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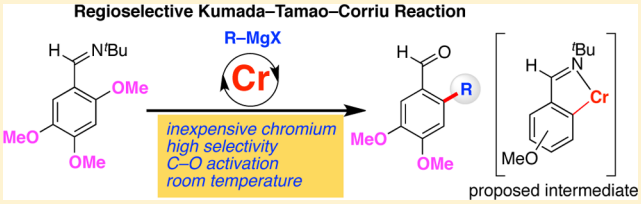
# Regio- and Chemoselective Kumada–Tamao–Corriu Reaction of Aryl Alkyl Ethers Catalyzed by Chromium Under Mild Conditions

Xuefeng Cong,[†] Huarong Tang,[†] and Xiaoming Zeng*[,†,‡]

[†]Center for Organic Chemistry, Frontier Institute of Science and Technology, Xi'an Jiaotong University, Xi'an 710054, China
[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

**ABSTRACT:** Acting as an environmentally benign synthetic tool, the cross-coupling reactions with aryl ethers via C–O bond activation have attracted broad interest. However, the functionalizations of C–O bonds are mainly limited to nickel catalysis, and selectivity has long been a prominent challenge when several C–O bonds are present in the one molecule. We report here the first chromium-catalyzed selective cross-coupling reactions of aryl ethers with Grignard reagents by the cleavage of C–O(alkyl) bonds. Diverse transformations were achieved using simple, inexpensive chromium(II) precatalyst combining imino auxiliary at room temperature. It offers a new avenue for buildup functionalized aromatic aldehydes with high efficiency and selectivity.

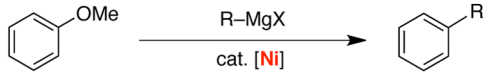



## 1. INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions are one of the most powerful tools in modern synthesis.[1] Among the numerous fundamental organic reactions, the Kumada–Tamao–Corriu reaction has emerged as a useful strategy for the formation of carbon–carbon bonds via the cross-coupling of an electrophile with a Grignard nucleophile.[2] Since a pioneering work by Wenkert at the end of the 1970s,[3] the coupling reactions with aryl ethers by the cleavage of C–O bonds have appeared as an ecological and atom-efficient method to create functionalized aromatic motifs, which has attracted broad interest because of the naturally abundant and nontoxic nature of phenol derivatives compared with their halide counterparts.[4−9] Despite several elegant examples described by Dankwardt,[10] Chatani,[11−17] and others[18−29] (Scheme 1a), the direct functionalization of aromatic ethers by the activation of C–O(alkyl) bonds remains a significant challenge and has been mainly limited to nickel catalysis. In particular, the cross-coupling reactions often suffer from a prominent selectivity obstacle when several C–O(alkyl) bonds coexist in the same molecule.[4,10] Noteworthy that multiple C–O bonds are frequently found in the motifs of drugs and biologically active molecules such as Uroxatral, cytotoxic dihydrochalcone, anticancer agent (**B**), and antitumor reagent (**C**) (Figure 1).[30] Kakiuchi[31,32] and Snieckus[33] disclosed that the selectivity issue can be circumvented by introducing an auxiliary into the scaffolds of aryl ethers to assist the transition metal in the activation of *ortho*-C–OMe bonds (Scheme 1b). Although considerable progress has been made, the expensive $RuH_2(CO)(PPh_3)_3$ catalyst is essential for ensuring the reaction will proceed effectively under harsh conditions. Alternative platforms with nonprecious, earth-abundant metals may provide the opportunity for developing a cost-effective, mild protocol to improve current methods. Considering that various organometallic nucleophiles such as B, Zn, and Sn reagents are prepared from the related Grignard reagents, using Grignard as a nucleophilic partner in the cross-coupling reactions would offer a direct route to form C–C bonds, despite its high sensitivity toward some functional groups. In fact, noncatalytic *ortho*-alkoxy group substitution by Grignard reagents on aromatic ketones or esters was described for the preparation of the relevant functionalized products.[34]

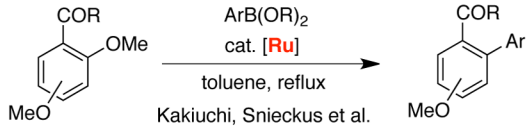
**Scheme 1. Cross-Coupling Reactions of Aryl Ethers**

