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Catalytic activation of unstrained C(aryl)-C(aryl) bonds in 2,2'-biphenols

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Abstract

Transition-metal catalysis has emerged as an important means for C-C activation allowing mild and selective transformations. However, the current scope of C-C bonds that can be activated is primarily restricted to either highly strained systems or more polarized C-C bonds. In contrast, catalytic activation of nonpolar and unstrained C-C moieties remains an unmet challenge. Here we report a general approach for catalytic activation of the unstrained C(aryl)-C(aryl) bonds in 2,2'-biphenols. The key is utilizing the phenol moiety as a handle to install phosphinites as a recyclable directing group. Using hydrogen gas as the reductant, mono-phenols are obtained with a low catalyst loading and high functional group tolerance. This approach has also been applied to the synthesis of 2,3,4-trisubstituted phenols. Further mechanistic study suggests that the C-C activation step is mediated by a rhodium(I) mono-hydride species. Finally, a preliminary study on breaking the inert biphenolic moieties in lignin models is illustrated.

Carbon skeletons exist ubiquitously in commodity chemicals, pharmaceuticals, agrochemicals, synthetic polymers, fuels and biomasses. To date, carbon-carbon bond (C-C) cleavage reactions have found important applications in strategic syntheses of complex organic molecules¹ and cracking of petroleum chemicals². Among various approaches to break a C-C bond, transition-metal (TM) catalysis has emerged as an important means³⁻¹⁰ allowing mild and selective transformations. However, the current scope of C-C bonds that can be activated is primarily restricted to either highly strained systems^{3,8,10}, in which strain release provides thermodynamic driving forces, or more polarized C-C bonds^{6,9}, such as carbon-cyanide (C-CN) and carbon-carbonyl (C-CO) bonds, in which the electrophilic

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Author Contributions

J.Z. and G.D. conceived and designed the experiments. J.Z. performed the experiments. J. W. performed the DFT calculation. J.Z., J.W. and G.D. co-wrote the manuscript.

Data availability. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition nos. CCDC 1848268 (**2z**), 1848266 ([Rh(**2a1**)Cl]₂), 1848267 (**8g**). Copies of the data can be obtained free of charge from www.ccdc.cam.ac.uk/structures/. All other data supporting the findings of this study are available within the Article and its Supplementary Information, or from the corresponding author upon reasonable request.

ASSOCIATED CONTENT

Additional information Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to G.D.

Competing interests

The authors declare no competing interests.

moiety serves as a handle for the initial reactivity. In contrast, catalytic activation of nonpolar and unstrained C–C moieties remains an unmet challenge.

While breaking hydrocarbon C–C chains has been carried out on multimillion ton scales in the petrochemical industry, i.e. the cracking processes², the related reaction for activating nonpolar unstrained C–C bonds with homogenous catalysis is rare. To the best of our knowledge, the only example of such a transformation was reported by Milstein and co-workers^{11,12} in which scission of an aryl–alkyl bond was achieved in a pincer-type substrate driven by forming a two-five-membered-fused rhodacycle (Fig. 1a). However, despite the prevalence of biaryl compounds, activation of unstrained aryl–aryl bonds remains an elusive transformation¹³, and the challenge is threefold. First, unlike ketones commonly used as substrates in C–C activation,^{6,9} the nonpolar aryl–aryl moiety lacks an electrophilic center for interacting with electron-rich TMs. Second, overlap between the biaryl C–C σ bond and TM d orbitals becomes more difficult due to the preferred twisted conformation of biaryls (for 2,2'-disubstitutedbiphenyl, the twist angle is close to 90°)¹⁴, which hinders the formation of the initial σ complex (Fig. 1b). Third, the bond-dissociation energy (BDE) of an aryl–aryl bond (often >110 kcal/mol) is significantly higher than typical C–C bonds (e.g. BDE of an acyl–alkyl bond is ca. 82 kcal/mol). Thus, one key factor to enable catalytic aryl–aryl bond activation is to control the conformation of the biaryl structure and bring low-valent TMs in close proximity to the targeted C–C σ bond. Herein, we report a general approach for catalytic activation of the unstrained C(aryl)–C(aryl) bonds in 2,2'-biphenols through utilizing the hydroxyl moieties as a handle to install recyclable directing groups (RDGs)¹⁵, which then guide TM insertion into the aryl–aryl bond (Fig. 1c).

