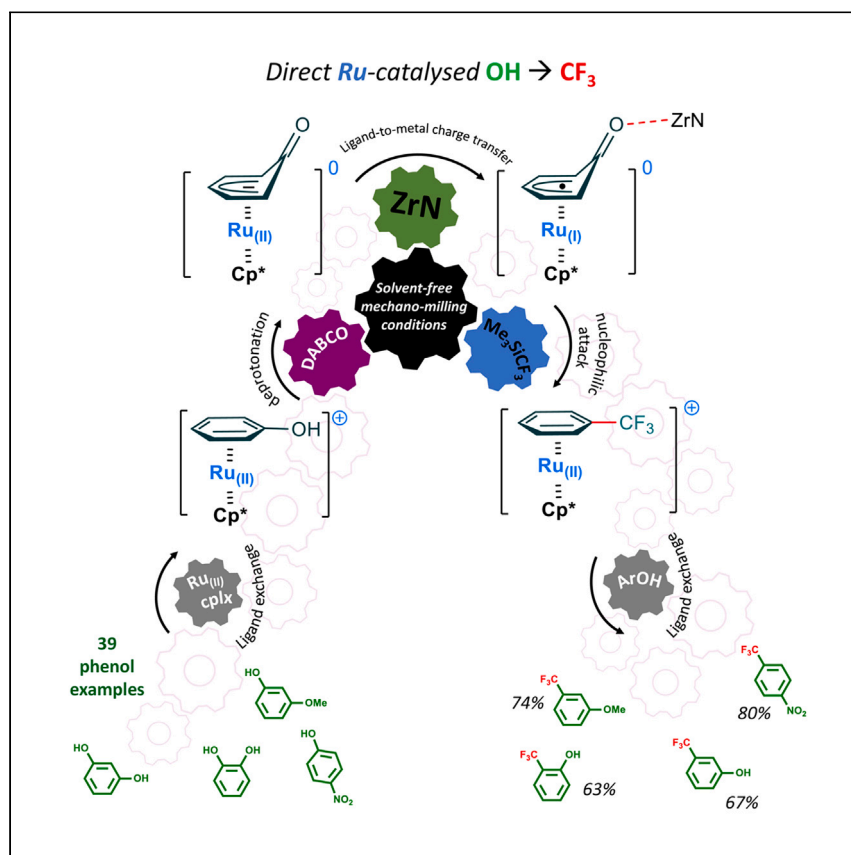


Article

# One-step Ru-catalyzed conversion of phenolic OH groups to trifluoromethyl under mechanochemical conditions



Iarsoshenko and co-workers report the conversion of otherwise unreactive phenols to pharmaceutically relevant CF<sub>3</sub>-aryls, enabling the direct treatment of cheap industrial lignin byproducts. The solvent-free solid-phase methodology and transition metal catalysis may offer an economical route to valuable products.

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### Highlights

Mechanochemical activation of phenols

Ru-catalyzed introduction of -CF<sub>3</sub>

ZrN additive enables ligand-to-metal charge transfer

## Article

# One-step Ru-catalyzed conversion of phenolic OH groups to trifluoromethyl under mechanochemical conditions

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## SUMMARY

**Direct and selective transformation of the phenolic hydroxy group in a concise way without prior derivatization is relevant in many industrial processes, particularly late-stage modification of pharmaceuticals and for lignin-material treatment. The introduction of fluorine has a profound impact on the molecular properties of both small molecules and biopolymers. Herein, we report a Ru-catalyzed transformation of phenols into trifluoromethyl-arenes under mechanochemical conditions. The protocol accepts a wide scope of starting materials and allows for gram-scale synthesis in excellent yields. The developed approach may offer an important alternative to known methods in the context of PASE (pot, atom, and step economy) synthesis and, therefore, green chemistry.**

## INTRODUCTION

The introduction of fluorine and fluorine-containing substituents into the structures of bioactive molecules is now a standard strategy in drug design to modify properties like binding affinity, pharmacokinetics, bioavailability, lipophilicity, steric properties, conformational constraint, and metabolic stability. The development of trifluoromethylation methods in the last decade has allowed for an extended fluorine scan and the introduction of novel drugs and drug candidates.<sup>1</sup> Among the total number of 369 fluorine chemotypes in structures of 340 fluoro-pharmaceuticals registered between the years 1954 and 2019, Ar-CF<sub>3</sub>, Het-CF<sub>3</sub>, and alkyl-CF<sub>3</sub> constitute about 19%.<sup>2</sup> Moreover, CF<sub>3</sub>-containing building blocks raise interest as precursors for -CHF- and -CF<sub>2</sub>- bridge formation,<sup>3,4</sup> as well as in mechanochemical variants of some useful transformations.<sup>5,6</sup> CF<sub>3</sub>-bearing compounds also find applications as agrochemicals<sup>7</sup> and in materials chemistry.<sup>8</sup>

