# Electrocatalytic Radical-Polar Crossover Hydroetherification of Alkenes with Phenols

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ABSTRACT: We disclose a general electrocatalytic hydroetherfication for modular synthesis of alkyl aryl ethers by utilizing a wide range of alkenes and phenols. The integration of the two involves an electrochemically instigated cobalt-hydride catalyzed radical–polar crossover of alkenes that enables the generation of key cationic intermediates, which could readily be entrapped by challenging nucleophilic phenols. We highlight the importance of precise control of the reaction potential by electrochemistry in conjunction with the decisive role of HFIP as the co-solvent to obtain optimal and exclusive chemoselectivity. Notably, this reaction system is pertinent to late-stage functionalization of pharmacophores that contain alkyl aryl ethers which has constantly been challenged since traditionally unconventional methods.

Alkyl aryl ethers has increasingly shown significant importance in agrochemical[1] and pharmaceutical industries[2-3] as their structural motifs in synthesis of biorelevant compounds have become ubiquitous (Figure 1A).[4-6] Early methods to synthesize alkyl aryl ethers include Williamson ether synthesis,[7] $S_NAr$[8] (nucleophilic aromatic substitution) and Mitsunobu[9]

reactions that all suffer from limitations to electronically unbiased or sterically hindered products. In response to these traditional methods, transition metal-mediated C($sp^2$)–O cross coupling of alcohols with aryl halides[10-19] has been most widely reported upon judicious choice of ligand and base additives to address challenging canonical step in either oxidative addition or reductive elimination.[20] As a complementary strategy in terms of retrosynthetic bond disconnection, C($sp^3$)–O cross coupling of phenols with redox-active esters (RAEs) in lieu of aryl halides has also been presented.[21]

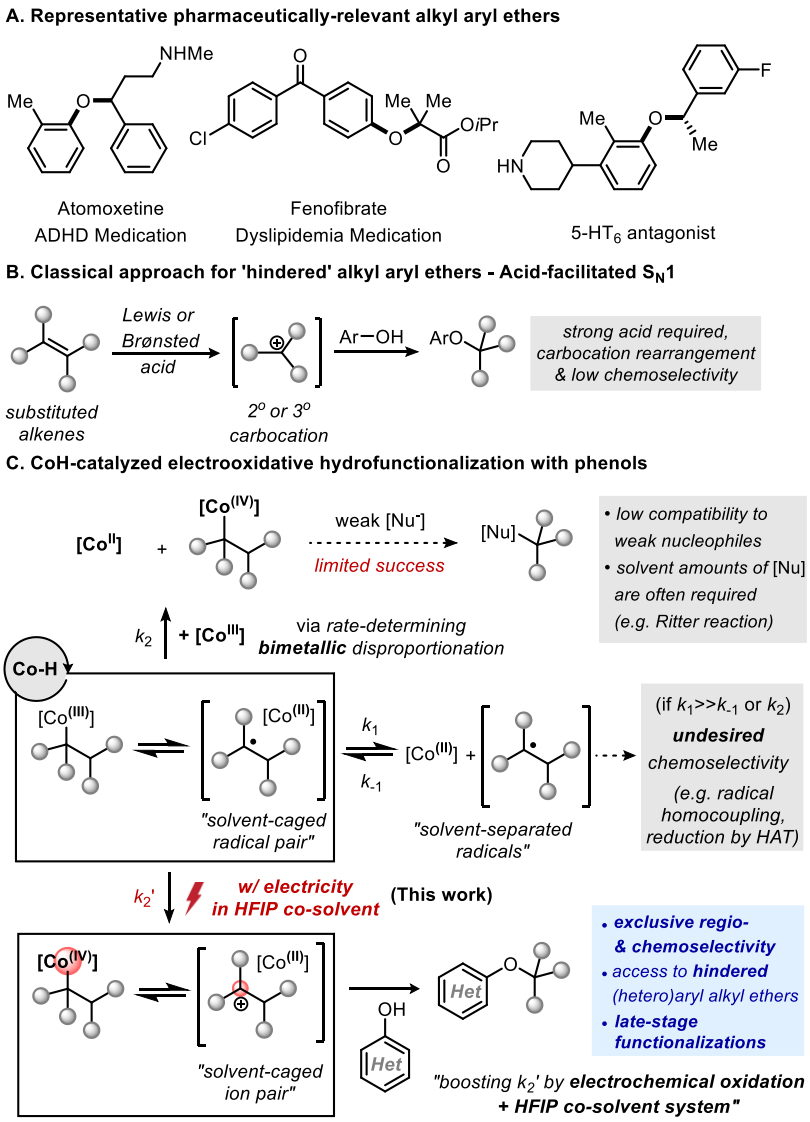



**Figure 1.** Synthetic Approaches to (Hindered) Alkyl Aryl Ethers.

On the other hand, alkyl aryl ethers can be formed by acid-catalyzed addition reactions of phenols with alkenes (Figure 1B).[22-23] As abundant precursors, alkenes can in principle offer a wide range of alkyl counterparts and are further complementary in forming sterically hindered ethers via highly substituted carbocation intermediates. However, such strong Lewis- or Brönsted acid catalyzed addition is predominantly accessible to only monosubstituted terminal alkenes while internal alkenes are less reactive and prone to isomerization.[24] Moreover, acid-catalyzed additions suffer from competitive chemoselectivity between forming the C−O bond and undesired C−C bond with *ortho* or *para* C−H bond of phenols.[25-29]

