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Rare-Earth $Y(OTf)_3$ Catalyzed Coupling Reaction of Ethers with Azaarenes

Yue-Hua Wu,[†] Nai-Xing Wang,*[,†] Tong Zhang,[†] Lei-Yang Zhang,[†] Xue-Wang Gao,[†] Bao-Cai Xu,*[,‡] Yalan Xing,*[,§] and Jian-Yi Chi[∥]

[†]Technical Institute of Physics and Chemistry & University of Chinese Academy of Sciences, Chinese Academy of Sciences, Beijing, 100190, China

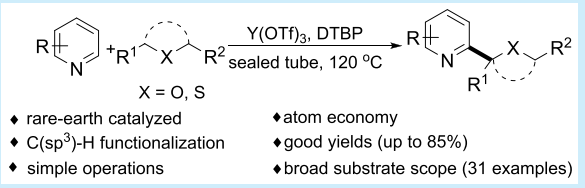
[‡]School of Food and Chemical Engineering, Beijing Technology and Business University, Beijing 100048, China

[§]Department of Chemistry, William Paterson University of New Jersey, Wayne, New Jersey 07470, United States

[∥]Baotou Rare Earth Research and Development Center, Chinese Academy of Sciences, Baotou, 014010, China

Supporting Information

ABSTRACT: Rare-earth catalysis has become a hot topic in the field of catalytic organic reaction. Chain ethers mostly have lower reactivity and lower boiling points which limited their reaction scope. Herein, we found a rare-earth $Y(OTf)_3$ can catalyze the coupling reaction of ethers especially chain ethers and thioethers with azaarenes. This protocol features simple operations, a broad substrate scope (31 examples), moderate to good yields (up to 85%), and atom economy.

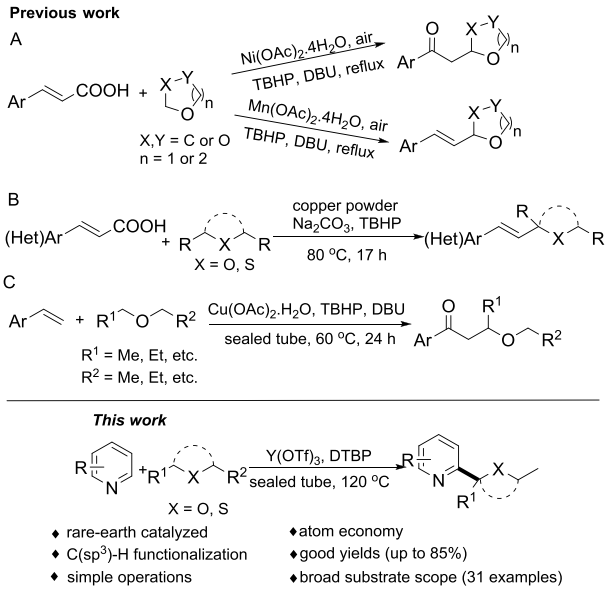


Transition metal catalyzed organic reactions have been widely studied for a long time.[1−3] Rare-earth catalysis has become a hot topic in the field of catalytic organic reaction.[4−6] Ethers are important moieties in a great number of biologically active compounds and pharmaceuticals.[7−11] Simple ethers, such as diethyl ether, and tetrahydrofuran, are bulk readily available chemicals which are often used as solvents for many reactions.[12−14] In the past few years, ethers were used as substrates in many α-C(sp^3)−H bond functionalization reactions via oxidative coupling processes.[15−20] Zhang[21] reported the bifunctionalization of styrenes with cyclic ethers, and Li[22] reported the 1,2-alkylarylation of styrenes with cyclic ethers and indoles. Only cyclic ethers are used in those reports. Therefore, α-C(sp^3)−H bond functionalized ethers, especially chain ethers, remain a challenge.[23]