Modern chemistry offers a whole toolbox for the introduction of the -CF<sub>3</sub> group into aromatic scaffolds.<sup>9</sup> The crudest method relies on -Cl to -F substitution using HF.<sup>10</sup> Aromatic carboxylic acids undergo deoxyfluorination in the presence of SF<sub>4</sub> and HF.<sup>11</sup> Modern medicinal chemistry methods require the presence of surrogate groups like -Hal,<sup>12,13</sup> -NO<sub>2</sub>,<sup>14</sup> or -B(OH)<sub>2</sub><sup>15,16</sup> and proceed via a TM-catalyzed mechanism. Reagents delivering -CF<sub>3</sub> as an electrophile, nucleophile, or free radical can be used, such as the Ruppert-Prakash reagent (TMSCF<sub>3</sub>), Togni reagent, Umemoto reagent, and Langlois reagent (CF<sub>3</sub>SO<sub>2</sub>Na). Direct or assisted C-H trifluoromethylation is achieved with Ag,<sup>17</sup> Cu,<sup>18</sup> Pd,<sup>19</sup> and Ni<sup>20</sup> catalysis, light-driven-assisted TM photocatalysis,<sup>21</sup> catalyst-free processes,<sup>22</sup> photoinduced processes,<sup>23</sup> peroxide-induced radical processes,<sup>24</sup> or alternating current electrolysis.<sup>25</sup> A Sandmeyer-type reaction involving Cu- and Ag-mediated protocols also adds anilines to the pool of possible starting materials.<sup>26,27</sup>

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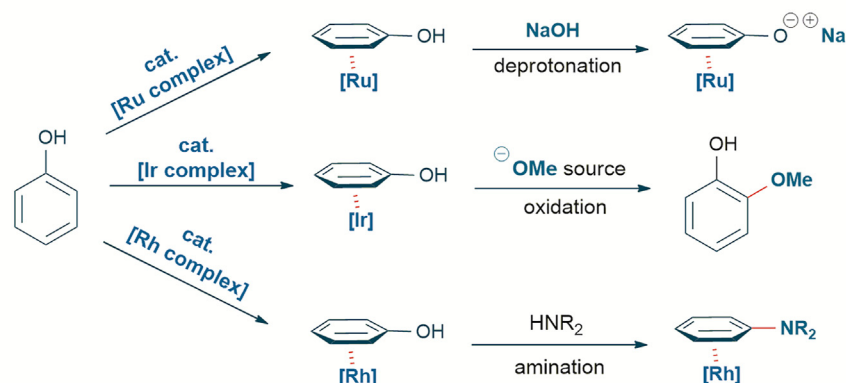
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<sup>10</sup>Lead contact

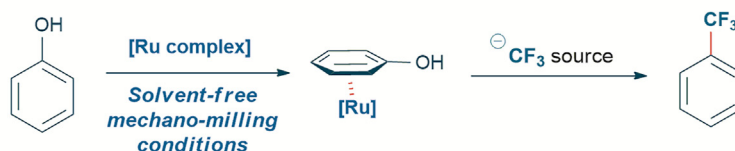
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**Previous works involving Ru, Ir and Rh catalysts:**



**General synthetic scenario - this work:**



**Scheme 1.** General synthetic scenarios for the formation and manipulation of  $\eta^6$ -phenol complexes with Ru, Ir, and Rh catalysts and the title transformation involving Ru catalyst under mechanochemical conditions

Despite numerous efforts and remarkable progress to achieve aromatic trifluoromethylation, most of the abovementioned methods suffer from one or other drawbacks such as limited substrate scope, harsh reaction conditions, low regioselectivity, and use of toxic/expensive reagents, explosive/unstable substrates, ligands, and catalysts. It is therefore obvious that an alternative and cost-effective trifluoromethylation approach using cheap and readily available starting materials/reagents under mechanochemical conditions needs to be developed.

Phenols and their derivatives are abundant motifs in nature and have been investigated in cross-couplings as electrophiles with a variety of nucleophiles.<sup>28–30</sup> Direct deoxyfluorination of phenols has been achieved utilizing PhenoFluor<sup>31</sup> and via aryl fluorosulfonates.<sup>32</sup> In the context of polymer preparation, industrial *in situ* fluorination of phenolic resins is achieved by harsh and non-selective methods.<sup>33,34</sup> Most polymers containing the  $-\text{CF}_3$  group are made from pre-modified building blocks<sup>35,36</sup> or with a perfluoro radical-generating reagent that can be used for simultaneous polymer initiation/trifluoromethylation<sup>37</sup> or as a post-modification reagent only.<sup>38</sup> Attempts have been made to manipulate the aromatic  $-\text{OH}$  group in lignin materials with TM catalysis. The most promising in this context, Ru,<sup>39</sup> Ir,<sup>40</sup> and Rh<sup>41</sup> can form sandwich complexes with phenols (Scheme 1).

