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Rhodium catalyzed template-assisted distal *para*-C–H olefination†

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Rhodium catalysis has been extensively used for *ortho*-C–H functionalization reactions, and successfully extended to *meta*-C–H functionalization. Its application to *para*-C–H activation remains an unmet challenge. Herein we disclose the first example of such a reaction, with the Rh-catalyzed *para*-C–H olefination of arenes. The use of a Si-linked cyanobiphenyl unit as a traceless directing group leads to highly *para*-selective arene–olefin couplings.

The transformation of carbon–hydrogen (C–H) bonds into diverse classes of carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds is a cornerstone of organic synthesis. There is intense interest in the discovery of new strategies for regioselective C–H functionalization.<sup>1</sup> A daunting challenge is imposed by the innate inertness of C–H bonds combined with the subtle reactivity differences among the C–H bonds of a given substrate. Directing group (DG)-assisted transition metal-catalyzed C–H activation has proven a successful strategy for regioselective C–H functionalizations in a general and predictable manner.<sup>2</sup> Most commonly coordination of a directing group to a transition metal to form a kinetically and thermodynamically stable 5- or 6-membered metallacycle is used to achieve *ortho*-C–H functionalization. In sharp contrast, distal C–H activation of *meta*<sup>3</sup> and *para*<sup>4</sup> sites is more challenging. In particular, *para*-C–H activation, which entails the formation of large macrocyclophane type metallacyclic intermediates, has remained elusive.<sup>5</sup> In a recent breakthrough, palladium-catalyzed systems employing a carefully designed ‘D-shaped’ directing group/linker template, based on a cyanobiphenyl motif, led to the first examples of distal *para*-C–H olefinations and acetoxylation.<sup>5,6</sup> Subsequent modifications of the 1<sup>st</sup> generation DGs through steric and electronic tuning led to 2<sup>nd</sup> generation DGs capable of effecting *para*-selective silylations<sup>7</sup> and acylations.<sup>8</sup>

To the best of our knowledge, for template assisted *para*-selective functionalization palladium catalysis has been

employed so far; albeit, other transition metals are also known to deliver *para*-selective functionalization relying on steric and electronic governance.<sup>5–9</sup> As part of our ongoing interest in C–H functionalization, we have now translated this reaction into the realm of rhodium catalysis and we report here the first example of a Rh-catalyzed *para*-C–H olefination. Existing Rh-catalyzed approaches to C–H activation,<sup>10</sup> using Rh(I)/Rh(III) redox cycles, are complementary to the Pd(0)/Pd(II) or Pd(II)/Pd(IV) cycles prevalent in palladium catalysis. The use of Rh offers benefits over Pd: (a) in contrast to Pd catalysis, which usually requires superstoichiometric quantities of silver salts, Rh catalysis can be performed with alternative, often cheaper, oxidants; (b) compared with Pd catalysis, which employ monoprotected amino acids (MPAA) as ligands, the different coordination environment of Rh is expected to provide advantageous opportunities for stereoselective synthesis; and (c) importantly, Rh-catalysis does not require use of hexafluoroisopropanol (HFIP), often unavoidable in Pd-catalysed distal C–H activation. With these thoughts in mind, we set about examining a Rh-catalyzed, DG-assisted distal *para*-C–H olefination, as shown in Scheme 1.

We commenced with the olefination of toluene scaffold DG<sub>1</sub> by ethyl acrylate (Scheme 2). Our first attempt, using

