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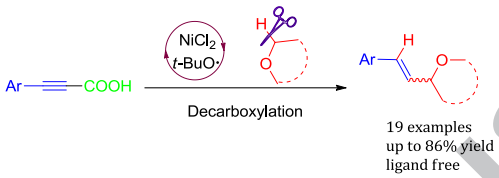

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$NiCl_2$-Catalyzed Radical Cross Decarboxylative Coupling between Arylpropiolic Acids and Cyclic Ethers

Zi-juan Wan[a] , Jin-yuan Wang and Jun Luo[a,] *

[a]*Affiliation 1, Address, City and Postal Code, Country School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing, 210094, China*

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ABSTRACT

A direct alkenylation of cyclic ethers *via* radical cross decarboxylative coupling process catalyzed by $NiCl_2$ and using DTBP as radical initiator and oxidant was developed. A variety of arylpropiolic acids and cyclic ethers were transformed into the corresponding 2-arylvinyl cyclic ethers in moderate to excellent yields. Mechanistic experiments were conducted to determine the nature of the reaction intermediates, and a plausible reaction mechanism involving $NiCl_2$-promoted radical process was proposed.

Catalytic transformation of numerous chemicals to valuable compounds *via* C-H functionalization is of great importance in organic synthesis [1]. Direct functionalization of C(sp^3)−H bonds in expectable and efficient manner has become a central challenge in modern organic chemistry for their relatively stronger bond dissociation energy (BDE) and lower polarity [2] than C(sp^2)−H functionalization [3]. Therefore, direct C(sp^3)−H functionalization of cyclic ethers attracts plenty of attention [4] since a large number of natural products, bearing 2-subsituted cyclic ether motif, exhibit a wide range of biological activities [5]. Furthermore, direct alkenylation of cyclic ethers through C(sp^3)−H functionalization is also significant because the products, arylvinyl cyclic ethers, are very important biologically active compounds (Figure 1) [6]. Recently, radical activation has proven to be an efficient pathway for converting C(sp^3)−H bonds to the corresponding radicals [7]. Using the strategy of organometallic C-H activation and oxidative radical cross-coupling, the direct C(sp^3)−H functionalization methods have grown exponentially [8].

In recent years, the transition metal-catalyzed cross decarboxylative coupling has become a powerful tool to prepare organic molecules [9]. Arylpropiolic acids were found to be a universal coupling partner for this kind of reaction .

Here we report a new protocol for direct alkenylation of cyclic ethers to prepare 2-arylvinyl cyclic ethers with high yield *via* radical initiated cross decarboxylative coupling catalyzed by $NiCl_2$.

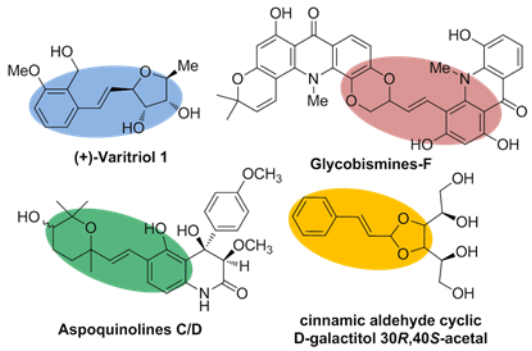


Figure 1. Selected biologically active 2-arylvinyl cyclic ethers.

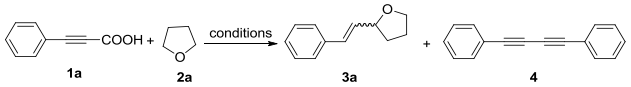
Our study started with the coupling of tetrahydrofuran (THF) with phenylpropiolic acid to prepare 2-styryltetrahydrofuran. Optimization of reaction conditions was inspected first and the results are listed in Table 1.