Compared to the aryl halides, which are one of the common aromatic feedstocks at present for the synthesis of trifluoromethyl arenes, phenols are considered comparatively sustainable and renewable aromatic feedstocks because of their wide availability from the lignin biomass and low cost of production. Thus, direct cross-coupling reactions involving the phenolic  $-\text{OH}$  group would be very interesting in light of cost effectiveness and environmental concerns, as phenols are much cheaper, more non-toxic, and more readily available than aryl halides. Furthermore,

the possibility of the generation of halogen waste using aryl halide precursors may also censor the synthetic utility with a perspective to environmental concerns. Until now, however, no methods have been known to substitute the inert phenolic -OH groups with -CF<sub>3</sub> without derivatization. Based on our previous attempts to realize catalytical processes under mechanochemical conditions,<sup>42–44</sup> we hypothesized that C–O bond activation could occur without prior derivatization of phenol in the solid phase via  $\pi$ -coordination activation.<sup>45–52</sup> Following the recently introduced direct deoxyfluorination,<sup>53</sup> we used the Cp\*Ru(Napht)BF<sub>4</sub> catalyst. The naphthalene ligand in this complex easily undergoes arene exchange by substituted benzenes, including phenols.<sup>54</sup> We were curious if mechanochemical friction would induce reactivity as expected according to the scenario in [Scheme 1](#).

Herein, we report optimizing a mechanochemical, Ru-catalyzed process to activate free phenols for -CF<sub>3</sub> substitution. The reaction successfully transformed 39 phenolic starting materials in high yields, also allowing for gram-scale synthesis (10 mmol, 3 examples).

## RESULTS AND DISCUSSION

### Optimization of reaction conditions

Generation of the active, anionic form of the Ruppert-Prakash reagent implied the addition of CsF. In the hope of stabilizing the  $\eta^5$ -phenoxo form, we introduced an adsorption material. A trial run using ZrO<sub>2</sub> resulted in a trace product ([Table S1](#), entry 12). We turned our attention to piezoelectric materials in light of the recent developments in mechanoredox reactions assisted by such nanoparticles.<sup>55</sup> Use of HfO<sub>2</sub> and BaBeO<sub>2</sub> resulted in no detectable product after 90 min of milling ([Table S1](#), entries 13 and 14). An increase in the yield was observed for HfN (57%, [Table S1](#), entry 11). Switching to zirconium nitride (ZrN), which has a high affinity to both oxygen and nitrogen, resulted in the highest yield (83%, [Table S1](#), entry 9). We also tried to introduce other Ru complexes, switching the ligands, which resulted only in a decrease in the reaction efficiency. The importance of the naphthyl ligand was confirmed, as [Cp\*Ru(PhCl)]PF<sub>6</sub> and Cp\*Ru(PhCl)BF<sub>4</sub> catalysts gave the product in 44% and 65% yields, respectively ([Table S1](#), entries 7 and 8), while [Cp\*RuCl]<sub>4</sub> and [Cp\*Ru(MeCN)<sub>3</sub>](BF<sub>4</sub>)<sub>2</sub> gave no product ([Table S1](#), entries 2 and 6). Furthermore, the dimeric [Cp\*RuCl<sub>2</sub>]<sub>2</sub> and [(*p*-cymene)RuCl<sub>2</sub>]<sub>2</sub> resulted in 34% and 18% yields ([Table S1](#), entries 1 and 3), while  $\eta^6$ -dimers [(C<sub>6</sub>H<sub>6</sub>)<sub>2</sub>RuCl<sub>2</sub>]<sub>2</sub> and [(C<sub>6</sub>H<sub>6</sub>)<sub>2</sub>Ru](BF<sub>4</sub>)<sub>2</sub> crippled the reaction completely ([Table S1](#), entries 4 and 5). The resulting optimal reaction conditions (ORCs) are specified in [Scheme 2](#). The milling vessel was heated from the outside using a heat gun. To achieve the desired internal temperature, the heat gun setting was adjusted according to the temperature measured inside of the milling jar immediately after opening (the heat gun was set to 100°C).<sup>56</sup> It was evidenced that elevated temperature is crucial for the transformation to occur and that the reaction conducted without any external heating gave no trace of the product ([Table S1](#), entry 10). The ZrN used in the reaction can be recovered by using modified workup conditions and reused several times without visible loss in the overall yield of the model compound. We also conducted the reaction by refluxing phenol with the reactants (R) in a selection of solvents in elevated temperatures for 24 h: toluene at reflux, benzene at reflux, 1,4-dioxane at reflux, xylenes at 130°C, DMF at 140°C, DMA at 155°C, and neat phenol at 165°C ([Table S1](#), entries 15–21). None of those attempts resulted in the desired product. ZrN is insoluble in most organic solvents; therefore, vigorous mixing was applied to agitate the suspension.

