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ARTICLE

Ruthenium(0)-Catalyzed Cross-Coupling of Aryl Methyl Ethers with Organoboranes by Selective C–O Cleavage

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The activation of C–O bonds in aryl methyl ethers is a fundamental method for cross-coupling of carbon–oxygen bonds, however, this process is highly challenging due to the high dissociation energy compared with other phenol derivatives. Herein, we report a mild Ru(0)-catalyzed cleavage of C(aryl)–O bonds enabled by a combination of $Ru_3(CO)_{12}$ catalyst and imine auxiliary. The method offers rapid entry to synthetically valuable biaryl aldehydes from abundant anisoles. Broad functional group tolerance is observed using this strategy, including unprecedented tolerance towards aryl bromides. The synthetic utility has been demonstrated in sequential processes to construct complex biaryls, exploiting the orthogonal selectivity of C–O bond activation. DFT studies were conducted to provide insight into the selectivity of C–O bond cleavage. The method establishes the mildest approach to C–OMe cross-coupling reported to date.

Introduction

The direct cross-coupling of C–O bonds in aryl methyl ethers is an important process in organic synthesis.[1] In contrast to the cross-coupling technologies utilizing aryl halides,[2] the development of methods for C–O bond activation has been recognized as a powerful tool due to the orthogonal nature of C–O bonds,[3] greater availability of common phenols than aryl halides, and more sustainable profile due to the avoidance of toxic halide by-products (Figure 1A).[4]

Traditional methods for activating C–O bonds have historically utilized sulfonates.[5] Recently, progress has been achieved using more stable sulfamate,[6] carbonate[7] and carbamate derivatives.[8] However, among the activating groups for phenols, aryl methyl ethers are by far the most inert and generate the least waste in the reaction.[9] Furthermore, neutral C–OMe bonds in anisoles represent one of the most prevalent motifs in organic synthesis.[1d] The activation of C–OMe bonds under mild conditions is highly challenging due to the high dissociation energy compared with activated phenol derivatives (101 kcal/mol, Ph–OMe).[10] While significant progress has been achieved using Ni catalysis,[1b,11] the development of chemoselective C–OMe bond activation methods using less nucleophilic catalysts has remained elusive.[12]

In principle, highly nucleophilic metals are required for direct oxidative addition of the C–OMe bond to transition-metals.[1,13] However, in these cases high nucleophilicity results in low functional group tolerance. Likewise, few studies have been reported on the kinetic and thermodynamic selectivity of C–OMe bond activation vs. other inert bonds.[14]

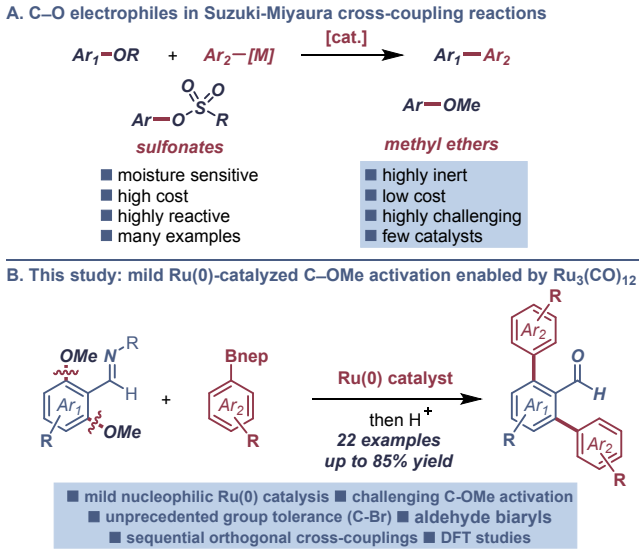

Figure 1. A) C–O electrophiles in Suzuki-Miyaura cross-coupling; B) This study: mild Ru(0)-catalyzed C–OMe activation enabled by $Ru_3(CO)_{12}$.

