C–H Alkylation

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# Regioselective C–H Alkylation of Anisoles with Olefins Catalyzed by Cationic Half-Sandwich Rare Earth Alkyl Complexes**

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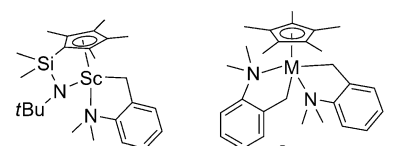
Anisole derivatives are important aromatic compounds, their structural motifs are observed in many useful materials, such as pharmaceuticals, natural products, and fluorescent dyes.[1] The development of efficient, selective processes for the synthesis of anisole derivatives is therefore of much interest and importance. Among the most straightforward and atom-economical routes to anisole derivatives is the C–H alkylation of anisoles with alkenes. However, such C–H bond alkylation approaches for the synthesis of anisole derivatives have met with limited success to date. The Friedel–Crafts reaction of anisoles with alkenes is a well-known route to alkylated anisole derivatives, but such Lewis acid catalyzed alkylation reactions generally suffer from poor regioselectivity and often give a mixture of *ortho*- and *para*-regioisomers with the *para*-regioisomer as the main product, owing to steric and electronic influences.[2–4] Recently, the late-transition-metal-catalyzed *ortho*-C–H alkylations of various aromatic compounds possessing a directing group have been reported.[5–7] However, these late-transition-metal catalysts seemed unsuitable for the *ortho*-selective C–H alkylation of anisoles, because the interaction between an ether group and the metal center is too weak to regioselectively direct the C–H bond activation. To the best of our knowledge, the catalytic *ortho*-selective C–H alkylation of anisoles with an alkene has not been previously reported.

In view of the strong oxophilicity of rare-earth metal ions[8,9] and the high activity of rare-earth alkyl species toward unsaturated C–C bonds,[10–12] we envisioned that the rare-earth alkyl complexes might serve as unique catalysts for the *ortho*-selective C–H alkylation of anisoles with alkenes. Herein, we report the rare-earth catalyzed C–H bond addition of anisoles to various olefins, which constitutes the first example of catalytic *ortho*-selective alkylation of an anisole compound with an alkene.

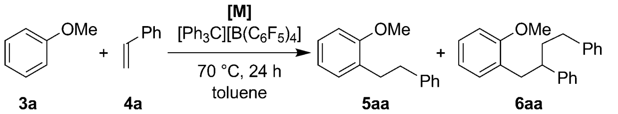


**1**

**2**-M
(M = Sc, Y, Sm, Gd, Lu)

***Figure 1.*** Half-sandwich rare-earth mono- and dialkyl complexes.

***Table 1:*** *ortho*-Alkylation of anisole with styrene catalyzed by rare-earth complexes.[a]



**3a** + **4a** → **5aa** + **6aa**

| Entry | [M] | Yield of **5aa** [%][b] | Yield of **6aa** [%][b] |
|---|---|---|---|
| 1[c] | **1** | 0 | 0 |
| 2 | **2**-Sc | 60 | 15 |
| 3 | **2**-Sc[d] | 58 | 12 |
| 4 | **2**-Y | 94 (91) | 2 |
| 5 | **2**-Gd | 91 | 1 |
| 6 | **2**-Sm | 1 | 0 |
| 7 | **2**-Lu | 17 | 0 |

[a] Reaction conditions: **[M]** (0.025 mmol), $[Ph_3C][B(C_6F_5)_4]$ (0.025 mmol), **3a** (1 mmol), **4a** (1.5 mmol), toluene (3 mL), 70 °C, 24 h, unless otherwise noted. [b] Yield (based on **3a**) measured by GC analysis. Yield of isolated product is given in parentheses. [c] With or without $[Ph_3C][B(C_6F_5)_4]$. [d] **4a** (1 mmol).

