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# A coupling reaction between tetrahydrofuran and olefins by Rh-catalyzed/Lewis acid-promoted C–H activation

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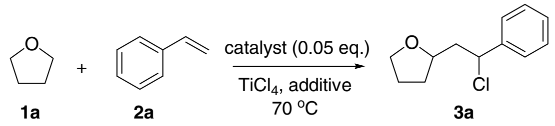
ABSTRACT

A novel coupling reaction between tetrahydrofuran and olefins is discovered, in which the consecutive C–C and C–Cl bond-forming process takes place via Rh-catalyzed/lewis acid-promoted C–H activation. This reaction could be developed into a straightforward and effective method for rapid access to 2-(2-chloro-2-arylethyl)-tetrahydrofuran compounds.

## 1. Introduction

The tetrahydrofuran (THF) moiety is the key structure feature of a large number of biologically active natural products.[1] Thus, synthesis of substituted THF has long been attractive to organic chemists. Recently, many groups have reported transition metal catalyzed intramolecular cyclization and tandem addition–cyclization to achieve THF derivatives.[2] However, direct transformation of commercially available THF to THF derivates has been a challenging subject and has rarely been reported.[3] In connection with our recent interest in sp$^3$ C–H bond activation of alcohols,[4] we speculated that the same transformation could occur on ethers.[5] Among the ethers we screened, cyclic ether (especially THF) coupled with styrene successfully under the catalysis of $RhCl(PPh_3)_3$ and the promotion of $TiCl_4$. To our surprise, an additional C–Cl bond was formed during this course (Eq. 1). This interesting result provides a direct and convenient procedure for preparation of 2-(2-chloro-2-arylethyl)-tetrahydrofuran derivatives with synthetically useful C–Cl bond, promoting us to investigate this cross-coupling protocol in detail.

**Table 1**
Optimization of reaction condition[a]



(1)

| Entry | Catalyst | **1a (equiv)** | Additive (equiv) | % Yield[b] (% Conv.)[c] |
|---|---|---|---|---|
| 1[d] | $RhCl(PPh_3)_3$ | 50 | – | 21 (80) |
| 2[d] | – | 50 | – | – |
| 3[d] | $RhCl(PPh_3)_3$ | 50 | TBHP (0.5) | 33 (95) |
| 4 | $RhCl(PPh_3)_3$ | 50 | TBHP (1.1) | 56 (100) |
| 5 | $Pd(OAc)_2$ | 50 | TBHP (1.1) | – |
| 6 | $Pd(PPh_3)_4$ | 50 | TBHP (1.1) | – |
| 7 | $RhCl_3$ | 50 | TBHP (1.1) | Trace |
| 8 | $RhCl(PPh_3)_3$ | 20 | TBHP (1.1) | 23 (70) |
| 9 | $RhCl(PPh_3)_3$ | 40 | TBHP (1.1) | 65 (100) |
| 10 | $RhCl(PPh_3)_3$ | 40 | $Bz_2O_2$ (1.0) | 16 (80) |

[a] Reaction condition: styrene **2a** (1.0 mmol), THF **1a** (20–50 mmol), catalyst (0.05 mmol), $TiCl_4$ (4.0 mmol), and TBHP (0.2 ml, ~1.1 mmol, ~5.5 M in decane) at 70 °C for 5 h.
[b] Isolated yields based on the consumed styrene.
[c] Reaction conversion determined by GC analysis.
[d] Using 2 mmol of $TiCl_4$.

Initially, the coupling of styrene with excessive THF was conducted in the presence of a catalytic amount of $RhCl(PPh_3)_3$ and two equivalents of $TiCl_4$, wherein only 21% isolated yield with 80% reaction conversion was obtained (Table 1, entry 1). The desired cross-coupling, however, did not proceed at all in the absence of $RhCl(PPh_3)_3$, and only the polymerization of starting styrene was observed (Table 1, entry 2). To our delight, when substoichiometric amount of *tert*-butyl hydroperoxide (TBHP) was employed,[6] both reaction conversion and product yield were improved (Table 1, entry 3). The yield increased to 56% when 4 equiv of $TiCl_4$ and 1.1 equiv of TBHP were employed (Table 1, entry 4). However,

