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Unusually high *ortho*-selectivity in electrophilic aromatic substitution promoted by $GaCl_3$†

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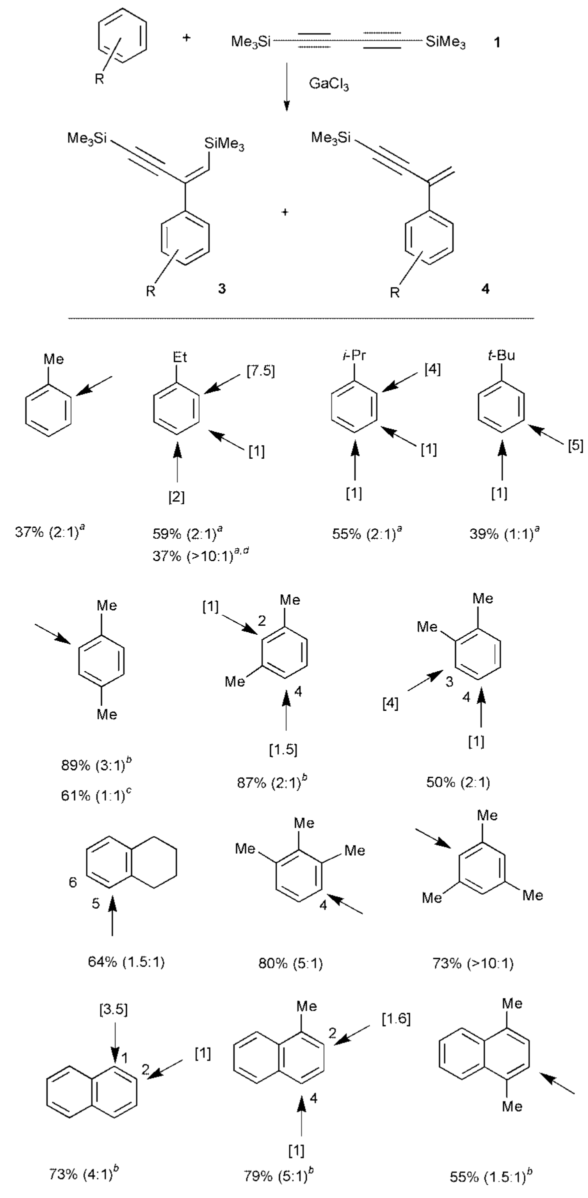
1,4-Bis(trimethylsilyl)buta-1,3-diyne in the presence of $GaCl_3$ reacts with aromatic hydrocarbons at −90 to −100 °C yielding 2-arylbut-1-en-3-ynes; the reactions exhibit an unusually high tendency to alkenylate the *o*-position of alkyl substituents; toluene, ethylbenzene and isopropylbenzene react predominantly to exclusively at the *o*-position while *o*-xylene and 1,2,3,4-tetrahydronaphthalene react at the 3 and 5-position, respectively.

Ortho–para selectivity in electrophilic aromatic substitution is an issue still not fully understood. Particularly, selective *o*-alkylation is rare, since a slight increase in the steric bulk of the substituent directs the reaction to the *p*-position.[1] Several benzene derivatives possessing heteroatom functionalities are known to exhibit such *o*-selectivity, which is ascribed to the interactions between the electrophile and the substituent.[2] Only modest levels of *o*-selectivity are observed in some reactions of toluene, where such an interaction is unavailable[3] while *o*-selectivity is rare for ethylbenzene or isopropylbenzene. Described here is an *o*-selective aromatic alkenylation reaction using $GaCl_3$ and 1,4-bis(trimethylsilyl)buta-1,3-diyne **1**. We previously reported the β-silylethenylation reaction of arenes with trimethylsilylethyne **2** in the presence of $GaCl_3$[4] involving C–C bond formation between an organogallium ethenyl cation and an arene exhibiting *para*-selectivity. By contrast, examination revealed that the electrophile derived from **1** shows an unusually high tendency to alkenylate the *o*-position of alkyl substituents.

