JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

UNIVERSITÉ PARIS SUD

Subscriber access provided by Bibliothèque de l'Université Paris-Sud

Article

Ruthenium-Catalyzed Reductive Cleavage of Unstrained Aryl#Aryl Bonds: Reaction Development and Mechanistic Study

Jun Zhu, Peng-hao Chen, Gang Lu, Peng Liu, and Guangbin Dong

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.9b11605 • Publication Date (Web): 01 Nov 2019

Downloaded from pubs.acs.org on November 2, 2019

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Ruthenium-Catalyzed Reductive Cleavage of Unstrained Aryl–Aryl Bonds: Reaction Development and Mechanistic Study

Jun Zhu[†⊥], Peng-hao Chen[‡⊥], Gang Lu*[§∥], Peng Liu*[∥]and Guangbin Dong*[†‡]

†Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States.

‡Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, United States.

§School of Chemistry and Chemical Engineering, Shandong University, 250100, Jinan, China

∥Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States.

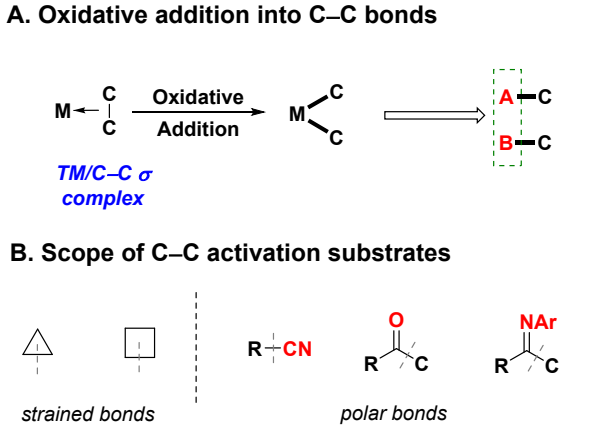
Abstract

Cleavage of carbon–carbon bonds has been found in some important industrial processes, e.g. petroleum cracking, and has inspired development of numerous synthetic methods. However, non-polar unstrained C(aryl)–C(aryl) bonds remain one of the toughest bonds to be activated. As a detailed study of a fundamental reaction mode, here a full story is described about our development of a Ru-catalyzed reductive cleavage of unstrained C(aryl)–C(aryl) bonds. A wide range of biaryl compounds that contain directing groups (DGs) at 2,2' positions can serve as effective substrates. Various heterocycles, such as pyridine, quinoline, pyrimidine and pyrazole, can be employed as DGs. Besides hydrogen gas, other reagents, such as Hantzsch ester, silanes and alcohols, can be employed as terminal reductants. The reaction is pH neutral and free of oxidants, thus a number of functional groups are tolerated. Notably, a one-pot C–C activation/C–C coupling has been realized. Computational and experimental mechanistic studies indicate that the reaction involves a ruthenium(II) monohydride-mediated C(aryl)–C(aryl) activation and the resting state of the catalyst is a η^4-coordinated ruthenium(II) dichloride complex, which could inspire development other transformations based on this reaction mode.

Introduction

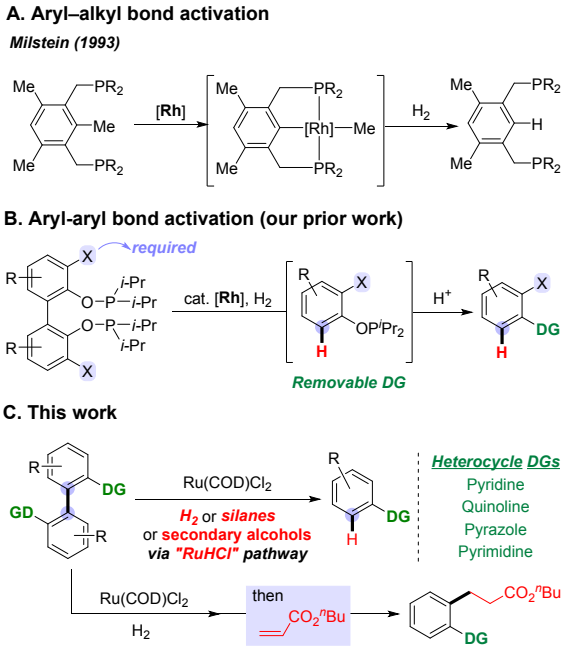
Oxidative addition of a transition metal (TM) into a carbon–carbon (C–C) bond represents an important means of activating C–C bonds, which has led to development of numerous synthetically valuable methods.[1] This process converts one relatively inert C–C bond into two more reactive C–TM bonds that can undergo further transformations, affording dual functionalization of both carbon terminuses (Scheme 1A).[2] To date, a number of catalytic C–C cleavage/functionalization methods have been developed based on such a mode of activation. However, the scope of C–C bonds that can undergo oxidative addition with TMs is still narrow (Scheme 1B). The major class of suitable substrates contains a three or four-membered ring, in which strain release becomes the main driving force for the C–C cleavage.[3] On the other hand, more polar C–C bonds, such as C–CN,[4] C–carbonyl and C–iminyl bonds in less strained substrates,[5] can also be activated by low valent TMs due to favorable interactions between

the low-lying σ* orbital in these moieties and TM filled d orbitals, which promotes forming the requisite C–C/TM σ complex.



Scheme 1. C–C Bond Activation via Oxidative Addition

In contrast, TM insertion into non-polar and unstrained C–C bonds has been extremely rare. In 1993, Milstein and co-workers reported a phosphine-directed activation of an aryl–alkyl bond in a pincer-type substrate, which was driven by forming a two-five-membered-fused rhodacycle (Scheme 2A).[6] The catalytic transformation was also developed a few years later by the same group.[7] Recently, Kakiuchi and coworkers developed a novel Rh-catalyzed cleavage of unstained aryl-allyl bonds, albeit through a β-carbon elimination mechanism.[8] Activation of unstrained aryl–aryl bonds has been elusive[9] until our recent work (Scheme 2B).[10] The C(aryl)–C(aryl) bonds in 2,2'-biphenols were catalytically cleaved with hydrogen gas using a rhodium catalyst and phosphinite directing groups (DGs). Despite this promising initial result, *ortho* substituents in the 2,2'-biphenol substrates were required for this transformation, and our general understanding of activating unstrained aryl–aryl bonds is still limited. A number of questions remain to be addressed. For example, can other types of DGs, besides those strongly coordinative phosphorus-based ones, be used in the C(aryl)–C(aryl) bond activation? Can other TMs besides expensive rhodium be employed as the catalyst? Can other reagents besides hydrogen gas react with the C–C cleavage intermediate? How does a metal catalyst approach the C(aryl)–C(aryl) bond to be cleaved? Answers to these questions could be important for expanding the substrate scope and reaction varieties of this transformation. In this full article, we describe a detailed development of a ruthenium-catalyzed reductive cleavage of unstrained C(aryl)–C(aryl) bonds and the mechanistic study of this reaction (Scheme 2C). Nitrogen-based heterocycles were found to be excellent DGs and, besides hydrogen gas, secondary alcohols and silanes could also be employed as the reductant for this transformation.

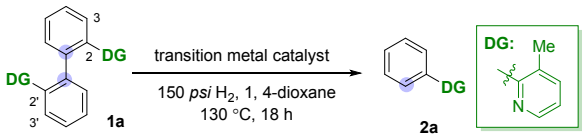


Scheme 2. Activation of Non-polar Unstrained C–C Bonds

Result and Discussion

Pyridine and related heterocycles have been frequently employed as DGs in catalytic C–H activation reactions.[11] They have also been used in C–C activation of ketones.[12] Thus, the 2,2'-(3-methylpyrdinyl) substituted biphenyl (**1a**) was chosen as the initial substrate. Rhodium-based catalysts were naturally examined first. Using $[Rh(C_2H_4)Cl]_2$, $[Rh(COD)Cl]_2$ or $Rh(COD)_2NTf_2$ as the catalyst, trace or no desired product was observed (Table 1, entries 1-3). However, adding NaI as the additive to the $[Rh(COD)Cl]_2$–catalyzed reaction, 39% yield of the desired C–C cleavage product was obtained (Table 1, entry 4). This result showed the feasibility of using pyridine as DGs for C(aryl)–C(aryl) bond activation, though the exact role of NaI is still unclear. Note that using the pyridine DG, *ortho* substitution at the 3,3' positions was not required, which is distinct from the prior 2,2'-biphenol activation.[10] This motivated us to test other readily available TM complexes as precatalysts for this transformation. While the Ni(0), Co(0), and Ir(I) complexes gave no desired cleavage product (entries 5-7), Ru(II) dichloride complexes nevertheless exhibited remarkable reactivity (entries 11-18). $RuCl_3 \cdot xH_2O$ showed moderate reactivity (entry 10), but $Ru_3(CO)_{12}$[12b] and Cp*Ru(COD)Cl were not reactive. Among various Ru complexes examined, $Ru(COD)Cl_2$ was found to be most efficient (entry 14). Besides 1,4-dioxane, other solvents, such as toluene and THF, were also suitable for this transformation (entries 15 and 16).

