.g.*, R^1, R^2 = alkyl, alkoxy, amino, halogen), possessing an electrophilic carbene carbon, are historically important organometallic reagents in organic syntheses and organometallic chemistry.[7] Surprisingly, however, few reports exist on the generation and use of *Schrock-type chromium carbene, i.e., chromium-alkylidene species*.[8]



This work (**Path D**, $M^1 = M^2 = Cr$)
Generation of nucleophilic chromocarbene equivalents

Figure 1. Generation of metal carbene species

The present study demonstrates the reactivity of *gem*-dichromiomethane species, which are as useful dianion species,[5,9] as Schrock-type chromium carbene equivalents *via* coupling and cyclization with 5-alkynylketones. The *in situ* preparation of *gem*-dichromiomethane species from reaction of $CrCl_2$ (8 equiv) and (diiodomethyl)trimethylsilane,[10] followed by treatment with 5-alkynylketone in THF at 70 °C, afforded alkynylcycloalkene **1a** as a single stereoisomer in 70% yield (Eq 1). Note that this cyclization of alkynylketones, which possess non-polar C≡C and polar keto C=O bonds, is very rare,[11] while the corresponding cyclization of alkynylaldehydes, which have more electrophilic formyl groups, is relatively common.[12] Previously, cyclization with Fischer-type electrophilic ruthenium carbene complexes generated *in situ* provided dihydropyrans (Eq 2, *Si* = $SiMe_3$, W = CO_2Me, *Ru* = Cp^*RuCl).[11b] In contrast, formation of **1a** in the current study could be explained by the sequential metathesis reaction[13] of carbene species to C≡C and C=O bonds (see Scheme 2 (vide infra)), implying that the generated carbene equivalents possessed Schrock-type nucleophilic reactivity. Although reactivity of *gem*-dichromiomethane species toward alkynes has been demonstrated



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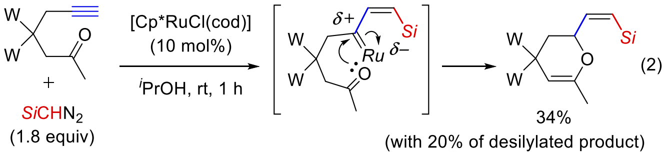
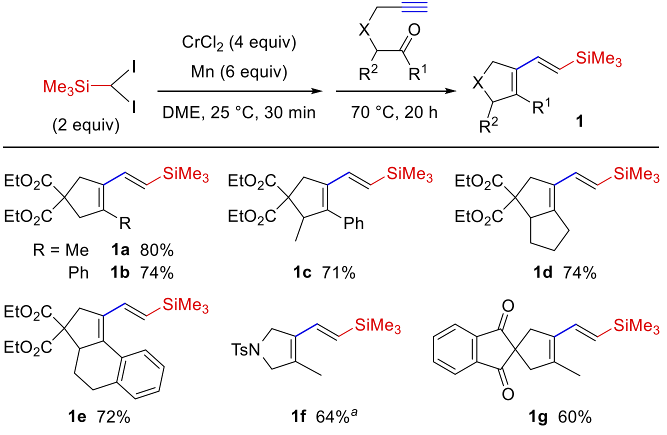
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x in our recent work on the transformation of 1,*n*-enynes,[14] the present results provide direct information about the reactivity of the generated carbene equivalents. The yield of **1a** increased to 85% by changing the solvent to DME (1,2-dimethoxyethane) (see Table S1 in ESI for optimization details). The amount of $CrCl_2$ could be reduced to 4 equiv using manganese powder to reduce the generated CrX_3 (X = Cl or I) back to CrX_2 (see Scheme 2),[15,16] resulting in isolation of **1a** in 80% yield (Table 1). The yield of **1a** decreased to 32% when the reaction was conducted at 50 °C, and an inseparable mixture was obtained with TMEDA, which was an effective additive for previously reported cyclopropanation of alkenes.[17]



Cyclization initiated by coupling of a chromosilylcarbene equivalent with C≡C bonds proceeded smoothly with phenyl ketones to produce **1b** and **1c** in 74% and 71% yield, respectively (Table 1). Note that aryl ketones could not be used as substrates in the previous intermolecular alkylidenations of carbonyl compounds.[18] Despite the more sterically hindered environment of ketocarbonyl groups, cyclization proceeded efficiently to afford fused bi- and tricycles **1d** and **1e** in high yields. The composition of the linkers between the alkynyl and carbonyl groups did not affect cyclization efficiency, and azacycle **1f** and spirocycle **1g**, respectively, were obtained, respectively. However, substituents at the propargyl position or alkyne terminal prevented the triple bond from participating in the present reaction.[19,20] In contrast, sequential cyclization with a diyne containing a keto carbonyl group provided the conjugated triene **2** in 64% yield (Scheme 1). The double bond geometry of **1** and **2** was *E* regardless of the structure of the precursor.