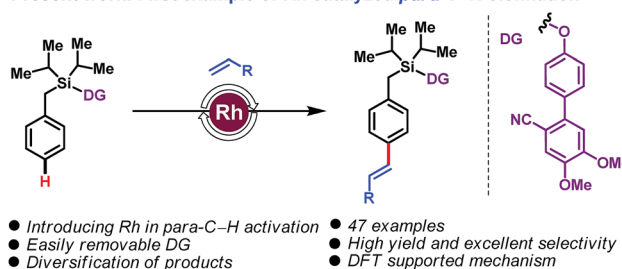
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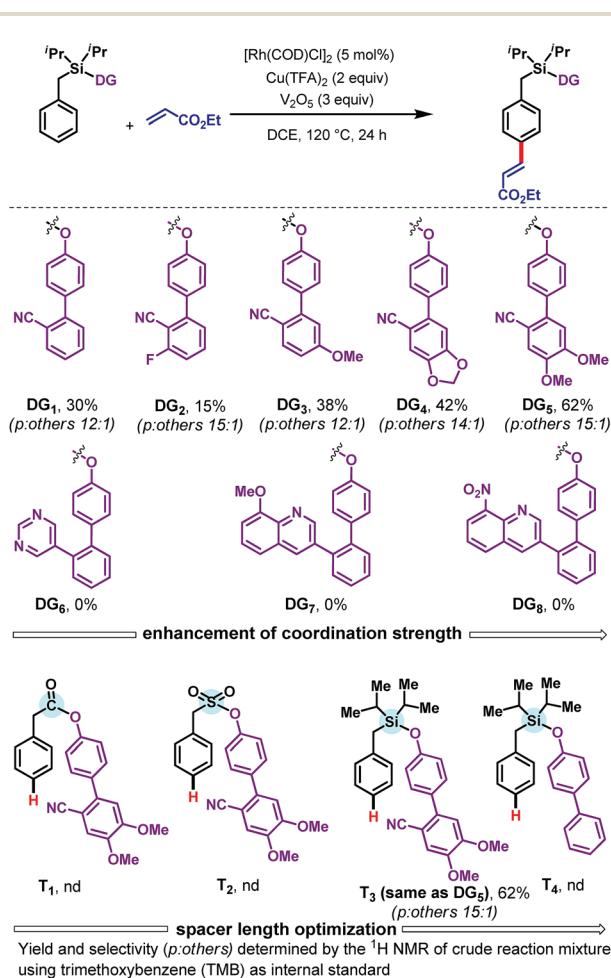
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Present work: First example of Rh catalyzed *para*-C–H olefinationScheme 1 Rh-catalyzed *para*-C–H olefination.

[Rh(COD)Cl]<sub>2</sub> (5 mol%) as catalyst, *N*-Ac-Gly-OH (10 mol%) as ligand, and AgOAc (3 equiv.) as oxidant, was unsuccessful. However, use of copper trifluoroacetate [Cu(TFA)<sub>2</sub>] as oxidant with V<sub>2</sub>O<sub>5</sub> as a co-oxidant provided the desired *para*-olefinated product in 30% yield. Encouraged by this initial result, we examined how the outcome could be improved by modifying the DG (Scheme 2). Analysis of cyano-based DGs (**DG**<sub>1</sub>–**DG**<sub>5</sub>) showed that the presence of an electron-withdrawing fluorine substituent (**DG**<sub>2</sub>) diminished the yield to 15% whereas an electron donating methoxy group (**DG**<sub>3</sub>) elevated the yield to 38%. By further enhancing the electron richness of the DG, the piperonal derivative **DG**<sub>4</sub> afforded a 42% yield of the olefinated product. The dimethoxy-substituted **DG**<sub>5</sub> gave a further improvement in yield, to 62%, with 15 : 1 *para* selectivity. The strong  $\sigma$ -donating DGs **DG**<sub>6</sub>–**DG**<sub>8</sub> failed to provide any of the desired olefinated products. A range of different tethers, containing carbonyl (**T**<sub>1</sub>), sulfonyl (**T**<sub>2</sub>), and silyl (**T**<sub>3</sub>) linkers, were tested, as was a nitrile-free biphenyl template (**T**<sub>4</sub>); only the silyl based template **T**<sub>3</sub> successfully delivered the desired olefinated product under the Rh-catalyzed conditions. These results indicate that the combination of sterically bulky silyl linker, nitrile group, and alkoxy groups present in **DG**<sub>5</sub> is crucial for obtaining good yields of the *para*-olefinated product.

