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. 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. 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 and para sites is more challenging. In particular, para-C–H activation, which entails the formation of large macrocyclic type metallacyclic intermediates, has remained elusive. 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 acetoxylations. Subsequent modifications of the 1st generation DGs through steric and electronic tuning led to 2nd generation DGs capable of effecting para-selective silylations and acylations.

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. 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, 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 stereo-selective 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 DG1 by ethyl acrylate (Scheme 2). Our first attempt, using

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di groups present in nation of sterically bulky silyl linker, nitrile group, and alkoxy catalyzed conditions. These results indicate that the combi-

Using best-performing directing group $\text{DG}_5$, we optimized the reaction with respect to oxidants. A wide variety of silver and copper salts were tested. In contrast to Pd-catalyzed olefina-

Table 1  Scope of olefin coupling partners$^a$  

| $\text{DG}$ | $\text{R}$ | Yield (%) | Ratio (para: others) |
|-----------|----------|-----------|---------------------|
| $\text{DG}_1$ | $\text{Me}_2\text{C}=$ | 75% | 15:1 |
| $\text{DG}_2$ | $\text{Ph}$ | 80% | 15:1 |
| $\text{DG}_3$ | $\text{Ph}$ | 78% | 15:1 |
| $\text{DG}_4$ | $\text{Me}$ | 74% | 7:1 |
| $\text{DG}_5$ | $\text{Me}$ | 71% | 10:1 |

$^a$ Ratio of para: others determined by the $^1\text{H}$ 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 \(15:1\) 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 DG5 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 DG5 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 DG5 alcohol. In principle, silanol 11 could be further used as a directing group for ortho functionalization. Therefore, the silyl-linked DG5 represents a traceless directing group enabling access to multifunctionalized arenes. While the para-olefinated product 6g has been treated with KF, KHCO₃ and H₂O₂, 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 2  | Scope of monosubstituted toluene derivatives<sup>a</sup> |
|----------|-------------------------------------------------------|
| ![Image](image1) | ![Image](image2) |
| ![Image](image3) | ![Image](image4) |
| ![Image](image5) | ![Image](image6) |
| ![Image](image7) | ![Image](image8) |
| ![Image](image9) | ![Image](image10) |
| ![Image](image11) | ![Image](image12) |
| ![Image](image13) | ![Image](image14) |
| ![Image](image15) | ![Image](image16) |
| ![Image](image17) | ![Image](image18) |

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

| Table 3  | Scope of disubstituted toluene derivatives in Rh-catalyzed para-C–H olefination<sup>a</sup> |
|----------|--------------------------------------------------------|
| ![Image](image19) | ![Image](image20) |
| ![Image](image21) | ![Image](image22) |
| ![Image](image23) | ![Image](image24) |
| ![Image](image25) | ![Image](image26) |
| ![Image](image27) | ![Image](image28) |
| ![Image](image29) | ![Image](image30) |
| ![Image](image31) | ![Image](image32) |

<sup>a</sup> Ratio of para: others determined by the ¹H NMR of crude reaction mixture.
Isotope labeling experiments were conducted involving an intermolecular competition using substrate 1a and its deuterated analogue D7-1a and a \( P_{H}/P_{D} \) value of 2.9 and \( k_{H}/k_{D} \) value of 2.6 were obtained (Scheme 4). 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. 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.

We explored the C–H activation process using density functional theory (DFT) (Fig. 1). Computations with the M06 functional using a model of DG 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. 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\(^{-1}\) lower in energy than the meta transition state TS1-meta. A fragment-based analysis of the TSS\(^1\) 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 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. Incorporation of two methoxy groups on the DG activates the substrate toward C–H bond breaking, lowering the barrier by 1.6 kcal mol\(^{-1}\) relative to TS1-para. A TS in which the nitrile is not bound to Rh was computed to be 23 kcal mol\(^{-1}\) higher in energy than TS1-para, indicating that the coordination of the nitrile to Rh strongly stabilizes the C–H activation transition state.
bond activation, computed with M06/6-311+G(d,p)-SDD//M06/6-31G(d,p)-LANL2DZ in SMD dichloroethane. Distances in Å, ΔG_rel in kcal mol⁻¹.

**Scheme 4** Experiments with a deuterium-labeled substrate.¹¹

**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 M06/6-311G(d,p)-SDD//M06/6-31G(d,p)-LANL2DZ in SMD dichloroethane. Distances in Å, ΔG_rel in kcal mol⁻¹.

**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 DG₃ 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.

12 We also considered several other mechanisms in which the CH bond cleavage step is mediated by either Rh(ni) or Rh(i), details are provided in the ESI†