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Digest Paper

Transition-metal-catalyzed etherification of unactivated C—H bonds

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ABSTRACT

The formation of C—O bonds is one of the fundamental transformations in organic chemistry. This digest summarizes recent advances in transition-metal-catalyzed etherification of unactivated C—H bonds. Etherification reactions with different directing groups and catalyst systems via C(sp^2)—H and C(sp^3)—H bonds activation are described.

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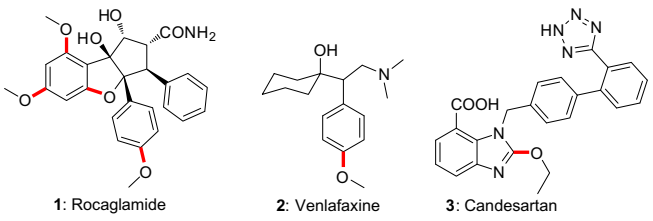
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Introduction

Ethers are common structural motifs in many natural products, pharmaceuticals, agrochemicals, etc. (Fig. 1).[1] Therefore, the development of practical and effective protocols to the synthesis of ethers has received tremendous interests. A large number of methods have been developed for the access of ethers, such as acid-catalyzed condensation of alcohols, the direct coupling of aryl halides with suitable alkoxides/alcohols to form the corresponding alkoxylated product (Williamson ether synthesis),[2] the Ullmann reaction,[3] and the Buchwald–Hartwig reaction (Scheme 1).[4] However, there are some disadvantages of these methods, such as the need for multiple reaction steps, excess amounts of metal salts and the production of metal halides as by-product.

Due to an increase of sustainable and environmental considerations, the formation of C—O bonds through the activation of C—H bonds has been developed rapidly.[5,6] Transition-metal catalyzed direct functionalization of inert C—H bond has undoubtedly emerged as a powerful tool for the step-economical construction

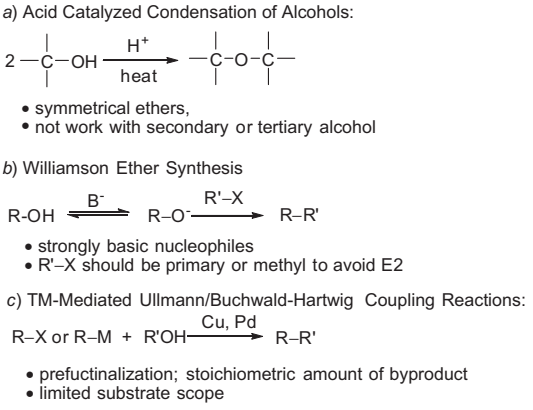


1: Rocaglamide **2**: Venlafaxine **3**: Candesartan

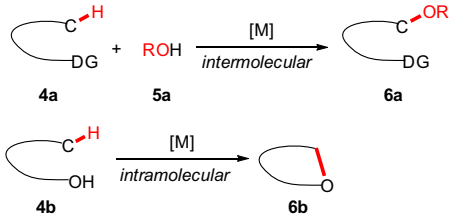
Figure 1. Pharmaceuticals that contain alkoxy functionalities.

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Scheme 1. Traditional methods for the synthesis of ethers.



Scheme 2. Transition-metal-catalyzed etherification of unactivated C—H bonds. M = transition metal.

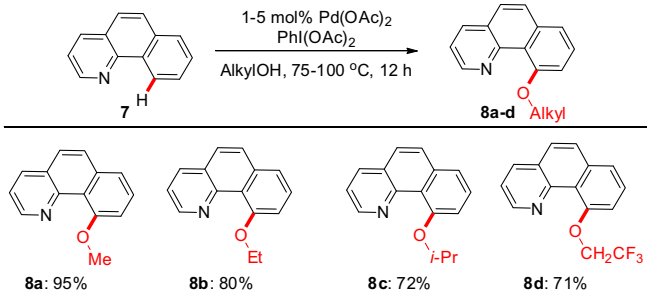
of complex organic molecules in modern organic chemistry,[7] because the direct transformation of C—H bonds provides unprecedented disconnections in the retro-synthetic analyses of complex target molecules, thus rendering synthetic routes more straightforward and atom-economical.[8]

In this review, we focus on recent advances in transition-metal catalyzed intermolecular and intramolecular alkoxylation and phenoxylation of unactivated C—H bonds, including C(sp^2)—H and C(sp^3)—H bonds (Scheme 2). Obviously, the reaction is highly valuable since it provides a complementary route to the construction of C—O bonds.