Result and discussion

To this end, phosphinites were chosen as RDGs^{16,17} as they can be conveniently installed to and removed (and in principle recycled) from phenols (Fig. 1c). Through carefully tuning the electronic and steric properties of the phosphinite RDGs, directed oxidative addition of the C(aryl)–C(aryl) bond with a low valent TM⁷, e.g. Rh(I), could be imagined to give a spiro-rhodacycle intermediate, which provides mono-phenol products upon hydrogenolysis and hydrolysis. Hence, we commenced our study with bisphosphinite **2** as the model substrate, which can be easily synthesized via phosphinylation of 2,2'-biphenol **1a** (Table 1). After examining a range of metal precatalysts, additives, and phosphorous groups, the C(aryl)–C(aryl) bond cleavage was successfully achieved using a low loading (0.5 mol%) of [Rh(C₂H₄)₂Cl]₂ with diisopropylphosphinite as the RDG under 50 psi H₂ atmosphere. The mono-phenol product (**3a**) was isolated in 77% yield upon workup on silica gel (entry 1). A series of control experiments were subsequently conducted to understand the role of each reactant. Unsurprisingly, in the absence of [Rh(C₂H₄)₂Cl]₂ or H₂, no desired product was obtained (entries 2 and 3). When using diphenylphosphinite as the RDG, only a trace amount of **3a** was observed (entry 4). We reasoned that the less electron-rich Ph₂P- moiety might impede the oxidative addition of the aryl–aryl bond to Rh; in contrast, the electron-rich dicyclohexylphosphinite RDG gave a comparable yield (entry 5). Reducing the H₂ pressure to 30 psi still offered 69% yield of mono-phenol **3a** (entry 6), and increasing the H₂ pressure marginally improved the yield (entry 7). It is noteworthy that the turnover number (TON) of Rh can reach 298 using 0.13 mol% RhH(PPh₃)₄ as the pre-catalyst (entry 8).

When the reaction was run at a lower temperature or using toluene as solvent, the yield slightly decreased (entries 9 and 10). Finally, other group 9 metals, such as Ir and Co, gave no desired product (entries 11 and 12).

To investigate the generality and robustness of the catalytic system, the substrate scope was then explored (Table 2). The biphenol compounds with substituents at the 5,5'-positions were tested first; it is encouraging that 5,5'-substituents with different lengths and branching properties all provided the desired mono-phenols in good yields. Substrates with bulky alkyl groups (**2i** and **2j**) required more forcing conditions (2.5 mol% [Rh] and 100 psi H₂) probably to promote rotation of the sterically hindered aryl-aryl bond, which is critical for forming the key C-C σ -complex intermediate. Besides having methoxyl groups at the 3,3'-positions, the corresponding alkyl- (**2r-2t**) or aryl- (**2w**) substituted substrates also provided the desired products in high efficiency. For comparison, the 3,3'-unsubstituted (**2u**) or bromo-substituted substrates (**2v**) showed very low reactivity probably caused by competing *ortho* C-H^{16,17} or C-Br bond activation, respectively. While substitution at the 6,6'-positions inhibited the reactivity under the current conditions likely due to increased steric hindrance around the aryl-aryl bond, the 4,4'-substituted biphenols (**2af** and **2ag**) are highly competent substrates. Moreover, a number of functional groups were found compatible, including electron-rich arenes (**2x**), furan (**2aa**), thiophenes (**2ab**), amides (**2o**), sulfonamides (**2p**), nitriles (**2q**, **2s**), silyl ethers (**2m**), esters (**2n**, **2t**), aryl fluorides (**2ac**), chlorides (**2ad**) and bromides (**2ae**, **2ag**). It is noteworthy that, while sulfur moieties often poison heterogeneous catalysts, in this homogeneous system the sulfur-containing substrates (**2w**, **2x**) still show good reactivity.

Both experimental and computational studies were next carried out to probe the reaction pathway, and the key question is how the C(aryl)-C(aryl) bond is cleaved during this reaction. Based on the previous organometallic studies on C-C activation^{11,18,19}, two pathways are possible. Path **a** involves a direct oxidative addition of the aryl-aryl bond to Rh(I)-Cl species to generate a diaryl-Rh(III) intermediate; further oxidative addition of H₂ and subsequent two C-H reductive elimination (formal σ -bond metathesis) result in two monomer products (Fig. 2a). Thus, path **a** involves a Rh(V) intermediate. Alternatively, the Rh(I)-Cl precatalyst can first react with H₂ to give a Rh(I) mono-hydride species, which is more electron-rich than the corresponding Rh(I)-Cl complex and can serve as the real catalyst in this reaction (path **b**). In this pathway, the Rh(I)-H first undergoes oxidative addition with the aryl-aryl bond to give a Rh(III) intermediate, followed by C-H reductive elimination to give one monomer and a Rh(I)-aryl species. The following oxidative addition of H₂ converts the Rh(I)-aryl species back to the Rh-H catalyst and meanwhile produces another equivalent of the monomer. Thus, path **b** only involves Rh(I) and Rh(III) intermediates.