Scheme 2 Evaluation of directing groups.<sup>11</sup>

Using best-performing directing group **DG**<sub>5</sub>, we optimized the reaction with respect to oxidants. A wide variety of silver and copper salts were tested.<sup>11</sup> In contrast to Pd-catalyzed olefinations, silver salts were found to be ineffectual in these Rh-catalyzed reactions, delivering the olefinated products in only trace amounts. Use of Cu(TFA)<sub>2</sub> as the oxidant in conjunction with V<sub>2</sub>O<sub>5</sub> as a co-oxidant gave a 62% yield of olefinated product with excellent (15 : 1) *para* selectivity. Use of CuCl<sub>2</sub> provided a lower (30%) yield of product, but a combination of CuCl<sub>2</sub>, V<sub>2</sub>O<sub>5</sub> and trifluoroacetic acid (TFA) furnished the olefinated product in excellent (85%) yield, with 15 : 1 *para* selectivity.<sup>11</sup> Interestingly, in the absence of either V<sub>2</sub>O<sub>5</sub> or TFA, the yield was significantly lower (40% and 30%, respectively). Other acidic additives such as acetic acid (AcOH), triflic acid (CF<sub>3</sub>SO<sub>3</sub>H) and pivalic acid (Piv-OH) failed to yield the *para*-olefinated product.<sup>11</sup>

With optimized conditions in hand, we explored the scope of the reaction with respect to olefin (Table 1), arene (Tables 2 and 3), and benzylic substituents (Table 4). With respect to the olefin coupling partner (Table 1), a range of acrylates reacted efficiently, including alkyl acrylates **2a–2d**, cyclohexyl acrylate **2e**, and trifluoroethyl acrylate **2f**. The olefinated products were obtained in excellent yields with synthetically useful *para*-selectivities ranging from 7 : 1 to 15 : 1. Apart from acrylates, vinyl sulfones including methyl vinyl sulfone (**2g**) and phenyl vinyl sulfone (**2h**) also gave the olefinated products, in 48% and 62% yields, respectively.

Next an array of substituted arenes was examined (Tables 2 and 3). For monosubstituted arenes, excellent yields and selectivities were obtained irrespective of the electronic nature of the substituent (Table 2). Both electron-rich and electron-deficient arenes were well tolerated, providing yields of up to 75% with up to 17 : 1 *para* selectivity.

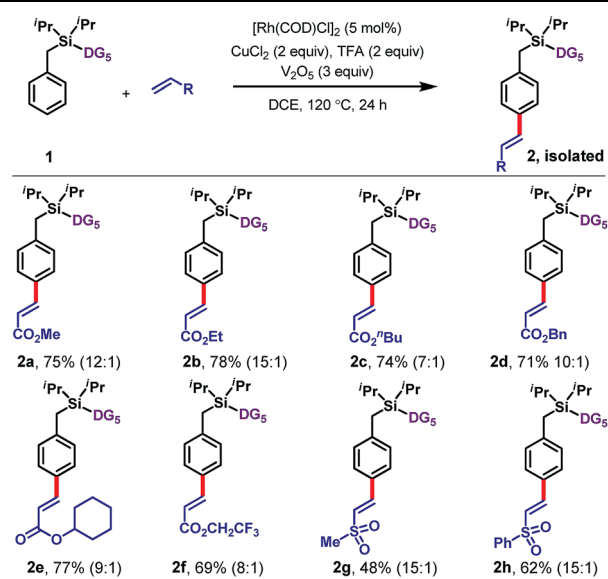
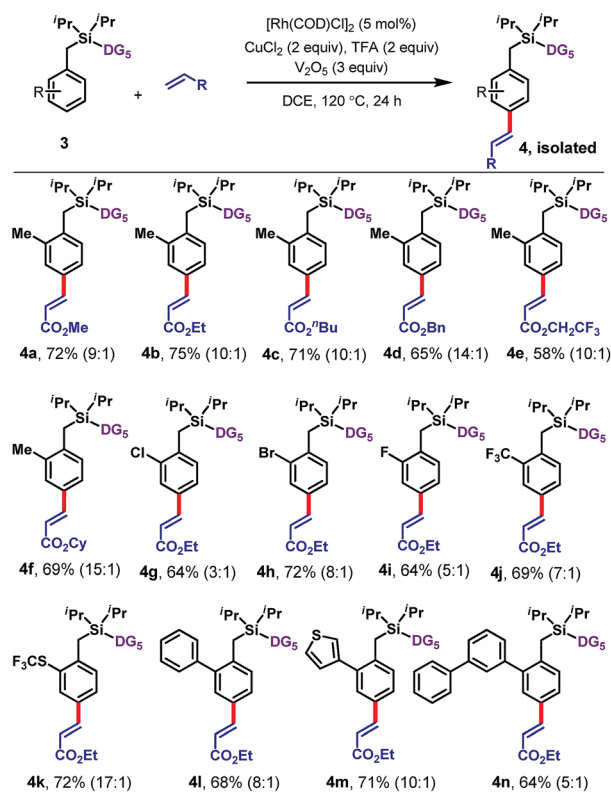
Table 1 Scope of olefin coupling partners<sup>a11</sup><sup>a</sup> Ratio of *para*: others determined by the <sup>1</sup>H NMR of crude reaction mixture.