Table 1. Selected Optimization Study for the Hydrogenation Condition

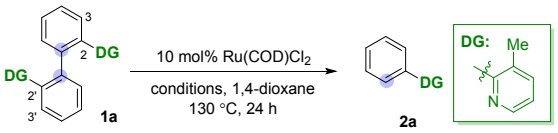


Entry[a]	Conditions	Yield[b]
1	10 mol% $[Rh(C_2H_4)Cl]_2$	trace
2	10 mol% $[Rh(COD)Cl]_2$	n.d.
3	10 mol% $[Rh(COD)Cl]_2$+100 mol% NaI	39%
4	20 mol% $Rh(COD)_2NTf_2$	n.d.
5	20 mol% $Ni(COD)_2$	n.d.
6	10 mol% $Co_2(CO)_8$	n.d.
7	10 mol% $[Ir(COD)Cl_2]_2$	n.d.
8	6.7 mol% $Ru_3(CO)_{12}$	n.d.
9	20 mol% Cp*Ru(COD)Cl	n.d.
10[c]	20 mol% $RuCl_3 \bullet xH_2O$	26%
11	10 mol% $[Ru(p\text{-cymeme})Cl_2]_2$	50%
12	10 mol% $[Ru(p\text{-cymeme})I_2]_2$	66%
13	20 mol% $Ru(COD)Cl_2$	89%
14	**10 mol% $Ru(COD)Cl_2$**	**89%(83%)**
15	10 mol% $Ru(COD)Cl_2$, Tol. as solvent	88%
16	10 mol% $Ru(COD)Cl_2$, THF as solvent	77%

[a] Reaction conditions: **1a** (0.1 mmol), 20 mol% monomer or 10 mol% dimer or 6.7 mol% trimer of metal catalyst, 1,4-dioxane (0.075 M), 130 °C, 18 h, Q-tube filled with 150 psi H_2 gas. [b] Unless otherwise noted, the yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as internal standard; n.d. = not detected; the yield in parentheses is isolated yield. [c] The catalyst loading was based on the formula of $RuCl_3$.

Alternative reductants besides H_2 gas were then sought, which, if successful, could provide a more convenient way to operate this C–C cleavage reaction (Table 2). To our delight, a variety of mild reductants was found reactive under this Ru-catalyzed condition, and afforded the desired product. For example, potassium formate salt and Hantzsch ester gave 9% and 58% yields of product **2a**, respectively (entries 2 and 3). Diverse secondary alcohols could also serve as a hydride source through a transfer hydrogenation process (entries 4-8). Among all the alcohols tested, cyclopentanol proved to be most efficient (entry 8), though an excess amount was needed for a higher conversion (entries 9-13). 84% yield was achieved using 50 equiv of cyclopentanol with toluene as solvent. In addition, a combination of silane and water (1:1) was found to be an excellent reductant (entries 14-18).[13] An optimal result (85% yield) was obtained when using 5.0 equiv of diphenylmethylsilane with 5.0 equiv of H_2O (entry 18).

Table 2. Screening for Alternative Reductants[a]

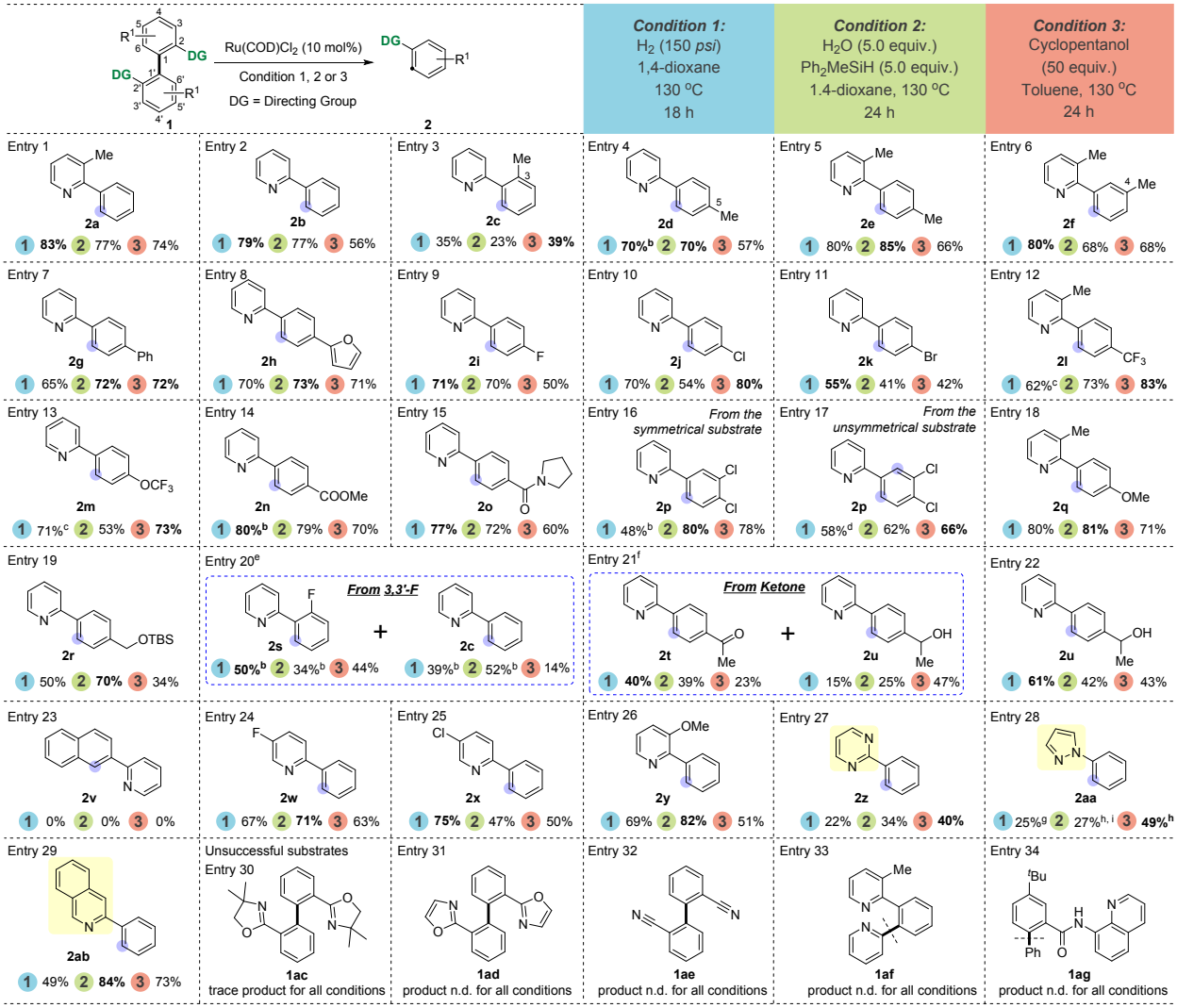


Entry[a]	Conditions	Yield[b]
1	10 *equiv.* $HCOONH_4$	n.d.
2	10 *equiv.* HCOOK	9%
3	10 *equiv.* Hantzsch ester	58%
4	10 *equiv.* diphenylmethanol	20%
5[c]	2-propanol	11%
6[c]	2-butanol	22%
7[c]	3-pentanol	47%
8[c]	cyclopentanol	70%
9	50 *equiv.* cyclopentanol	66%
10	30 *equiv.* cyclopentanol	62%
11	10 *equiv.* cyclopentanol	51%
12	50 *equiv.* cyclopentanol, Tol as solvent	84% (81%)
13	50 *equiv.* cyclopentanol, THF as solvent	46%
14	10 *equiv.* $(TMS)_3SiH$ + 10 *equiv.* H_2O	12%
15	10 *equiv.* Et_3SiH + 10 *equiv.* H_2O	28%
16	10 *equiv.* $PhMe_2SiH$ + 10 *equiv.* H_2O	42%
17	10 *equiv.* Ph_2MeSiH + 10 *equiv.* H_2O	80%
18	5 *equiv.* Ph_2MeSiH + 5 *equiv.* H_2O	85% (78%)

[a] Reaction condition: **1a** (0.1 mmol), 10 mol% $Ru(COD)Cl_2$, 1,4-dioxane or other solvents (1.0 mL), 130 °C, 24 h, sealed vial. [b] Unless otherwise noted, the yields were determined by ^1H NMR using 1,1,2,2-tetrachloroethane as internal standard; n.d. = not detected; the yields in parentheses are isolated yields. [c] The indicated alcohols were used as solvent.