We have recently found that the silylene-linked half-sandwich rare-earth alkyl complexes such as **1** (Figure 1) could serve as unique catalysts for the *ortho*-selective C–H silylation of anisoles with hydrosilanes, because the coordination of the methoxy group to the rare-earth metal ion can direct the C–H activation to selectively take place at the *ortho*-position.[9] At first, we chose complex **1** as a catalyst to examine the reaction of anisole with styrene and ethylene, but no alkylation product was observed (See Table 1, entry 1). To facilitate the insertion of a C=C double bond into a possible metal–anisyl active species,[9] we then turned to the cationic rare-earth alkyl complexes, which have shown high activity for olefin polymerization.[10,11] To our delight, the cationic half-sandwich scandium alkyl species, generated by the reaction of the half-sandwich scandium dialkyl complex **2**-Sc[11f] with an equivalent of $[Ph_3C][B(C_6F_5)_4]$,[13] showed high catalytic activity and selectivity for the *ortho*-C–H alkylation of anisole with styrene, which afforded the 1:1 addition product **5aa** as a major product (60%) and a small amount (15%) of the 1:2 addition product **6aa** formed by insertion of two molecules of styrene into an *ortho*-C–H bond of anisole (entry 2). When the yttrium (**2**-Y) or gadolinium (**2**-Gd) analogue was used instead of **2**-Sc, the yield of the mono-

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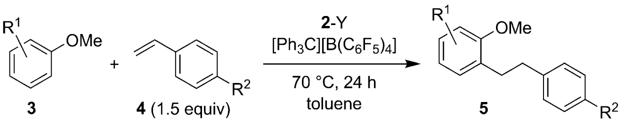
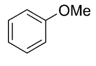
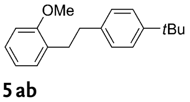
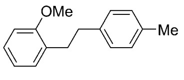
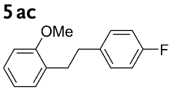
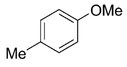
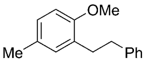
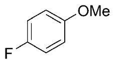
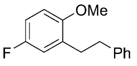
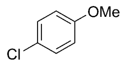
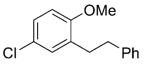
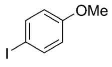
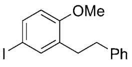
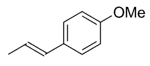
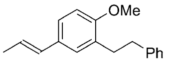
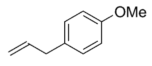
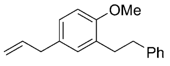
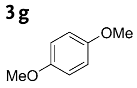
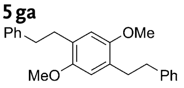
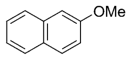
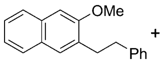
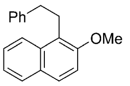
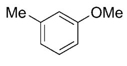
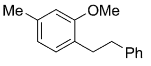
***Table 2:*** *ortho*-Alkylation of various substituted anisoles with styrenes.[a]



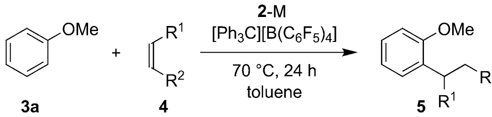
| Entry | Substrate | **4** (R$^2$) | Product | Yield [%][b] |
|---|---|---|---|---|
| 1 |  **3a** | **4b** (*t*Bu) |  **5ab** | 92 |
| 2 | **3a** | **4c** (Me) |  **5ac** | 93 |
| 3 | **3a** | **4d** (F) |  **5ad** | 51 |
| 4 | **3a** | **4d** (F) | **5ad** | 79[c] |
| 5 |  **3b** | **4a** (H) |  **5ba** | 90 |
| 6[d] |  **3c** | **4a** (H) |  **5ca** | 88 |
| 7 |  **3d** | **4a** (H) |  **5da** | 87 |
| 8 |  **3e** | **4a** (H) |  **5ea** | 77 (86)[e] |
| 9 |  **3f** | **4a** (H) |  **5fa** | 84 |
| 10 |  **3g** | **4a** (H) |  **5ga** | 86 |
| 11 |  **3h** | **4a** (H) |  **5ha** | 93[f] |
| 12 |  **3i** | **4a** (H) |  **5ia** +  **5ia'** | 92 (6:1)[g] |
| 13 |  **3j** | **4a** (H) |  **5ja** | 90 |