Recently, our group has successfully developed several strategies of C(sp^3)−H functionalization of ethers (Scheme. 1). We previously reported Ni- and Mn-catalyzed decarboxylative cross-coupling of α,β-unsaturated carboxylic acids with cyclic ethers (Scheme. 1A).[24] When $Ni(OAc)_2{\cdot}4H_2O$ was used as a catalyst, oxyalkylation was achieved. and $Mn(OAc)_2{\cdot}4H_2O$ promoted the alkenylation. We also disclosed the C(sp^3)−H bond functionalization of chain ethers with α,β-unsaturated carboxylic acids (Scheme 1B).[25] Additionally, we developed a $Cu(OAc)_2{\cdot}H_2O$ mediated functionalization of the unactivated C(sp^3)−H bond of chain ethers with styrenes using *tert*-butyl hydroperoxide (TBHP) as a radical initiator (Scheme. 1C).[26]

Cross-dehydrogenative coupling (CDC) has become one of the most straightforward strategies in C−H bond functionalization without the need for prefunctionalization of reactants.[23,27−30] Li and co-workers published a CDC reaction of pyridines and cycloalkanes, which was known as a Minisci-type reaction.[31−35] Although the alkylation products were obtained in moderate yields, most pyridines as substrates afford almost equal amounts of mono- and bis-alkylation products, and only bis-alkylation products were obtained in some cases, which showed low regioselectivity.[36] The substrates were limited to

Scheme 1. C(sp^3)−H Functionalization of Ethers



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cycloalkanes, and the detailed mechanism was not investigated. Later, Lei and co-workers developed a selectfluor promoted CDC reaction of pyridines with cycloalkanes.[37] Another alkylation of pyridine derivatives using $K_2S_2O_8$ was disclosed by Barriault and co-workers.[38] However, this method lacks regioselectivity. Coupling of ethers with azaarenes is important from a practical point of view. Herein, we would like to describe the coupling reaction of ethers and azaarenes.

Results and Discussion

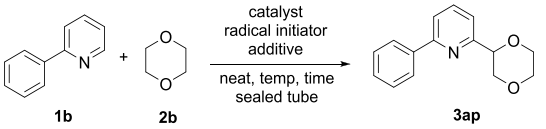
We began our study of the coupling reaction of the chain ethers with azaarenes. The optimization investigation was performed using 2-methylpyridine and diethyl ether as model substrates, and the results are shown in Table S1. However, the yield was up to 54%. Then more reactive 1,4-dioxane and 2-phenylpyridine were used as the substrates for the optimization studies, and the results are shown in Table 1.

After screening metal catalysts (entries 1−4), **3ap** was achieved in 36% yield (entry 2). Only trace amount of product was obtained when $Cu(OAc)_2{\cdot}H_2O$ was used as the catalyst (entry 4). The results showed that $Y(OTf)_3$ was the most powerful catalyst. To our delight, the reaction could also run without DBU (entry 5). When no $Y(OTf)_3$ catalyst was added, trace amount of product was obtained, which showed that the rare-earth catalyst is essential for this reaction (entry 6). The rare-earth yttrium ion belongs to a hard Lewis acid, which exhibits strong ability to coordinate with compounds containing a N or an O atom. We speculated that, in this case, the azaarenes and ethers can be pulled together by the yttrium ion to react more smoothly. Subsequently, we found that TBHP was less effective (entries 7). By screening the reaction time, the results showed that prolonging the reaction time could further increase the yield of **3ap** to 57% (entries 8, 9). Next, we studied the catalyst loading of $Y(OTf)_3$ and found that reducing or increasing the amount of the catalyst did not affect the reaction yield significantly (entries 10, 11). However, changing the amount of DTBP has a great impact on the yield of the reaction. When 3.0 equiv of DTBP were used, the yield of **3ap** was further improved to 65% (entries 12, 13). Then, when the reaction was carried out at 90 °C, the yield of **3ap** dropped dramatically (entries 14−16). We also tried a photocatalytic reaction. **3ap** was obtained with Na_2-eosin Y as a photosensitizer under blue light at room temperature (entries 17, 18). It is worth noting that when the reaction was performed at gram scale, **3ap** was obtained in 57% yield (entry 19). When using 2,6-dimethylpyridine instead of 2-phenylpyridine, the corresponding product was obtained in 85% yield (entry 20).