With three high yielding conditions in hand, the substrate scope was investigated next (Table 3). First, besides 3-methylpyrdine, simple pyridine can also serve as an effective DG (entry 2). Substitutions on the arene at 3, 4 or 5 positions were all tolerated (entries 3-6), and the yield was lower for the 3,3'-disubstiutted substrates likely due to the steric hindrance (**2c**). In addition, phenyl and furyl-substituted substrates (**2g** and **2h**) showed good reactivity. A range of functionalization groups, such as fluoride (**2i**), chloride (**2j** and **2p**), bromide (**2k**), trifluoromethyl (**2l**), OCF_3 (**2m**), ester (**2n**), amide (**2o**), OMe (**2q**) and silyl ether (**2r**) were found compatible. Interestingly, when a fluorine substituent is *ortho* to the DG (entry 20), partial C–F bond activation/cleavage product was obtained;[14] for comparison, fluorine substitutions at other positions (**2i** and **2w**) were intact. When a ketone moiety was present (entry 21), partial reduction to the corresponding alcohol was observed, particularly under the transfer hydrogenation conditions. Unsurprisingly, alcohol moieties (**2u**) were tolerated. The bulkier binaphthyl-derived substrate was not reactive, likely due to the steric hindrance around of the C(aryl)–C(aryl) bond (entry 23). Regarding the scope of DGs, substituted pyridines with various electronic properties exhibited similar reactivity (entries 24-26). Gratifyingly, other heteroarenes, including pyrimidine (entry 27), 5-membered pyrazole (entry 28) and quinoline (entry 29), were found as competent DGs. More labile oxazoline (**1ac**), oxazole (**1ad**) and nitrile (**1ae**) were ineffective. Finally, attempts to cleave an aryl–pyridyl bond or use a mono bidentate DG were unfruitful at this stage (entries 33 and 34).

Table 3. The Substrate Scope [a]

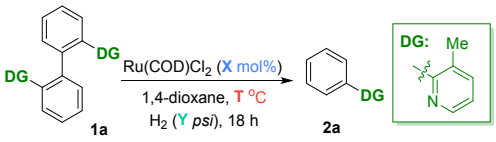


[a]**Condition 1**: biaryl **1** (0.1-0.2 mmol), $Ru(COD)Cl_2$ (10 mol %), 1,4-dioxane (0.075 M), 130 °C, 18 h, Q-tube filled with 150 psi H_2 gas; **Condition 2**: biaryl **1** (0.1-0.2 mmol), $Ru(COD)Cl_2$ (10 mol %), 5.0 equiv of Ph_2MeSiH, 5.0 equiv of H_2O, 1,4-dioxane (1.0 mL/0.1 mmol **1**), 130 °C, 24 h, sealed vial; **Condition 3**: biaryl **1** (0.1-0.2 mmol), $Ru(COD)Cl_2$ (10 mol %), 50 equiv of cyclopentanol, toluene (1.0 mL/0.1 mmol **1**), 130 °C, 24 h, sealed vial. All yields are isolation yields. [b]Reaction time was 6 h. [c]Reaction time was 3 h. [d]Reaction time was 11 h. [e]The total yields are isolation yields, and the ratio of the two products were determined by ^1H NMR. [f]The two products were both observed and isolated from the reaction system. [g]$Ru(COD)Cl_2$ (20 mol %), 160 °C. [h]$Ru(COD)Cl_2$ (20 mol %), 150 °C. [i]$(EtO)_3SiH$ (5.0 equiv) was used instead of Ph_2MeSiH. n.d. = not detected.

The limits of the catalyst loading and reaction temperature under the hydrogenation condition was further investigated (Table 4). Reducing the Ru loading from 10 mol% to 2.5 mol% only marginally affected the yield (entry 1, Table 4); further lowering the catalyst loading to 1 mol% still afforded 55%

yield of the product (entry 2, Table 4). It was surprising that, at a lower temperature (110 °C), a higher yield (90%) was obtained (entry 4, Table 4). Further decreasing the temperature to 70 °C still showed moderate reactivity (entries 4-6, Table 4). The hydrogen pressure could be further reduced to 70 psi without affecting the reaction efficiency (entries 7 and 8, Table 4). A lower yield (65%) was obtained when 30 psi of hydrogen was used (entry 9, Table 4).

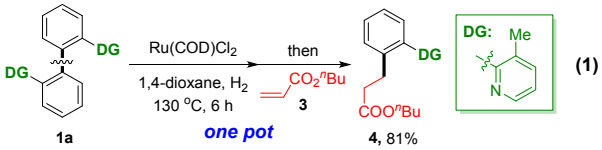
Table 4. Exploring the limits of hydrogenolysis of the C(aryl)−C(aryl) Bonds



Entry[a]	X (mol%)	T (°C)	Y (*psi*)	Yield[b]
1[c]	2.5	130	150	80%
2[d]	**1.0**	130	150	55%
3[e]	10	130	150	83%
4	10	110	150	90%
5	10	90	150	59%
6	10	**70**	150	33%
7	10	130	110	90%
8	10	130	70	89%
9	10	130	**30**	65%

[a]Conditions: **1a** (0.2 mmol), Ru(COD)Cl_2, 1,4-dioxane (*C*cat = 0.0075 M), 18 h, Q-tube filled with H_2 gas. [b]Isolated yield. [c]0.4 mmol **1a** was used. [d]1.0 mmol **1a** was used. [e]0.1 mmol **1a** was used.

In addition, a one-pot C−C activation/C−C formation approach has also been established (Eq 1). After the hydrogenolysis of the aryl−aryl bond, the ruthenium catalyst was found to remain active. Subsequent addition of acrylate allowed for mono *ortho* alkylation of the C−C cleavage product in a high yield.[15] This result shows the potential to couple aryl−aryl bond activation with subsequent functionalization using a single catalyst.



Mechanistic Studies

The mechanism of the Ru-catalyzed aryl−aryl bond activation was explored using a combination of computational and experimental efforts. Three possible reaction pathways are proposed (Figure 1). **Path a** involves insertion of a Ru(II) dichloride species ("$RuCl_2$") into the aryl−aryl bond to give a Ru(IV) intermediate, which then undergoes hydrogenolysis to give the monomer product. **Path b** is initiated by a Ru(II) monohydride monochloride species ("RuHCl"), generated via mono-hydrogenation of the ruthenium dichloride precursor.[16] Oxidative addition of the "RuHCl" into the aryl−aryl bond followed by C−H reductive elimination affords one monomer product, and the resulting ruthenium aryl intermediate

then reacts with H_2 to deliver the other monomer product and regenerate the "RuHCl" catalyst. **Path c** is based on a Ru(II) dihydride ("RuH_2") species, generated from double hydrogenation of the "$RuCl_2$" precursor.[17] Similarly, insertion of the "RuH_2" intermediate into the aryl–aryl bond, followed by double C–H reductive elimination, should afford two monomer products. The resulting Ru(0) can then react with H_2 to regenerate the "RuH_2" species (for a discussion of an alternative Ru(0)-initiated pathway, see the Supporting Information).