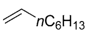
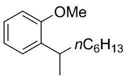
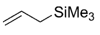
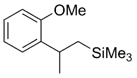
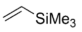
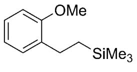
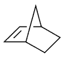
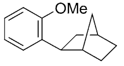
[a] Reaction conditions: **2**-Y (0.025 mmol), $[Ph_3C][B(C_6F_5)_4]$ (0.025 mmol), **3** (1 mmol), **4** (1.5 mmol), toluene (3 mL), 70 °C, 24 h, unless otherwise noted. [b] Yield of isolated product (based on **3**). [c] **3a** (0.5 mmol), **4d** (1.5 mmol). Yield determined by GC analysis. [d] **2**-Y (0.04 mmol), $[Ph_3C][B(C_6F_5)_4]$ (0.04 mmol) and **4a** (2 mmol) were used. [e] Yield determined by $^1$H NMR spectroscopy is given in parentheses. [f] **3h** (0.5 mmol) was used. [g] The product ratio (**5ia**/**5ia'**) determined by $^1$H NMR spectroscopy is given in parentheses.

insertion product **5aa** was increased to 91–94 % under the same conditions (entries 4 and 5), probably because **2**-Y and **2**-Gd are less effective for the polymerization (or continuous insertion) of styrene.[11a] In all of these reactions, the alkylation took place at only one of the two *ortho*-C–H positions of anisole; *meta*, *para*, and di-*ortho*-alkylation were all not observed. The lutetium and samarium complexes **2**-Lu and **2**-Sm were less effective under the same conditions (entries 6 and 7). Neither the neutral rare-earth dialkyl complexes nor $[Ph_3C][B(C_6F_5)_4]$ alone afforded the alkylation product, which shows that a cationic rare-earth alkyl species is essential in the present reaction.

Complex **2**-Y was then utilized to examine the reactions of various substituted anisoles and styrenes. Some representative results are summarized in Table 2. As with styrene, 4-*tert*-butylstyrene (**4b**) and 4-methylstyrene (**4c**) also reacted selectively with the *ortho*-C–H bond of anisole to give in high yields the linear alkylation products **5ab** and **5ac**, respectively, in the presence of 2.5 mol % of **2**-Y/$[Ph_3C][B(C_6F_5)_4]$ (Table 2, entries 1 and 2). 4-Fluorostyrene (**4d**) seemed less reactive and needed a higher catalyst loading (5 %) and a higher feed (3 equiv to anisole) to give a higher yield of the alkylation product **5ad** (entries 3 and 4). The reaction of styrene with various substituted anisole derivatives also took place exclusively at the *ortho* position of the methoxy group. The aromatic C–I, C–Cl and C–F bonds survived the catalytic reaction conditions to selectively give the corresponding halogen-containing alkylated products (entries 6–8). Allyl and propenyl groups are also compatible with this catalyst (entries 9 and 10). In the case of 1,4-dimethoxybenzene (**3h**), the reaction took place at one of the two *ortho* positions of each MeO group to selectively give the *para*-dialkylated product **5ha** (entry 11). In the case of 2-methoxynaphthalene (**3i**), which has two different *ortho*-C–H bonds, the alkylation at the 3-C–H bond predominated over that at the more active

***Table 3:*** *ortho*-Alkylation of anisole with various olefins.[a]



| Entry | **2**-M | Olefin (equiv) | Product | Yield [%][b] |
|---|---|---|---|---|
| 1 | **2**-Sc |  **4e** (2) |  **5ae** | 82 |
| 2 | **2**-Y | **4e** (2) | **5ae** | (21) |
| 3 | **2**-Sc |  **4f** (4) |  **5af** | 80 |
| 4 | **2**-Sc |  **4g** (1.4) |  **5ag** | 64 |
| 5 | **2**-Sc |  **4h** (2) |  **5ah** | 95 |

[a] Reaction conditions: **2**-M (0.025 mmol), $[Ph_3C][B(C_6F_5)_4]$ (0.025 mmol), **3a** (1 mmol), **4** (1.4–4 mmol), toluene (3 mL), 70 °C, 24 h. [b] Yield of isolated product (based on **3a**). Yield measured by GC analysis is given in parentheses.