In this context, catalytic hydroetherification of a wide range of alkenes with phenols as the nucleophile is particularly attractive due to the accessibility to hindered alkyl aryl ethers but remains to be scarce.[18,30] In addition, these approaches mostly rely on rare noble transition metals and has yet been compatible to synthesize key structural motifs in bioactive and pharmaceutical compounds.[31-32] To this end, we were drawn to the possibility that a catalytic system under mild conditions that can generate diverse cationic alkyl intermediates to their respective olefins and compatible to a wide variety of phenolic nucleophiles.

Recently, Pronin, Shigehisa, Hiroya, Zhu and others have successfully expanded Mukaiyama's hydrogen atom transfer from a metal hydride (MHAT) paradigm[33-36] to nucleophilic alkene hydrofunctionalization under oxidizing conditions (Figure 1C, upper part).[37-42] These methods however involve the use of chemical oxidants with minimal control over the oxidizing potential that dictates the bimetallic catalyst-controlled oxidation,[43] which consequently necessitates the use of solvent amounts of nucleophiles to engage with unactivated multisubstituted alkenes.[44-46] In addition, this rate-determining bimetallic disproportionation ($k_2$) often deteriorates the desired nucleophilic entrapment particularly when weak nucleophiles are employed. This is mainly due to

solvent cage escape process ($k_1$) leading to the formation of solvent-separated radicals, which can irreversibly be driven to unwanted side reactions (Figure 1C, middle part).[43, 46-47] Thus, the development of a new catalytic strategy that allows proficient and controllable generation of high-valent cobalt(IV)-alkyl species or carbocations from the corresponding alkenes over solvent-cage escape process remains a major challenge for hydrofunctionalization with important but challenging nucleophiles such as phenols.[47-49]

Herein we report a cobalt-catalyzed electrochemical radical polar crossover hydroetherification of alkenes in which a controllable electricity under HFIP co-solvent system drives systematic consecutive oxidations of cobalt catalyst to generate carbocationic species from a comprehensive class of olefins, which would subsequently be entrapped by phenols to afford the desired alkyl aryl ethers (Figure 1C, lower part). We envisioned that the preferential use of alcoholic solvents such as HFIP would increase the microviscosity of the reaction system[46], thereby eventually acquiring optimal chemoselectivity. By manipulating the oxidation potential at a required minimum, the system herein is found to be compatible with oxidatively sensitive phenols including heterocyclic derivatives with exclusive chemoselectivity towards C−O bond formation. Furthermore, this operationally simple protocol also allowed facile and modular access to pharmaceutical ethers via late stage functionalization.

To design an electrochemical system for the generation of high valent cationic species, we envisioned a prospective catalytic cycle wherein a Co(II) salen catalyst **I** would first be anodically oxidized to form Co(III)-hydride **III** upon addition of Si–H bond of hydrosilane **II** (Figure 2A, anodic event 1).[50] This Co(III)-hydride **III** would perform alkene MHAT with simultaneous formation of a metallo/organic radical pair **IV**, which is known as "solvent-caged radical pair".[46] The second anodic oxidation of either **IV** or cage collapse intermediate **V** would occur to form the

corresponding Co(IV) intermediate **VI** or solvent cage ion pair **VII**, respectively (Figure 2A, anodic event 2), while undesired side reactions such as hydrogen atom transfer (HAT) or homocoupling is also conceivable with the cage escape free radical intermediate. Capture of the resultant intermediates (**VI** or **VII**) by the phenol nucleophile would furnish the desired alkyl aryl ether product.