(a) Kumada–Tamao–Corriu reaction of aryl methyl ethers

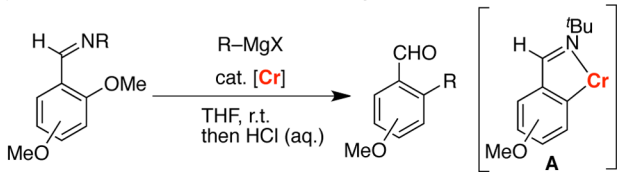



*suffering from a regioselectivity obstacle when several C–O bonds are present in the same molecule*

(b) Addressing the selectivity challenge:




(c) this work: cost-effective chromium catalysis under mild conditions

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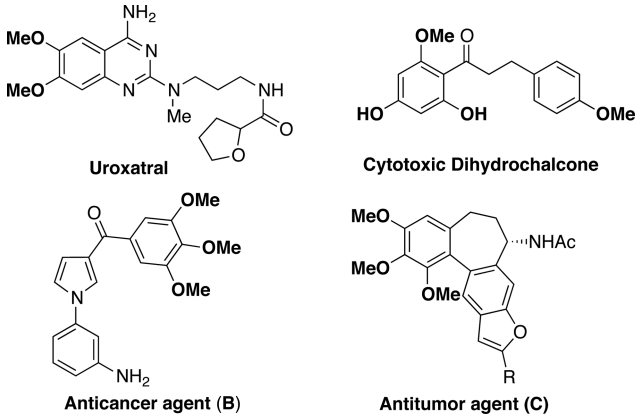



**Figure 1.** Illustration of exemplified drug and bioactive molecules containing multiple C−O bonds.

In recent years, the use of first-row transition metals such as nickel, iron, and cobalt as low-cost alternatives to precious-metal catalysts in cross-coupling reactions has received immense attention.[1,35,36] By contrast, the catalytic capability of the group 6 metal chromium in cross-coupling reactions has rarely been investigated,[37−46] with the exception of chromium-promoted polymerization.[47] In particular, the unique oxophilicity of chromium may endow it with a new opportunity in the cleavage of inert C−O(alkyl) bonds.[48,49] In this article, we demonstrate the first chromium-catalyzed cross-coupling reactions of aryl ethers with Grignard reagents by cleaving inert C−O(alkyl) bonds under mild conditions (Scheme 1c). The simple and inexpensive chromium(II) chloride serving as the precatalyst accompanied by an imino auxiliary to promote the diverse functionalization of C−O(alkyl) bonds can achieve high regio- and chemoselectivity. The methodology provides an alternative avenue to regiospecific installation of fundamental aryl and alkyl fragments at the scaffolds of aromatic aldehydes via the transformation of C−O bonds.

## 2. RESULTS AND DISCUSSION

To achieve the selective functionalization of unreactive aryl ethers with chromium under ambient conditions, we postulated that a highly active low-valent species might be required because of its unique ability to insert into unactivated chemical bonds via the formation of intermediate **A** (Scheme 1c).[50,51] Thus, inexpensive chromium(II) chloride was chosen as the precatalyst for studying the auxiliary effects on the cross-coupling of phenyl methyl ethers with phenylmagnesium bromide. The latter may play an additional role as a reductive reagent to react with chromium(II) in producing low-valent active species.[52] As shown in Figure 2, common directing auxiliaries such as 8-aminoquinolinyl, carbonyl, amidyl, and pyridyl are inefficient in assisting chromium to activate C−O bonds. The phenyl-substituted imino scaffold shows good performance in helping chromium to cleave the C−O bond, leading to the coupling product **3a** in a 25% yield. Replacing the phenyl group with 4-methoxyphenyl and benzyl remarkably increases the reaction rate, but forms a large amount of diarylated compounds. To our delight, using the electron-rich and bulky *tert*-butyl group suppresses the coupling reaction of the C−H bond without losing efficiency in functionalization of the C−O bond, producing **3a** in 96% yield. However, substrates containing a 2,6-diisopropylphenyl and 2-methoxyphenyl group on the imino scaffold only give trace amounts of **3a**. Note that

