Site-Selective Magnesiation of Multi-Fluorinated Arenes Catalyzed by Rhodium–Aluminum Bimetallic Complexes

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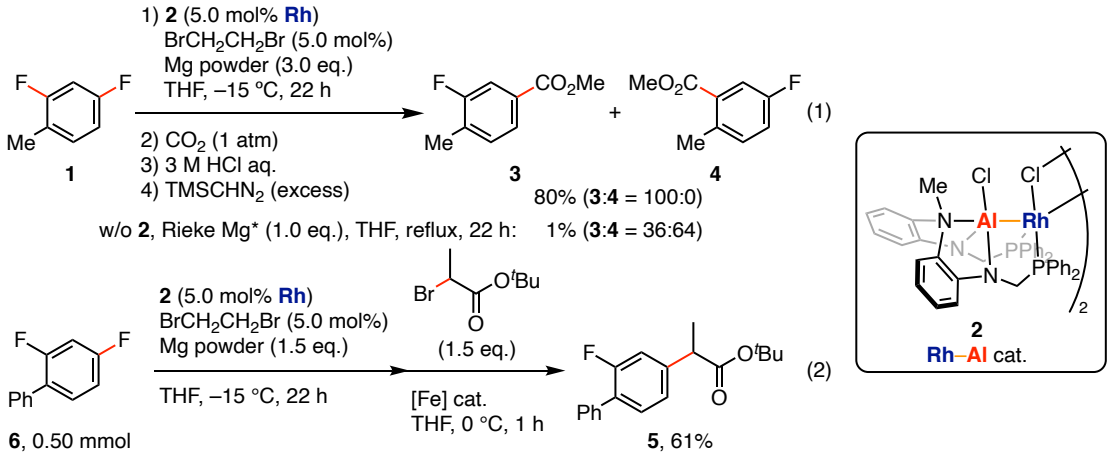
Fluorinated arenes are key building blocks for functional molecules. Transition metal-catalyzed site-selective carbon–fluorine bond functionalization of multi-fluorinated arenes can be an attractive method to build up fluorinated arenes due to ready availability of multi-fluorinated arenes.[1] However, it is difficult to control its site-selectivity without coordinating directing groups.[2] Here, we report a site-selective magnesiation of carbon–fluorine bonds of multi-fluorinated arenes by rhodium–aluminum bimetallic complexes.

The magnesiation of 2,4-difluorotoluene (**1**) with Mg powder (3.0 eq.) in the presence of Rh–Al complex **2** (5.0 mol% Rh) and 1,2-dibromoethane (5.0 mol%) in THF at –15 ºC for 22 h followed by treatment with CO_2 and $TMSCHN_2$ afforded the corresponding C4-functionalized product **3** in 80% yield without formation of its isomer **4** (Eq. 1). On the other hand, a mixture of **3** and **4** was obtained when Rieke Mg was used for the magnesiation step.[3] The present method allows rapid access to a synthetic precursor of an anti-inflammatory medicine, Flurbiprofen (**5**): the site-selective magnesiation of **6** followed by an iron-catalyzed cross-coupling[4] of the resulting arylmagnesium with *tert*-butyl 2-bromopropionate gave **5** in 61% yield (Eq. 2).



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