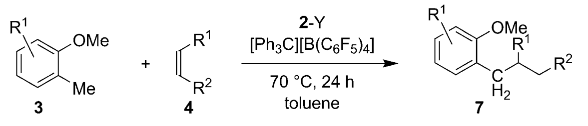
(acidic) 1-C–H bond, to give two regioisomers (**5ia** and **5ia′**) in a 6:1 molar ratio (entry 12). This is probably due to the steric influence of the hydrogen atom at the 8 position. The steric factor became further dominant in the reaction of 3-methylanisole (**3j**), which led to the alkylation taking place only at the less sterically demanding 6-C–H bond to give **5ja** exclusively (entry 13). In the case of 2-methylanisole, only a trace amount of the alkylation product was observed, whereas 1,2-dimethoxybenzene did not react with styrene under the same conditions.

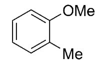
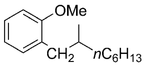
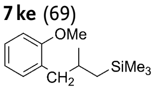
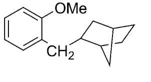
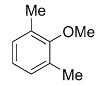
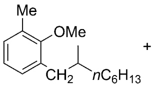
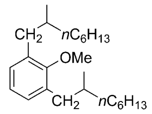
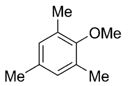
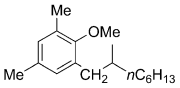
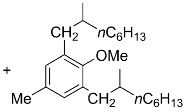
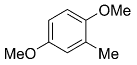
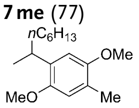
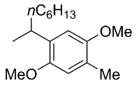
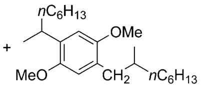
In the reaction of anisole with 1-octene (**4e**), complex **2**-Sc showed a higher activity than **2**-Y to selectively give the branched alkylation product **5ae** (Table 3, entries 1 and 2). Allyltrimethylsilane (**4f**) could also serve as an alkylation agent for anisole to give the corresponding alkylation product **5af** in a similar fashion (entry 3). In the case of vinyltrimethylsilane (**4g**), the linear alkylation product **5ag** was exclusively obtained (entry 4). The reaction of norbornene (**4h**) with anisole gave the norbornyl-substituted product **5ah** in almost quantitative yield (entry 5). The reaction of ethylene (1 atm) with anisole gave an oligomer product, probably because of the tendency (relatively high activity) of ethylene towards polymerization (successive insertion).

Although 2-methylanisole (**3k**) did not react with styrene, its reaction with 1-octene (**4e**) proceeded under similar conditions. However, the alkylation took place selectively at the sp$^3$ benzylic C–H bond rather than at the aromatic sp$^2$ C–H bond.[8b,14] Complex **2**-Y seemed more effective than **2**-Sc for this benzylic C–H alkylation reaction (Table 4, entries 1–3). The reactions of 2-methylanisole (**3k**) with allyltrimethylsilane (**4f**) and norbornene (**4h**) also exclusively gave the benzylic C–H alkylation products when **2**-Y/$[Ph_3C][B(C_6F_5)_4]$ was used as the catalyst (entries 4 and 5). In the reactions of 2,6-dimethylanisole (**3l**) and 2,4,6-trimethylanisole (**3m**) with 1-octene, the alkylation took place predominantly at one of the two *ortho*-methyl groups to give the monoalkylated products **7le** and **7me**, respectively, as the major products (77%). A small amount (5%) of dialkylated products (**8le** and **8me**) resulting from alkylation at both *ortho*-methyl groups was also obtained in these cases (entries 6 and 7). No alkylation at the *para*-methyl group was observed in the case of 2,4,6-trimethylanisole, which suggests that the interaction between the methoxy group and the catalyst metal center is essential in the present alkylation reactions. For 2,5-dimethoxytoluene (**3n**) with 1-octene, the alkylation took place only at the 5 position of the phenyl ring to give **5ne**, albeit with a low conversion (17%; entry 8), which suggests that, if sterically allowed, the C–H activation at an *ortho*-sp$^2$ C–H bond is preferred to that at an sp$^3$ C–H bond. When **2**-Sc was used instead of **2**-Y in this reaction, a much higher conversion was obtained to give the sp$^2$ C–H alkylation product **5ne** in 77% yield with a small amount of the benzylic sp$^3$ C–H alkylation product **5ne′** (9%; entry 9). 2-Ethylanisole did not react with 1-octene at either the benzylic or the *ortho*-sp$^2$ C–H position under same conditions.