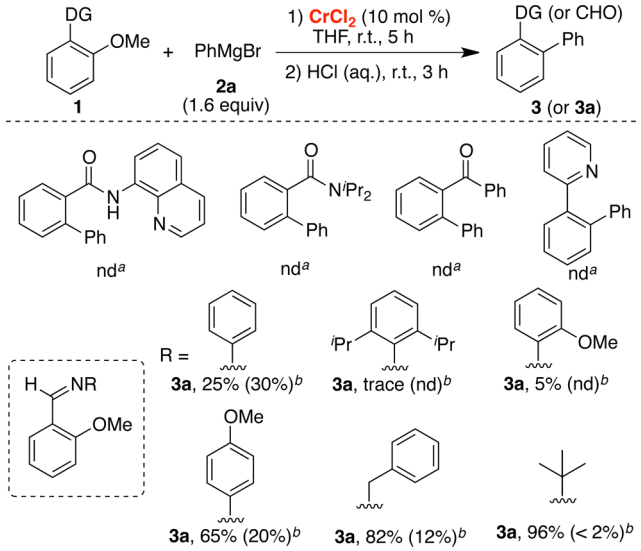
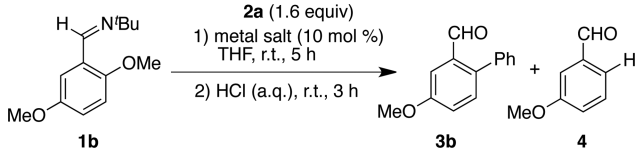



**Figure 2.** Evaluation of the auxiliary effect on the cross-coupling reactions of C−OMe bonds. Conditions: **1** (0.25 mmol), PhMgBr (0.4 mmol), $CrCl_2$ (0.025 mmol, 99.99% purity), THF (0.25 M), 25 °C, 5 h; then quenched with HCl/$H_2O$ (3 M), 25 °C, 3 h. Isolated yields of the coupling products are given. (*a*) Not detected. (*b*) Yield of the diarylated product in parentheses that was formed via a consecutive functionalization of *ortho*-C−O and C−H bonds.

these reactions furnish diphenyl as a byproduct in <5% yields, indicating that a two-electron reduction from $L_nCrPh_2$ could be considered for the formation of a low-valent chromium species in situ.[52]

It was revealed that the reaction did not proceed in the absence of chromium(II) chloride (Table 1, entry 1). This result suggests that a nucleophilic aromatic substitution with Grignard reagent involving a Meyers-type reaction mechanism can be excluded in the transformation.[53] $CrCl_3$ displays high reactivity in the promotion of the C−O bond-activation/cross-coupling reaction (entry 3). In contrast, a low performance was observed when using $Cr(acac)_3$, indicating an important

**Table 1. Effect of First-Row Transition-Metal Salts on the Selective Kumada−Tamao−Corriu Reaction of Aryl Ether[a,b]**




| entry | metal salt | yield (%) 3b | 4 |
|---|---|---|---|
| 1 | none | nd[c] | nd[c] |
| 2 | **$CrCl_2$** | 91 | nd[c] |
| 3 | **$CrCl_3$** | 90 | <5[d] |
| 4 | $Cr(acac)_3$ | <3[d] | nd[c] |
| 5 | $CoCl_2$ | 5 | nd[c] |
| 6 | $FeCl_2$ | nd[c] | nd[c] |
| 7 | $Ni(COD)_2$ | nd[c] | 10 |
| 8 | $NiCl_2(PPh_3)_2$ | nd[c] | <5[d] |

[a]Reactions were conducted on a 0.25 mmol scale. [b]Isolated yield. [c]Not detected. [d]Estimated by GC analysis. The purities of metal salts: $CrCl_2$ (99.99%), $CrCl_3$ (99.99%), $Cr(acac)_3$ (97%), $CoCl_2$ (99.9%), and $FeCl_2$ (98%).



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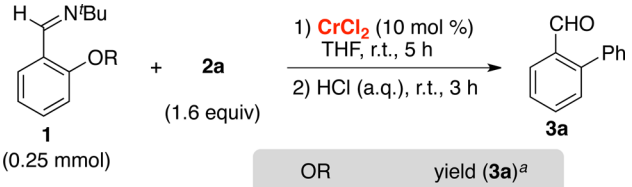
chloride anion effect of the chromium precatalyst on the generation of the catalytically active species in situ (entry 4). Other first-row transition metals, such as $FeCl_2$ and $CoCl_2$, are inefficient for the conversion (entries 5 and 6). Meanwhile, the employment of nickel complexes of $Ni(COD)_2$ and $NiCl_2(PPh_3)_2$ results in an unexpected compound **4** via the hydrodeoxygenation reaction of C−O bond (entries 7 and 8).[54] In addition to methoxy, ethoxy, phenoxy, and tosylate are also suitable leaving groups, although slightly inferior results were obtained in these cases (Scheme 2).