Herein, we report a mild Ru(0)-catalyzed cleavage of C(aryl)–O bonds enabled by a combination of $Ru_3(CO)_{12}$ catalyst and imine auxiliary (Figure 1B). Our laboratory has been interested in ruthenium catalysis as a versatile platform for activation of inert bonds.[15] We identified a system based on mildly nucleophilic $Ru_3(CO)_{12}$ that enables activation of C–OMe bonds. Notable features of our study include: (1) exceedingly mild conditions for C–OMe activation with unprecedented functional group tolerance, including aryl bromides; (2) rapid entry to

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synthetically valuable biaryl aldehydes from abundant anisoles by exploiting orthogonal C–O bond activation; (3) DFT studies providing insight into the selectivity of C–O bond activation. It is important to note that the final di-*ortho*-substituted biaryl products are widely utilized in medicinal chemistry research and the synthesis of OLED materials.[2c]

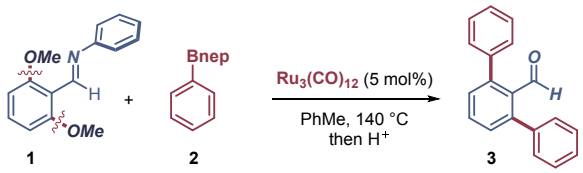
Results and discussion

Selected optimization results are presented in Table 1. We selected cross-coupling of *N*-imine of 2,6-dimethoxybenzaldehyde (**1a**) with neopentyl phenyl boronate (**2a**) as a model system. We proposed that an approach using readily removable imine auxiliary in combination with very selective ruthenium carbonyl $Ru_3(CO)_{12}$ catalyst could provide a mild and functional group tolerant strategy for C–OMe activation. Ruthenium(0) chelation to a readily modifiable imine directing group forms thermodynamically stable chelates facilitating C–OMe activation. The cross-coupling produces biaryl aldehydes that are readily amenable for synthetic manipulation.

After extensive optimization, best results were obtained using *N*-Ph imine and Ph–Bnep as nucleophile in toluene at 140 °C providing the diarylation product in 73% yield (Table 1, entry 1, 95:5 selectivity). It is noteworthy that the product was obtained with 1:2 diarylation selectivity, indicating that C–OMe activation is faster than catalyst de-coordination (*vide infra*). Importantly, screening of other Ru and Rh catalysts, including [Ru–H] catalysts that are inherently prone for coordination to carbonyl groups and significantly less chemoselective resulted in product formation (Table 1, entries 2-5). Furthermore, evaluation of different imine directing groups revealed that *N*-Ph imine is the preferred auxiliary (Table 1, entries 6-8). Importantly, in these cases the product was obtained with >10:1 di:mono arylation selectivity. Moreover, screening of different solvents indicated that toluene is the preferred solvent, however, dioxane can be used for less soluble substrates with similar efficiency (Table 1, entries 9-12). Furthermore, we established that neopentyl aryl boronate is the preferred nucleophile, while pinacol aryl boronate is less efficient and other nucleophiles are ineffective (Table 1, entries 12-15). Finally, experiments at lower temperature indicated that 140 °C (Table 1, entry 16) and excess of aryl boronate (Table 1, entry 17) are required for the cross-coupling. Importantly, in these cases the product was obtained with 5:1 and 4:1 di:mono arylation selectivity, respectively, indicating that C–OMe activation is thermodynamically preferred under these conditions (*vide infra*). Further, it should be noted that $Ru(CO)_2(PPh_3)_3$ is not an effective catalyst. In general, phosphine containing Ru(0) and Ru(II) catalysts are not suitable for this bond activation. It is also interesting to note that PhB-nep is more effective than PhB-pin. We think that PhB-nep facilitates transmetallation step.