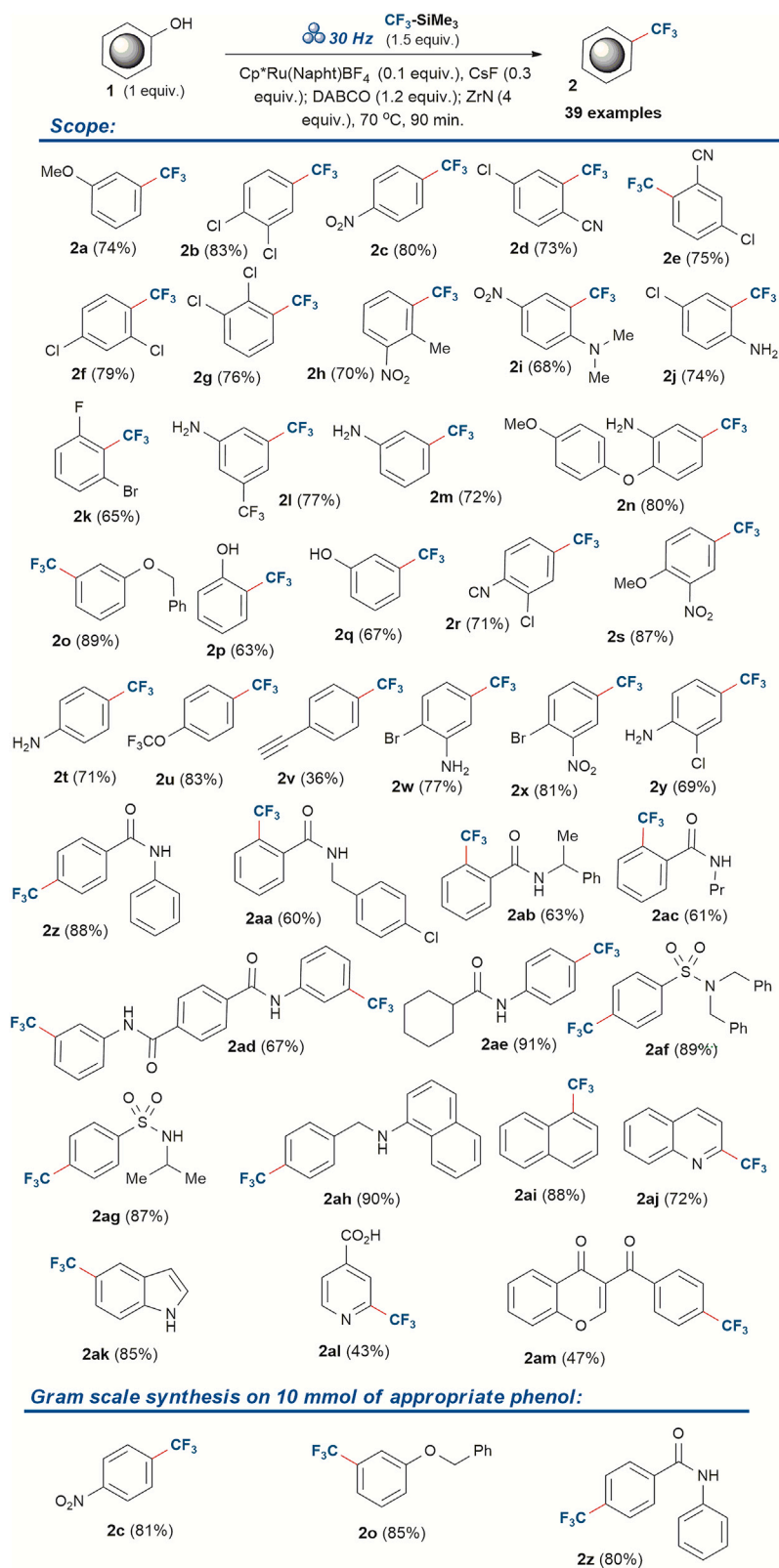
### Assessment of the reaction scope

With the ORCs in hand, we moved to scope assessment. In total, 39 phenols with simple as well as more voluminous substituents were subjected to the mechanochemical