**Scheme 2. Influence of OR Leaving Groups on the Selective Kumada−Tamao−Corriu Reaction of Aryl Ether**



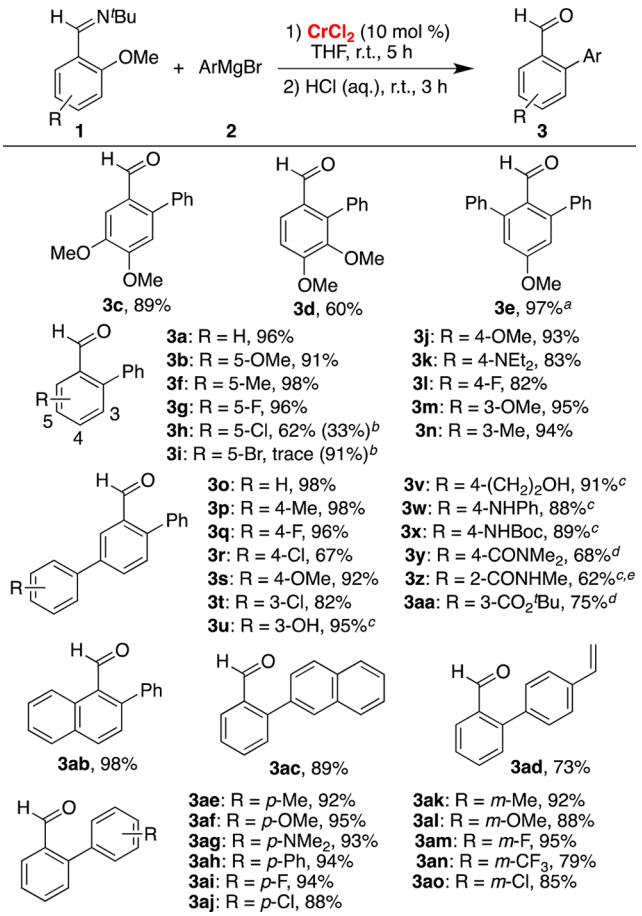

| OR | yield (**3a**)[a] |
|---|---|
| OMe | 96% |
| OEt | 91% |
| OPh | 92% |
| OTs | 75% |
| OBn | 16% |

[a] Isolated yield.

With the optimized reaction conditions in hand, the substrate scope of the chromium-catalyzed arylation of aryl methyl ethers was probed next (Scheme 3). We were pleased to find that the cross-coupling reactions proceed in high regio- and chemoselectivity. Only the *ortho*-C−OMe bonds adjacent to the imino scaffold are efficiently functionalized to produce C−C bonds, while other C−OMe bonds on the aromatic rings remained intact (**3c**−**3e**). Of these, the reaction with 2,4,6-trimethoxyl-substituted aldimine results in a synchronous transformation of two *ortho*-C−OMe bonds, forming the terphenyl-containing carbaldehyde **3e** in a 97% yield. Both the electron-rich and electron-deficient aromatic ethers undergo the conversion smoothly, affording *ortho*-arylated aromatic aldehydes in good to excellent yields (60−98%). A diverse range of functional groups, such as methoxy, fluoride, chloride, trifluoromethyl, amino, and alkenyl, are well tolerated by the reaction system. However, the conversion was completely shut down with bromide-containing aromatic ethers (**3i**). This may be attributed to a preferential oxidative addition of the C−Br bond over the inert C−OMe bond, resulting in a high-valent chromium species that lacks catalytic activity toward activation of the C−O bond. Notably, the cross-coupling is not sensitive to the steric hindrance around the *ortho*-C−O scaffold, and 6-methoxy or methyl-containing biphenyl-2-carbaldehyde (**3m** and **3n**) can be easily prepared by this protocol. Furthermore, the methodology allows access to functionalized *p*-terphenyl structural motifs from 4-phenyl-substituted aromatic ethers. Synthetically appealing structural motifs including hydroxyl, amino, amide, and ester groups can be well retained in the coupling reaction (**3u**−**3aa**). In addition, variation of substituents on the aromatic Grignard reagents has no obvious influence on the conversion of C−OMe bonds (**3ac**−**3ao**).