In the presence of di-*tert*-butyl peroxide (DTBP, 1.2 equiv.), the desired product 2-styryltetrahydrofuran (**3a**) was obtained in 42% yield (Table 1, entry 1). A variety of catalysts including $NiCl_2$, $Ni(acac)_2$, CuCl and $CuCl_2$ were tested. It was found that $NiCl_2$ afforded **3a** in higher yield than $Ni(acac)_2$ (Table 1, entries 2 and 3), while CuCl and $CuCl_2$ gave 1,4-diphenylbutadiyne (**4**) as the major product (Table 1, entries 4 and 5). The category of base affects the reaction significantly. Among the based used, potassium carbonate gave the highest yield of 79% and by-product **4** was not detected (Table 1, entry 6). Sodium carbonate shows negative effect on the reaction (Table 1, entry 7). Bases with stronger basicity than potassium carbonate lower the yield

* Corresponding author. Tel.: +86-25-84315514; fax: +86-25-84315030; e-mail: luojun@njust.edu.cn.

dramatically (Table 1, entries 8-10). The reason might be assigned to the fact that phenylpropiolic acid was partially even completely neutralized to potassium phenylpropiolate, which is completely insoluble in the reaction mixture, by strong bases. Organic tertiary amines such as triethylamine and DBU afford low and moderate yield and slight **4** was detected (Table 1, entries 11 and 12). Having the above results in hand, the effect of radical initiators such as *tert*-butyl hydroperoxide (TBHP), 3-chloroperoxybenzoic acid (*m*CPBA), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 2,2'-azobis(2-methylpropionitrile) (AIBN) and benzoyl peroxide (BPO) on the reaction was investigated. The results indicated that all the initiators were inferior to DTBP (Table 1, entries 13-17). When a classical ligand 2,2'-bipyridine was added, 1,4-diphenylbutadiyne (**4**) was obtained as major product (Table 1, entry 18).

Table 1. Optimization of Reaction Conditions [a]



Entry	Catalyst	Base	radical initiator	Yield(**3a**/**4**)(%) [b]
1	-	-	DTBP	42/<5
2	$NiCl_2$	-	DTBP	65/21
3	$Ni(acac)_2$	-	DTBP	51/23
4	CuCl	-	DTBP	32/65
5	$CuCl_2$	-	DTBP	31/58
6	$NiCl_2$	K_2CO_3	DTBP	79/ND [c]
7	$NiCl_2$	Na_2CO_3	DTBP	43/ND
8	$NiCl_2$	Cs_2CO_3	DTBP	21/ND
9	$NiCl_2$	*t*-BuOK	DTBP	ND/ND
10	$NiCl_2$	NaOAc	DTBP	47/ND
11	$NiCl_2$	NEt_3	DTBP	28/<5
12	$NiCl_2$	DBU	DTBP	56/<5
13	$NiCl_2$	K_2CO_3	TBHP [d]	59/ND
14	$NiCl_2$	K_2CO_3	*m*CPBA	ND/ND
15	$NiCl_2$	K_2CO_3	DDQ	ND/ND
16	$NiCl_2$	K_2CO_3	AIBN	68/ND
17	$NiCl_2$	K_2CO_3	BPO	54/ND
18 [e]	$NiCl_2$	K_2CO_3	DTBP	33/48

[a] General reaction conditions : **1a** (0.5 mmol), catalyst (10 mol%), radical initiator (1.2 equiv.), base (1.1 equiv.), THF (3 mL), 120 °C, 24 h, N_2 atmosphere.

[b] Isolated yield.

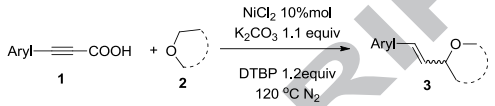
[c] ND=Not detected.