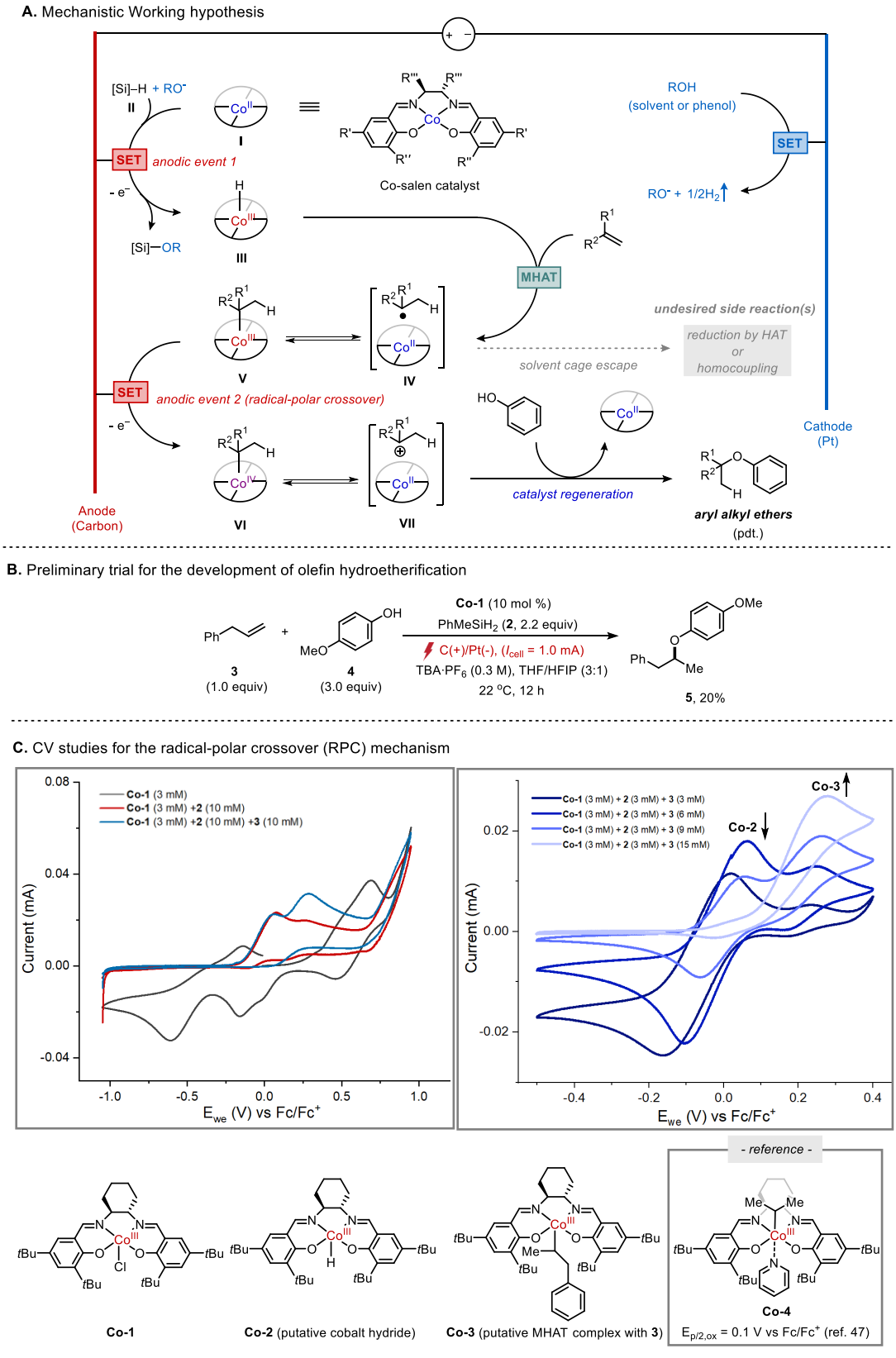
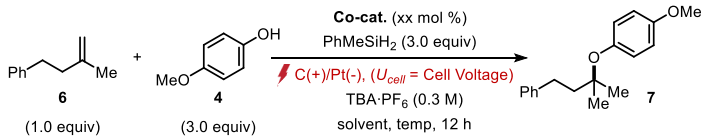