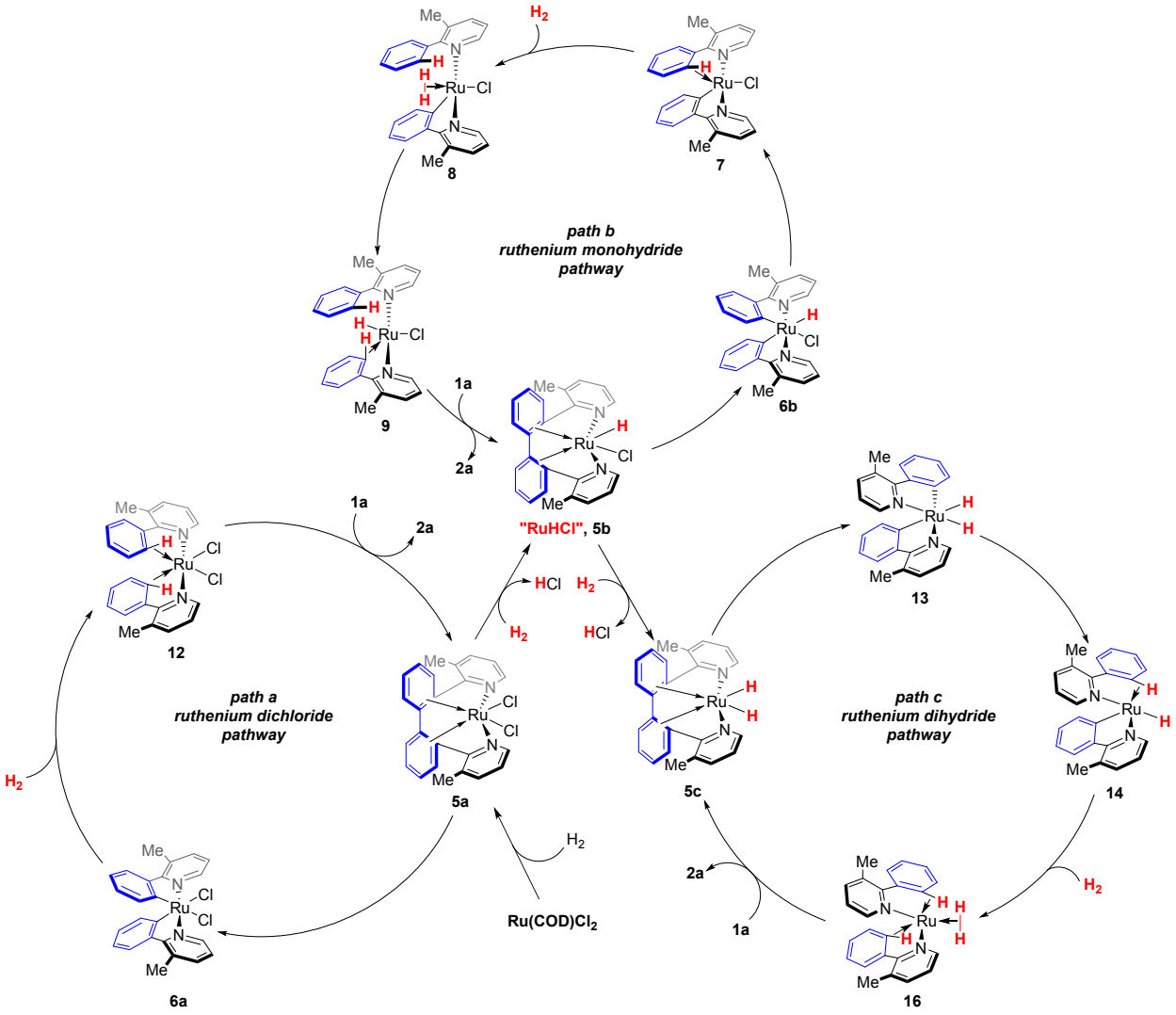


Figure 1. Proposed Possible Reaction Pathways.

DFT calculation. To differentiate the three possible pathways, density functional theory (DFT) calculations were performed. It was found that the "RuHCl" pathway (**path b**) was the most favorable. The computed energy profile in Figure 2 shows that "RuHCl" complex **5b** is the active catalyst species in the catalytic cycle, which is formed from the endothermic reaction of $RuCl_2$ species **5a** with H_2 via **TS1** with a barrier of 21.3 kcal/mol. In both **5a** and **5b**, the two pyridine DGs adopt a *trans* geometry. This places the target aryl–aryl bond in closer proximity to the Ru, which is evidenced by the short Ru···C

distances of 2.3-2.6 Å in **5a** and **5b** (*vide infra*, Figure 5, the X-ray structure of 5**ah**). This agostic C–C/Ru coordination leads to a low barrier of 12.2 kcal/mol for the subsequent C(aryl)–C(aryl) oxidative addition transition state **TS2b** with respect to **5b**. The overall activation free energy of **TS2b** is 24.5 kcal/mol with respect to the resting state **5a**. In contrast, the experimentally observed low reactivity of bi-aryl substrates with only one pyridine substituent (e.g. **1af**) can be attributed to the lack of the agostic C–C coordination with the Ru (see Figure S7.2.2 for detailed computational results). The necessity of two DGs for the C(aryl)–C(aryl) bond cleavage has also been demonstrated in the catalytic activation of the C(aryl)–C(aryl) bonds of 2,2'-biphenols by installing phosphinites as DGs in our prior study.[10] After the C–C cleavage step, the ensuing C–H reductive elimination (**TS3**) and σ-bond metathesis with H_2 (**TS4**) both occur with low barriers, leading to two monomer products (**2a**) and regenerating the "RuHCl" catalyst (**5b**).

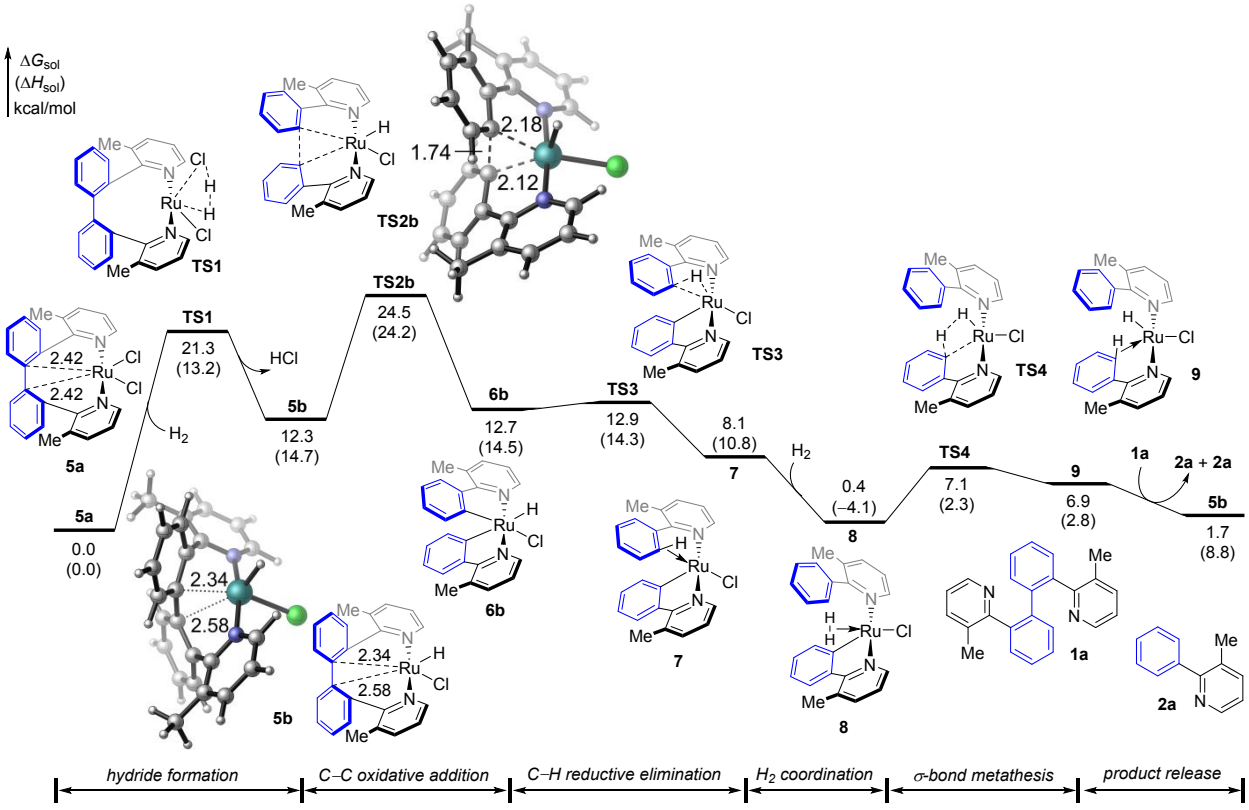


Figure 2. DFT-computed reaction energy profile of the C(aryl)−C(aryl) bond activation of substrate **1a** catalyzed by a Ru monohydride monochloride catalyst (path b).

The possibility of the "$RuCl_2$" and "RuH_2" pathways are also considered and the key results are summarized in Figure 3. In the "$RuCl_2$" pathway (path a, Figure 3A), although the oxidative addition of C(aryl)–C(aryl) (**TS2a**) requires a relatively low barrier of 20.8 kcal/mol with respect to the "$RuCl_2$" species **5a**, the resulting octahedral Ru intermediate **6a** is coordinatively saturated and thus incapable of binding with H_2 and undergoing hydrogenolysis of the Ru–C(aryl) bonds. The transition state **TS5** for H_2 cleavage has a barrier of 28.6 kcal/mol, even higher than that of the C(aryl)–C(aryl) cleavage (**TS2b**) in the "RuHCl" pathways (Figure 2). Our calculations indicated several other possible pathways of **6a**

reacting with H_2, including the one via dissociation of one of the pyridine DGs or one chloride ligand,[18] all require high barriers (see details in the Supporting Information, Figure S7.2.3). Figure 3B shows that the formation of the RuH_2 complex **5c** from **5a** is endergonic by 34.8 kcal/mol. This results in a highly disfavored C(aryl)–C(aryl) oxidative addition transition state **TS2c** ($\Delta G^{\ddagger}$ = 53.0 kcal/mol with respect to **5a**) via the ruthenium dihydride complex (see details in Figure S7.2.4). Taken together, these computational results indicate that the "$RuCl_2$" and "RuH_2" pathways are both disfavored. In addition, our DFT calculations show that although the reductive elimination of RuH_2 (**5c**) to form a Ru(0) species is energetically feasible, the Ru(0) pathway requires very high activation barriers for the C(aryl)–C(aryl) oxidative addition and the further hydrogenolysis steps (see details in Figure S7.2.5). Therefore, the DFT calculations suggested the "RuHCl" pathway (**path b**, Figure 1) is the most feasible.