With the optimal conditions in hand, the substrate scope was investigated (Figure 1). First, a series of ethers were investigated. Chain ethers, such as diethyl ether and dibutyl ether, methy butyl ether, methy *tert*-butyl ether, and anisole, underwent the reaction smoothly and produced the corresponding products **3aa**−**3af** in moderate yields. Compared **3aa** with **3ab**, we found that the reactivity of 2-phenylpyridine was lower than 2-methylpyridine. In addition, when 1,2-diethoxyethane was used as the starting material, **3ag** and **3ah** were obtained in 33% and 14%, respectively, which showed that the steric effect was the major factor. And due to the large steric hindrance, diisopropyl ether only gave a trace amount of the product (**3ai**).

Cyclic ethers such as tetrahydropyran and tetrahydrofuran reacted smoothly to give the desired products (**3aj**−**3al**).

Table 1. Optimization of the Reaction Conditions of Coupling Reaction of the Cyclic Ethers[a]



1b 2b 3ap

entry	cat. (mol %)	radical initiator (equiv)	additive (equiv)	temp (°C)	time (h)	yield[b] (%)
1	$Sc(OTf)_3$ (5.0)	DTBP (2.0)	DBU (1.5)	120	12	33
2	$Y(OTf)_3$ (5.0)	DTBP (2.0)	DBU (1.5)	120	12	36
3	$Ce(OTf)_3$ (5.0)	DTBP (2.0)	DBU (1.5)	120	12	26
4	$Cu(OAc)_2{\cdot}H_2O$ (5.0)	DTBP (2.0)	DBU (1.5)	120	12	trace
5	$Y(OTf)_3$ (5.0)	DTBP (2.0)		120	12	35
6		DTBP (2.0)		120	12	trace
7	$Y(OTf)_3$ (5.0)	TBHP (2.0)		120	12	trace
8	$Y(OTf)_3$ (5.0)	DTBP (2.0)		120	8	31
9	$Y(OTf)_3$ (5.0)	DTBP (2.0)		120	24	57
10	$Y(OTf)_3$ (3.0)	DTBP (2.0)		120	24	56
11	$Y(OTf)_3$ (1.0)	DTBP (2.0)		120	24	58
12	$Y(OTf)_3$ (3.0)	DTBP (1.0)		120	24	34
13	$Y(OTf)_3$ (3.0)	DTBP (3.0)		120	24	65
14	$Y(OTf)_3$ (3.0)	DTBP (3.0)		130	24	58
15	$Y(OTf)_3$ (3.0)	DTBP (3.0)		110	24	32
16	$Y(OTf)_3$ (3.0)	DTBP (3.0)		90	24	trace
17[c]	$Y(OTf)_3$ (3.0)	DTBP (3.0)	Na_2-eosin Y	30	12	trace
18[c]	$Y(OTf)_3$ (3.0)	DTBP (3.0)	Acid red 94	30	12	n.r.
19[d]	$Y(OTf)_3$ (3.0)	DTBP (3.0)		120	24	57
20[e]	$Y(OTf)_3$ (3.0)	DTBP (3.0)		120	24	85

[a]Reaction conditions: 2-phenylpyridine **1b** (0.2 mmol, 1.0 equiv), 1,4-dioxane **2b** (0.25 mL) in sealed tube. [b]Isolated yields. [c]Under blue light. [d]Gram scale (10 mmol scale). [e]Using 2,6-dimethylpyridine instead of 2-phenylpyridine.