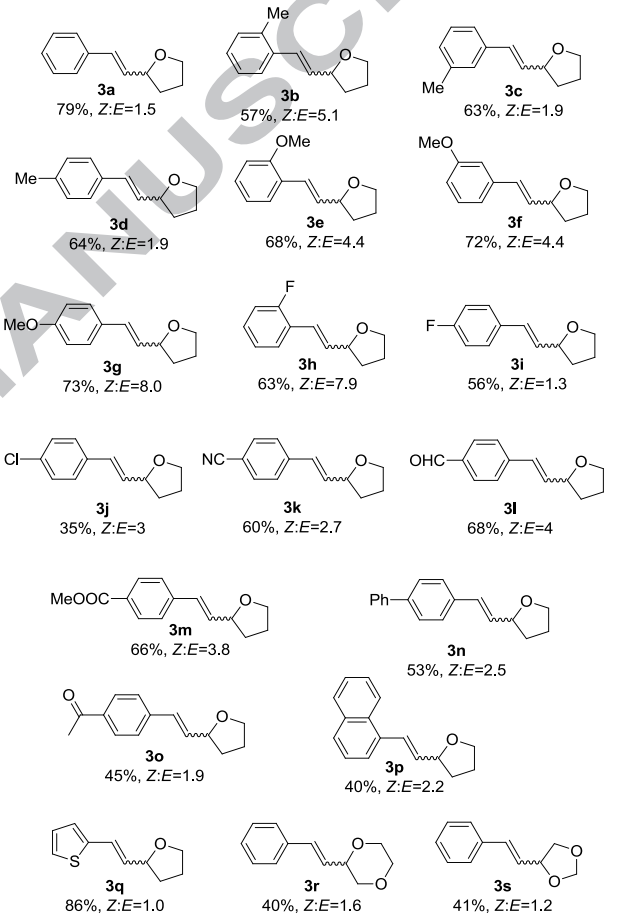
[d] TBHP (5–6 M in decane).

[e] 2,2'-bipy (20 mol%) was used as ligand.

With the optimized reaction conditions in hand, a variety of arylpropiolic acids were selected to couple with cyclic ethers and the results are listed in Table 2. It was observed that the reaction of THF with phenylpropiolic acid containing electron-donating groups such as methoxy and methyl underwent smoothly and generated the corresponding products **3b-g** in good yields (57–73%). Meanwhile, the reaction of THF with phenylpropiolic acid bearing electron-withdrawing groups also proceeded well and afforded the desired products **3h-3o** in 35-68% yields. The steric hindrance did not interfere with this transformation too much (**3b-i**). However, in comparison with *meta*- and *para*-substituted substrates, the *ortho*-isomers afforded a little lower yields but much higher *Z/E* ratios. To our surprise, when 2-thiophenepropiolic acid was used, the corresponding product **3q** was obtained in an amazing high yield of 86%. But 2-naphthalenepropiolic acid gave **3p** in an unsatisfactory yield of 40%. Considering the importance of direct functionalization of different ethers, other simple cyclic ethers including 1,4-dioxane (**3r**) and 1,3-dioxolane (**3s**) were also tested to couple with phenylpropiolic acid under optimized conditions, unfortunately, the yields were relative low (Table 2, **3r** and **3s**).

Table 2. Substrate scope [a b]





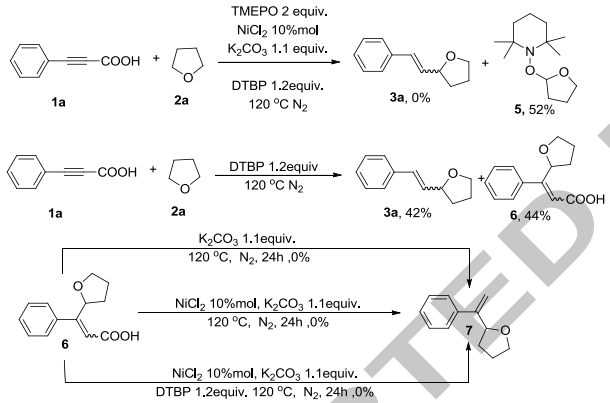
[a] Reaction conditions: **1** (0.5 mmol), $NiCl_2$ (10 mol %), DTBP(1.2 equiv.), K_2CO_3 (1.1 equiv.), **2** (3 mL), 120 °C, 24 h, N_2 atmosphere.