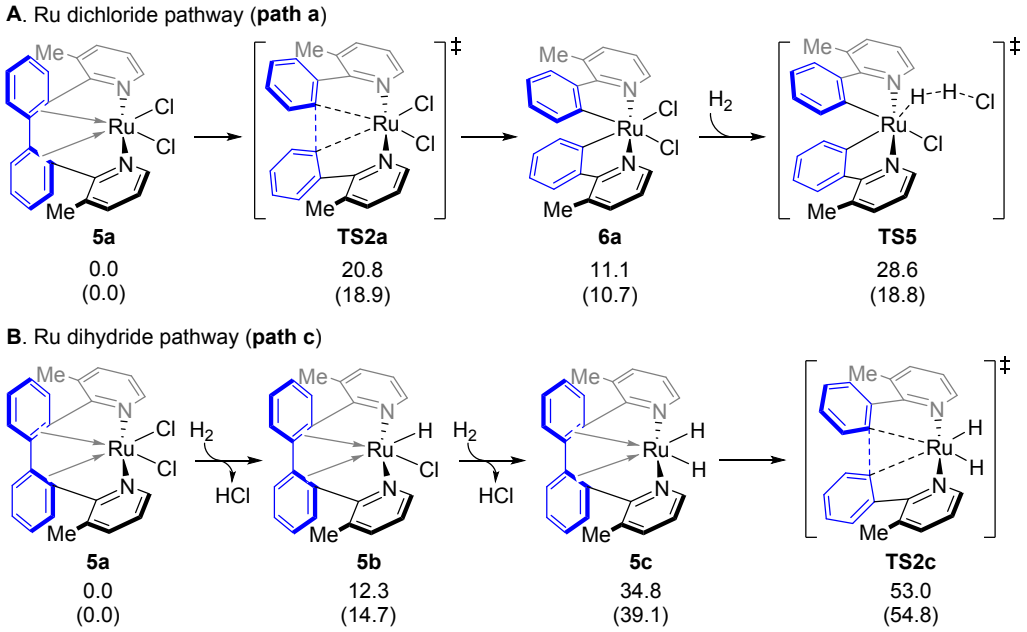
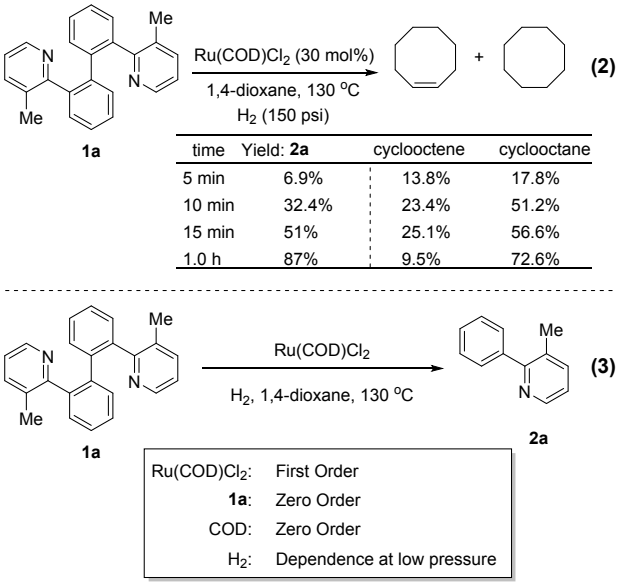


Figure 3. DFT computed pathways for the C(aryl)−C(aryl) bond activation of substrate **1a** catalyzed by Ru dichloride and Ru dihydride catalysts. Gibbs free energies and enthalpies (in parentheses) are in kcal/mol with respect to the $RuCl_2$ complex **5a**.

Kinetic studies. To validate the computational results that favor the "RuHCl"-mediated C−C activation pathway, the following kinetic studies were performed. First, the fate of 1,5-cyclooctadiene (COD) on the Ru precatalyst was determined. It was found that the COD ligand was hydrogenated to cyclooctene and cyclooctane in high efficiency at the beginning of the reaction (Scheme 3, Eq 2). This result indicated that COD is likely not involved in the catalytic cycle. Second, the kinetic profile of the reaction with substrate **1a** was measured. The initial-rate method was employed to determine the reaction order of each component. The reaction was found to exhibit first order dependence on the concentration of $Ru(COD)Cl_2$, zero order on [substrate **1a**] and [COD], and pseudo zero order on [H_2] under a higher pressure; but some rate dependence on [H_2] was observed under a relatively low H_2 gas pressure (<40 psi) (Scheme 3, Eq 3 and see Supporting Information, Table S5.2.3 for details).[19] These kinetic data are consistent with the DFT calculation (*vide supra*, Figure 2), which suggests that the oxidative addition step

is the turnover-limiting step (TLS).



Scheme 3. Kinetic Studies with the Model Substrate

In addition, Hammett plot analysis was conducted to investigate the sensitivity of the reaction to electronic changes (Figure 4).[20] The results indicated that the electron-withdrawing substituents on the arenes could promote the reaction to some extent, while electron-donating groups slowed down the reaction. This observation is also consistent with the DFT calculated results, in which the oxidative addition step is predicted to be the TLS, as the electron-deficient bonds typically promote oxidative addition.

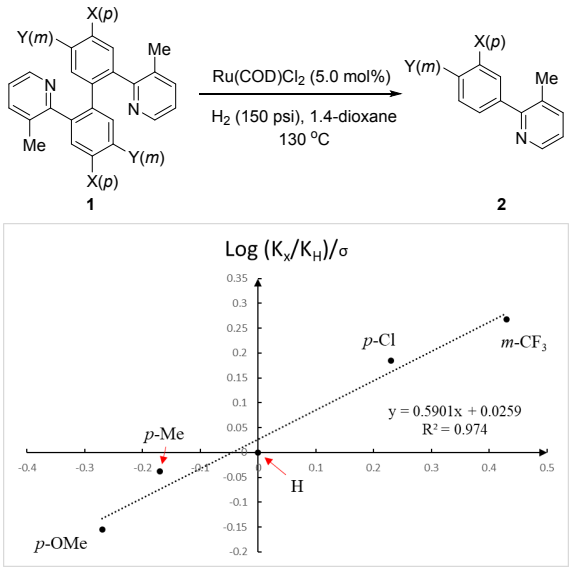


Figure 4. Hammett Plot

Resting state. Considerable endeavors have been made to capture the DFT calculated resting state, "$RuCl_2$" species **5a**. After numerous attempts, heating a mixture of substrate **1ah** and 30 mol% of $Ru(COD)Cl_2$ under 150 psi H_2 atmosphere in 1,4-dioxane at 130 °C for 20 min afforded a dark green

metal complex (**5ah**). The structure of complex **5ah** was unambiguously determined by X-ray crystallography (Figure 5), which is consistent with the proposed "$RuCl_2$" resting state by DFT (*vide supra*, Figure 2). In complex **5ah**, the metal center exhibits octahedral geometry with the two pyridine DGs adopting a *trans* spatial relationship. An interesting η^4-coordination mode between two arene π bonds and the Ru center was observed;[21] in particular, the bond lengths between the Ru center and the carbons to be cleaved are short: ca 2.2 Å. Thus, this structure shows that the Ru(II) center is very close to the target C(aryl)−C(aryl) bond. Compared to d^8 Rh(I) that favors a square planar geometry, the d^6 Ru(II) can easily form a 18 electron complex through coordination with two arene π bonds. The agostic interaction with the C(aryl)−C(aryl) bond, as illustrated in the structure of **5ah**, is anticipated to be important for the desired C−C bond activation.