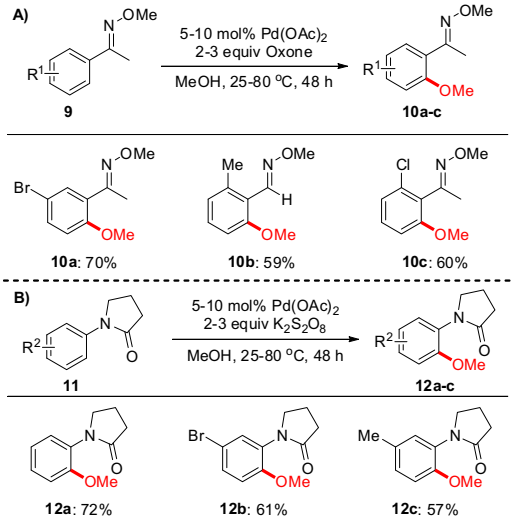
Palladium–catalyzed etherification of unactivated CH bonds

Palladium-catalyzed etherification of C(sp^2)—H bonds

In 2004, Sanford and co-workers reported a Pd-catalyzed procedure for the transformation of C—H bonds to ethers (Scheme 3).[9] Initially, they found that the combination of 1 equiv of benzo-[*h*]quinoline with $PhI(OAc)_2$ (2 equiv) and 2 mol % $Pd(OAc)_2$ in CH_3CN at 75 °C for 12 h afford the monoacetoxylated product and the analogous phenol in high yield. They also found when alcohols were used as solvents, a range of sterically and electronically diverse alkyl–aryl ethers were produced in good yields. A Pd(II)/Pd(IV) catalytic cycle was postulated for this transformation.



Scheme 3. Pd-catalyzed alkoxylation of benzo[*h*]quinoline.

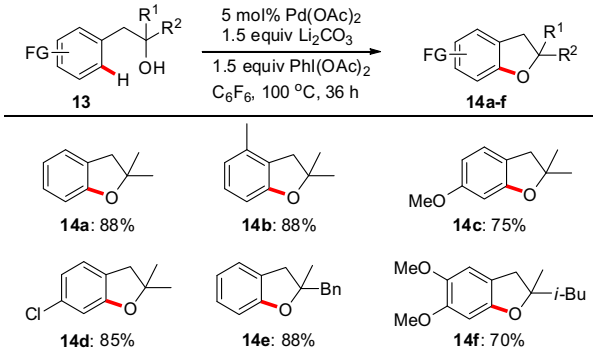


Scheme 4. Pd-catalyzed methoxylation reported by Sanford.

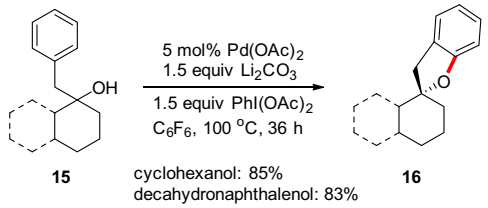
The iodine(III) oxidant is expensive and forms stoichiometric quantities of toxic PhI with each catalytic turnover. In consideration of these factors, Sanford and co-workers rationalized that the Pd(IV) intermediate could be accessed by the use of other peroxide-based oxidants.[10] Consistent with this hypothesis, they found that $Pd(OAc)_2$ catalyzed C—H bond methoxylation with Oxone or $K_2S_2O_8$ as oxidants could be applied to a broad range of arene substrates (Scheme 4).

Many natural products and pharmaceuticals contain dihydrobenzofuran rings. The synthesis of these structural skeletons via Pd- and Cu-catalyzed intramolecular coupling of aryl halides with alcohols has been reported by Buchwald and other groups.[11,12] However, intramolecular reactions of hydroxyl groups with C—H bonds to form C—O bond had not been reported until recently. In 2010, Yu and co-workers reported the first Pd(II)-catalyzed hydroxyl-directed C—H activation reaction to form C—O bonds.[13] The transformations reported by Yu could be extended to compounds containing a variety of different function groups, including both electron-donating groups, such as OMe and Me, and electron-withdrawing groups, such as Cl (Scheme 5).

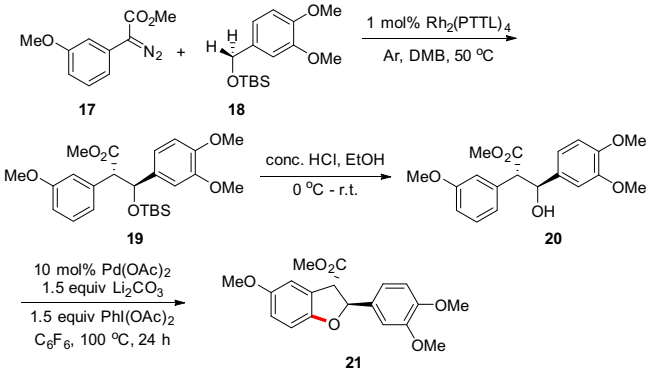
Remarkably, this reaction could also be applied to the synthesis of natural products and drug molecules containing spirocyclic dihydrobenzofurans (Scheme 6).



Scheme 5. Palladium-catalyzed C—H activation/C—O cyclization reaction reported by Yu.



Scheme 6. Pd(II)-catalyzed C—O cyclization in the formation of spirocyclic core skeleton.

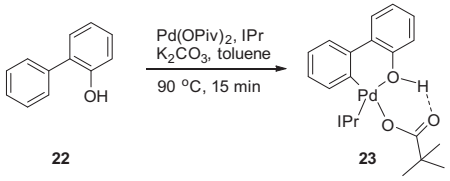


Scheme 7. Synthesis of dihydrobenzofuran via sequential C—H functionalization.