**Figure 2.** Design of Electrocatalytic System for Hydroetherification of Alkenes with Phenols.

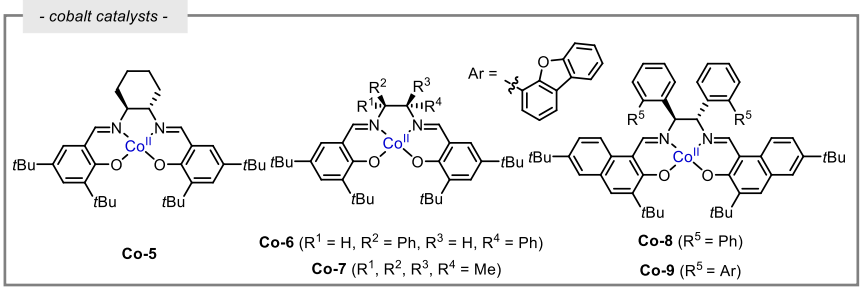
Initial exploration of the reaction using allylbenzene (**3**), 10 mol% of Co(III) salen catalyst **Co-1** with 3.0 equiv of methylphenylsilane (**2**) and TBA·$PF_6$ electrolyte in THF/HFIP co-solvent upon electrolysis under constant current of 1 mA gave 20% of the desired hydroetherification product **5** as a promising lead result (Figure 2B). This observation led us to examine the oxidation step involved in the generation of requisite intermediates that display reactivity reminiscent of a carbocation using cyclic voltammetry (CV). CVs were performed using 3 mM cobalt catalyst in the absence (gray line), in the presence of excess amount of silane **2** (red line) and in the presence of 10 mM of both **2** and **3** (blue line) in THF/HFIP (3:1) at a scan rate of 100 mV/s (Figure 2C, left box). A quasi-reversible feature at –0.15 V shown for the **Co-1** (gray line) in the absence of silane and alkene where designated as Co(II)/Co(III) redox couple. The addition of 3.3 equiv of **2** resulted in a significant change, displaying an irreversible oxidation with a peak potential of 0.05 V (red line) which we attributed to the oxidation of Co(III)–H species (**Co-2**). Notably, the addition of **3** resulted in a decrease in current of this feature as well as a shift in anodic peak potential, with the appearance of an additional redox wave (blue line, $E_{p,ox}$ = 0.27 V). Accordingly, the CV behavior of **Co-1** was further interrogated under more precise control of concentration of **3** (Figure 2C, right box). In this experiment, a sequential increase in current at the second redox feature with a simultaneous decrease at the first oxidation peak was observed as more **3** is added. This is indicative of the generation of putative MHAT complex **Co-3**, which is proposed to be capable of generating corresponding Co(IV) or carbocation intermediate upon electrochemical oxidation. Indeed, the observed oxidation peak potential of putative **Co-3** intermediate is found to be on par with that of previously reported Co(III)-alkyl complex **Co-4** ($E_p$ = 0.11 V vs $Fc/Fc^+$).[47] In closer scrutiny, higher scan rates display corresponding increases in current amplitude of the second redox feature (Figure S3), complementing our mechanistic hypothesis. The cage-escape process

($k_1$) is under competition with the oxidation of **Co-3** ($k_2$) and since MHAT process is fast enough to form **Co-3** upon first oxidation, we believe these higher scan rates facilitate higher portions of **Co-3** to be oxidized over cage-escape (Figure 1C). Based on these voltammetric studies, we hypothesized that the electrochemical oxidation of putative MHAT Co(III)-alkyl intermediate can bypass the bimetallic disproportionation mechanism which has been dictated by the use of chemical oxidants.[43]

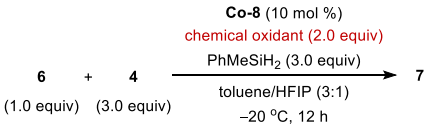
**A.** Optimization for the hydroetherification for 'hindered' alkyl aryl ether synthesis

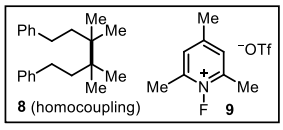



| entry | **Co-cat.** (mol %) | $U_{cell}$ | solvent | temp (°C) | yield (%) |
|---|---|---|---|---|---|
| 1 | **Co-5** (10) | 2.3 V ($E_{a,i}$ = 0.5 V) | THF/HFIP (3:1) | 22 | 35 |
| 2 | **Co-6** (10) | 2.3 V | THF/HFIP (3:1) | 22 | 44 |
| 3 | **Co-6** (10) | 2.3 V | toluene/HFIP (3:1) | 22 | 62 |
| 4 | **Co-7** (10) | 2.3 V | toluene/HFIP (3:1) | 22 | <5 |
| 5 | **Co-8** (10) | 2.3 V | toluene/HFIP (3:1) | 22 | 67 |
| 6 | **Co-9** (10) | 2.3 V | toluene/HFIP (3:1) | 22 | 21 |
| 7 | **Co-8** (10) | 2.3 V | toluene/HFIP (3:1) | 0 | 83 |
| 8 | **Co-8** (10) | 2.3 V ($E_{a,i}$ = 0.5 V) | toluene/HFIP (3:1) | –20 | 97 (92) |
| 9 | **Co-8** (10) | 3.0 V ($E_{a,i}$ = 0.8 V) | toluene/HFIP (3:1) | –20 | 61 |
| 10 | **Co-8** (5) | 2.3 V | toluene/HFIP (3:1) | –20 | 78 |
| 11 | **Co-8** (10) | 2.3 V | toluene | –20 | 23 (29 of **8**) |




**B.** Control experiments (chemical oxidant instead of anodic oxidation)




| chemical oxidant | conversion of **6** (%) | yield (**7**/**8**, %) |
|---|---|---|
| anode | 99 | 92/- |
| **9** | 99 | 54/20 |
| NFSI | 99 | 29/21 |
| $PhI(OAc)_2$ | 72 | <5/28 |
| Oxone | 99 | 26/32 |
| TBHP | 93 | <5/21 |
| $O_2$ (balloon) | 68 | 41/27 |
| $Cu(OAc)_2$ | 70 | 37/12 |
| CAN | 75 | 22/22 |
| $Fc^+BF_4^-$ | 74 | 15/5 |