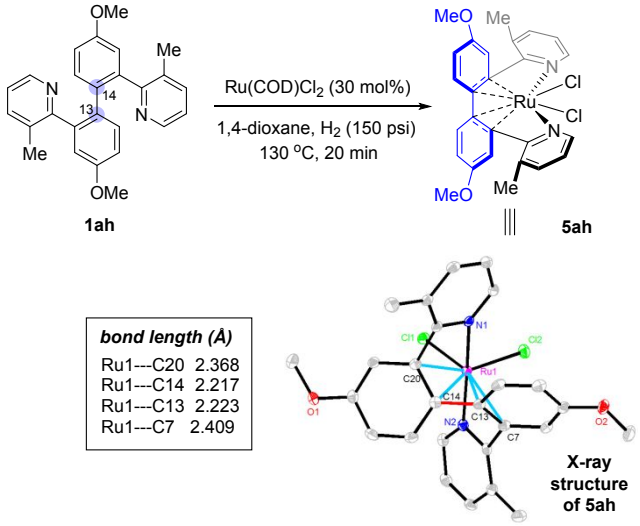
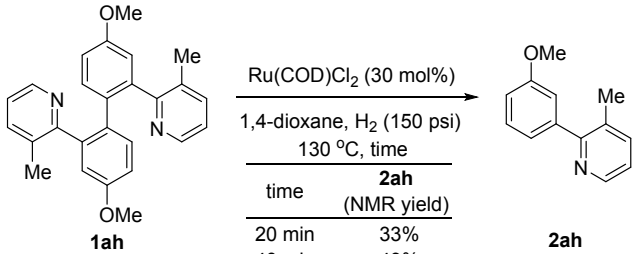


Figure 5. Capture of the Resting State of the Catalyst

In addition, the reaction of substrate **1ah** was monitored by ^{1}H-NMR, in which the "$RuCl_2$" species **5ah** was observable from the very beginning to almost the end of the reaction by comparing the ^{1}H-NMR spectra of the crude mixture with that of the isolated **5ah** (Figure 6).



time	**2ah** (NMR yield)
20 min	33%
40 min	49%
60 min	68%
100 min	87%
140 min	90%

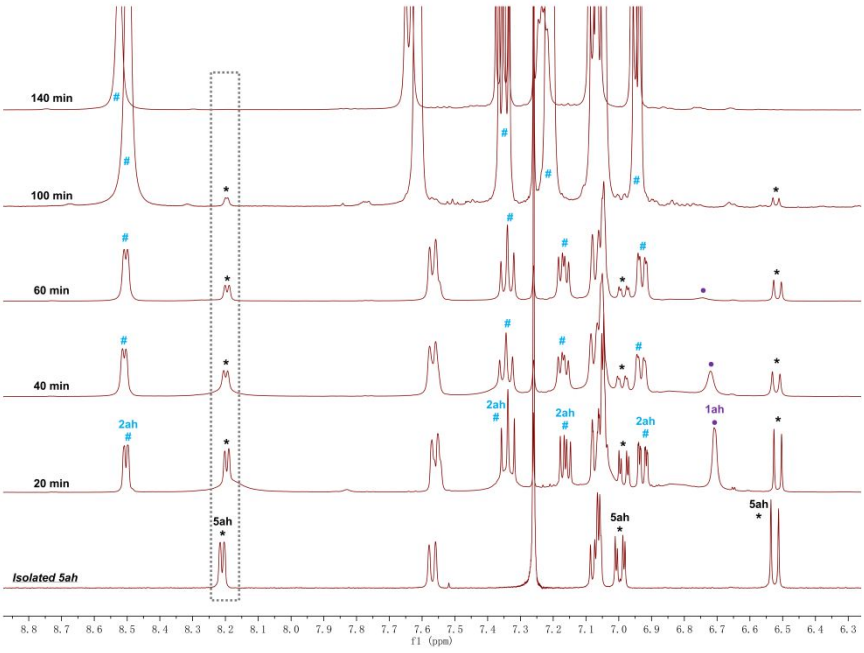
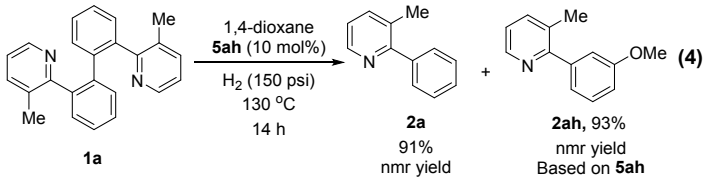
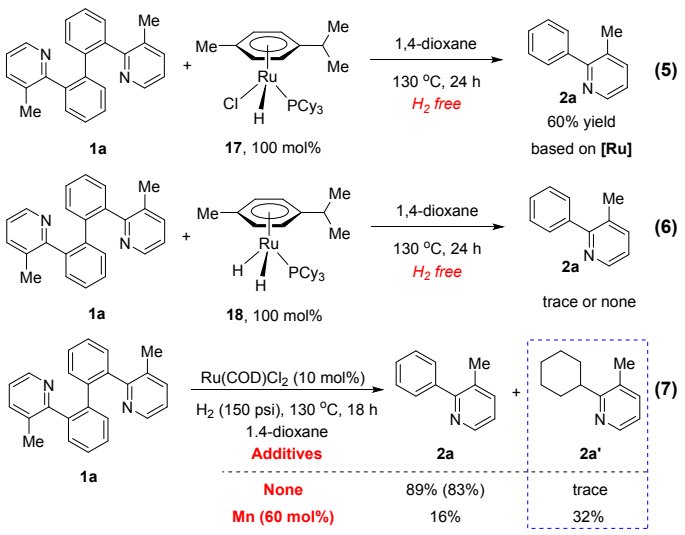


Figure 6. Monitoring the Reaction of Substrate 1ah

Moreover, complex **5ah** is catalytically active. When 10 mol% of the **5ah** was employed as the catalyst under otherwise identical conditions, 91% yield of the desired product was obtained (Eq 4). Therefore, all the above observations are consistent with the proposal of having the "$RuCl_2$" species (**5a**) as the resting state of the catalyst.



Other control experiments. To explore the "RuHCl"-mediated reaction pathway, a ruthenium monohydride monochloride complex **17** was synthesized and subjected to the reaction with substrate **1a** in the absence of hydrogen gas (scheme 4, Eq 5).[22] To our delight, 60% yield of the desired monomer product was obtained based on the hydride complex.[23] For comparison, the analogous ruthenium dihydride complex **18**[24] gave only trace product via LC-MS analysis under the same reaction conditions (Scheme 4, Eq 6). These results suggest the important role of the chloride ligand in the Ru-catalyzed C(aryl)–C(aryl) bond activation.



Scheme 4. Further Control Experiments

To further examine the possibility of the Ru(0)-initiated pathway, a control experiment was run with 60 mol% of Mn added to the reaction, as Mn metal is known to be capable of reducing Ru(II) to Ru(0) (Scheme 4, Eq 7).[25] To our surprise, the reaction with Mn not only gave a lower overall yield on the C–C cleavage products, but also generated a significant amount of arene hydrogenation product **2a'**. It is intriguing that the neutral benzene ring is selectively reduced instead of the more electron-deficient pyridine ring, implying a possible directed hydrogenation by a Ru(0) catalyst.[26] For comparison, such an over-reduction product was almost not observed under the standard reaction conditions. This experiment suggests that the Ru(0) is unlikely to be the actual catalyst for the activation of the C(aryl)–C(aryl) bonds.

Conclusion

In summary, to explore a fundamental reaction mode, we have conducted a detailed study of an unusual Ru-catalyzed activation of unstrained C(aryl)–C(aryl) bonds. The reaction limits and substrate scopes have been carefully examined. Besides hydrogen gas, a number of other reagents, such as Hantzsch ester, silanes and alcohols, have also been found effective to serve as terminal reductants for the reductive cleavage. Various heterocycles, such as pyridine, quinoline, pyrimidine and pyrazole, can be employed as DGs. In addition, a range of functional groups are compatible under the reaction conditions. Moreover, a one-pot C–C activation/C–C coupling has been realized. Finally, the reaction mechanism has been investigated through collaborative efforts between DFT calculations and experiments. The involvement of a ruthenium(II) monohydride-mediated C(aryl)–C(aryl) activation and a η^4-coordinated ruthenium(II) complex as the resting state should have broad implications beyond this work. The knowledge obtained in this study may improve our understanding on activating strong, non-polar and unstrained chemical bonds. Efforts on expanding the reaction mode to non-reductive processes are ongoing in our laboratories.

ASSOCIATED CONTENT

Text, figures, tables, and CIF files giving experimental procedures, kinetics data, and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.
Experimental procedures; spectral data (PDF)
Crystallographic data for **5ah**
Computational details, additional computational results, and Cartesian coordinates

AUTHOR INFORMATION

Corresponding Author

*ganglu@sdu.edu.cn
*pengliu@pitt.edu
*gbdong@uchicago.edu

Author Contributions

⊥These authors contributed equally.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENT

NIGMS (1R01GM124414-01A1) (G.D.) and the National Science Foundation (CHE-1654122) (P.L.) are acknowledged for research support. G.L. thanks Shandong University for financial support. Dr. Ki-Young Yoon and Dr. Alexander Filatov are acknowledged for X-ray crystallography. Dr. Jianchun Wang is thanked for helpful discussions. Calculations were performed at the Center for Research Computing at the University of Pittsburgh and the Ex-treme Science and Engineering Discovery Environment (XSEDE) supported by the NSF.