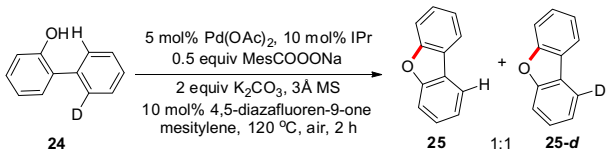
The aforementioned methodology was applied to the enantioselective synthesis of highly functionalized 2,3-dihydrobenzofurans by the collaborate of the Davies and Yu groups in 2013.[14] In general, the reaction protocol proceeded with a three-step sequence: enantioselective intermolecular benzylic C—H insertion, the removal of TBS group, and C—H activation/C—O cyclization (Scheme 7).

In 2011, Liu reported a phenol-directed C—H activation/C—O cyclization to the synthesis of dibenzofurans via a Pd(0)/Pd(II) catalytic cycle using air as an oxidant.[15] Notably, Yu's protocol is not applicable because phenols are susceptible to oxidation. Initially, they found that the reaction was significantly improved when sodium pivalate was added. It is reported that the pivalate coordinated to Pd(II) as an anionic ligand which could promote C—H activation by acting as a proton shuttle.[7c] Upon the treatment of **22** with a stoichiometric amount of $Pd(OPiv)_2$ at 90 °C, a four-coordinate Pd(II) complex was obtained, which unambiguously revealed that the phenol group coordinated with Pd(II) as a neutral σ donor (Scheme 8).

When the Pd(II) complex **23** was heated at 90 °C for 24 h, only a trace amount of product was obtained. However, the yield was improved to 58% when the reaction temperature was increased to 120 °C. These observations indicated that C—O reductive elimination from the Pd(II) center was the most difficult step in this reaction. Furthermore an intramolecular KIE (kinetic isotope effect) value of 1 was obtained when **24** was subjected to the reaction conditions (Scheme 9). This experiment further supported that



Scheme 8. Formation of four-coordinate Pd(II) complex **23**.

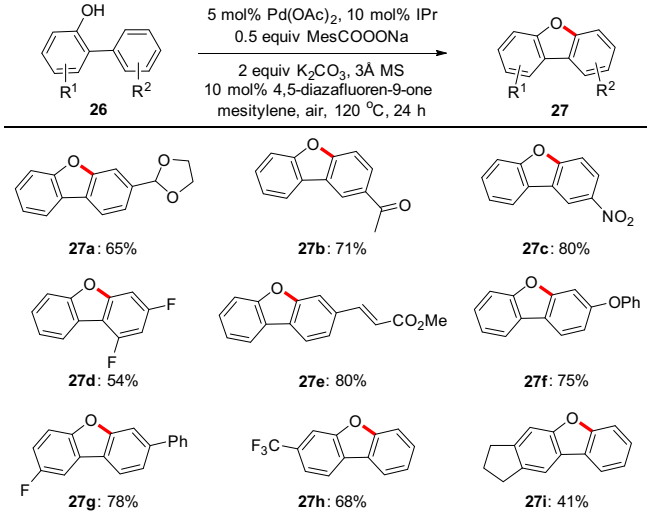


Scheme 9. Intramolecular kinetic isotope effect.

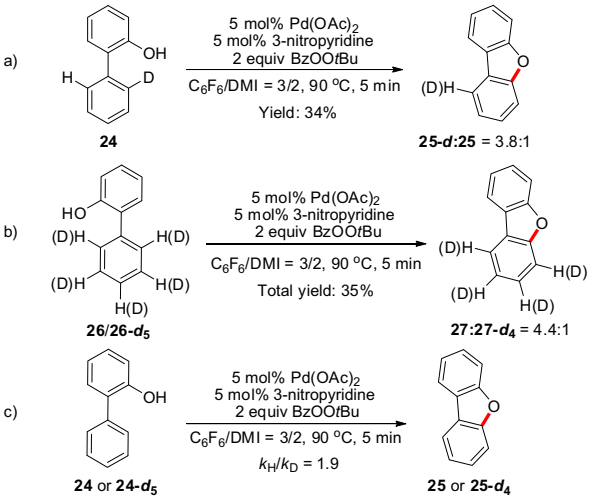
the turnover-limiting step was C—O reductive elimination instead of C—H activation. Moreover, the addition of 4,5-diazafluoren-9-one may help the aerobic oxidation of Pd(0) to regenerate Pd(II).[16]

The optimized reaction conditions were extended to a variety of 2-aryl phenols and the desired products were afforded in modest to good yields (Scheme 10). Both of the aromatic rings could be substituted with electron-donating groups such as ketal, ether, and electron-withdrawing groups such as ketone, nitro, fluoride, chloride, and trifluoromethyl.