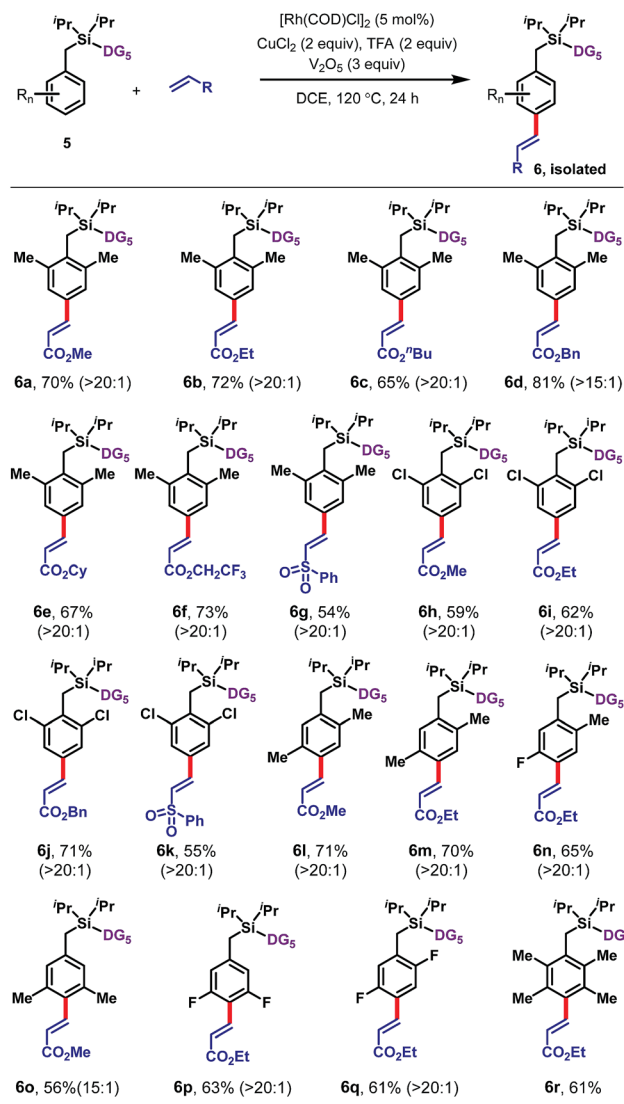
Table 2 Scope of monosubstituted toluene derivatives<sup>a11</sup>

<sup>a</sup> Ratio of *para*: others determined by the <sup>1</sup>H NMR of crude reaction mixture.

Disubstituted arenes were also extremely well tolerated (Table 3). The reaction was successfully applied to a range of 2,2-, 2,5-, 3,5- and 2,6-disubstituted toluenes containing methyl, fluoro, and/or chloro substituents (6a–6q). The selectivities of these reactions were generally higher than those observed for monosubstituted arenes, with all  $\geq 15 : 1$  *para* selective. Even a tetramethyl-substituted arene was tolerated, reacting with ethyl acrylate to give **6r** in 61% yield.

The protocol is also applicable to  $\alpha$ -substituted toluene derivatives (Table 4). Substrates bearing methyl, phenyl, or substituted phenyl substituents at the benzylic position reacted with methyl or ethyl acrylate to afford *para*-olefinated products **8a–8d**. The reaction also worked well with a more complex olefin coupling partner, namely, the acrylate derived from cholesterol, which furnished **8e–8g** in 59–68% yield.