REFERENCES

[1] For books and recent reviews, see: (a) Murakami, M.; Ito, Y., *Cleavage of Carbon–Carbon Single Bonds by Transition Metals*. In *Top. Organomet. Chem.* 1999; Vol. 3, pp 97. (b) Dong, G. (ed.) C–C Bond Activation. Vol. 346 of *Top. Curr. Chem.* (Springer, 2014). (c) Murakami, M. (ed.) Cleavage of carbon-carbon single bonds by transition metals (Wiley-VCH Verlag GmbH & Co. KGaA, 2015). (d) Perthuisot, C.; Edelbach, B. L.; Zubris, D. L.; Simhai, N.; Iverson, C. N.; Müller, C.; Satoh, T.; Jones, W. D. Cleavage of the carbon–carbon bond in biphenylene using transition metals. *J. Mol. Catal. A: Chem.* **2002,** *189*, 157-168. (e) Ruhland, K. Transition-Metal-Mediated Cleavage and Activation of C–C Single Bonds. *Eur. J. Org. Chem.* **2012,** *2012*, 2683-2706.

[2] For recent reviews on "cut and sew" chemistry review, see: (a) Chen, P.-h.; Dong, G. Cyclobutenones and Benzocyclobutenones: Versatile Synthons in Organic Synthesis. *Chem. Eur. J.* **2016,** *22*, 18290-18315. (b) Chen, P.-h.; Billett, B. A.; Tsukamoto, T.; Dong, G. "Cut and Sew" Transformations via Transition-Metal-Catalyzed Carbon–Carbon Bond Activation. *ACS Catal.* **2017,** *7*, 1340-1360.

[3] For recent reviews on activation of three membered and four membered rings, see: (a) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. Cyclobutanes in Catalysis. *Angew. Chem. Int. Ed.* **2011,** *50*, 7740-7752. (b) Mack, D. J.; Njardarson, J. T. Recent Advances in the Metal-Catalyzed Ring Expansions of Three- and Four-Membered Rings. *ACS Catal.* **2013,** *3*, 272-286. (c) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies That Exploit C–C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev.* **2017,** *117*, 9404-9432.

[4] For recent book and review on C-CN bond activation, see: (a) Nakao, Y., Catalytic C–CN Bond Activation. In *C-C Bond Activation*, Dong, G., Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 2014; pp 33-58. (b) Wen, Q.; Lu, P.; Wang, Y. Recent advances in transition-metal-catalyzed C–CN bond activations. *RSC Adv.* **2014,** *4*, 47806-47826.

[5] For recent reviews on less strained C-C activation, see: (a) Rybtchinski, B.; Milstein, D. Metal Insertion into C−C Bonds in Solution. *Angew. Chem. Int. Ed.* **1999,** *38*, 870-883. (b) van der Boom, M. E.; Milstein, D. Cyclometalated Phosphine-Based Pincer Complexes: Mechanistic Insight in Catalysis, Coordination, and Bond Activation. *Chem. Rev.* **2003,** *103*, 1759-1792. (c) Jun, C.-H. Transition metal-catalyzed carbon–carbon bond activation. *Chem. Soc. Rev.* **2004,** *33*, 610-618. (d) Park, Y. J.; Park, J.-W.; Jun, C.-H. Metal−Organic Cooperative Catalysis in C−H and C−C Bond Activation and Its Concurrent Recovery. *Acc. Chem. Res.* **2008,** *41*, 222-234. (e) Chen, F.; Wang, T.; Jiao, N. Recent Advances in Transition-Metal-Catalyzed Functionalization of Unstrained Carbon–Carbon Bonds. *Chem. Rev.* **2014,** *114*, 8613-8661. (f) Kim, D.-S.; Park, W.-J.; Jun, C.-H. Metal–Organic Cooperative Catalysis in C–H and C–C Bond Activation. *Chem. Rev.* **2017,** *117*, 8977-9015.

[6] (a) Gozin, M.; Weisman, A.; Ben-David, Y.; Milstein, D. Activation of a carbon–carbon bond in solution by transition-metal insertion. *Nature* **1993,** *364*, 699-701. (b) Gozin, M.; Aizenberg, M.; Liou, S.-Y.; Weisman, A.; Ben-David, Y.; Milstein, D. Transfer of methylene groups promoted by metal complexation. *Nature* **1994,** *370*, 42-44. (c) Liou, S.-Y.; Gozin, M.; Milstein,

D. Directly Observed Oxidative Addition of a Strong Carbon-Carbon Bond to a Soluble Metal Complex. *J. Am. Chem. Soc.* **1995,** *117*, 9774-9775.

[7] Liou, S.-Y.; E. van der Boom, M.; Milstein, D. Catalytic selective cleavage of a strong C–C single bond by rhodium in solution. *Chem. Commun.* **1998**, 687-688.

[8] Onodera, S.; Ishikawa, S.; Kochi, T.; Kakiuchi, F. Direct Alkenylation of Allylbenzenes via Chelation-Assisted C–C Bond Cleavage. *J. Am. Chem. Soc.* **2018,** *140*, 9788-9792.

[9] Ruhland, K.; Obenhuber, A.; Hoffmann, S. D. Cleavage of Unstrained C(sp^2)—C(sp^2) Single Bonds with Ni^0 Complexes Using Chelating Assistance. *Organometallics* **2008,** *27*, 3482-3495.

[10] Zhu, J.; Wang, J.; Dong, G. Catalytic activation of unstrained C(aryl)–C(aryl) bonds in 2,2'-biphenols. *Nat. Chem.* **2019,** *11*, 45-51.

[11] For recent reviews on directed C-H activation, see: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Palladium(II)-Catalyzed C-H Activation/C-C Cross-Coupling Reactions: Versatility and Practicality. *Angew. Chem. Int. Ed.* **2009,** *48*, 5094-5115. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C−C Bond Formation via Heteroatom-Directed C−H Bond Activation. *Chem. Rev.* **2010,** *110*, 624-655. (c) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chem. Rev.* **2010,** *110*, 1147-1169. (d) Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. Recent advances in directed C–H functionalizations using monodentate nitrogen-based directing groups. *Org. Chem. Front.* **2014,** *1*, 843-895. (e) Daugulis, O.; Roane, J.; Tran, L. D. Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon–Hydrogen Bonds. *Acc. Chem. Res.* **2015,** *48*, 1053-1064.

[12] For C-C activation directed by pyridine and other heterocycles, see: (a) Suggs, J. W.; Jun, C. H. Directed cleavage of carbon-carbon bonds by transition metals: the α-bonds of ketones. *J. Am. Chem. Soc.* **1984,** *106*, 3054-3056. (b) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. $Ru_3(CO)_{12}$-Catalyzed Decarbonylative Cleavage of a C−C Bond of Alkyl Phenyl Ketones. *J. Am. Chem. Soc.* **1999,** *121*, 8645-8646. (c) Jun, C.-H.; Lee, H. Catalytic Carbon−Carbon Bond Activation of Unstrained Ketone by Soluble Transition-Metal Complex. *J. Am. Chem. Soc.* **1999,** *121*, 880-881. (d) Jun, C.-H.; Lee, D.-Y.; Kim, Y.-H.; Lee, H. Catalytic Carbon−Carbon Bond Activation of sec-Alcohols by a Rhodium(I) Complex. *Organometallics* **2001,** *20*, 2928-2931. (e) Jun, C.-H.; Lee, H.; Lim, S.-G. The C−C Bond Activation and Skeletal Rearrangement of Cycloalkanone Imine by Rh(I) Catalysts. *J. Am. Chem. Soc.* **2001,** *123*, 751-752. (f) Jun, C.-H.; Moon, C. W.; Lee, H.; Lee, D.-Y. Chelation-assisted carbon–carbon bond activation by Rh(I) catalysts. *J. Mol. Catal. A: Chem.* **2002,** *189*, 145-156. (g) Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Shi, Z.-J. Pyridinyl Directed Alkenylation with Olefins via Rh(III)-Catalyzed C–C Bond Cleavage of Secondary Arylmethanols. *J. Am. Chem. Soc.* **2011,** *133*, 15244-15247. (h) Chen, K.; Li, H.; Li, Y.; Zhang, X.-S.; Lei, Z.-Q.; Shi, Z.-J. Direct oxidative arylation via rhodium-catalyzed C–C bond cleavage of secondary alcohols with arylsilanes. *Chem. Sci.* **2012,** *3*, 1645-1649. (i) Lei, Z.-Q.; Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Sun, J.; Shi, Z.-J. Extrusion of CO from Aryl Ketones: Rhodium(I)-Catalyzed C-C Bond Cleavage Directed by a Pyridine Group. *Angew. Chem. Int. Ed.* **2012,** *51*, 2690-2694. (j) Ko, H. M.; Dong, G. Cooperative activation of cyclobutanones and olefins leads to bridged ring systems by a catalytic [4+2] coupling. *Nat. Chem.* **2014,** *6*, 739. (k) Xia, Y.; Lu, G.; Liu, P.; Dong, G. Catalytic activation of carbon–carbon bonds in cyclopentanones. *Nature* **2016,** *539*, 546. (l) Xia, Y.; Wang, J.; Dong, G. Distal-Bond-Selective C−C Activation of Ring-Fused Cyclopentanones: An Efficient Access to Spiroindanones. *Angew. Chem. Int. Ed.* **2017,** *56*, 2376-2380. (m) Xia, Y.; Wang, J.; Dong, G. Suzuki–Miyaura Coupling of Simple Ketones via Activation of Unstrained Carbon–Carbon Bonds. *J. Am. Chem. Soc.* **2018,** *140*, 5347-5351. (n) Zhao, T.-T.; Xu, W.-H.; Zheng, Z.-J.; Xu, P.-F.; Wei, H. Directed Decarbonylation of Unstrained Aryl Ketones via Nickel-Catalyzed C—C Bond Cleavage. *J. Am. Chem. Soc.* **2018,** *140*, 586-589.