When the 2-methyltetrahydrofuran reacted with 2-phenylpyridine, the coupling product was obtained exclusively at the C5 of the 2-methyltetrahydrofuran (**3am**). Since there are two chiral centers in **3am**, two diastereomers were generated (d.r. = 5:3; see Supporting Information). Using 1,3-dioxolane as substrate, **3an** and **3ao** were obtained in 18% and 55%, respectively. The reason might be that the hydrogen on the C2 of the 1,3-dioxolane is more easily removed to generate the radical (**3ao**).

Subsequently, an array of the pyridine moiety bearing electron-donating groups such as 2-methyl, 2,3-dimethyl, 2,3-cyclopenteno, 2,5-dimethyl, and 2,6-dimethyl groups were found to provide the desired products **3aq**−**3au** in favorable yields. Due to the only reactive site at C4 of the 2,6-

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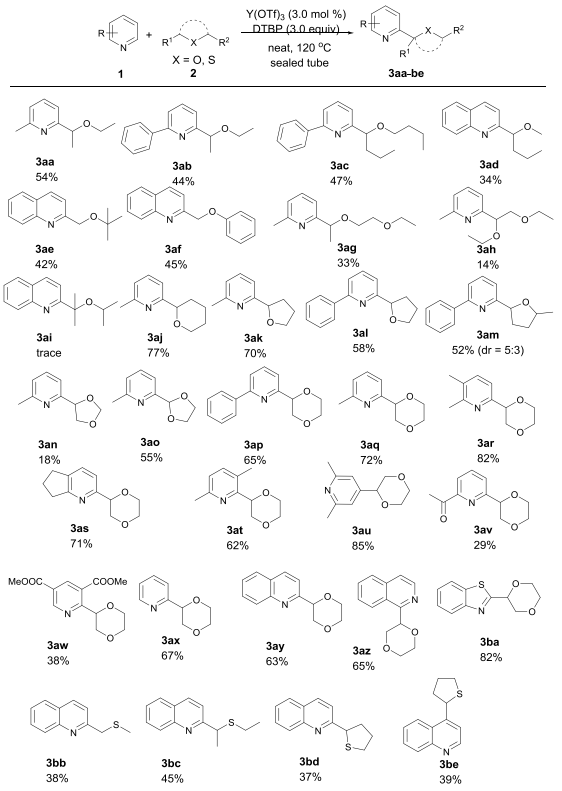


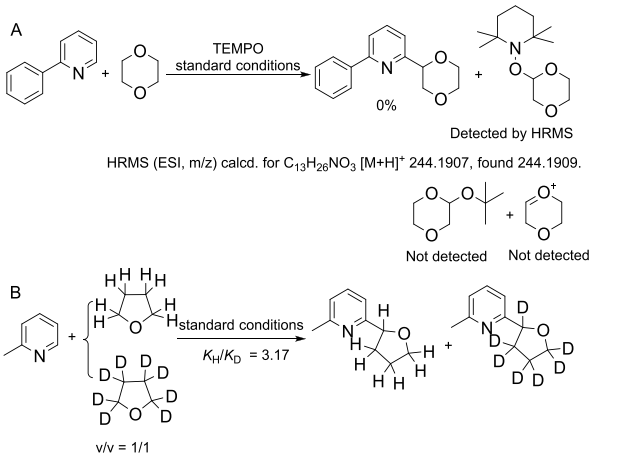
Figure 1. Substrate scope for the reaction of azaarenes and ethers.[a] [a] Reaction conditions (for the chain ethers): **1** (0.2 mmol, 1.0 equiv), **2** (0.25 mL) $Y(OTf)_3$ (5.0 mol %), DTBP (3.0 equiv), in sealed tube at 120 °C for 24 h; (for the cyclic ethers and thioethers): **1** (0.2 mmol, 1.0 equiv), **2** (0.25 mL) $Y(OTf)_3$ (3.0 mol %), DTBP (3.0 equiv), in sealed tube at 120 °C for 24 h, unless otherwise noted.

dimethylpyridine, **3au** was obtained in 85% yield. And the pyridine moiety bearing an electron-withdrawing group such as 2-acetylpyridine and dimethylpyridine-3,5-dicarboxylate could give corresponding products **3av** and **3aw** in lower yield. Furthermore, pyridine, quinoline, isoquinoline, and benzothiazole smoothly underwent the reaction and achieved good yields (**3ax**–**3ba**).