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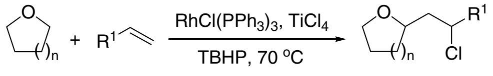
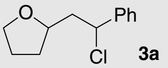
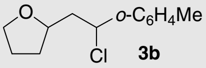
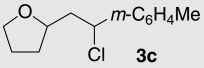
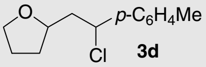
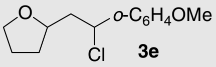
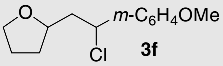
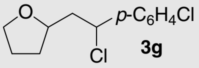
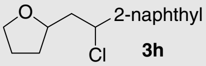
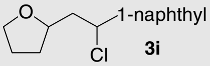
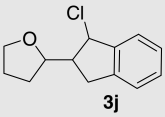
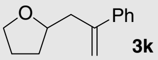
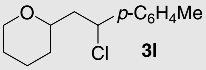
$Bz_2O_2$ was not effective in this coupling (Table 1, entry 10). Among the catalysts further examined, $RhCl_3$ gave trace amount of the desired product (Table 1, entry 7), and the use of other transition metal catalyst such as $Pd(OAc)_2$ or $Pd(PPh_3)_4$ resulted in no reaction (Table 1, entries 5 and 6). It should be noted that the THF loading also has somewhat influence on this reaction (Table 1, entries 8 and 9), and currently the employment of 40 equiv of THF afforded the best result with an increasing isolated yield of 65%. Among the lewis acids investigated such as $AlCl_3$, $SnCl_4$ and $SbCl_5$,[7] only $TiCl_4$ was found to be successful for this transformation.

Based on the above-optimized conditions (Table 1, entry 9), the scope of this reaction was then examined and different vinyl-substituted arenes **2** were subjected to the reaction with **1**. As shown in Table 2, different substituents on the aromatic ring were compatible with this coupling reaction. Vinyl-substituted arenes containing the electron-donating group proved to be effective and the corresponding products **3** were formed in moderate to good yields (entries 1–6). When a styrene bearing an electron-withdrawing substituent such as *para*-chloro styrene was used (entry 7); however, the starting alkene could not be consumed completely, even with longer reaction time (8 h), giving product **3g** only in 30% yield with 60% of the substrate recovered, which clearly demonstrated the unfavorable electronic effect on the aromatic ring of styrene. Moreover, vinyl-substituted naphthalenes (entries 8 and 9) and indene (entry 10) also proved to be effective, and the desired products **3h**–**j** were obtained in moderate yields. In addition, reaction of α-methyl substituted styrene with THF **1a** was tested (entry 11), but the expected product was not obtained. Instead, the terminal olefin **3k** was formed through the kinetically controlled elimination process. Furthermore, THP as a cyclic ether was investigated in this coupling reaction, and the desired product **3l** was obtained in a lower yield (35%). The dimerization of the alkene was the main side reaction.[8] However, while using 1,4-dioxane and 1,3,5-trioxane as cyclic ether, the coupling reaction did not occur under the present conditions. Acyclic aliphatic ether such as diethyl ether was not effective, affording the coupling product in very low yield (~10%).

**Table 2**
Coupling reaction of olefins and ethers[a]



**1** **2** **3**

| Entry | Substrate | Product | % Yield[b] |
|---|---|---|---|
| 1 | $n = 1$, $R^1$ = Ph |  **3a** | 65 (1:0.5) |
| 2 | $n = 1$, $R^1$ = *o*-$C_6H_4Me$ |  **3b** | 55 (1:0.5) |
| 3 | $n = 1$, $R^1$ = *m*-$C_6H_4Me$ |  **3c** | 45 (1:0.7) |
| 4 | $n = 1$, $R^1$ = *p*-$C_6H_4Me$ |  **3d** | 75 (1:0.5) |
| 5 | $n = 1$, $R^1$ = *o*-$C_6H_4OMe$ |  **3e** | 60 (1:0.7) |
| 6 | $n = 1$, $R^1$ = *m*-$C_6H_4OMe$ |  **3f** | 63 (1:0.8) |
| 7 | $n = 1$, $R^1$ = *p*-$C_6H_4Cl$ |  **3g** | 30(40)[c] (1:0.6) |
| 8 | $n = 1$, $R^1$ = 2-naphthyl |  **3h** | 56 (1:0.9) |
| 9 | $n = 1$, $R^1$ = 1-naphthyl |  **3i** | 50 (1:0.9) |
| 10[d] | $n = 1$, Indene |  **3j** | 51 |
| 11[d] | $n = 1$, α-methyl styrene |  **3k** | 54 |
| 12[d] | $n = 2$, $R^1$ = *p*-$C_6H_4Me$ |  **3l** | 35 (1:0.8) |

[a] Standard reaction conditions **1** (40.0 mmol), **2** (1.0 mmol), $RhCl(PPh_3)_3$ (0.05 mmol), $TiCl_4$ (4.0 mmol) and TBHP (0.2 ml, ~1.1 mmol) at 70 °C for 5 h.

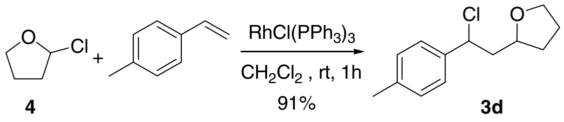
[b] Isolated yields calculated on the basis of alkene **2**; the ratio of two diastereoisomers determined by $^1H$ NMR is given in parentheses.