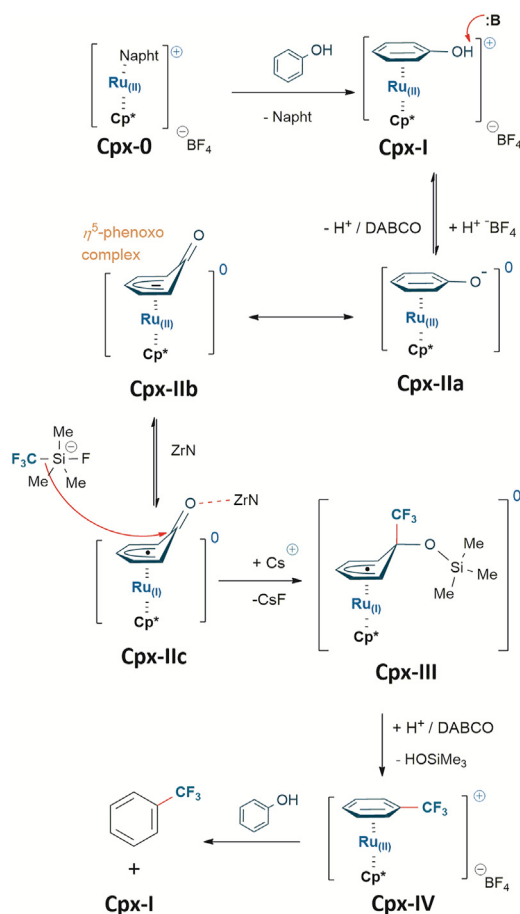
protocol under the ORCs, including arenes with useful and reactive handles like  $-\text{NO}_2$ ,  $-\text{COOH}$ ,  $-\text{CN}$ ,  $-\text{Br}$ ,  $-\text{Cl}$ ,  $-\text{NH}_2$ , and amide. In the majority of cases, the yields of the expected products oscillated between 70% and 90%. The somewhat lower yields (around 60%–70%) observed for phenols **1i**, **1aa**, **1ab**, and **1ac** can be attributed to the presence of larger moieties in the *o*-position with respect to the  $-\text{OH}$  group or two *o*-substituents, in the case of 2-bromo-6-fluorophenol **1k**. In the case of *N*<sup>1</sup>,*N*<sup>4</sup>-bis(3-hydroxyphenyl)-terephthalamide **1ad**, two consecutive reaction acts are needed to produce **2ad**, which can explain the slightly lower yield (67%). Catechol **1p** and resorcinol **1q** were also included in the scope of starting materials. Single-substituted products **2p** and **2q** were obtained in 63% and 67% yields, respectively. The possible second reaction act leading to the doubly substituted byproducts accounts for the lower yields in those cases as well. However, it is difficult to confirm this by isolation of the byproducts due to their volatility under the workup conditions (adsorption of the crude mixture on silica and subsequent drying on rotavapor). The 2-hydroxyisonicotinic acid **1al** was converted to the  $-\text{CF}_3$  derivative in 43%. This starting material is not a typical phenol and can coordinate with the Ru catalyst in more than one mode, which can interfere with the main process. In the case of 3-(4-hydroxybenzoyl)-4*H*-chromen-4-one **1am**, product **2am** was obtained in 47% isolated yield. To evidence the usefulness of our mechanochemical protocol on a larger scale, we attempted a gram-scale synthesis. Compounds **2c**, **2o**, and **2z** were obtained from 10 mmol of the corresponding phenols in 81%, 85%, and 80% yields, respectively (bottom of [Scheme 2](#)).