In contrast to the benzylic C–H alkylation of 2-methylanisole (Table 4, entry 5), the reaction of the less sterically demanding 2,3-dihydrobenzofuran (**3o**) with norbornene selectively took place at the *ortho* sp$^2$ C–H bond (rather than at the benzylic C–H) to give **5oh** in almost quantitative yield (Scheme 1). Similarly, the reaction of 1,4-benzodioxane (**3p**) with norbornene selectively gave the 2,5-dialkyalted product **5ph**, whereas no reaction between 1,2-dimethoxybenzene and norbornene was observed under the same conditions.

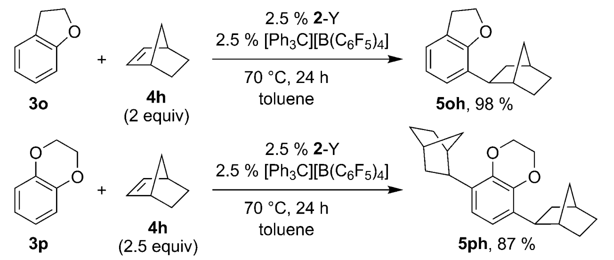
*Table 4:* Alkylation of *ortho*-methylanisoles.[a]



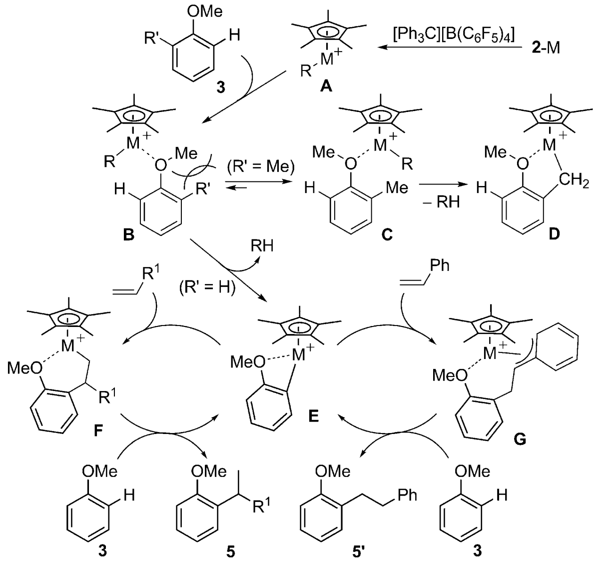
| Entry | **3** | **4** | Product (yield [%])[b] | |
|---|---|---|---|---|
| 1[c,d] | <br>**3k** | **4e** | <br>**7ke** (30) | |
| 2[d] | **3k** | **4e** | **7ke** (50) | |
| 3 | **3k** | **4e** | **7ke** (69) | |
| 4 | **3k** | **4f** | <br>**7kf** (57) | |
| 5[e] | **3k** | **4h** | <br>**7kh** (83) | |
| 6 | <br>**3l** | **4e** | <br>**7le** (77) | + <br>**8le** (5) |
| 7 | <br>**3m** | **4e** | <br>**7me** (77) | + <br>**8me** (5) |
| 8 | <br>**3n** | **4e** | <br>**5ne** (17) | |
| 9[f] | **3n** | **4e** | <br>**5ne** (77) | + <br>**5ne′** (9) |