With the optimized conditions in hand, the scope of this C–OMe activation was next investigated (Scheme 1). As shown, a range of functionalized aryl neopentyl boronates can serve as viable coupling partners under our conditions. This cross-coupling is uniformly compatible with electronically-diverse nucleophiles, including electron-neutral (**3a**), electron-rich (**3b–3d**), conjugated (**3e**) and electron-deficient nucleophiles (**3f–3k**). Notably, the reaction is fully regioselective for the cross-coupling of the C–OMe electrophilic group adjacent to the directing auxiliary (**3b**). This positional selectivity represents a clear advantage of the approach and is not feasible with more nucleophilic metals, such as Ni. Furthermore, the functional

Table 1. Optimization of Reaction Conditions[a]



1 2 3

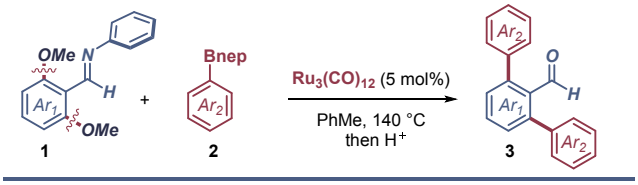
entry	variation from the standard conditions	yield[b] (%)
1	no change	73
2	$RuH_2(CO)(PPh_3)_3$	<2
3	$RuH_2(PPh_3)_4$	<2
4	$RhCl(PPh_3)_3$	<2
5	$[Rh(cod)Cl]_2$	<2
6	*N*-Me instead of *N*-Ph	64
7	*N*-*t*-Bu instead of *N*-Ph	50
8	*N*-2,6-Me_2-C_6H_3 instead of *N*-Ph	25
9	dioxane instead of toluene	64
10	acetone instead of toluene	18
11	pinacolone instead of toluene	21
12	*i*-PrOH instead of toluene	<2
13	Ph-Bpin instead of Ph-Bnep	19
14	Ph-$B(OH)_2$ instead of Ph-Bnep	<2
15	Ph-$Si(OMe)_4$ instead of Ph-Bnep	<2
16	120 °C instead of 140 °C	28
17	Ph-Bnep 1.0 equiv instead of 2.5 equiv	21

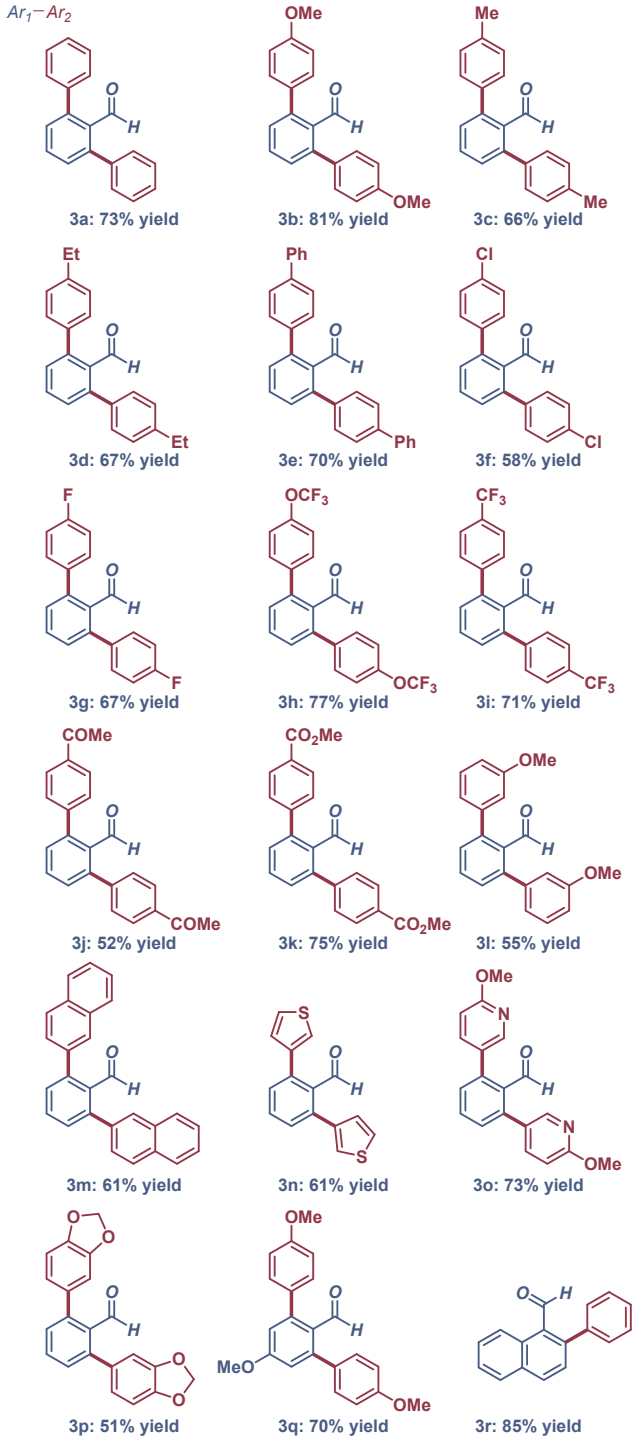
[a]Conditions: imine (1.0 equiv), PhBnep (2.5 equiv), catalyst (5 mol%), toluene (1.0 M), 140 °C. [b]Determined by ^{1}H NMR and GC. Bnep = 5,5-dimethyl-1,3,2-dioxaborolane. See SI for details.