**Figure 3.** Reaction Parameter Optimization.

We examined the viability of this protocol toward more sterically demanding 1,1-disubstituted alkenes for the synthesis of hindered alkyl aryl ether (Figure 3A). Accordingly, we chose alkene **6** as the model substrate. The Co(II) analogues were employed as the catalyst precursor due to the ease of preparation and feasibility of being oxidized under anodic oxidation conditions to generate corresponding Co(III)-hydrides.[48] Combining the phenol **4** with **6** together with 10 mol % of **Co-5** as the catalyst with 3.0 equiv of silane **2** in THF/HFIP (3:1) solution under the application of constant cell voltage of 2.3 V (corresponding to an initial anodic potential $E_{a,i}$ ~ 0.5 V vs $Fc^{+/0}$) furnished the hydroetherification product **7** in 35% yield (entry 1). A marginal increase in reactivity was observed with **Co-6** as the catalyst (entry 2). Among a variety of solvent systems screened, we found that employing toluene/HFIP co-solvent dramatically increased reactivity (entry 3, see Supporting Information (SI) for full data). Further evaluation of cobalt catalysts led to an improvement in reaction efficiency particularly with **Co-8** catalyst, which provided **7** in 67% yield (entries 4–6). We note that the yields were improved with a decrease in reaction temperature, providing 92% of isolated yield of **7** under –20 °C (entries 7–8). The increase of voltage input from 2.3 V to 3.0 V ($E_{a,i}$ from ~ 0.5 V to 0.8 V vs $Fc^{+/0}$) resulted in decrease in reaction efficiency with poor mass balance presumably due to unwanted side reactions caused by high anodic potential (entry 9). We also found that the model reaction was smoothly proceeded under reduced catalyst loading (5 mol %) or decreased equivalents of phenol (1.0 equiv) albeit in slight decrease in product yields (entry 10, see also Table S1, entry 21). Finally, significant decrease in product yield (23%) and the formation of radical homocoupling side product **8** (29%) in the absence of HFIP and toluene as the sole solvent (entry 11) is resultingly indicative of the crucial role of HFIP as the co-solvent.

Subsequently, a set of control experiments was conducted under a series of conventionally employed chemical oxidants without an electrical input for comparative purposes (Figure 3B). None of these chemical oxidants promoted the reaction efficiency comparable to our electrochemical protocol, while significant amounts of homocoupled side product **8** were obtained in most cases. This may suggest the use of such chemical oxidants partially obviates the second SET of the reaction, *via* radical polar crossover, when outcompeted by other side reaction pathways. This highlights employing electrical current as the oxidant circumvents any unwanted pathways and its crucial role in chemoselectivity of our reaction. Indeed, this radical-polar crossover strategy as a salient feature of electrochemistry has received attention in both net-oxidative and net-reductive organic transformations. [51-54]