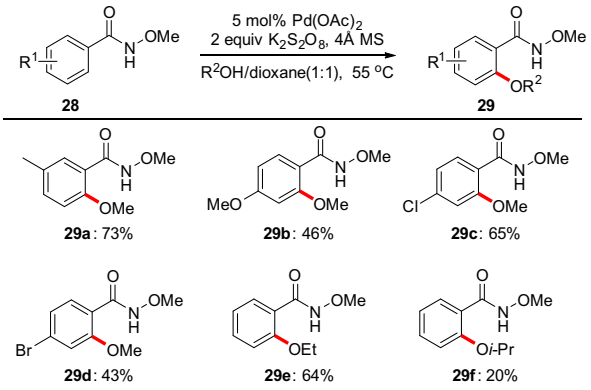
Shortly after, Yoshikai et al. reported a similar transformation using 3-nitropyridine as ligand, and *tert*-butyl peroxybenzoate (BzO*O*t*B*u) as oxidant.[17] The KIE experiments of this transformation have provided clear evidence that C—H bond cleavage is not only



Scheme 10. Palladium catalyzed C—H activation/C—O cyclization reported by Liu.



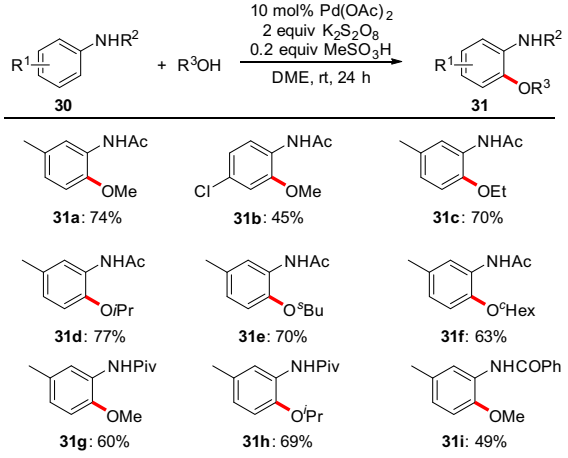
Scheme 11. Intramolecular and intermolecular kinetic isotope effect studies.



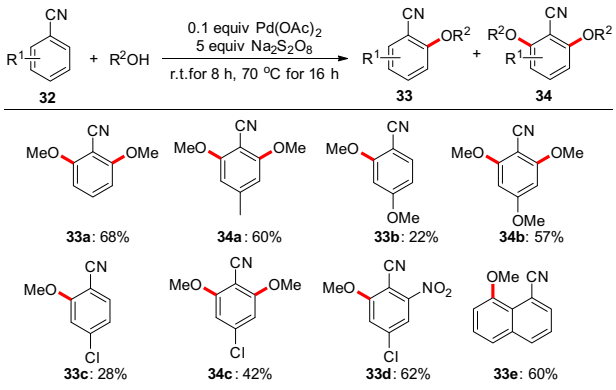
Scheme 12. Palladium-catalyzed *ortho*-alkoxylation of *N*-methoxybenzamides by Wang.

the rate-limiting step, but also the irreversible step of the reaction (Scheme 11). The control experiment revealed that the stirring of **22** with a stoichiometric amount of $Pd(OAc)_2$ under the reaction conditions but without BzOO*t*Bu did not give the desired product at all. Therefore, they proposed that this reaction most likely proceeded through a Pd(II)/Pd((IV) catalytic cycle.

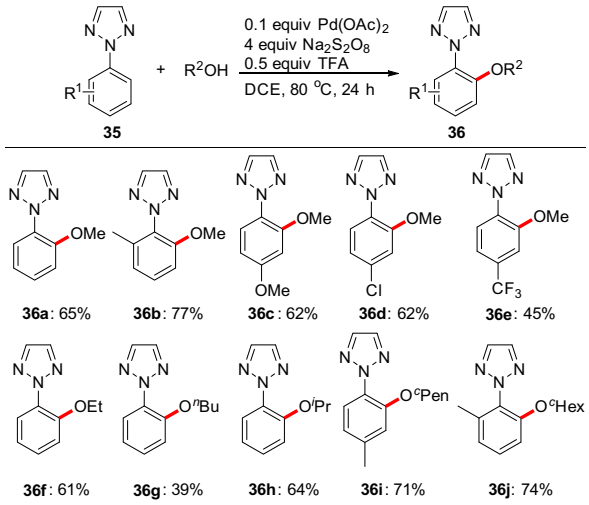
In 2010, Wang and co-workers described the alkoxylation of aromatic C—H bonds directed by *N*-methoxyamides.[18] This protocol could be applied to the methoxylation of a variety of different substrates bearing electron-donating groups, such as Me and OMe, and electron-withdrawing groups, such as Cl and Br.



Scheme 13. Palladium-catalyzed *ortho*-alkoxylation of anilides.



Scheme 14. Palladium-catalyzed alkoxylation of arylnitriles.