In order to differentiate the two pathways, the following experiments have been conducted. First, treatment of the substrate derived from Ph₂PCl with [Rh(C₂H₄)₂Cl]₂ provided a Rh(I) complex containing chloride bridges (Fig. 2b); however, heating the similar complex prepared from *i*-Pr₂PCl in the absence of H₂ only gave a trace amount of C-C activation product. The DFT calculation (Supplementary Section 14) shows that direct oxidative addition of the aryl-aryl bond to the Rh(I)-Cl species (path **a**) can be reversible and

endothermic; in addition, the subsequent H₂ oxidative addition to give the Rh(V) intermediate requires a high energy barrier of 34.2 kcal/mol. Alternatively, in path **b**, the reaction of Rh(I)–Cl with H₂ should generate one equivalent of HCl²⁰. It is known that HCl would rapidly consume phosphinites through P–O bond cleavage (*vide infra*, Fig. 3d), thus detrimental to the reaction. Indeed, when a higher [Rh(C₂H₄)₂Cl]₂ loading was used, the yield of C–C cleavage product was dramatically reduced, whereas adding bases under these conditions can restore the good yields (Fig. 2c). These observations suggest that HCl was formed in this reaction. The role of bases is proposed to be two-fold: first, they could promote the formation of the Rh mono-hydride species via reacting with the HCl generated from [Rh(C₂H₄)₂Cl]₂²⁰; second, it could also protect the phosphinite substrate from P–O bond cleavage. In addition, reaction of bisphosphinite **2c** with Rh(PPh₃)₄H led to a putative Rh–hydride species, which upon heating directly afforded a good yield of the monomer product in the absence of any chloride or H₂ (Fig. 2d). This result strongly supports the Rh–hydride-mediated C–C bond activation pathway (path **b**). Moreover, consistent with the experiments, the DFT calculation shows that path **b** is more energetically favorable than path **a**, and the turnover-limiting step for path **b** is calculated to be the C–C cleavage step with a barrier of 28.1 kcal/mol (Supplementary Section 14). To further support path **b**, we hypothesized that, if the C–C bond can be activated by a Rh–H species, by analogy it could also be activated by a Rh–aryl/alkyl species. Treatment of the substrate-Rh(I)Cl adduct with PhLi in pentane led to transmetalation and precipitation of LiCl salt, and upon heating the putative Rh–Ph species in 1,4-dioxane, as expected, provided the desired biaryl product (**4c**). This observation demonstrates that oxidative addition of a strong aryl–aryl bond to Rh(I)–Ph species is feasible, which should open the door for developing new C–C forming reactions via aryl–aryl bond activation. Altogether, the results from the mechanistic study support C–C activation through path **b**.

The synthetic utility of this method was first explored in the synthesis of 2,3,4-trisubstituted phenols. Given that electrophilic substitution of phenols is generally *para* and *ortho* selective, functionalization at the *meta* position is often realized via directing group (DG)-based approaches^{21,22}. If phenol substrate **5** with a DG at the C4 position is used (Fig. 3a), the less bulky C5 position would be much more reactive than the C3 position from the steric prospect and the C6 position would be more reactive from the electronic viewpoint. Thus, it is difficult to access 2,3,4-trisubstituted phenols through direct functionalization at the C3 position of substrate **5**. To address this challenge, we hypothesized that, using the corresponding 2,2'-dimer (via one-step preparation from the monomer) as the substrate, the desired C3 selectivity could be realized as the biaryl moiety should effectively block both the C5 and C6 positions; subsequent C–C cleavage using this hydrogenolysis method should provide 2,3,4-trisubstituted phenols. To test this hypothesis, substrate **5a**, prepared in one step from the commercially available 4-bromo-2-methylanisole, was employed as the substrate, and C–H halogenation was attempted as halogen substituents could be conveniently converted to various other FGs. As expected, direct subsection of substrate **5a** to the Rh-catalyzed C–H bromination conditions developed by Glorius,²³ followed by deprotection, only led to the 2,4,5-substituted phenol (**7a**). However, using substrate **6a** prepared via a gold-catalyzed dimerization of **5a**²⁴, followed by the sequence of a Rh-catalyzed C–H halogenation, deprotection and the key aryl–aryl cleavage, the desired 2,3,4-