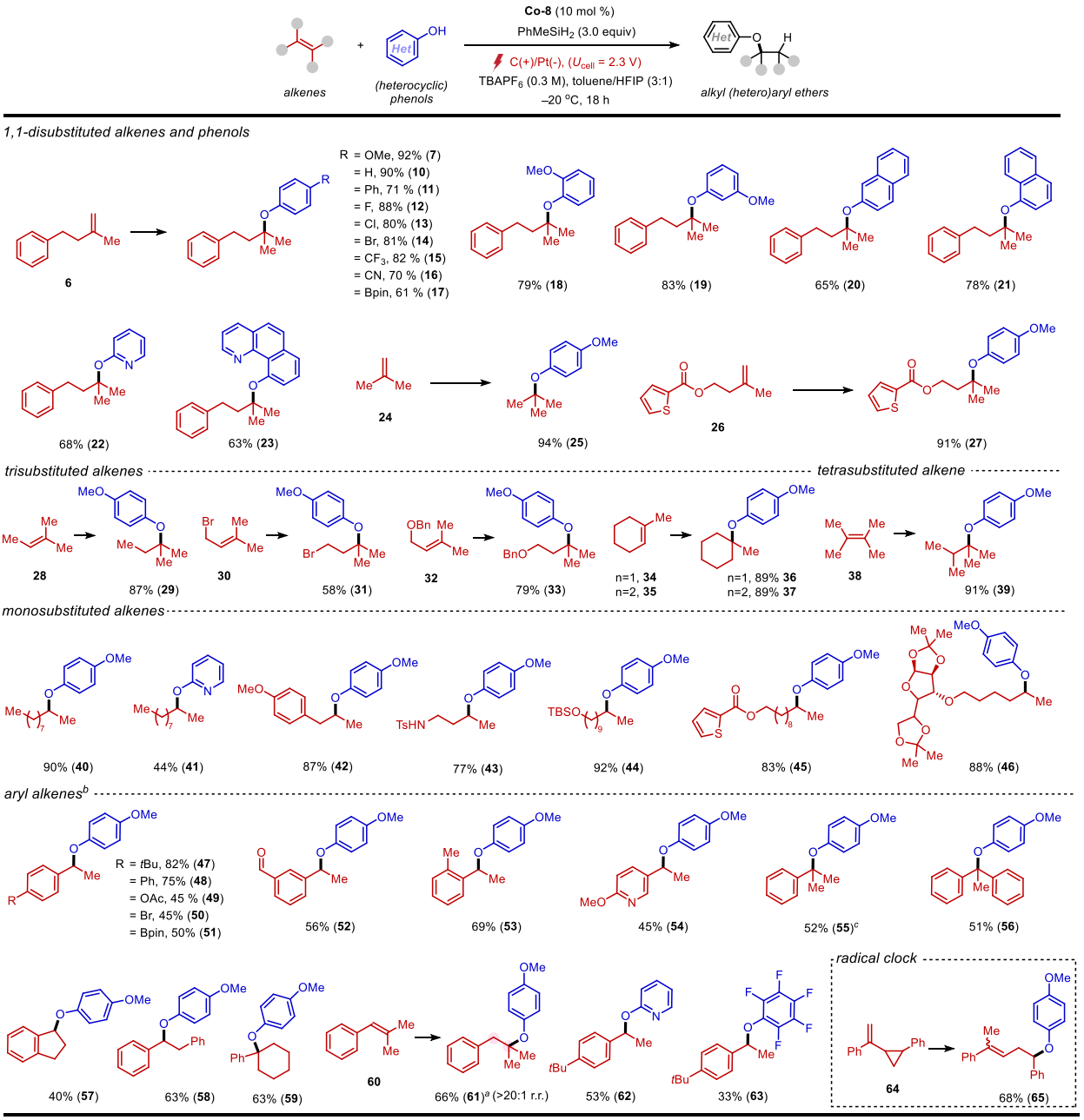
We then sought to evaluate the reaction scope with respect to both phenols and alkenes (Table 1). Along with **4**, uniformly high reactivities were observed upon variation of the *para* substituent of the phenol (**7, 10**–**17**). The substituents on *ortho* or *meta* position did not affect the reaction efficiency (**18**–**19**). The reaction accommodated naphthols as the oxygen nucleophiles (**20**–**21**). It was notable to see that hydroxy-substituted heterocycles were also compatible to afford corresponding alkyl heteroaryl ether products (**22**–**23**). An isobutene (**24**) was also a competent substrate as well, enabling a simple *O-tert*-butylation of phenol. The hydroetherification also tolerated thiophene moiety to afford product **27**.

Following our investigations on 1,1-disubstituted alkenes, we further applied this methodology to more sterically congested alkene substrates. We found that the protocol herein was effective to both acyclic (**28**, **30, 32**) and cyclic (**34-35**) trisubstituted alkenes. Notably, tetrasubstituted alkene **38** also underwent hydroetherification smoothly to produce the corresponding tertiary alkyl aryl

ether **39** in good yield. This result further supports the intermediacy of the carbocation generated by an electrochemical radical-polar crossover mechanism.

Besides multisubstituted alkenes, a series of monosubstituted alkenes underwent hydroetherification with phenols. Products **40** and **41**, only containing a simple alkyl chain, were afforded in excellent yields. A variety of functional groups including methoxyarene (**42**), sulfonamide (**43**), silyl protected alcohol (**44**), thiophenyl ester (**45**) or even fructose derivative (**46**) smoothly participated the reaction without difficulty.