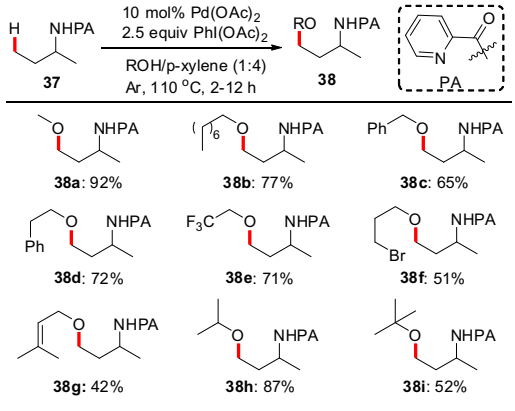
Scheme 15. Palladium catalyzed *ortho*-alkoxylation of 2-aryl-1,2,3-triazoles.

When other alcohols were used as solvents, the corresponding alkoxylated products were obtained in moderate yields (Scheme 12).

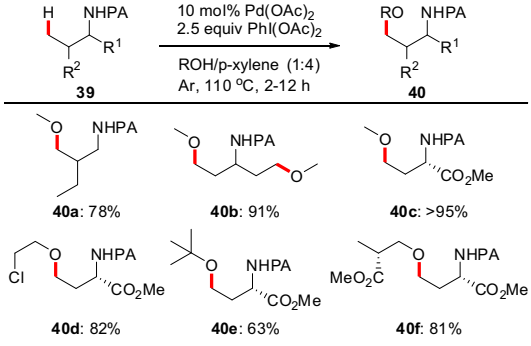
Encouraged by the work of de Vries, van Leeuwen, and co-workers that *p*-toluenesulfonic acid (PTSA) could promote the Pd-catalyzed C—H activation reaction of anilides,[19] Wang achieved the alkoxylation of acetanilides in the presence of CH_3SO_3H.[20] A large number of primary alcohols, such as *n*-PrOH, *n*-BuOH, and $MeOCH_2CH_2OH$ could be used as the alkoxylating reagents. Moreover, secondary alcohols, such as *i*-PrOH, 2-butanol, cyclohexanol, and cyclopentanol, also proceeded well in this catalytic system. Anilides bearing other protecting groups, such as *N*-(*m*-tolyl)pivalamide and *N*-(*m*-tolyl)benzamide, could also afford the desired products (Scheme 13).

The cyano group was first employed as a weak-coordinating directing group by Yu recently.[21] Encouraged by this report, Sun reported a Pd-catalyzed *ortho*-alkoxylation of arylnitrile using cyano as the directing group.[22] A broad range of aromatic nitriles bearing either electron-donating or electron-withdrawing groups could be alkoxylated, however, it was difficult to control the mono- and di-alkoxylation (Scheme 14). The same group also reported a palladium-catalyzed alkoxylation of 2-aryloxypyridines in the presence of $PhI(OAc)_2$ as oxidant.[23]

More recently, Kuang and co-workers demonstrated the palladium-catalyzed alkoxylation of C(sp^2)—H bond with the assistance of 1,2,3-triazole.[24] A variety of 2-aryl-1,2,3-triazoles could be alkoxylated by primary and secondary alcohols, such as



Scheme 16. Palladium-catalyzed alkoxylation of methyl C(sp^3)—H reported by Chen.



Scheme 17. Palladium-catalyzed alkoxylation of methyl C(sp^3)—H.

EtOH, *n*-BuOH, benzyl alcohol, *i*-PrOH, cyclopentanol, and cyclohexanol (Scheme 15). One limitation of this transformation is that the directing group could not be removed.

Pd-catalyzed *ortho*-alkoxylation of *N*-tosylbenzamides using $PhI(OAc)_2$ as the oxidant was reported by Fabis group recently.[25] The alkoxylation reaction proceeds smoothly at room temperature using methanol as the solvent. However, the scope of the reaction is largely restricted to the use of non-hindered alcohols.

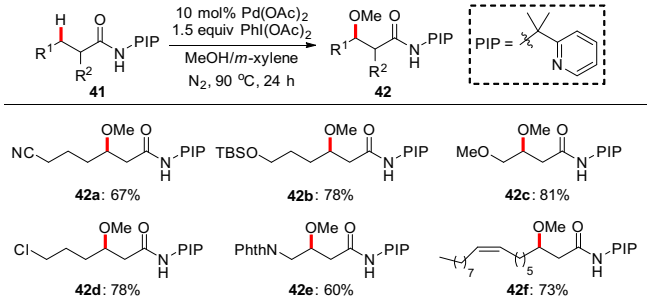
Palladium-catalyzed alkoxylations of C(sp^3)—H bonds

Despite these successes in palladium-catalyzed alkoxylation of C(sp^2)—H bonds, the C—H alkoxylation of unactivated C(sp^3)—H bonds remains to be a great challenge. Not until 2012 did the Chen group report the first example the C—H alkoxylation of unactivated C(sp^3)—H bonds with a broad substrate scope employing a picolinamide directing group.[26] When investigating the C—H amination reaction systems, the Chen group observed that the concentration of OAc ligands in solution affects the reaction pathway and thus the product distribution. Inspired by this observation, they found that the use of alcohols as nucleophiles to replace the coordinated acetoxyl ligand could give the alkoxylated products in good yields under the optimized conditions.