group tolerance towards electrophilic handles (**3f**) and carbonyl groups (**3j–3k**) provides a valuable advantage over other systems. It is noteworthy that the method provides access to fluorine containing biaryls featuring aldehyde handle for functionalization (**3g–3i**) that are very common in medicinal chemistry and materials science. Meta-substitution is well-tolerated (**3l**), providing yet another example of positional selectivity of C–OMe activation. Furthermore, polyaromatic (**3m**) as well as heterocyclic boronates, such as thienyl, pyridyl and benzo[*d*][1,3]dioxole (**3n–3p**) are compatible with high levels of efficiency. Note that these heterobiaryls represent privileged motifs in medicinal chemistry.

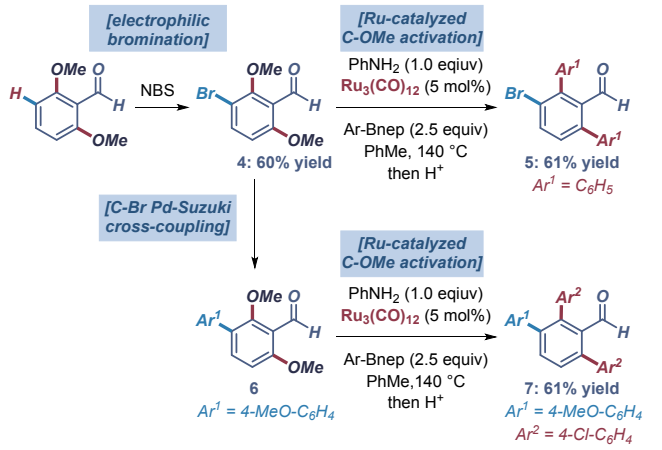
Finally, the method is also compatible with more electron-rich trimethoxybenzaldehyde (**3q**) (*vide infra*) with exclusive selectivity for the ortho-positions, while the cross-coupling of 1-Np-2-MeO-electrophile provided the product in 85% yield, demonstrating mono-arylation selectivity. At present stage, heterocycles are not suitable as C–OMe activation substrates.

The special advantage of this mild Ru(0)-catalyzed C–OMe activation is compatibility with sensitive functional groups that can be installed through orthogonal properties of aryl methyl ethers and exploited in sequential cross-couplings (Scheme 2).

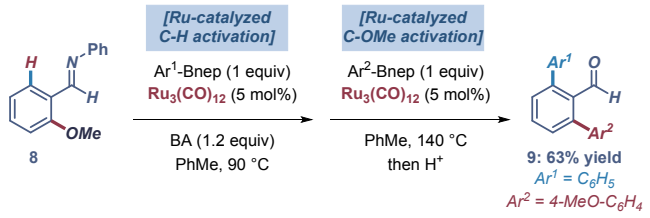




Scheme 1. Ru(0)-Catalyzed C–OMe Activation. Conditions: imine (1.0 equiv), PhBnep (2.5 equiv), catalyst (5 mol%), PhMe (1.0 M), 140 °C, 10 h. Isolated after hydrolysis. See SI for details.