The success of the cross-coupling reactions of C−OMe bonds with aromatic nucleophiles stimulated us to explore the

**Scheme 3. Chromium-Catalyzed Selective Cross-Coupling of Aryl Methyl Ethers with Aromatic Grignard Reagents**




Reaction conditions: **1** (0.25 mmol), **2** (0.4 mmol), $CrCl_2$ (0.025 mmol), rt, 5 h; and then quenched with HCl (aq), 3 h. Isolated yields were given. [a]PhMgBr (0.8 mmol) was employed. [b]Recovery of the starting aromatic aldehyde containing *ortho*-C−OMe bond. [c]PhMgBr (0.75 mmol) was employed. [d]12 h. [e]24 h.

alkylation of aryl methyl ethers. Gratifyingly, by treating naphthyl ether with methylmagnesium chloride, the cross-coupling proceeds effectively under the same catalytic conditions, producing the methylated compound **6a** in a 96% yield (Scheme 4). Variation of the counterion of the alkyl Grignard reagents to bromide did not affect the transformation. Other primary alkyl partners, including ethyl-, heptyl-, and benzyl-substituted Grignard reagents, allow for direct couplings with C−OMe bonds, leading to the desired products **6b**−**6d** in preparatively useful yields. In addition, secondary Grignard reagents are suitable nucleophilic partners for alkylation (**6e**−**6g**), although a mixture of primary and secondary coupling products was obtained when using isopropylmagnesium chloride. Because of the great steric hindrance, the cross-coupling with tertiary alkyl partners has long been a formidable challenge in the organic community.[55,56] Importantly, the bulky *tert*-butyl group can be incorporated into the *ortho* position of 1-naphthaldehyde (**6h**) in our case, concomitantly forming a regioisomeric compound (**6h′**).

Different from the functionalization of acyclic C−O bonds, the cross-coupling reaction by cleavage of a *cyclo*-C−O bond allows for keeping a synthetically useful hydroxyl-tethered chain in the scaffold of the final products, thus offering an improved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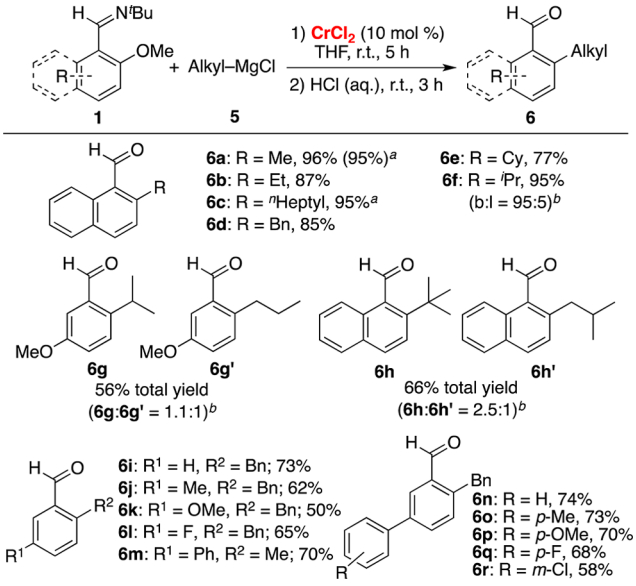
**Scheme 4. Regioselective Alkylation of Aryl Methyl Ethers**




Reaction conditions: **1** (0.25 mmol), **5** (0.5 mmol), $CrCl_2$ (0.025 mmol), rt, 5 h; and then quenched with HCl (aq), 3 h. Isolated yields were given. [a]RMgBr(0.5 mmol) was employed. [b]The regioisomeric ratio was determined by $^1H$ NMR analysis.