### Reaction mechanism elucidation

As shown in [Scheme 3](#), we present the most plausible mechanism for the titled transformation. The initial arene exchange of the naphthalene by phenol in the **Cpx-0** complex is well established in the literature.<sup>54</sup> The high propensity of the naphthyl ligand to exchange (with respect to chlorobenzene or acetonitrile) was also evidenced during the optimization of the conditions ([Table S1](#)). Previous studies on the trifluoromethylation of  $\pi$ -complexes of arenes by Walton et al. show that the electron-withdrawing effect of the  $\eta^6$ -coordination of arene to the  $\text{CpRu}^+$  catalyst allows for nucleophilic substitution of the  $-\text{NO}_2$  leaving group with  $-\text{CF}_3$ .<sup>14</sup> Upon deprotonation of the Ru-coordinated phenol in **Cpx-I** (in the presence of a DABCO base), the neutral **Cpx-IIa** is formed, which exists in resonance with the  $\eta^5$ -phenoxo complex **Cpx-IIb**. Further, **Cpx-IIb** is stabilized by the interaction with the solid adsorbent,<sup>57</sup> in our case the highly oxophilic ZrN.<sup>58</sup> This material, having cationic vacancies (oxygen substitutions), under mechanical conditions may induce ligand-to-metal charge transfer (LMCT) to Ru(II), which formally reduces the metal to Ru(I) in **Cpx-IIc** and generates a phenoxyl radical ligand. Photoinduction of the Ru(II)\*-to-Ru(I) transition is described in the literature.<sup>59</sup> Furthermore, LMCT has been described and extensively studied for sandwich-type complexes.<sup>60,61</sup> In our case, the mechanical mode of activation would be the first example of incorporating mechanochemistry instead of photochemistry to induce LMCT in a sandwich-type complex. In the next step, the nucleophilic attack of the anionic form of the Ruppert-Prakash reagent on the  $\delta^+$  carbon in  $\text{C}=\text{O}$  takes place. Bond rearrangement leads to the formation of **Cpx-III**, which in turn liberates silanol  $\text{Me}_3\text{SiOH}$  upon interaction with HB. Protonation induces the electron density to fall back and return Ru(I) to the Ru(II) state. The resulting cationic  $\eta^6$ -(trifluoromethyl)arene complex **Cpx-IV** enters an aryl exchange step with phenolic starting material, liberating the product and reconstituting the active complex **Cpx-I** for another turnover. This last step was confirmed by the trial reaction with a model complex  $[\text{Cp}^*\text{Ru}(\text{PhCl})]\text{BF}_4$  having chlorobenzene, in place of the  $\text{CF}_3$  product, undergoing exchange by phenol ([Table S1](#), entry 8). In order to validate the proposed reaction mechanism, we performed the stoichiometric reaction between the Ru complex (1 equiv) and phenol **1b** (1 equiv)



**Scheme 2. Reaction scope and results of the gram-scale experiments**



**Scheme 3. Proposed plausible mechanism of the title transformation**

with 1.5 equiv of the trimethyl(trifluoromethyl)silane; in this case, the compound **2b** was isolated in 61% yield.

Density functional theory (DFT) calculations were carried out to support the postulated mechanism for the introduction of the CF<sub>3</sub> group via formal activation of the C–OH bond in the phenols. DFT study was performed to get an insight into the kinetic barriers and thermodynamics associated with the different reaction steps. We used a model where the pentamethylcyclopentadienyl Cp\* ligand (anionic, 6e<sup>−</sup>) was substituted for a less sterically demanding Cp ligand. The mechanism starts with the reaction of the naphthalene-Ru-Cp\* sandwich complex with phenol (C<sub>6</sub>H<sub>5</sub>OH), where naphthalene is replaced by phenol, forming the phenol-Ru-Cp\* (Int1) sandwich complex, which is observed at 8.10 kcal/mol, as compared to initial R. As presented in Figure 1, the reaction proceeds with the removal of a proton from the phenol, resulting in the formation of a phenoxo complex (Int2), which is further stabilized by 23.66 kcal/mol with respect to the initial R. The C–OH bond distance at Int1 is 1.36 Å, which reduces to 1.25 Å in the case of the C=O bond (Int2).

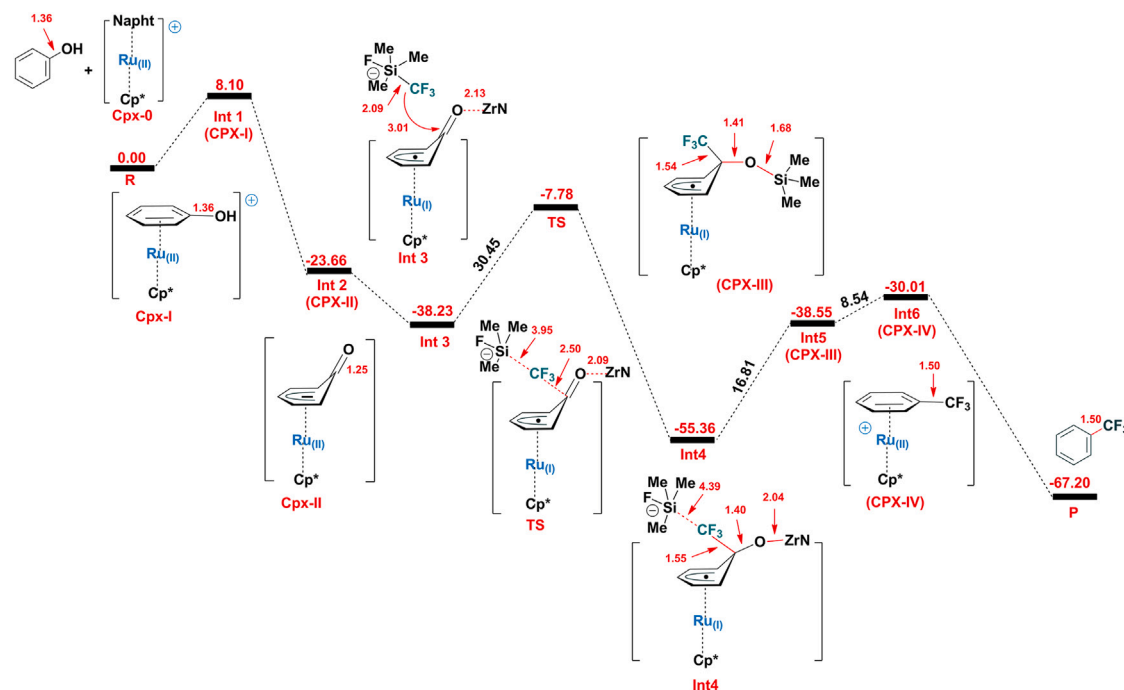
The removal of oxygen from the Int2 complex is not possible or feasible without the addition of a catalyst. Moreover, the ZrN catalyst based on low-cost Earth-abundant elements is a highly promising alternative to expensive and scarce platinum (Pt) catalysts.<sup>58</sup> Upon the addition of ZrN, the introduction of the trifluoromethyl (CF<sub>3</sub>) group