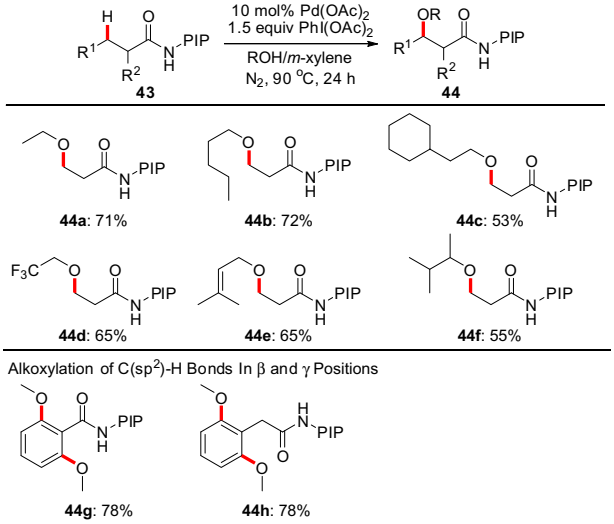
Primary alcohols, such as MeOH, *n*-PrOH, BnOH, CF_3CH_2OH and even *n*-octyl alcohol, could be used and provided the desired products in good to excellent yields. Secondary alcohols, such as *i*-PrOH and cyclohexanol, proceed well with prolonged reaction time. Notably, even *t*-BuOH afforded *tert*-butyl ether product (**38i**) in 52% yield (Scheme 16).

Substrates with or without α-substituents but bearing 1° γ-C(sp^3)—H groups can be methoxylated under the standard reaction conditions (Scheme 17). In addition, both the γ-*o*-C(sp^2)—H and δ-*o*-C(sp^2)—H bonds of the aromatic substrates can also be alkoxylated in moderate to high yields.

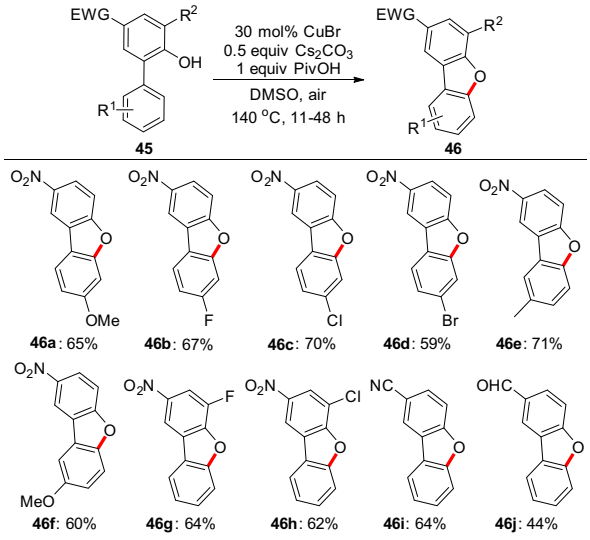
Compared to methyl C(sp^3)—H bonds, methylene C(sp^3)—H bonds are more resistant to be activated due to high steric



Scheme 18. Palladium-catalyzed methoxylation of methylene C(sp^3)—H bonds.

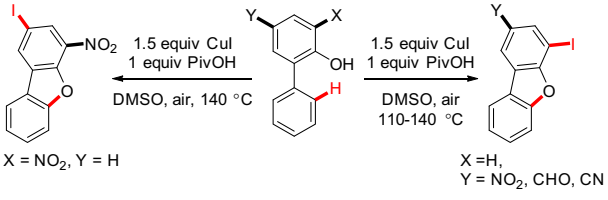


Scheme 19. Palladium-Catalyzed alkoxylation of C(sp^3)—H bonds with various alcohols.

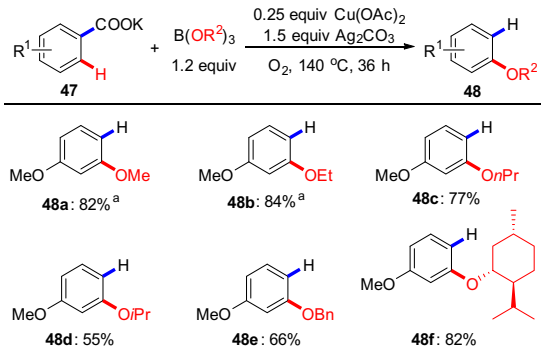


Scheme 20. CuBr-Catalyzed cycloetherification of 2-arylphenols.

hindrance and intrinsic inertness. In 2005, the seminal work by the Daugulis group reported that the *N*,*N*-bidentate directing groups could significantly facilitate the activation of methylene C(sp^3)—H bonds and therefore, a diverse collection of novel C(sp^3)—H functionalization reactions have been developed.[27] Inspired by this elegant work, we envisioned that the alkoxylation of unactivated methylene C(sp^3)—H bonds could be achieved by the judicious choice of an appropriate bidentate directing group. We commenced



Scheme 21. CuI-mediated sequential iodination/cycloetherification of *o*-arylphenols.



Scheme 22. Copper-catalyzed decarboxylative alkoxylation of aromatic carboxylates.