Arene (5 mol equiv.) and **1** (1 mol equiv.) were reacted with $GaCl_3$ (2 mol equiv.) in CH_2Cl_2 at −90 to −100 °C for 1–2 h.‡ THF was then added, and the mixture stirred for 0.5 h at −90 to −100 °C. Aqueous workup gave (*Z*)-1,4-bis(trimethylsilyl)-2-arylbut-1-en-3-yne **3** and 4-trimethylsilyl-2-arylbut-1-en-3-yne **4** (method A) as shown in Scheme 1.[5] For some arenes such as *p*-xylene or *m*-xylene, addition of another portion of $GaCl_3$ (2 mol equiv.) increases the total yield (method B). The reaction can be carried out using an equimolar amount of *p*-xylene and **1** with only a slight decrease in the yield. Addition of THF prior to the water improves the yield of the products. The (*Z*)-stereochemistry of **3** was determined by NOE studies. The reaction sites of the arenes were confirmed unambiguously by spectroscopic methods. The isomer distribution of **3** is similar to that of **4**. The olefinic trimethylsilyl group of **3** can be removed producing **4** by careful treatment with CF_3CO_2H in a mixture of diethyl ether and water with the temperature gradually increased from −78 °C to room temperature. For example, (*Z*)-1,4-bis(trimethylsilyl)-2-(2,5-dimethylphenyl)-but-1-en-3-yne **7** was monodesilylated in 70% yield. Reactions of **1**, which is a stable alternative to buta-1,3-diyne, have attracted considerable attention in organic synthesis. For example, silicon substitution with electrophiles occurs in the presence of Lewis acids or methyllithium giving diyne compounds.[6] Organometal addition producing enynes has also been reported.[7] Electrophilic addition to **1** as well as to the parent buta-1,3-diyne has been little studied.[8]

It may be reasonably assumed, based on the employment of similar reagents and reaction conditions, that the present reaction and the β-silylethenylation[4] involve similar electrophilic substitution mechanisms. However, several differences are noted. First, the orientation of these reactions differs considerably. The directing effect of the methyl group to its *o*-position is unusually high in the present reaction; indeed toluene



Scheme 1 Yield of **3** + **4** is shown. Figures in parentheses indicate the ratio of **3** : **4**. →: Reaction site. [ ]: Isomer ratio of **3**. [a] 20 mol equiv. of arene used. [b] Method B employed. [c] 1 mol equiv. of arene used. [d] 1,4-Bis(triethylsilyl) buta-1,3-diyne used, the isomer ratio is very similar to the reaction of **1**.

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† Electronic supplementary information (ESI) available: full experimental and spectroscopic data. See http://www.rsc.org/suppdata/cc/b0/b003215h/

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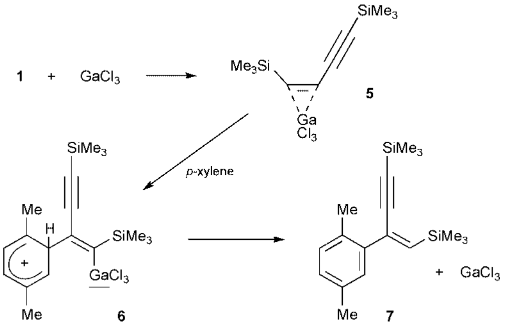
reacts exclusively at the *o*-position. This is in contrast to the observation that the β-silylethenylation predominantly occurs at the *p*-position.[4] Ethylbenzene and isopropylbenzene also predominantly react at the *o*-position. Notably, *tert*-butylbenzene gives the *m*-isomer as the major product. Disubstituted benzenes also show a tendency to react at positions adjacent to the alkyl substituents; *o*-xylene is predominantly alkenylated at the 3-position, 1,2,3,4-tetrahydronaphthalene exclusively reacts at the 5-position while a considerable proportion of *m*-xylene reacts at the 2-position. The dominant reaction sites in β-silylethenylation are at the 4-, 6- and 4-positions for these three substrates, respectively.[4] It is known from detritiation experiments that the *p*-position in toluene is about twice as reactive as the *o*-position.[9] Similarly, the 4-position of *o*-xylene, the 6-position of 1,2,3,4-tetrahydronaphthalene and the 4-position of *m*-xylene are more reactive than the others.[9] Detritiation is considered to reflect the reactivity of the aromatic sites excluding steric effects. The orientation of β-silylethenylation using **2**, therefore, can be understood by taking into account both electronic and steric effects. The orientation of the present reaction using **1** is unusual with reaction at the less reactive and more hindered sites predominating. The following examples also show the anomalous orientation of this reaction. 1-Methylnaphthalene predominantly reacts at the 2-position. While 1,3,5-trimethylbenzene is inert to β-silylethenylation, the reaction of **1** proceeds smoothly. The substituent on the silicon atom of **1** is not essential for *o*-selectivity, since 1,4-bis(triethylsilyl)buta-1,3-diyne reacts with ethylbenzene also at the *o*-position.