**Table 1**. Substrate Scopes[a]



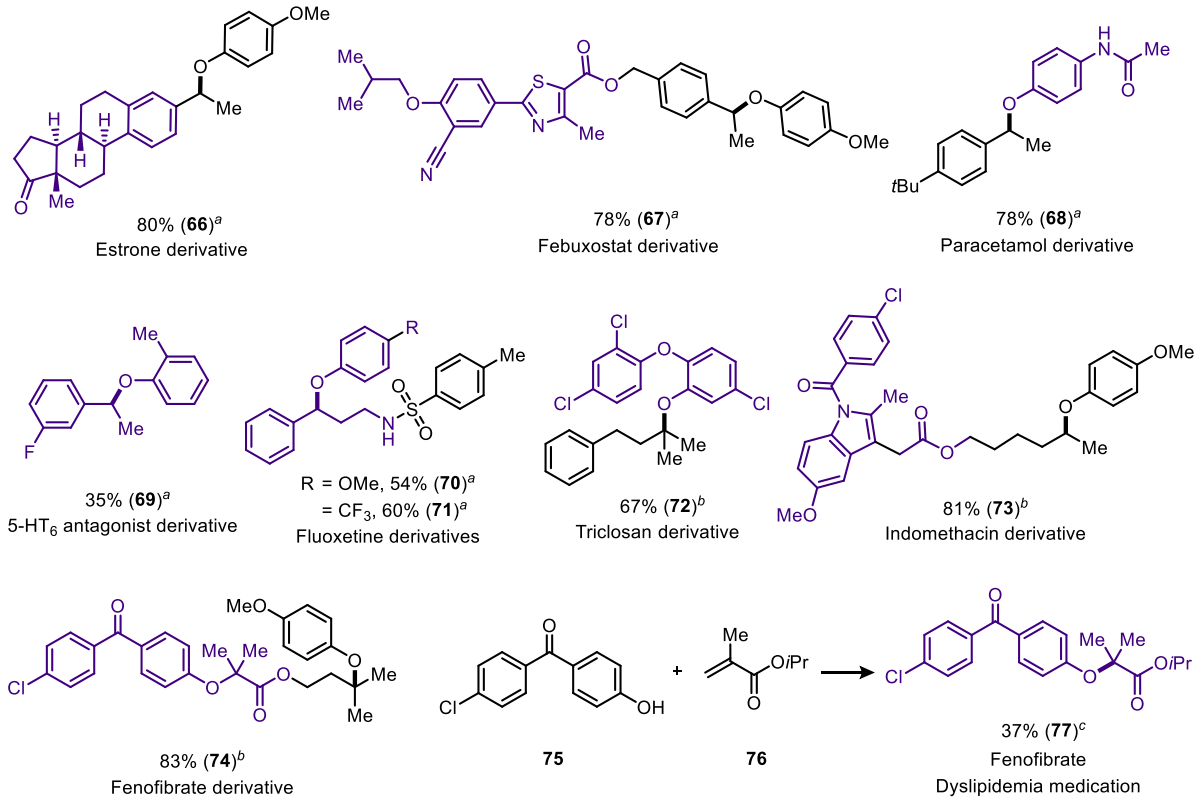

[a]alkenes (0.6 mmol), phenols (1.8 mmol), **Co-8** (10 mol %), $PhMeSiH_2$ (**2**, 1.8 mmol) and TBA·$PF_6$ (1.2 mmol) in toluene/HFIP (4.0 mL, 3:1) at –20 °C under $N_2$ atmosphere. [b]alkenes (0.6 mmol), phenols (1.8 mmol), **Co-8** (8 mol %), 1,1,3,3-Tetramethyldisiloxane (TMDSO, 1.8 mmol) and $LiClO_4$ (1.2 mmol) in 2-MeTHF/HFIP (4.0 mL, 1:1) at –20 °C under $N_2$ atmosphere. [c]**Co-5** (5 mol %) was used instead of **Co-8** (8 mol %) otherwise identical to the styrene reaction conditions. Isolated yields are reported.

This hydroetherification method also proved efficient in engaging styrenes as substrates, which are considered to be more challenging due to the unfavorable homocoupling or reduction caused

by intrinsically high stability of benzylic radicals generated by cage-escape mechanism (*vide supra*, Figure 2A).[39,42] Under slightly modified reaction conditions, styrenes bearing a series of functional groups at the para position were converted to the desired ether products in moderate to good yields (**47–51**). Vinylarenes possessing oxidatively sensitive functional groups on either *meta*- or *ortho*- position were smoothly converted into desired products (**52–53**). Vinyl-substituted pyridine also underwent the hydroetherification (**54**). The method herein could be applied to the disubstitued aryl alkenes (**55–58**) and trisubstituted cyclic aryl alkene (**59**). In addition, it was found that hydroetherification of β,β-disubstituted styrene (**60**) proceeded at the β-position with an exclusive regioselectivity (**61**), again suggesting the generation of the carbocationic intermediate. It should be noted that the vinylarenes were also compatible with heterocyclic (**62**) or electronically biased phenols (**63**) as coupling partners. Lastly, radical clock substrate **64** underwent rupture of the three-membered ring under standard reaction conditions to furnish **65**, suggesting key radical intermediacy prior to the generation of carbocation.

The high functional group tolerance of our hydroetherification method was highlighted by its application in late-stage functionalization of natural product structures and densely functionalized pharmacophores (Table 2). A wide range of bio-relevant structures were all transformed into corresponding hydroetherification product with ease (**66–74**). It is worth noting that fenofibrate (**77**), an oral medication for dyslipidemia could directly be synthesized in a single hydroetherification step, highlighting the utility of our method as a tool for late-stage drug synthesis and modification.