The DG<sub>5</sub> directing group can be readily removed from the olefinated product in several ways (Scheme 3). Treatment of **2b** with TBAF furnished the desilylated product **9** in 92% yield and allowed the DG<sub>5</sub> alcohol **10** to be recovered in 88% yield for reutilization. Alternatively, treatment of **2b** with *p*-TSA generated the corresponding silanol derivative **11** in 82% yield along with an 85% recovery of the DG<sub>5</sub> alcohol. In principle, silanol **11** could be further used as a directing group for *ortho* functionalization. Therefore, the silyl-linked DG<sub>5</sub> represents

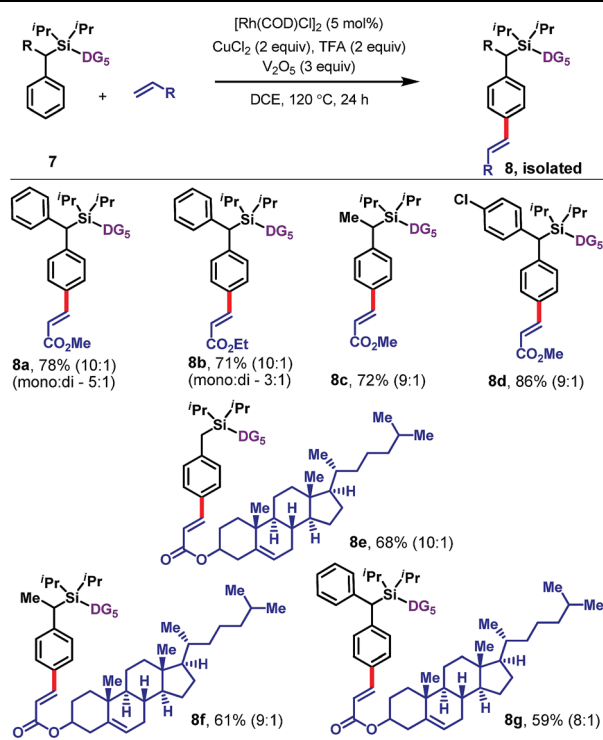
Table 3 Scope of disubstituted toluene derivatives in Rh-catalyzed *para*-C–H olefination<sup>a11</sup>

<sup>a</sup> Ratio of *para*: others determined by the <sup>1</sup>H NMR of crude reaction mixture.

a traceless directing group enabling access to multi-functionalized arenes. While the *para*-olefinated product **6g** has been treated with KF, KHCO<sub>3</sub> and H<sub>2</sub>O<sub>2</sub>, it produced the corresponding silanol (**12**). The silanol derivative was then employed under modified Tamao's oxidation condition to produce corresponding benzyl alcohol (**13**). Another derivative **2c** was treated under similar condition to provide the benzyl alcohol which subsequently oxidized to the corresponding benzaldehyde derivative (**14**) in 76% yield. The silyl based template can act as a nucleophile in presence of TBAF. To demonstrate that, 4-nitrobenzaldehyde (**15**) and 2-naphthaldehyde (**17**) was treated with *para*-olefinated product **2e** and **6c**, respectively to produce corresponding benzyl alcohols (**16** and **18** in 83% and 72%, respectively).



Table 4 Scope of  $\alpha$ -substituted toluene derivatives and more complex olefin coupling partners<sup>a</sup>