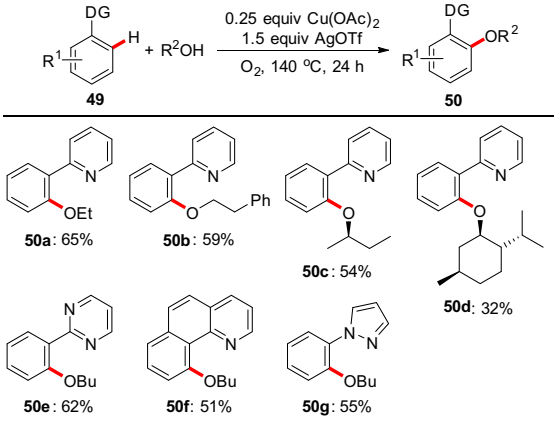
our studies by employing 8-aminoquinoline derived amide as substrate, however, alkoxylation of the quinolone C(sp^2)—H proceeded predominantly. After extensive optimization, we were delighted to find that the use of the 2-(pyridine-2-yl)isopropyl (PIP) directing group was efficient for this transformation.[28a,29] Preliminary DFT calculations revealed that the *gem*-dimethyl structure of this directing group was essential for the C—H activation and cyclopalladation process.[28]

The optimized reaction conditions are compatible with a broad range of aliphatic amides bearing various functional groups such as nitrile, ethers, chloride, and Phth-protected amines. Notably, the oleic acid derivative could also be methoxylated at the β position in good yield (Scheme 18).

This protocol was found to be compatible with a large number of alcohols. Generally, linear or branched primary alcohols afforded the corresponding alkoxylated products in good yields. Secondary alcohols could also be applied in the alkoxylation reaction, albeit in slightly lower yield (Scheme 19). It is worth noting that this reaction protocol could also be applied to the alkoxylation of C(sp^2)—H bonds in β and γ positions.

Copper-catalyzed etherification of unactivated C—H bonds

Recently, tremendous efforts have been devoted to copper-catalyzed/mediated oxidative C—H functionalization due to the cheapness, abundance, and relatively low toxicity of copper salts.[30] In 2006, the pioneering work by Yu demonstrated the first example of aryloxylation of 2-phenylpyridine with 4-cyanophenol.[31] Inspired by this work, Zhu et al. postulated that a copper-catalyzed C—H activation/cycloetherification of 2-arylphenols could also be feasible, providing a complementary route to dibenzofurans.[32] Electron-deficient phenols, such as 4-nitro-2-phenylphenols, 4-cyano-2-phenylphenol, and 4-formyl-2-phenylphenol all proceeded smoothly to give dibenzofurans under optimized conditions (Scheme 20). However, cycloetherification of 2-phenylphenol with various copper catalysts under aerobic conditions were failed since the electron-rich substrate is labile under these conditions. Preliminary studies revealed that an irreversible, rate-limiting concerted-metalation-deprotonation (CMD) process is most likely involved in this reaction.



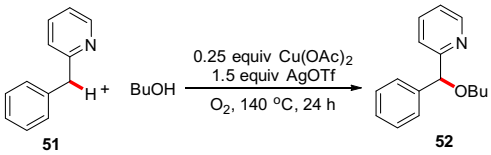
Scheme 23. Copper-catalyzed *ortho*-alkoxylations of aryl C—H directed by N-chelating auxiliaries.

The same group also found that when CuBr was replaced by CuI, 2- or 4-iododibenzofurans were obtained through CuI-mediated sequential iodination/cycloetherification of 2-arylphenols (Scheme 21).[33] Further studies suggested that iodination reaction took place prior to C—O cyclization.

In 2013, Goossen and co-workers reported the synthesis of aryl ethers via *ortho*-alkoxylation of aromatic carboxylates followed by protodecarboxylation (Scheme 22).[34] They found that copper acetate and silver carbonate are the most effective catalyst systems and without either copper or silver, the reaction did not proceed. Silver carbonate was crucial for this transformation not only for the decarboxylation, but also for the methoxylation process, as proposed by the authors. The alkyl aryl ethers were obtained in good yields with both of primary and secondary alkoxides. Notably, chiral alkoxides were transferred with complete retention of configuration (**48f**). Furthermore, this protocol was compatible with aromatic carboxylic acids bearing a wide range of functional groups, including keto, cyano, nitro, sulfonyl, N-heterocyclic, and bromo.

Inspired by the copper-mediated phenoxylation of 2-phenylpyridine developed by Yu[31] and the observation by Ribas and Stahl that aryl-copper was methoxylated by the addition of methanol,[35] Goossen and co-workers reported the copper/silver-mediated dehydrogenative coupling of arenes with alcohols (Scheme 23).[36] Both linear and branched alcohols reacted smoothly with 2-phenylpyridine and chiral alcohols reacted with the retention of configuration. Besides 2-pyridyl, other N-chelating directing groups, such as pyrimidine, benzoquinoline, and pyrazole, can also be applied as the directing groups. Mechanistic studies revealed that C—H activation step is rate-limiting and irreversible. However, the directing groups cannot be removed or modified.