substituted phenols were obtained with good efficiency. Further, the Br or I moiety were easily transformed to a number of other common FGs via cross couplings, such as aryls (**8a**, **8b**), alkynyl (**8d**), vinyl (**8e**), allyl (**8f**), and hetero-aryls (**8g**, **8h**) groups. The amide DG could also be converted to other FGs, such as an amine (**8c**). Therefore, the key for the success of this synthetic strategy is the use of dimerization as a “traceless” protecting tool to deliver unusual site-selectivity, which is enabled by this new C–C activation method.

On the other hand, the C–C activation protocol is also scalable. On a gram scale, 83% yield was obtained using 1 mol% $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ under 100 psi H_2 (Fig. 3b). Furthermore, a one-pot procedure was also established to allow in-situ RDG installation and subsequent hydrogenolysis, in which free 2,2'-biphenols can be directly employed as the substrate (Fig. 3c). Lastly, while using a catalytic RDG remains challenging at this stage, the diisopropylphosphino RDG moiety could nevertheless be recycled (Fig. 3d). After the C–C activation, the diisopropylphosphino moiety was found to remain bounded to the mono-phenol product; simple treatment of the reaction mixture with dry HCl led to quantitative protonation of the mono-phenol phosphinite **3c'** to give free phenol product **3c** in a good yield and the regenerated *i*-Pr₂PCl reagent can be recovered by distillation.

Given that the 2,2'-biphenol moiety has been often found in lignin extracted from softwood²⁵, the use of the C(aryl)–C(aryl) activation method was also investigated in a model study for cleaving the biaryl linkages in lignin, i.e. the “5-5” and “dibenzodioxocin” moieties (Fig. 4a). Converting lignin to valued-added products has been attractive from both economic and environmental viewpoints. While breakthroughs have been obtained lately on cleaving the polar C–O bonds (e.g. the “β-O-4” linkage) in lignin^{26–32} much fewer progresses have been achieved for selective disconnection of less polar but more robust C–C bonds^{25,33}, which also commonly present in both extracted and industrial lignins^{34,35}. To our knowledge, selectively breaking the aryl–aryl bonds in “5-5” and/or “dibenzodioxocin” structures has not been reported in either a real system or a model study to date. Considering that most biaryl moieties in native lignin, suggested by recent studies³⁵, exist in the form of a “dibenzodioxocin” structural motif, we first explored the feasibility of converting the “dibenzodioxocin” linkage to the “5-5” (free phenol) form through a catalytic C–O bond cleavage³⁶. Inspired by Hartwig’s Pd/C-catalyzed C–O cleavage method³⁰, “dibenzodioxocin” model compound **9** was subjected to the hydrogen-free conditions with a mixture of 1,4-dioxane/*p*-cymene (1:1) as the solvent (Fig. 4b). Gratifyingly, using either Pd/C or Ru/C²⁹ as the catalyst, the desired “5-5” model **1c** was provided in good yields. Moreover, improved efficiency (81% yield) was obtained when the reaction was run under a low pressure of H_2 in methanol with the Ru/C catalyst. With a reliable procedure of transforming “dibenzodioxocin” to “5-5” moieties in hand, we were motivated to examine the possibility of cleaving biphenolic lignin dimers extracted from natural wood (Fig. 4c). Treatment of wet sawdust (2.5 g × 14 batches) of spruce wood with Ru/C and H_2 at 250 °C in MeOH gave 82.9 mg of a crude mixture containing ca. 40.6 mg of lignin dimer **1c**. Further reaction of the crude mixture with Et₃N and *i*-Pr₂PCl, followed by the Rh-catalyzed C–C activation, afforded 28.6 mg of pure phenol monomer **3c** in 70% yield based on extracted **1c**, corresponding to a 0.08% w/w overall yield of the product based on the

biomass used. Since this process is conducted in a glove box, it at present only serves to highlight the potential of aryl–aryl bond cleavage in 2,2'-biphenols for lignin valorization.