Scheme 2. Sequential Electrophilic Bromination/Pd-Catalyzed Suzuki Cross-Coupling/Ru(0)-Catalyzed C–OMe Activation.



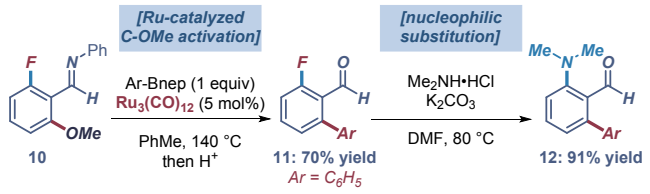
Scheme 3. Sequential Ru(0)-Catalyzed C–H/C–OMe Activation.

As such, electrophilic bromination of 2,6-dimethoxybenzaldehyde regioselectively furnishes bromo aldehyde (**4**) through the directing effect of the methoxy groups. Remarkably, the Ru(0) C–OMe proceeds in the presence of the aryl bromide to give the diarylated bromo aldehyde (**5**), featuring two functional handles for further derivatization. *To our knowledge, this is the first example of selective C–OMe activation in the presence of aryl bromide.* Furthermore, the intermediate bromo aldehyde (**4**) could be cross-coupled under the standard Suzuki conditions in the presence of aryl methyl ethers to afford biaryl (**6**). This product undergoes C–OMe activation under our standard conditions to afford tetraphenyl (**7**) with a formyl functional handle. These orthogonal activation scenarios provide a clear benefit for implementation in further derivatization strategies by integrated electrophilic functionalization/C–OMe cleavage.

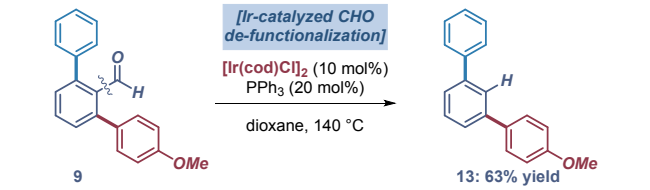
Intrigued by the unprecedented chemoselectivity of C–OMe activation process, we conducted comparative studies to test the facility of C–H vs. C–OMe activation under Ru(0) catalysis (Scheme 3). Importantly, we found that the C–H activation could take place fully chemoselectively in the presence of the C–OMe bond using BA (BA = benzylideneacetone) as a mild Ru–H acceptor. Critically, this process allows to use the same Ru(0) catalyst for sequential C–H/C–OMe activation-cross-coupling to furnish differentiated terphenyls. This Ru(0)-catalyzed C–H/C–OMe functionalization represents an exciting finding for the

future usage of C–OMe activation techniques that is not easily accessible by other methods.

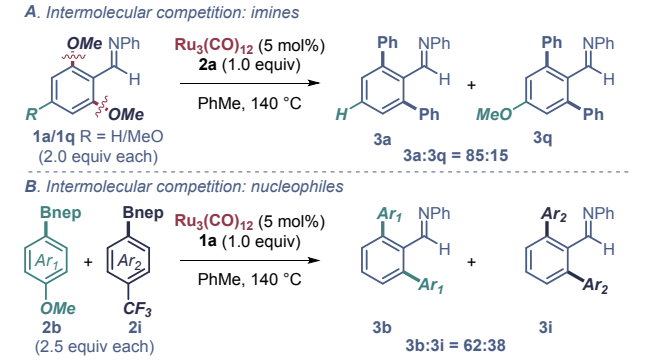
Moreover, we were interested to test the facility of C–OMe vs. C–F activation under Ru(0) catalysis (Scheme 4). Interestingly, we found that C–OMe activation takes place fully chemoselectively in the presence of an ortho-C–F bond also poised for oxidative addition to Ru(0). The product (**11**) contains a fluoro-biaryl aldehyde functional handle that can be utilized in S_NAr functionalization to furnish amino-biaryl aldehyde (**12**). Overall, these transformations demonstrate orthogonal