Table 1. Coupling and cyclization of 5-alkynylketones with *gem*-(dichromio)silylmethane



R = Me **1a** 80%
Ph **1b** 74%

1c 71%

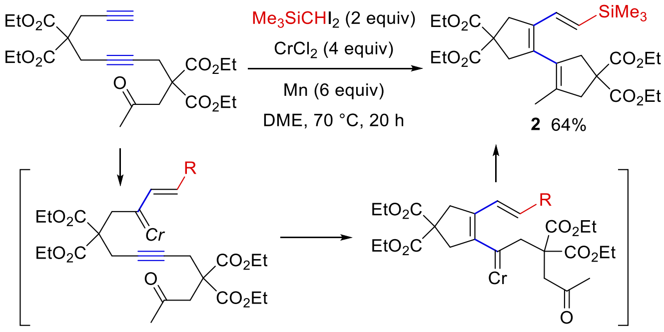
1d 74%

1e 72%

1f 64%[a]

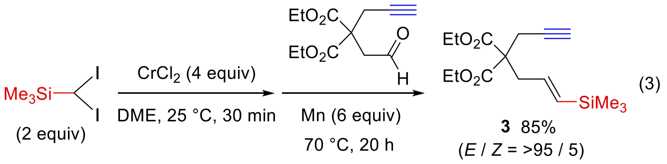
1g 60%

[a] For 7 h.

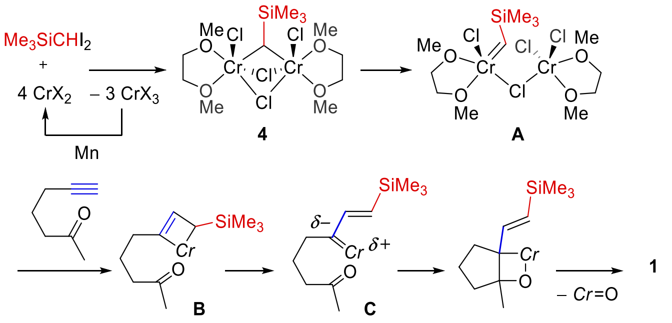


Scheme 1. Sequential cyclization initiated by coupling with diyne

When 5-alkynylaldehyde was used as a precursor, direct alkylidenation furnished **3** without affecting the terminal triple bond (Eq 3). The results obtained so far indicated that the affinity of the *gem*-di(chromio)silylmethane species was in the order of formyl group (CHO) > ethynyl group (C≡CH) > keto carbonyl group (RC(=O)R').



The reaction mechanism for the current coupling and cyclization reaction is proposed in Scheme 2. *gem*-(Dichromio)silylmethane species **4** generated *in-situ* by sequential single-electron transfers from 4 equiv of $CrCl_2$ may generate chromium alkylidene species **A**. Chromacyclobutene intermediate **B** generated *via* formal [2+2]cycloaddition of alkynylketones with **A** is then converted to alkenylchromacarbene species **C**,[14] which subsequently undergoes intramolecular alkylidenation of the pendant keto carbonyl group to furnish alkenylcycloalkene **1**.[21] Note that the generated **C** is a Schrock-type carbene species, and formation of the corresponding dihydropyrans as shown in Eq 2 was not observed.



Scheme 2. Plausible reaction mechanism for the formation of **1** (*Cr* = CrCl(dme)(ClCrCl$_2$(dme)), X = Cl or I)

Although attempts to obtain direct information about the generation of chromium alkylidene species **A** was unsuccessful, the isolation and structural characterization of a key reactive species, *gem*-(dichromio)silylmethane **4**, stabilized by coordination of DME, was achieved. Note that only a trace amount of **4** was detected in DME at 70 °C due to its competitive decomposition to (*E*)-1,2-bis(trimethylsilyl)ethene in the absence of alkynylketones (Eq 4).[22] However, an authentic sample of **4** was obtained by ligand exchange of the THF-coordinated *gem*-(dichromio)silylmethane **4'** prepared in THF at 25 °C (Eq 5).[23] A single crystal suitable for X-ray crystallographic analysis was obtained by recrystallization from a DME solution layered with hexane. The solid-state structure of **4** in

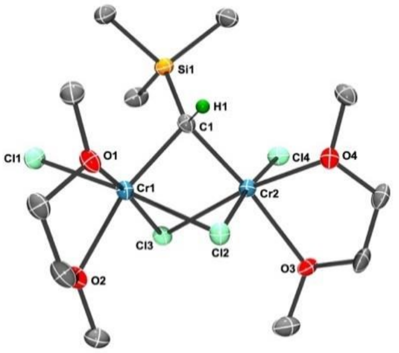
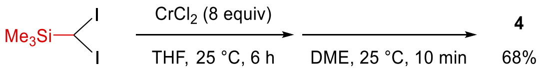
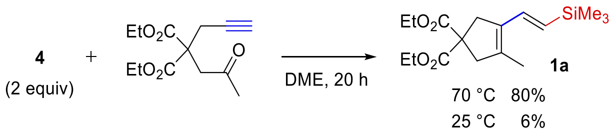


Figure 2. POV-ray drawing of **4** with thermal ellipsoids at the 50% probability level. Hydrogen atoms with the exception of H1 and co-crystallized solvent molecules have been omitted for clarity.