Second, a difference in the behavior of **1** and **2** is observed in deuteration experiments. When the reaction of *p*-xylene and **1** was quenched with D_2O, product **7** was not deuterated at the olefin moiety. Whereas β-silylethenylation using **2** produced a β-deuterated product.[4] Since the reaction of **1**, as for **2**, is likely to proceed *via* the organogallium electrophile **5**, an arenium cation **6** should be formed (Scheme 2). The above result of the deuteration experiment suggests that protodegallation of **6** takes place in the reaction mixture, regenerating $GaCl_3$. Unfortunately, 10 or 50 mol% of $GaCl_3$ does not effectively promote the catalytic reaction.§



Scheme 2

Third, the present reaction proceeds at a temperature lower than that for β-silylethenylation.[4] While the latter reaction does not take place at −90 °C, the former reaction occurs efficiently even at −100 °C. The electrophilic species derived from **1** appears to be more reactive than that from **2**.

A higher polyyne compound can also be used for alkenylation. Reaction of 1,8-bis(triethylsilyl)octa-1,3,5,7-tetrayne **8**[10] and toluene yields 2-aryloct-1-en-3,5,7-triyne **9** (Scheme 3). Since the *p*-product predominated here, the anomalous orientation in the reaction of **1** can be attributed, at least in part, to its diyne structure.

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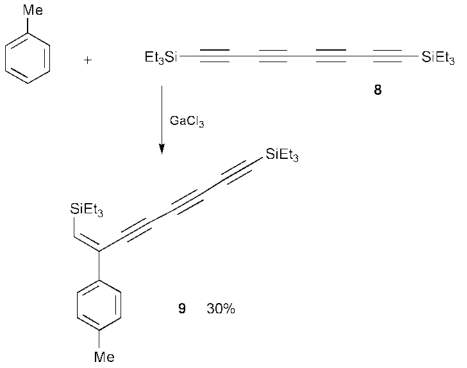

Scheme 3

Notes and references

‡ *Typical procedure*: under an argon atmosphere, to a stirred solution of *p*-xylene (0.31 mL, 2.5 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of $GaCl_3$ (1.0 M in methylcyclohexane, 1.0 mL) at −98 °C. To this mixture, **1** (97 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was added slowly, and stirring was continued for 1 h at this temperature. Then THF (3 mL) was added, and after 30 min water was added. A standard workup gave **7** (74 mg, 49%) and 4-trimethylsilyl-2-(2,5-dimethylphenyl)but-1-en-3-yne (10 mg, 9%).

§ There are lines of evidence for product inhibition: (i) When **7** (2 mol equiv.) was added to the reaction mixture of *m*-xylene (2 mol equiv.), **1** (2 mol equiv.) and $GaCl_3$ (1 mol equiv.) at −90 °C, alkenylation was totally inhibited with recovery of **7** in 84% yield. In contrast, 17% of the product derived from *m*-xylene was obtained in the absence of **7** under the same conditions. (ii) Compound **7** and $GaCl_3$ react to form an orange solution in methylcyclohexane at −100 °C, which fades on addition of THF. Reversible complex formation was also detected by *in situ* IR. **7**: IR (methylcyclohexane, −95 °C) 1248, 843 cm^{-1}. **7**•$GaCl_3$ complex: IR (methylcyclohexane, −95 °C) 1252, 839 cm^{-1}. For complex formation of $GaCl_3$ and aromatic hydrocarbons, see ref. 11.

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