[a] Reaction conditions: **2**-Y (0.025 mmol), $[Ph_3C][B(C_6F_5)_4]$ (0.025 mmol), **3** (1 mmol), **4** (4 mmol), toluene (3 mL), 70°C, 24 h. [b] Yield of isolated product (based on **3**). [c] **2**-Sc was used instead of **2**-Y. [d] **4e** (2 mmol). [e] **4h** (1.1 mmol). [f] **4e** (2 mmol). **2**-Sc was used instead of **2**-Y.

A possible mechanism for the present catalytic alkylation of anisoles is shown in Scheme 2. The coordination of the oxygen atom of anisole compound **3** to the metal center of the cationic alkyl species **A**, which is generated from the neutral dialkyl precursor **2**-M and $[Ph_3C][B(C_6F_5)_4]$, would give **B**. In the case of an anisole compound without substituents at the *ortho* positions (R′ = H), the *ortho*-C–H bond could be activated to give the anisyl species **E**.[9,15,16] The 2,1-insertion of a 1-alkene into the metal–anisyl bond in **E** to afford **F** would be sterically favored, which, upon deprotonation of another molecule of anisole **3**, should yield the branched alkylation product **5** and regenerate **E**. In the case of styrene,



***Scheme 1.*** Alkylation of cyclic aromatic ethers **3o** and **3p** with norbornene (**4h**).



***Scheme 2.*** A possible mechanism for the catalytic C–H alkylation of anisoles with olefins.

1,2-insertion would be preferred, because a stable benzallylic species such as **G** could possibly be formed, which, after deprotonation with **3**, should give the linear alkylation product **5'**. In the reaction with vinylsilane, the 1,2-insertion would also probably be favored owing to the electronic effect of the silyl group, thus affording the linear product (Table 3, entry 4).

In the case of 2-methyl-substituted anisoles such as **3k** (R' = Me), the coordination to the metal center would take place in such a fashion that the methyl group of the methoxy unit is oriented away from the *ortho*-methyl group to give **C** because of steric repulsion between the two methyl groups,[9] thus leading to benzylic C–H activation to afford **D**. The insertion of an olefin in **D** could take place analogously to that in **E**.

In summary, we have demonstrated that the cationic rare-earth alkyl species generated from half-sandwich rare-earth dialkyl complexes (such as **2**-M) and [Ph$_3$C][B(C$_6$F$_5$)$_4$] can serve as a unique catalyst for the C–H alkylation of anisoles with alkenes. The reaction of anisole derivatives without a substituent at the *ortho* position with various olefins takes place regioselectively at the *ortho*-sp$^2$ C–H bond to afford the corresponding *ortho*-monoalkylated anisole derivatives. In the case of 2-methyl-substituted anisole derivatives, the alkylation occurs exclusively at the benzylic sp$^3$ C–H bond. Functional groups such as halogens, allyl groups, and propenyl groups are compatible with this catalyst system. Studies on the further application of this catalytic C–H activation/insertion process are in progress.[17]

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**Keywords:** alkenes · alkylation · anisoles · C-H activation · rare-earth complexes

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[15] An intramolecular kinetic isotope effect was not observed ($k_H/k_D = 1.0$) in the reaction of 4-methyl[2-D]anisole with styrene, which suggests that C−H bond cleavage is not involved in the rate-determining step (see the Supporting Information).

[16] The formation of a Sc–anisyl species in the reaction of **2**-Sc/$[C_6H_5NMe_2H][B(C_6F_5)_4]$ with anisole was confirmed by $^1H$ NMR analysis. See the Supporting Information for details.

[17] *N,N*-Dimethylaniline could also react with 1-octene and norbornene under similar conditions to give the corresponding *ortho*-alkylation products in 81% and 86% yields, respectively. Further studies are in progress and will be reported in due course.