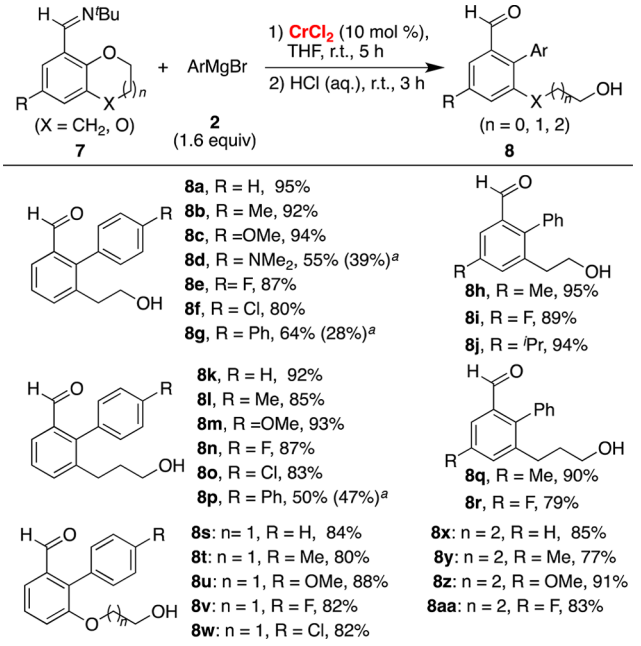
atom efficiency during the buildup of structurally diversified molecules without wasting the alkoxyl groups.[57] However, methods for the functionalization of 1-oxygen-containing benzoheterocycles by the activation of *cyclo*-C−O bonds are scarce. Strikingly, the chromium-catalyzed protocol shows high efficiency in the ring-opening/cross-coupling of 2,3-dihydrobenzofuran by the assistance of the imino group, giving rise to hydroxyl-tethered diphenyl carbaldehyde (**8a**) in a 95% yield (Scheme 5). The coupling reactions with a wide range of substituted phenyl Grignard reagents occur smoothly under standard conditions (**8b**−**8g**). Moreover, variation of substituents on the motifs of benzocycles did not influence the conversion (**8h**−**8j**). Starting from 8-amino-bearing chromans, 3-hydroxypropyl-tethered aromatic aldehydes **8k**−**8r** can be facilely accessed by this protocol. Starting from 2,3-dihydrobenzo[*b*][1,4]dioxine, only the *ortho-cyclo*-C−O bond adjacent to the imino group was cleaved to give 2-hydroxyethoxy-tethered products **8s**−**8w**.

Of particular interest is that the double ring-opening/cross-coupling reactions with bis(2,3-dihydrobenzofuran) and bis(chroman) take place smoothly in our protocol, allowing rapid access to complex dihydroxyl-tethered dicarbaldehydes **10a** and **10b** via cleavage of two *ortho-cyclo*-C−O bonds (Scheme 6a). In addition, the two *para*-C−OMe bonds on the aromatic ring could also couple with the phenyl Grignard reagent to form terphenyl-bearing dicarbaldehyde **12**, providing an alternative avenue to prepare blue organic light-emitting diode material molecule (Scheme 6b).[58]

The cross-coupling reaction of aryl ether can be performed on a gram scale without detrition to its efficiency (eq1). Further functionalization of the resulting coupling product was successful by an intramolecular oxidative coupling, leading to biologically interesting 9*H*-fluoren-9-one derivative **13**.[59]

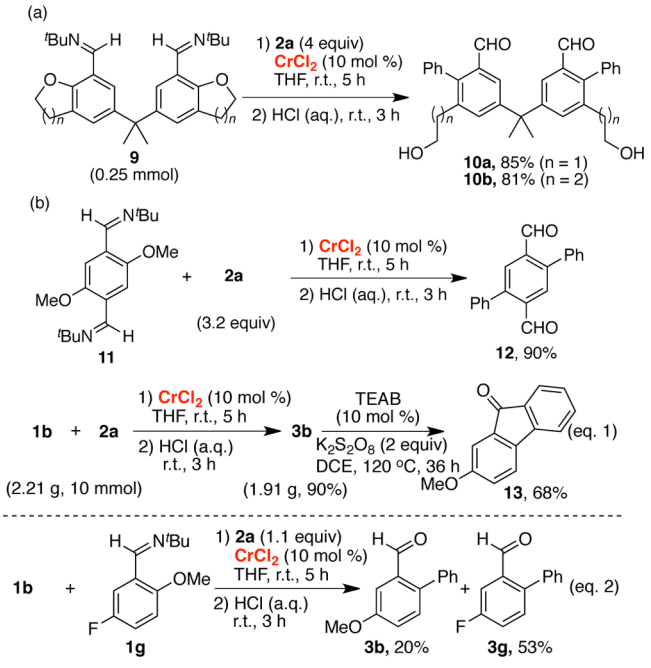
To understand the role of Grignard reagents in the reactions besides being a coupling partner, we performed a control experiment by replacing organozinc reagents that were