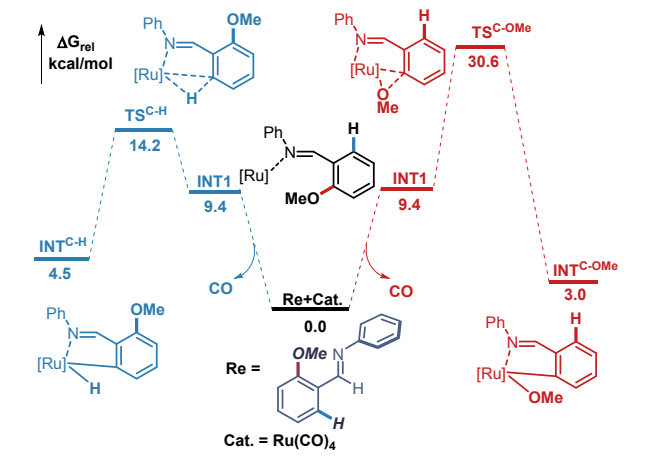
Scheme 4. Sequential Ru(0)-Catalyzed C–OMe Activation/Nucleophilic Aromatic Substitution.



Scheme 5. Ir-Catalyzed CHO Defunctionalization.



Scheme 6. Mechanistic Studies.



Scheme 7. Free Energy Profiles for the Selectivity of C–H and C–OMe Activation.

properties of the functional groups enabled by mild Ru(0) catalysis that underpin a wide range of chemical processes.

A special characteristic of this catalyst system is the ability to promote C–H, C–F and C–OMe activation with differential activity. Specifically, C–H activation requires hydrogen acceptor, while C–F activation gives the optimum results in the presence of a carbonate base. This allows for selectivity between C–F/C–OMe and C–H/C–OMe activations. In general, the order of reactivity is as follows: C–H > C–OMe > C–F.

Furthermore, the aldehyde functional handle can be successfully accommodated in transition-metal-catalyzed de-functionalization to furnish differentiated meta-terphenyls (Scheme 5).[16] Meta-terphenyls, such as (**13**), have found a broad range of applications in organometallic chemistry and biochemistry due to well-defined pocket created by the flanking aromatic rings.[17]

To gain preliminary insight into the reaction selectivity, we conducted intermolecular competition experiments (Scheme 6). Competitions between differently substituted electrophiles (Scheme 6A) showed that less electron-rich substrates are inherently more reactive (**3a**:**3q** = 85:15). Furthermore, competition experiments with electronically-diverse nucleophiles (Scheme 6B) showed that electron-rich boronates are inherently more reactive (**3b**:**3i**, 62:38). These results are consistent with C–OMe oxidative addition to Ru(0) and transmetallation as kinetically relevant steps in the mechanism (*vide infra*).

Intrigued by the features of this Ru(0)-catalyzed C–OMe functionalized, we conducted DFT studies to gain insight into the C–OMe selectivity of this process (Scheme 7). The calculation results show that the activation energy of C-H activation (**TS^{C-H}**) is 14.2 kcal/mol lower than 30.6 kcal/mol of C-OMe activation (**TS^{C-OMe}**). These calculated results are in agreement with the experiments.

Conclusions

In conclusion, we have reported mild Ru(0)-catalyzed cleavage of C(aryl)–O bonds in aryl methyl ethers. This reaction has been enabled by a combination of highly selective $Ru_3(CO)_{12}$ catalyst and imine auxiliary to thermodynamically facilitate C–OMe cleavage. The reaction furnished synthetically important biaryl aldehydes and proceeds with excellent functional group tolerance that is not available by other methods for C–OMe activation. The utility has been demonstrated in orthogonal sequential cross-couplings utilizing C–OMe functional group to direct the process. DFT studies provided insight into the selectivity of C–OMe activation. Studies on expanding the scope to coordinating substrates and development of new Ru catalyst systems are ongoing in our laboratories and will be reported in due course. We anticipate that this process will advance the implementation of Ru-catalyzed C–O functionalizations in organic synthesis.

Conflicts of interest

There are no conflicts to declare.

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