Conclusion

In summary, catalytic activation of aryl–aryl bonds in 2,2'-biphenols is enabled by a RDG strategy. The reaction is chemoselective and scalable with a low catalyst loading. The preliminary synthetic utility of this biaryl-activation method is described in realization of an unconventional site-selectivity for the synthesis of 2,3,4-trisubstituted phenols. In addition, demonstration of the methods usage in breaking lignin aryl–aryl linkages is still at the proof-of-concept stage. It is anticipated that the mechanistic insights obtained from this study should have broad implications for discovering new catalytic methods for activating nonpolar and unstrained C–C bonds in common organic compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1|. Catalytic activation of nonpolar unstrained C–C bonds.

a, Milstein's seminal work on cleavage of the C(aryl)–C(alkyl) bond in a pincer ligand. **b**, Challenge for biaryl substrates: unlike activation of the C(aryl)–C(alkyl) bond, the twisted conformation of biaryls hinders the formation of the initial σ complex. **c**, Strategy of catalytic activation of unstrained C(aryl)–C(aryl) bonds of 2,2'-biphenols: the phenol moieties are used as the handle.

Figure 2]. Exploratory mechanistic study.

a, Two proposed mechanistic pathways for the C–C activation step. Path **a** starts with a Rh–Cl species and involves a formal Rh(V) intermediate; path **b** involves a Rh–H-mediated oxidative addition of the aryl–aryl bond. For computed activation energy, see Supplementary Section 14 for the DFT study. **b**, Stoichiometric Rh–Cl-mediated transformations in the absence of H₂ afforded a trace amount of product after heating, and the chlorine bridged dirhodium complex could be obtained at room temperature. **c**, A higher [Rh(C₂H₄)₂Cl]₂ loading led to significantly reduced yields and adding bases restored the yields. **d**,

Stoichiometric reactions with Rh–H and Rh–Ph species. Stoichiometric Rh(PPh₃)₄H afforded product **3c** in a moderate yield in the absence of H₂. PhLi could be used to transfer a phenyl group to the aryl–aryl bond. These results support path **b**

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Figure 3]. Catalytic reductive cleavage of C(aryl)–C(aryl) bonds in 2,2'-biphenols.

a. Synthesis of 2,3,4-trisubstituted phenols. This method could be useful to prepare 2,3,4-trisubstituted phenols from substrate **5a**. In contrast, the direct C–H activation approach only gives the 2,4,5-substituted product. For experimental details, see Supplementary Section 4.

b. Scalability. The reaction can be run on a gram scale with a good yield. **c.** The reaction can be run in one pot directly from 2,2'-biphenols. **d.** The RDG moiety can be recycled. Simple treatment of the reaction mixture after C–C activation with dry HCl regenerates *i*-Pr₂PCl

with a quantitative conversion. The lower isolated yield of *i*-Pr₂PCl is mainly caused by its volatility during the handling and purification.

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Figure 4|. Model study for the cleavage of aryl–aryl bonds in lignin dimers.

a, Representative structure of softwood lignin, highlighting “5-5” and “dibenzodioxocin” units, which are arguably the most difficult linkers to be cleaved; in contrast, cleavage of the β -O-4 linkage has been widely studied. **b**, Conversion of “dibenzodioxocin” to “5-5” linkages. **c**, Conversion of wet spruce sawdust (2.5 g $\times$ 14 batches) to lignin monomers. For experimental details, see Supplementary Section 12.

Table 1|

Selected optimization of reaction conditions.

Entry ^a	Changes	Yield(%) ^b	Entry ^a	Changes	Yield(%) ^b
1	as above	77	7	150 psi H ₂	79
2	no [Rh]	nd	8 ^{c,d}	0.13 mol% RhH(PPh ₃) ₄	39
3	50 psi Ar instead of H ₂	nd	9 ^c	130 °C	70
4	R = Ph instead of <i>i</i> -Pr	trace	10 ^c	toluene as solvent	71
5	R = Cy instead of <i>i</i> -Pr	58	11 ^c	[Ir(COD)Cl] ₂ (2.5 mol%)	nd
6	30 psi H ₂	69	12 ^c	CO ₂ (CO) ₈ (2.5 mol%)	nd

* Reaction conditions:

^a All reactions were run on a 0.3 mmol scale; [Rh] = [Rh(C₂H₄)₂Cl]₂; nd = not detected.^b Isolated yields.^c 150 psi H₂.^d 1.2 mmol of **2a** were used and GC yield was obtained.

Table 2|

Substrate scope for the reductive C–C cleavage of 2,2'-biphenols.

* Reaction conditions: **2** (0.3 mmol), $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (0.0015 mmol), H_2 (50 psi), 150 °C, 24 h. All reactions were worked up on silica gel. All yields are isolated yields.

^a 2.5 mol% $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$, 100 psi H_2 was used.

^b 0.2 mmol **2** was used.