via activation to the C=O bond of the phenoxo complex occurs, yielding a transition state (TS). The Int3 is stabilized at 38.23 kcal/mol with respect to the reference point. The oxygen atom of the phenoxo ligand interacts with ZrN at an interaction distance of 2.13 Å. The CF<sub>3</sub> group is obtained by adding trimethyl(trifluoromethyl)silane fluoride (TMTSF), as shown in Figure 1. At Int3, the interaction distance between TMTSF and the Ru complex is 3.01 Å. Additionally, we performed the natural bond orbital (NBO) analysis to evaluate the mode of charge transfer while moving from Int2 to Int3. The NBO charge on Ru at Int2 is  $-0.015 e^-$ , whereas this charge at Int3 is calculated as  $-0.247 e^-$ . Therefore, NBO analysis reveals the accumulation of charge over Ru while moving from Int2 to Int3, which supports the LMCT in this mechanism.

The activation barrier for CF<sub>3</sub> transfer (TS) is 30.45 kcal/mol with respect to Int3. The CF<sub>3</sub> group interacts with the carbon atom of the radical-bearing ring with an interaction distance of 2.50 Å, whereas the Si–C bond distance is increased from 2.09 to 3.95 Å at the TS (see Figure 1). The activation barrier for the obtained TS (30.45 kcal/mol) is quite feasible to achieve under mechanochemical conditions.<sup>62</sup> Moreover, we also attempted to locate TSs in the absence of ZrN, as well as the Ru-cyclopentadienyl complex. The activation barrier in the absence of Ru-cyclopentadienyl is 33.96 kcal/mol, which is reduced to 30.45 kcal/mol upon the addition of Ru-cyclopentadienyl. Furthermore, in the absence of ZrN, no TS was located, which indicates that the addition of CF<sub>3</sub> is not possible without the ZrN additive. The product of this reaction (Int4) is stable at 55.36 kcal/mol with respect to the initial R. The negative value of the stabilization energy associated with Int4 indicates that this product is thermodynamically highly stable. The bond length of F<sub>3</sub>C–C is 1.55 Å at Int4. After Int4, the reaction is followed by the replacement of ZrN with trimethylsilane, which results in the formal reduction of the radical-bearing ring (Int5). Int5 is 38.55 kcal/mol more stable with respect to the R. Int5 is converted to Int6 by the removal of trimethylsilanol. Moreover, Int6 is thermodynamically more stable with respect to the R by 30.01 kcal/mol. The F<sub>3</sub>C–C bond length reduces from 1.55 to 1.54 Å while moving from Int5 to Int6, respectively. The final product, benzotrifluoride or trifluorotoluene in our case, is stable at 67.20 kcal/mol, as compared to that of the starting R.

The DFT mechanistic study indicates that the introduction of the CF<sub>3</sub> group via a formal activation of the C–OH bond (phenols) through the Ru catalyst takes place in a single step under mechanochemical conditions. Moreover, the conversion is not possible without the explicit presence of ZrN, which further facilitates the process. The thermodynamic and kinetic analysis of the studied steps clearly illustrates that the Ru-catalyzed conversion of phenolic OH groups to trifluoromethyl is a viable process because the activation barrier is easily accessible under mechanochemical reaction conditions.