**Scheme 5. Ring-Opening/Cross-Coupling Reaction via the Activation of *cyclo*-C−O Bonds**




Reaction conditions: **7** (0.25 mmol), **2** (0.5 mmol), $CrCl_2$ (0.025 mmol), rt, 5 h; and then quenched with HCl (aq), 3 h. Isolated yields were given. [a]Recovery of the starting aromatic aldehyde containing cyclic *ortho*-C−O(alkyl) bond.

**Scheme 6. Dual C−O Bond Activation**




generated in situ from the reaction of $ZnCl_2$·TMEDA with PhMgBr (see Supporting Information for details).[60] Noteworthy is that the cross-coupling reaction of the *ortho*-C−OMe bond with the organozinc did not proceed, whereas the addition of TMEDA to the reaction system has no influence on the coupling of the C−O bond with the phenyl Grignard reagent. These results show that organomagnesium plays a



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particularly important role in the promotion of the coupling reactions.

In order to further gain insight into the nature of the catalytically active chromium species, stoichiometric reactions by treating $CrCl_2$ with different amount of phenyl Grignard reagent were conducted. Note that biphenyl was isolated in 90% yield by using 2 equiv of PhMgBr (see Supporting Information). However, the use of excess Grignard reagent (3 or 4 equiv) cannot obviously increase the yield of the homocoupling product. These results indicate that a two-electron reduction can be considered with the formation of an active low-valent chromium species, which may be responsible for the coupling reaction of C−O bond with Grignard reagent,[52] whereas the replacement of Grignard by $Ph_2Zn$ led to low conversions of biphenyl, evidencing a less reducing of organozinc as compared to organomagnesium. Furthermore, the competitive experiment showed that the cross-coupling reaction of C−OMe bonds was strongly affected by the electronic properties of the aromatic ethers, supporting an electron-deficient aryl-favored transformation (eq2).

## 3. CONCLUSIONS

In conclusion, an unprecedented chromium-catalyzed regio- and chemoselective functionalization of aromatic ethers by the cleavage of unactivated C−O(alkyl) bonds is developed. Diverse transformations of C−O(alkyl) bonds, including arylation, alkylation and ring-opening/cross-coupling reactions, were achieved with a simple and inexpensive chromium(II) chloride as the precatalyst combining with a Grignard reagent. For the first time, the unique ability of activating C−O(alkyl) bonds with chromium is demonstrated with the assistance of amino groups, which offers a highly selective protocol to install fundamental aryl and alkyl scaffolds at the *ortho* position of aromatic aldehydes via the transformation of C−O(alkyl) bonds. Despite the indispensable imino auxiliary for achieving these reactions with high efficiency and selectivity, the method allows for the retention of a synthetically useful aldehyde scaffold in the products, granting an entry for late-stage functionalization. Further mechanistic studies by the isolation and characterization of active intermediates are undergoing.

## 4. EXPERIMENTAL SECTION

**General Procedure for the Chromium-Catalyzed Kumada−Tamao−Corriu Reaction of Aryl Methyl Ethers.** A dried Schlenk tube was charged with an *ortho*-methoxy-containing aromatic aldimine **1** (0.25 mmol) and $CrCl_2$ (3 mg, 0.025 mmol), followed by adding freshly distilled THF (0.5−0.6 mL) by syringe under a nitrogen atmosphere. After stirring at room temperature for 5 min, Grignard reagent (0.4−0.5 mL, 0.8−1.0 M in THF, 0.40 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 5 h. After quenching with 3 M HCl (1 mL), the resulting mixture was stirred at room temperature for another 3 h and then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$ and concentrated under vacuum. The residue was purified using flash chromatography on silica gel (gradient eluent of EtOAc in petroleum ether) to give the desired product.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08621.

Experimental procedures and characterization data for all products, including $^1H$ and $^{13}C$ NMR spectra (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*zengxiaoming@mail.xjtu.edu.cn


### Notes

The authors declare no competing financial interest.

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