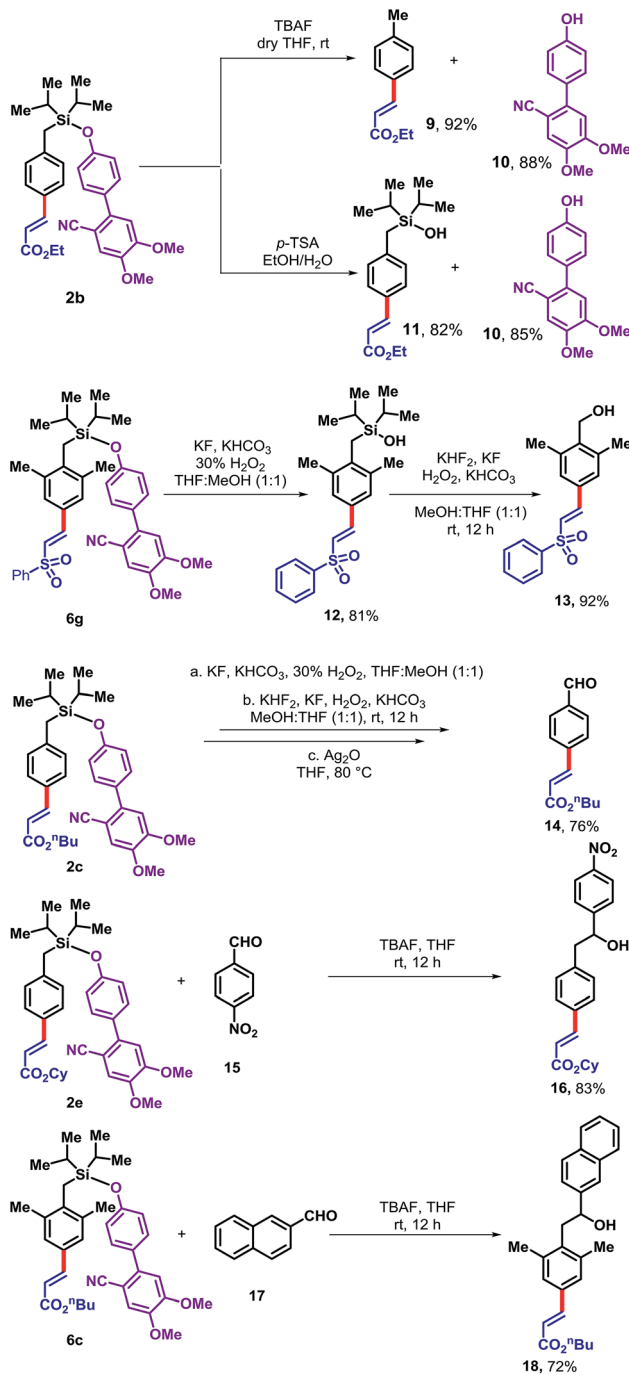


<sup>a</sup> Ratio of *para*: others determined by the <sup>1</sup>H NMR of crude reaction mixture.

Isotope labeling experiments were conducted involving an intermolecular competition using substrate **1a** and its deuterated analogue **D-1a** and a  $P_{\text{H}}/P_{\text{D}}$  value of 2.9 and  $k_{\text{H}}/k_{\text{D}}$  value of 2.6 were obtained (Scheme 4).<sup>11</sup> Furthermore, a detailed kinetic study indicated that the reaction was first order with respect to the substrate and zero order with respect to the olefin.<sup>11</sup> Together, these results suggest that the C–H bond activation is likely to be the rate-determining step of the catalytic cycle. A plausible catalytic cycle for the *para*-olefination is shown in Scheme 5. In this mechanism, the Rh(I) catalyst precursor is first oxidized to Rh(III). The main steps in the cycle consist of C–H activation, migratory insertion,  $\beta$ -hydride elimination, and reductive elimination.<sup>11</sup>

We explored the C–H activation process using density functional theory (DFT) (Fig. 1). Computations with the M06 functional using a model of **DG<sub>1</sub>** with trifluoroacetate anion as the base predicted that the C–H bond activation follows an electrophilic aromatic substitution pathway, with a distinct intermediate **Int1**, rather than a concerted metalation–deprotonation pathway.<sup>10p,12</sup> Transition structures for C–H bond breaking at the *para* and *meta* positions are shown in Fig. 1.