Moreover, they also found that this reaction protocol can also be applied to the alkoxylation of benzylic C—H bonds (Eq. 1).

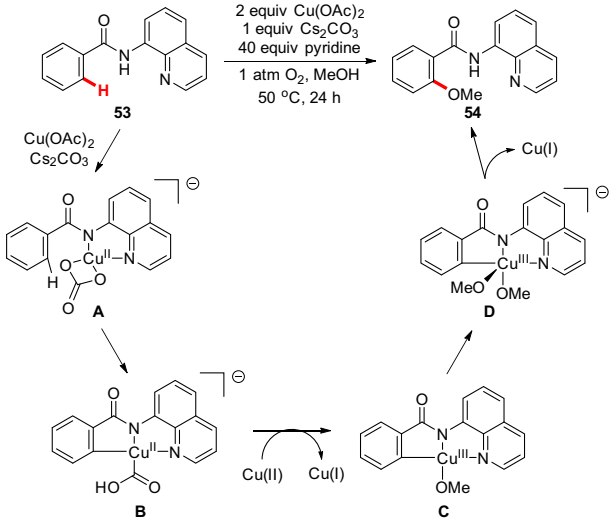


(1)

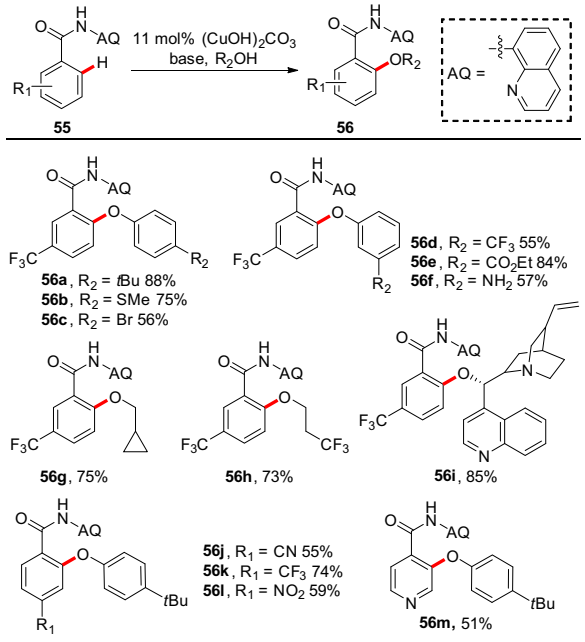
In an instructive study of copper-mediated C—H oxidation, Stahl reported a $Cu(OAc)_2$-mediated methoxylation of *N*-(8-quinolinyl)benzamide using methanol as solvent. Experimental and computational studies suggest that a basic ligand induced, rate-limiting organometallic C—H activation step is most likely involved in this protocol (Scheme 24).[37]

Shortly after, Daugulis and co-workers reported $(CuOH)_2CO_3$-catalyzed etherification of unactivated aryl C—H bonds by employing removable bidentate directing groups.[38] The reaction scope of phenols, aliphatic alcohols, and aminoquinoline benzamides are quite general and a variety of functional groups, such as chloride, bromide, amino, trifluoromethyl, ester, and even iodide, were tolerated under the optimized conditions (Scheme 25). They also found that picolinamide can also serve as an efficient directing group.

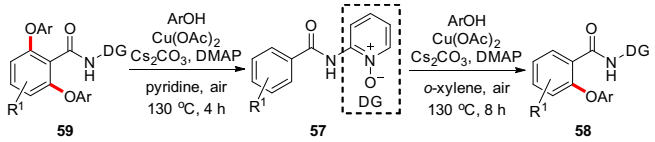
More recently, the Song group reported a copper-mediated mono- and diaryloxylation of benzamides by employing a remov-



Scheme 24. $Cu(OAc)_2$-mediated methoxylation of *N*-(8-quinolinyl)benzamide.



Scheme 25. Copper-catalyzed aryloxylation and alkoxylation of $C(sp^2)$—H.



Scheme 26. Copper-catalyzed mono- and diaryloxylation of $C(sp^2)$—H.

able *N*,*O*-bidentate directing group (Scheme 26).[39] Mechanistic studies indicated that the cleavage of C—H bond is reversible and is involved in the rate-determining step.

Conclusions

The synthesis of ethers via transition-metal-catalyzed direct functionalization of unactivated C—H bonds has attracted increased interest in recent years. From a synthetic point of view, these protocols offer novel and economical approaches to functionalized ethers, although some reactions still suffered from limited substrate scope, harsh reaction conditions, high catalyst loading and the use of synthetically restrict directing groups. Besides, there are also some fundamental challenges to be addressed. First, the development of an efficient catalyst system for the alkoxylation of unactivated $C(sp^3)$—H bonds is highly desirable. Second, the application of these transformations into the total synthesis of natural products and late-modification of complex molecules is still in its infancy. Finally, an insightful understanding of the detailed mechanism could lead to the design of more efficient catalyst systems.

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