At last, we studied the thioethers such as dimethylsulfane, diethylsulfane, and tetrahydrothiophene to react with quinoline, the corresponding coupling products **3bb**–**3be** were obtained in moderate yield. It is worth noting that the products of thioethers are still sulfides, which are not further oxidized to sulfoxides and sulfones.

To gain further insight into the reaction mechanism, mechanistic studies were designed and conducted (Scheme 2). Initially, 3.0 equiv of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) were added to the reaction system under the standard conditions. It was found that the transformation was completely inhibited, and the adduct of TEMPO and radical generated from 1,4-dioxane was detected by HRMS-ESI. Ethers can be transformed into acetal in the presence of TBHP. And the acetal can further generate an oxocarbenium to react with other nucleophiles.[39] However, the acetal and corresponding cyclic oxocarbenium were not detected by HRMS. These results suggested that the present reaction should involve a free radical process (Scheme. 1A). Then the deuterated intermolecular competing kinetics isotope experiment was performed using deuterated THF as substrate. By integrating ^{1}H NMR, the K_H/K_D = 3.17, which suggested

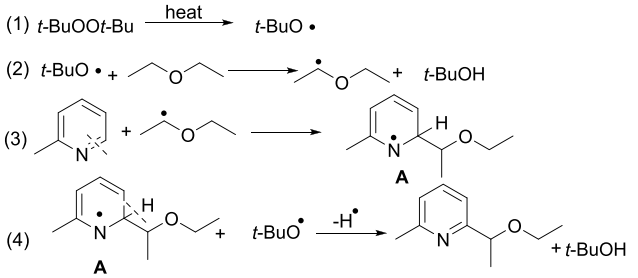
Scheme 2. Mechanism Studies



that α-C(sp^3)–H bond cleavage of ether is involved in the rate-determining step (Scheme. 2B).

Based on the mechanistic studies, a plausible reaction mechanism was proposed (Scheme 3). For example, in the

Scheme 3. Plausible Reaction Mechanism



case of the reaction of diethyl ether and 2-methylpyridine, under heat, the DTBP decomposed into two *tert*-butylperoxyl radicals. Then, the *tert*-butylperoxyl radical turned the ether into a carbon-centered radical. The ether radical then combined with 2-methylpyridine to give intermediate **A**. The intermediate **A** was further oxidized by DTBP to generate the product.

Since the reaction is a free radical reaction, stereoselectivity control of the reaction meets a great challenge. First, chiral ligands and catalysts such as BINOL, BINAP, L-proline, and cyclohexanediamine were added to the reaction system. However, none of these reactions gave any stereoselectivity. Subsequently, three methods were tried to slow down the reaction rate (see Supporting Information): (a) the reaction temperature was dropped from 120 to 90 °C; (b) 0.2 equiv of TEMPO was added to the reaction system to capture some of the newly generated free radicals; (c) the reaction was carried out under photocatalyzed conditions at room temperature. No positive result was achieved. Although the approaches we used gave no stereoselectivity, chemists interested in the stereoselectivity control of radical reactions could learn from the strategies that we provided.

Conclusions

In summary, we have developed a rare-earth $Y(OTf)_3$ catalyzed coupling reaction of ethers, including chain ethers, cyclic ethers, and thioethers, with azaarenes to generate corresponding alkylation products in moderate to high yields

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with good functional group tolerance. Further studies regarding the coupling reaction occurring in the neighborhood of other functionalities are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02763.

Experimental procedures and copies of spectra for all the compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nxwang@mail.ipc.ac.cn.
*E-mail: xubac@163.com.
*E-mail: xingy@wpunj.edu.

ORCID

Nai-Xing Wang: 0000-0001-9520-3254

Notes

The authors declare no competing financial interest.

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