[c] Substrate conversion determined by GC analysis.

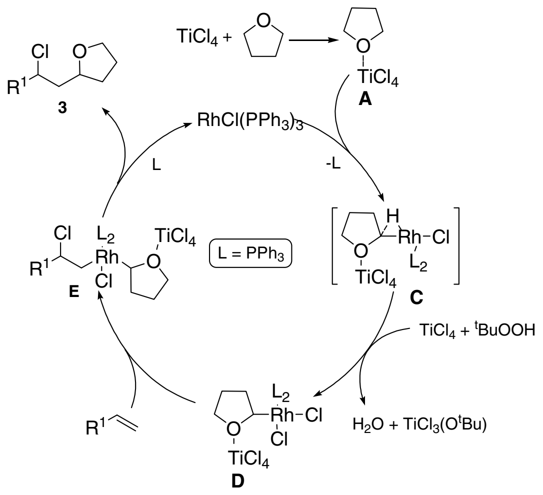
[d] Using 2.0 mmol of $TiCl_4$ (1.0 M in $CH_2Cl_2$).

To propose a possible reaction mechanism, some supporting experiments were then conducted. As shown in Scheme 1, the known 2-chlorotetrahydrofuran **4**[9] instead of THF was subjected to the current coupling reaction, and the desired addition product **3d** could be achieved in 91% yield, which partially demonstrated that may be the alpha-C–H activation of THF was firstly involved in this coupling reaction in the presence of catalyst $RhCl(PPh_3)_3$. Additionally, it was found that addition of $PPh_3$ (0.01 equiv) has a large detrimental effect on the catalytic performance,[7] implying that the presence of $PPh_3$ could prohibit the ligand dissociation and exchange.

Based on the above experimental results, a tentative mechanism was thus proposed in Scheme 2. Firstly, oxygen atom of THF could preferentially coordinate with Lewis acid $TiCl_4$,[10] and then Rh-catalyzed alpha-C–H activation of THF could take place



**Scheme 1.** Cross-coupling of 2-chlorotetrahydrofuran and *p*-methyl styrene. Using 5 mmol of 2-chlorotetrahydrofuran and 1 mmol of *p*-methyl styrene in 4 mL $CH_2Cl_2$.



**Scheme 2.** Proposed mechanism on the coupling of tetrahydrofuran and olefins.

through intermediate **C** followed by the cooperation of $TiCl_4$ and TBHP, generating the key species **D**. During this process, TBHP may act as an effective hydride acceptor[11] to accelerate the C–H activation from **C** to **D**.[12] Subsequently, the alkene coordination/insertion into the Rh–Cl bond[13] in a less hindered fashion could afford the intermediate **E**, which could undergo reductive elimination to provide the desired product **3** with the release of Rh(I) catalyst into the next cycle.

In conclusion, we have developed a novel Rh-catalyzed/Lewis acid-promoted coupling reaction between THF and vinyl-substituted arenes. This reaction may proceed via a process including the alpha-C–H activation of THF and successive C–C bond and C–Cl bond formation. A series of 2-(2-chloro-2-arylethyl)-tetrahydrofuran have been synthesized from simple and readily available starting materials. Further studies toward the insight into the reaction mechanism, the expansion of the substrate scope and the synthetic application is currently ongoing in our group.

## 2 General procedure

To the freshly distilled cooled (−78 °C) THF (3.2 mL, 40.0 mmol) was added $TiCl_4$ ($4.4\times10^{-1}$ mL, 4.0 mmol) carefully under argon. The resulting light yellow mixture was stirred and warmed to 0 °C within 30 min, then $RhCl(PPh_3)_3$ (46.3 mg, $0.5\times10^{-1}$ mmol), styrene (117.0 μL, 1.0 mmol), and TBHP (0.2 mL, ~1.1 mmol) were sequentially added. After the reaction mixture was stirred at 70 °C until the substrate was consumed completely (~5 h), the reaction mixture was cooled to rt and filtered through a short silica gel column using $CH_2Cl_2/Et_2O$ as eluent. After evaporation of the solvent, the residue was purified by flash chromatography (petroleum ether/AcOEt = 20:1) to afford **3a** (136.5 mg, 65% yield, diastereomeric ratio 1:0.5).

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.057.

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4. For Rh-catalyzed $sp^3$ C–H bond activation see: (a) Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A.; Zhao, Y. M.; Xia, W. J. *J. Am. Chem. Soc.* **2005**, *127*, 10836–10837; (b) For Pd-catalyzed $sp^3$ C–H bond activation see: Jiang, Y. J.; Tu, Y. Q.; Zhang, E.; Zhang, S. Y.; Cao, K.; Shi, L. *Adv. Synth. Catal.* DOI: 10.1002/adsc.200700439.
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6. *Caution!* Mixing a metal salt and peroxide can cause an explosion.
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