Figure 2 contained a dinuclear chromium coordinated with a DME bridged by a methine carbon. Comparison of a previously isolated *gem*-(dichromio)silylmethane complex having a TMEDA ligand[5c] indicated that bond the lengths for C–Cr(dme) (2.051(4) Å, 2.062(4) Å) were slightly shorter than that for C–Cr(tmeda), (2.082(3) Å). Despite the shorter C–Cr distances and less hindered environments around the chromium center of **4** compared to those for the TMEDA-coordinated species, the weaker σ-donation ability of DME may result in facile ligand dissociation to provide a vacant site for the coordination of alkynylketones. This is one of the reasons why DME-coordinated *gem*-(dichromio)silylmethane **4** showed better performance for the transformation of alkynylketones than TMEDA-coordinated species (Table S1 in ESI, entries 4 vs 8). Solution susceptibility measurements obtained using Evans' method[24] revealed that complex **4** had $S = 3$ ($\mu_{\mathrm{eff}} = 6.64\ \mu_{\mathrm{B}}$), where each chromium(III) center had a d^3 high-spin configuration with no metal-metal bond, similar to the TMEDA-coordinated species ($\mu_{\mathrm{eff}} = 6.75\ \mu_{\mathrm{B}}$).[5c] The reactivity of **4** as a key precursor to the chromium alkylidene species was demonstrated in the addition and cyclization leading to **1a** (Eq 6). The reaction proceeded efficiently at 70 °C, which indicated that heating was required for both the generation of **4** and the addition to alkynylketones. As expected, (*E*)-1,2-bis(trimethylsilyl)ethene was formed quantitatively in the absence of alkylketones.



(5)



(6)

In conclusion, the present study demonstrated the rare generation of alkylidene equivalents from *gem*-dimetalloalkanes (Path D in Figure 1). *gem*-Dichromiomethanes acted as a chromiumalkylidene equivalent to promote carbene/alkyne metathesis[13] followed by capture by polar C=O bonds to yield functionalized carbo- and heterocycles. Formation of alkeynylcycloalkenes *via* the attack of an alkenylcarbene intermediate to a carbonyl group indicated that the carbene equivalents generated possessed Schrock-type nucleophilic reactivity. Application of this strategy for preparation of early transition metal-based alkylidene species is ongoing.

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Conflicts of interest

There are no conflicts to declare.

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20 Reactions with other *gem*-dichromiomethanes having boryl, stannyl, iodo, and alkyl groups were examined, yields of the expected alkenylcycloalkenes were unfortunately less than 30%. The presence of the relatively bulky silyl group seems to be important to stabilize the *gem*-dichromiomethanes and chromium alkylidene species. Because the present reaction requires heating to 70 °C, it is likely that the *gem*-dichromiomethane species without appropriate substituents decomposed during the reaction with alkynylketones.

21 Sequential alkyne insertion occurred in the reaction with simple terminal alkynes without forming the corresponding cyclopropenes. On the other hand, reaction of simple ketones gave the corresponding olefins albeit in low yields. Given this high reactivity toward ethynyl groups, cycloisomerisation of enynes generated via the direct alkylidenation of keto carbonyl group in the initial stage is unlikely as a reaction mechanism. The possibility of intramolecular [2+2]cycloaddition of alkynylketones followed by alkylidenation might be another potential mechanism, but this route is also unlikely because formation of the key intermediate, 1-cyclopentene-1-carbaldehydes, was never observed.

22 The byproduct, $Me_3SiCH{=}CHSiMe_3$, might be formed *via* radical or chromium-mediated coupling reaction of alkylidene species **A**. Because formation of the corresponding phosphonium ylide, $Me_3SiCH{=}PMe_3$, was not observed in the presence of PMe_3, dimerization of the metal-free carbene species can be ruled out as a possible reaction mechanism.

23 *gem*-(Dichromio)silylmethane was generated at 25 °C in THF, whereas heating to 70 °C was required in DME. The THF-coordinated *gem*-(dichromio)silylmethane **4’** could not be structurally characterized due to the amorphous character of the solid obtained and the difficulty of separating it from the byproduct $CrCl_2I(thf)_3$.

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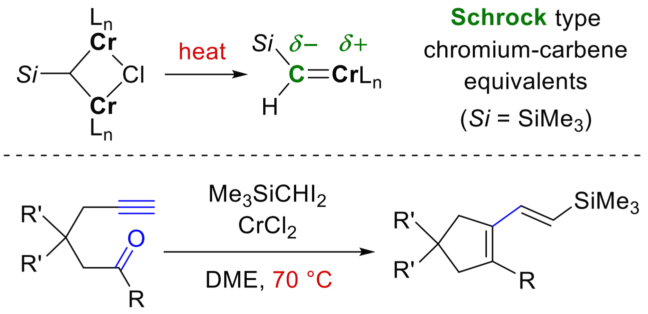

Sequential metathesis reaction with C≡C and C=O.