[b] Isolated yield.

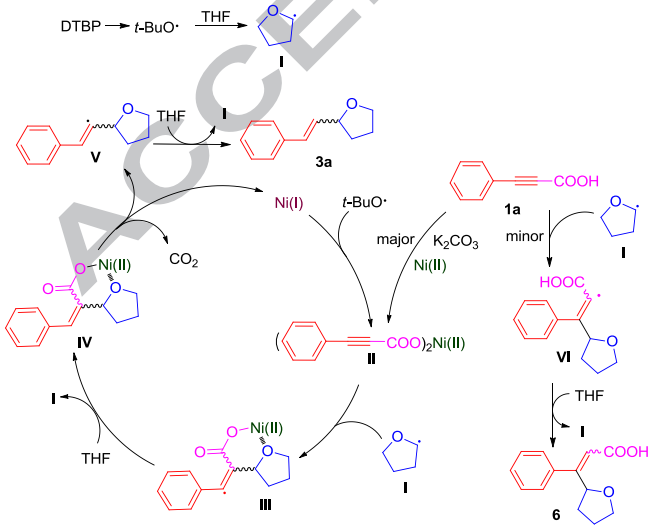
[c] *Z/E* ratios were determined by ^1H NMR based on Ref. 10b.

Then, control experiments were performed to probe the reaction mechanism (Scheme 1). Adding the typical radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) completely inhibited the reaction. Almost no desired product was detected at all, however, along with the formation of a radical-trapping product (**5**) in 52% yield. The results indicate that this reaction must proceed *via* a radical procedure. When $NiCl_2$ and K_2CO_3 were not added, a by-product of cinnamic acid **6** was isolated in 44% yield while 42% of **3a** was detected. The by-product **6** could not be decarboxylated smoothly under the three conditions.

On the basis of the above results and the literature reports [10], a plausible mechanism containing a radical oxidative coupling process is illustrated in Scheme 2. Using the reaction of phenylpropiolic acid (**1a**) and THF as an example, the reaction should be initiated by the cleavage of DTBP to gives a *tert*-butoxy radical, which abstracts a hydrogen atom from THF to afford radical **I**. The radical **I** may engage on two competing pathways, i.e., addition to the 2-position carbon in intermediate **II**, generated from the reaction of phenylpropiolic acid (**1a**) with potassium carbonate and nickel chloride, to produce intermediate **III**. The other pathway is addition to the 3-position carbon in phenylpropiolic acid (**1a**) to generate the intermediate **VI,** which produces the stable cinnamic acid **6** through hydrogen abstraction of THF. The intermediate **III** then proceeds *via* an abstraction of THF to generate intermediate **IV**, which undergoes an elimination through a single electron transfer process to release carbon dioxide, alkenyl radical **V** and Ni(I). Alkenyl radical **V** abstracts a hydrogen atom from THF to generate the product **3a**. Ni(II) would be regenerated by oxidation of Ni(I) with a *tert*-butoxy radical and converted to intermediate **II** to complete the catalytic cycle. Ni(II) might have two roles in this reaction: one is the formation of salt with phenylpropiolic acid to facilitate the 2-position attack by **I**; the other is to facilitate the radical decarboxylatioin of intermediate **III**.



Scheme 1. Control experiments



Scheme 2. Plausible mechanism of the cross decarboxylative coupling.

In conclusion, we have described a direct alkenylation of cyclic ether *via* cross radical decarboxylative coupling process catalyzed by $NiCl_2$ and using DTBP as radical initiator and oxidant. This catalytic system is suitable for the coupling reactions between a wide range of arylpropiolic acid and cyclic ethers. Based on the control experiments, a radical mechanism was proposed.

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Highlights

- Ligand-free NiCl2-catalyzed direct alkenylation of cyclic ethers.
- A radical cross decarboxylative coupling strategy was applied.
- Mechanistic experiments were conducted to establish a plausible reaction mechanis.