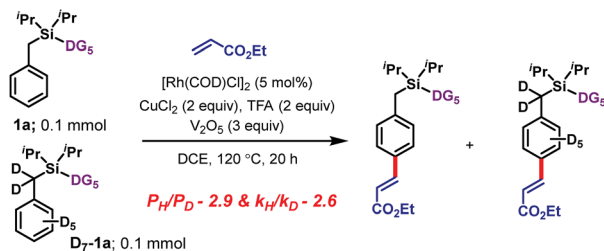
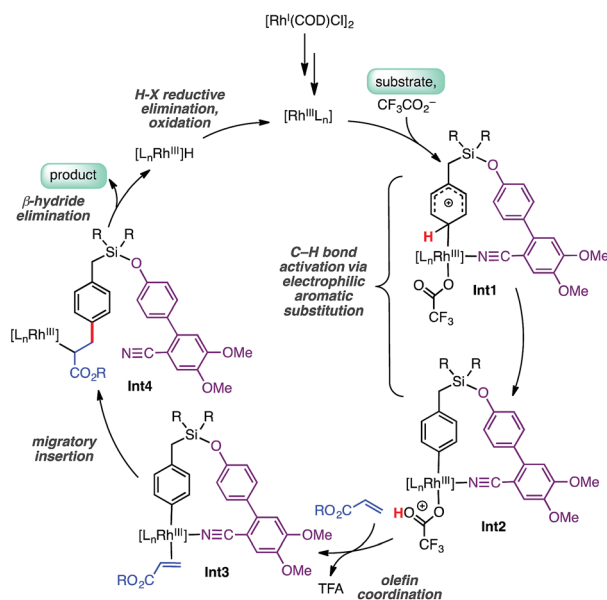
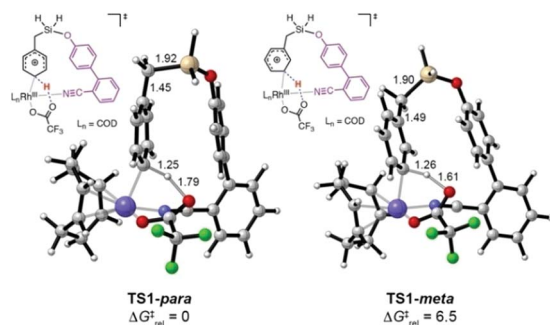
The *para* transition state, **TS1-*para***, is 6.5 kcal mol<sup>−1</sup> lower in energy than the *meta* transition state **TS1-*meta***. A fragment-based analysis of the TSs<sup>12</sup> reveals that the preference for *para*-C–H activation is due to a  $\beta$ -silicon effect. The interaction of the arene with Rh(III) endows it with arenium cation character, and this interaction is strengthened in **TS1-*para*** because



Scheme 3 Removal of the directing group and diversification of the *para*-olefinated products.<sup>11</sup>

the C–Si bond (which lies perpendicular to the ring) stabilizes the positive charge through hyperconjugation. Computations also revealed the roles of the DG methoxy and nitrile substituents.<sup>12</sup> Incorporation of two methoxy groups on the DG activates the substrate toward C–H bond breaking, lowering the barrier by 1.6 kcal mol<sup>−1</sup> relative to **TS1-*para***. A TS in which the nitrile is not bound to Rh was computed to be 23 kcal mol<sup>−1</sup> higher in energy than **TS1-*para***, indicating that the coordination of the nitrile to Rh strongly stabilizes the C–H activation transition state.



Scheme 4 Experiments with a deuterium-labeled substrate.<sup>11</sup>Scheme 5 Possible catalytic cycle for *para*-selective Rh-catalyzed olefination.Fig. 1 Transition states for Rh(III)-mediated *para*-C–H and *meta*-C–H bond activation, computed with M06/6-311+G(d,p)-SDD//M06/6-31G(d,p)-LANL2DZ in SMD dichloroethane. Distances in Å,  $\Delta G_{rel}^\ddagger$  in kcal mol<sup>-1</sup>.

## Conclusions

In summary, herein we have reported the first example of a Rh-catalyzed distal *para*-C–H functionalization reaction. The Rh-catalyzed olefination of toluenes using the Si-linked DG<sub>5</sub> directing group displays broad substrate tolerance. Electron-

rich and electron-deficient arenes are coupled with electron-deficient olefins in high yield and selectivity. Mechanistic studies are consistent with a catalytic cycle in which the C–H bond activation is rate-determining. This work reveals the potential of Rh catalysis to diversify the scope of functionalizations in the realm of remote *para*-C–H activation.

## Conflicts of interest

The authors declare no conflict of interest.

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- 11 See the ESI† for detailed descriptions.
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