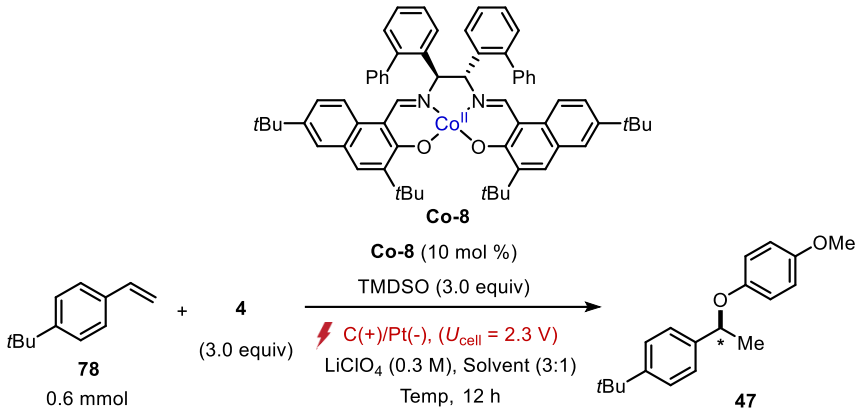
**Table 2.** Functionalization of natural product and drug derivatives[a]




[a]alkenes (0.6 mmol), phenols (1.8 mmol), **Co-8** (8 mol %), 1,1,3,3-Tetramethyldisiloxane (TMDSO, 1.8 mmol) and $LiClO_4$ (1.2 mmol) in 2-MeTHF/HFIP (4.0 mL, 1:1) at –20 °C under $N_2$ atmosphere. [b]alkenes (0.6 mmol), phenols (1.8 mmol), **Co-8** (10 mol %), $PhMeSiH_2$ (**2**, 1.8 mmol) and TBA·$PF_6$ (1.2 mmol) in toluene/HFIP (4.0 mL, 3:1) at 20 °C under $N_2$ atmosphere. [c]TBA·$PF_6$ (1.2 mmol) in toluene/acetone/HFIP (5 mL, 2:2:1) with 5.0 equiv of phenol otherwise the reaction conditions is identical to a. Isolated yields are reported.

Finally, we observed measurable, albeit modest, enantioselectivity for hydroetherification reactions involving monosubstituted alkene **78** (Figure 4)[55]. 16% of enantiomeric excess (e.e.) was achieved under optimized reaction conditions (entry 1, Figure 4) while the highest e.e. of 40% was observed when the reaction was conducted under –40 °C (entry 3) in MeCN. Such asymmetric induction safely excludes the possibility of the target aryl alkyl ether **47** formed solely via free carbocation intermediacy and therefore the $S_N2$-type displacement of Co(IV)-alkyl intermediate **VI** (Figure 2A) by phenol should also be considered.

In retrospect, while highly-substituted alkenes are unable to undergo nucleophilic displacement by phenol from tertiary-alkyl Co(IV) intermediate **VI**, the observed stereoselectivity from Figure 4 sheds light to the possibility of both intermediates **VI** and **VII** depending on the employed alkene substrates. Ultimately, these results support our voltametric studies (Figure 2C) in proving the *quasi*-reversible feature of second redox wave, in which the erosion of reversibility originates in the irreversible cage escape to generate free carbocation.[44-46]




| Entry | Solvent | Temp. (°C) | Yield of **47** (%) | e.r. |
|---|---|---|---|---|
| 1 | 2-MeTHF/HFIP (1:1) | –20 | 82 | 58:42 |
| 2 | 2-MeTHF/HFIP (1:1) | –40 | 56 | 59:41 |
| 3 | MeCN | –40 | 27 | 70:30 |

**Figure 4.** Preliminary Result for Stereoselective Hydroetherification of Alkenes with Phenols.

In summary, we present a modular approach to synthesizing alkyl aryl ethers by integrating a wide range of alkenes and phenols. This protocol involves successive oxidative SET reactions to enable conventional radical polar crossover reactions to allow direct entrapment of cationic alkyl intermediates by challenging nucleophilic phenols. The experimental data suggest that using an electrochemical anode as the oxidant may not only be sustainable but also optimal for high reactivity and chemoselectivity. This versatile hydroetherification method can be manipulated to target complex molecules including bioactive compounds, suggesting that the strategy for

nucleophilic phenols as synthetic drug precursors would enlarge a library of potentially new pharmaceutical agents.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

## ASSOCIATED CONTENT

**Supporting Information**.

The following files are available free of charge.

Materials and methods, synthetic procedures, voltammetric study, optimization of reaction conditions and full characterization of new compounds, spectroscopic data, and NMR spectra (PDF)

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DEDICATION

This work is dedicated to Professor Sukbok Chang on the occasion of his 60th birthday.

ABBREVIATIONS

TBA—tetrabutylammonium, TMDSO—1,1,3,3-Tetramethyldisiloxane. HFIP—1,1,1,3,3,3-Hexafluoro-2-propanol, CAN—ceric ammonium nitrate, TBHP—*tert*-Butyl hydroperoxide.

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55. A more comprehensive investigation of enantioselectivity of target alkyl aryl ethers **42** and **47** from monosubstituted alkenes is demonstrated in the SI (Figure S6-S11).