In conclusion, we have developed a direct Ru-catalyzed transformation of phenolic -OH groups to -CF<sub>3</sub> under mechanochemical conditions. One example of a hormone derivative, bearing a 4-hydroxybenzoyl group, gave the expected product in 47% yield, confirming that our method accepts complex, fragile molecules to some extent and can be useful in late-stage modifications. The successful gram-scale experiments gave the products in excellent yields, making our protocol an important method in the preparation of trifluoromethylated intermediates. The presented transformation is yet another example of the benefits of mechanochemical processes in terms of pot, atom, and step economy and forms a basis for further investigations into solid-phase, one-pot, multistep reaction strings and applied methods in lignin treatment.



**Figure 1. Energy profile diagram for Ru-catalyzed conversion of phenolic OH groups to trifluoromethyl**

All energy values are reported in kcal/mol from isolated reactants at 0.00 kcal/mol as reference. All bond lengths are in Å.

## EXPERIMENTAL PROCEDURES

### Resource availability

#### Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Viktor O. Iaroshenko ([iva108@gmail.com](mailto:iva108@gmail.com)).

#### Materials availability

All materials generated in this study are available from the lead contact without restriction.

#### Data and code availability

The authors declare that the data supporting the findings of this study are available within the article and the [supplemental information](#). Additional requests for data or information will be fulfilled by the lead contact.

### Reaction procedure with optimized reaction conditions

The general procedure for the synthesis of trifluoromethyl arenes **2** starting from phenols **1** is as follows: in a glovebox under the constant purge of argon, a 5 mL grinding vessel (made of stainless steel) equipped with two balls (made of stainless steel, diameter: 5 mm) was loaded consecutively with the phenol starting material **1** (1 mmol, 1 equiv), catalyst Cp\*Ru(Napht)BF<sub>4</sub> (38 mg, 0.1 mmol, 0.1 equiv), CF<sub>3</sub>SiMe<sub>3</sub> (213 mg, 1.5 mmol, 1.5 equiv), CsF (46 mg, 0.3 mmol, 0.3 equiv), DABCO (135 mg, 1.2 mmol, 1.2 equiv), and ZrN (421 mg, 4 mmol, 4 equiv). The reaction vessel was properly capped. Finally, the vessel was installed on the mill and subjected to milling at 30 Hz for 90 min at 70°C. The temperature was maintained using a hot air jet from a commercially available heat gun installed a few centimeters above the vessel. The heat gun setting was calibrated beforehand to achieve the desired internal temperature of the reaction. The vessel was allowed to cool down before opening. The

content of the vessel was generously treated with distilled water, filtrated, and properly dried in vacuum. The resulting crude product was directly subjected to gradient flash chromatography on silica gel to isolate the desired product 2.

The gram-scale synthesis was performed on 10 mmol of the starting phenol 1 in 25 mL grinding vessel using three 10 mm balls.

### Computational methodology

In the current mechanistic study, all the DFT simulations were performed using the Gaussian09 package.<sup>63</sup> The structure optimizations were performed with the B3LYP functional implemented in DFT. B3LYP is an effective and computationally low-cost DFT functional frequently implemented for the quantum chemical simulations of electronic characteristics, thermodynamic stabilities, and mechanistic studies.<sup>62,64,65</sup> Furthermore, the B3LYP functional is a reliable and accurate functional in the field of catalysis.<sup>66,67</sup> GenECP methods were used for the geometry optimization of all the studied compounds, where the LanL2DZ basis set was assigned to ruthenium and zirconium (heavy atom) and the 6-31G(d,p) basis set was assigned to all other lighter atoms. Moreover, the nature of optimized geometries over the potential energy surface was confirmed through frequency analysis, i.e., the presence of one negative or imaginary frequency confirms the saddle point, whereas the absence of an imaginary frequency reveals the minima nature of reacting species. Additionally, in the case of the TS, the animation of imaginary frequency was also analyzed to confirm that the eigen vector of the TS corresponded to motion along the reaction axis.<sup>68</sup> All the energy values reported here are in kcal/mol, whereas the reported bond distances for all studied structures are presented in Å.

### SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.xcrp.2024.102062>.

### ACKNOWLEDGMENTS

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### AUTHOR CONTRIBUTIONS

Conceptualization, S.M. and V.O.I.; methodology, S.M., V.O.I., and M.J.; investigation, S.M., M.J., O.S., S.S., K.A., V.B.P., and V.O.I.; writing – original draft, M.J., V.B.P., S.M., and V.O.I.; writing – review & editing, M.J., V.B.P., S.M., and V.O.I.; funding acquisition, S.M. and V.O.I.; resources, V.O.I.; supervision, S.M. and V.O.I.

### DECLARATION OF INTERESTS

The authors declare no competing interests.

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