[13] (a) Rendler, S.; Oestreich, M. Hypervalent Silicon as a Reactive Site in Selective Bond-Forming Processes. *Synthesis* **2005,** *2005*, 1727-1747. (b) Jia, Z.; Liu, M.; Li, X.; Chan, A. S. C.; Li, C.-J. Highly Efficient Reduction of Aldehydes with Silanes in Water Catalyzed by Silver. *Synlett* **2013,** *24*, 2049-2056. (c) Yan, M.; Jin, T.; Chen, Q.; Ho, H. E.; Fujita, T.; Chen, L.-Y.; Bao, M.; Chen, M.-W.; Asao, N.; Yamamoto, Y. Unsupported Nanoporous Gold Catalyst for Highly Selective Hydrogenation of Quinolines. *Org. Lett.* **2013,** *15*, 1484-1487.

[14] (a) Yutaka, I.; Naoto, C.; Shuhei, Y.; Shinji, M. Rhodium-Catalyzed Si-F Exchange Reaction between Fluorobenzenes and a Disilane. Catalytic Reaction Involving Cleavage of C-F Bonds. *Chem. Lett.* **1998,** *27*, 157-158. (b) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. Nickel-Catalyzed Suzuki–Miyaura Reaction of Aryl Fluorides. *J. Am. Chem. Soc.* **2011,** *133*, 19505-19511. (c) Ahrens, T.; Kohlmann, J.; Ahrens, M.; Braun, T. Functionalization of Fluorinated Molecules by Transition-Metal-Mediated C–F Bond Activation To Access Fluorinated Building Blocks. *Chem. Rev.* **2015,** *115*, 931-972.

[15] For selected Ru-catalyzed C-H acrylate coupling, see: Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. Ruthenium(II)-Catalyzed C–H Bond Activation and Functionalization. *Chem. Rev.* **2012,** *112*, 5879-5918.

[16] Jung, S.; Ilg, K.; Brandt, C. D.; Wolf, J.; Werner, H. A series of ruthenium(ii) complexes containing the bulky, functionalized trialkylphosphines $tBu_2PCH_2XC_6H_5$ as ligands. *J. Chem. Soc., Dalton Trans.* **2002**, 318-327. (b) Kuznetsov, V. F.; Abdur-Rashid, K.; Lough, A. J.; Gusev, D. G. Carbene vs Olefin Products of C−H Activation on Ruthenium via Competing α- and β-H Elimination. *J. Am. Chem. Soc.* **2006,** *128*, 14388-14396. (c) Morilla, M. E.; Rodríguez, P.; Belderrain, T. R.; Graiff, C.; Tiripicchio, A.; Nicasio, M. C.; Pérez, P. J. Synthesis, Characterization, and Reactivity of Ruthenium Diene/Diamine Complexes Including Catalytic Hydrogenation of Ketones. *Inorg. Chem.* **2007,** *46*, 9405-9414.

[17] (a) Nolan, S. P.; Belderrain, T. R.; Grubbs, R. H. Convenient Synthesis of Ruthenium(II) Dihydride Phosphine Complexes $Ru(H)_2(PP)_2$ and $Ru(H)_2(PR_3)x$ (x = 3 and 4). *Organometallics* **1997**, *16*, 5569-5571. (b) Shen, J.; Stevens, E. D.; Nolan, S. P. Synthesis and Reactivity of the Ruthenium(II) Dihydride $Ru(Ph_2PNMeNMePPh_2)_2H_2$. *Organometallics* **1998**, *17*, 3875-3882.

[18] Lu, Y.; Liu, Z.; Guo, J.; Qu, S.; Zhao, R.; Wang, Z.-X. A DFT study unveils the secret of how H_2 is activated in the N-formylation of amines with CO_2 and H_2 catalyzed by Ru(ii) pincer complexes in the absence of exogenous additives. *Chem. Commun.* **2017**, *53*, 12148-12151.

[19] We reasoned that under a low H_2 pressure the concentration of the "RuHCl" species (**5b**) is in equilibrium with the resting state (**5a**), thus showing rate dependence with the H_2 pressure. In contrast, under a high H_2 pressure, a situation of "saturation kinetics" could take place; therefore, the initial rate is less dependent on the [H_2].

[20] Stowers, K. J.; Sanford, M. S., Mechanistic Comparison between Pd-Catalyzed Ligand-Directed C−H Chlorination and C−H Acetoxylation. *Org. Lett.* **2009,** *11*, 4584-4587.

[21] A structurally related Ru(II) biaryl bispyridyl complex with a η^4-coordination was reported by Ryabov and Lagadec through a biaryl coupling reaction, see: Saavedra-Díaz, O.; Cerón-Camacho, R.; Hernández, S.; Ryabov, A. D.; Le Lagadec, R. Denial of Tris(C,N-cyclometalated) Ruthenacycle: Nine-Membered η^6-N,N-trans or η^2-N,N-cis RuII Chelates of 2,2′-Bis(2-pyridinyl)-1,1′-biphenyl. *Eur. J. Inorg. Chem.* **2008,** *2008*, 4866-4869.

[22] Solari, E.; Gauthier, S.; Scopelliti, R.; Severin, K. Multifaceted Chemistry of $[(Cymene)RuCl_2]_2$ and PCy_3. *Organometallics* **2009,** *28*, 4519-4526..

[23] Complex **17** can promote hydrogen transfer from 1,4-dioxane. For details, see the Supporting Information.

[24] Demerseman, B.; Mbaye, M. D.; Sémeril, D.; Toupet, L.; Bruneau, C.; Dixneuf, P. H. Direct Preparation of $[Ru(\eta^2\text{-}O_2CO)(\eta^6\text{-arene})(L)]$ Carbonate Complexes (L = Phosphane, Carbene) and Their Use as Precursors of $[RuH_2(p\text{-cymene})(PCy_3)]$ and $[Ru(\eta^6\text{-arene})(L)(MeCN)_2][BF_4]_2$: X-ray Crystal Structure Determination of $[Ru(\eta^2\text{-}O_2CO)(p\text{-cymene})(PCy_3)]\cdot 1/2CH_2Cl_2$ and $[Ru(\eta^2\text{-}O_2CO)(\eta^6\text{-}C_6Me_6)(PMe_3)]\cdot H_2O$. *Eur. J. Inorg. Chem.* **2006,** *2006*, 1174-1181.

[25] McKinney, R. J.; Colton, M. C. Homogeneous ruthenium-catalyzed acrylate dimerization. Isolation, characterization and crystal structure of the catalytic precursor bis(dimethyl muconate)(trimethyl phosphite)ruthenium(0). *Organometallics* **1986,** *5*, 1080-1085.

[26] (a) Prechtl, M. H. G.; Scariot, M.; Scholten, J. D.; Machado, G.; Teixeira, S. R.; Dupont, J. Nanoscale Ru(0) Particles: Arene Hydrogenation Catalysts in Imidazolium Ionic Liquids. *Inorg. Chem.* **2008,** *47*, 8995-9001. (b) Touge, T.; Arai, T. Asymmetric Hydrogenation of Unprotected Indoles Catalyzed by η^6-Arene/N-Me-sulfonyldiamine–Ru(II) Complexes. *J. Am. Chem. Soc.* **2016,** *138*, 11299-11305. (c) Rakers, L.; Martínez-Prieto, L. M.; López-Vinasco, A. M.; Philippot, K.; van Leeuwen, P. W. N. M.; Chaudret, B.; Glorius, F. Ruthenium nanoparticles ligated by cholesterol-derived NHCs and their application in the hydrogenation of arenes. *Chem. Commun.* **2018,** *54*, 7070-7073.