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# Iron-catalyzed ene-type propargylation of diarylethylenes with propargyl alcohols<sup>†</sup>

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The diarylalkenyl propargylic complex framework has been found in many natural products and medicinal regents. Herein, we have disclosed an unprecedented FeCl<sub>3</sub> catalyzed ene-type reaction of propargylic alcohols with 1,1-diaryl alkenes which enabled us to furnish a diarylalkenyl propargylic complex framework in moderate to high chemical yields (up to 98%).

## Introduction

Iron as one of the most abundant metals on the earth and has attracted much attention in modern catalysis because of its unique reactivity towards carbon–carbon and carbon–heteroatom bond formation. Owing to its inexpensive and environmental benign characteristics, considerable effort has focused on iron catalysis which resulted in a series of novel iron-catalyzed organic transformations.<sup>1</sup>

The propargylic moiety is a widely distributed structure in medicinal and organic chemistry due to the high synthetic value of the alkyne functionality. The electron-rich triple bond, in combination with the fairly acidic features of the terminal acetylenic hydrogen atom, makes it a versatile entity for further chemical transformation.<sup>2</sup> This makes propargylic moieties suitable precursors for the synthesis of highly substituted 1,1-diarylalkanes. In addition, various natural products, fine chemicals and pharmaceuticals containing propargylic subunits as components of their structures have been reported.3 Consequently, efficient routes to this important scaffold are constantly needed. One attractive method is the Brønsted acid catalyzed propargylation.<sup>4</sup> Another efficient way for making this propargylic moiety is the direct propargylation of arenes or heteroarenes with propargyl alcohols via metal catalyzed Friedel-Crafts (F-C) reactions (eqn (1)). Since the discovery by Nicolas in 1987,5 the propargylation of aromatic systems have attracted much attention. In 2002, Uemura and coworkers discovered that a stoichiometric amount of Ru-allenylidene reacted with 2-methylfuran leading to the rapid formation of 5-propargylated 2-methylfuran.<sup>6a</sup> Subsequently

a variant of these catalytic transformations was developed by using ruthenium complexes.<sup>6b-f</sup> In 2004, Toste and co-workers developed a mild rhenium-catalyzed propargylation of electronrich arenes.7 Although an example of iron-catalyzed nucleophilic substitution of propargylic alcohols was disclosed by Zhan group in 2006,<sup>8</sup> diarylethylene-type nucleophiles were not included in this contribution. More recently, Yoshimatsu et al. developed a scandium-catalyzed propargylation.9 Besides arenes and heteroarenes, allylsilane and vinyl silvl ethers were also used as nucleophiles in this transformation. While the methods described above used  $\alpha$ -arylated propargylic alcohols as highly reactive alkylation reagents, all the above reports of the arylation of  $\alpha$ -substituted propargyl groups are based on the Friedel-Crafts reaction. Herein, we document a FeCl<sub>3</sub>-catalyzed ene-type substituted alkylation reaction of propargyl alcohols bearing not only a terminal group but also a internal alkyne group (eqn (2)). To the best of our knowledge, this is the first report of an ene-type reaction triggered propargylation of 1,1-diarylethylene with propargyl alcohol.



### **Results and discussion**

We began our investigation by examining the FeCl<sub>3</sub> catalyzed twocomponent reaction of alkenes and 1-phenyl-2-propyn-1-ol. The initial experiment results showed that the use of a catalytic amount of anhydrous FeCl<sub>3</sub> (10 mol%) could not enable a reaction between styrene and 1-phenyl-2-propyn-1-ol (Scheme 1, 48 h, no reaction). Meanwhile, we also tested the reaction activity of *trans*-stilbene and cyclopentene. The results showed that a sluggish reaction or no reaction happened in 48 h (Scheme 1, <5% yield or 0% yield, respectively). Surprisingly, if 1,1-diphenylethylene was used

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Scheme 1 Investigation of the ene-type reaction.

to replace the above alkenes, the reaction went smoothly and efficiently (Scheme 1, 2 h, 74% yield). However, when we tried to use a strong electron-withdrawing group (Cl) or a electrondonating group (Me) to replace the phenyl group (Scheme 1, 1,1-dichloroethylene and 2-methylpropene), no desired compound was achieved (Scheme 1, no reaction, respectively). We deduced that the phenyl group played a critical role in stabilizing the carbon cation after the ene-type reaction.

Having this finding in hand, we started to optimize the reaction parameters of this ene-type substitution reaction. During our investigation of the metal salt (10 mol%) catalyzed reaction of 1,1diphenylethylene 1a with 1-phenylprop-2-yn-1-ol 2a in CH<sub>3</sub>CN (1 mL) at 80 °C for 2 h, FeCl<sub>3</sub>·6H<sub>2</sub>O was discovered to be the most efficient catalyst and promoted the highest yield of 3a with 77% (Table 1, entry 2). Subsequently, we examined other reaction parameters by varying temperature and solvent in order to improve the reaction efficiency. The results are summarized in Table 2. In general, higher reaction yields were obtained with less polar solvents (Table 2, entries 7-9, 54-70%). No reaction happened when highly polar solvents were used as reaction media (Table 2, entries 12 and 13). In addition, oxygen-containing solvents were also not suitable for reaction media in this process (Table 2, entries 10 and 11, <10% yield, respectively). We deduced that oxygencontaining solvents, such as THF and 1,4-dioxane, coordinated with the iron catalyst resulting in the loss of iron catalytic activity. Lower temperature did not favor this process and caused the loss of reaction yields to some degree (Table 2, entries 4 and 5, 60 °C and 25 °C, 70% and 58%, respectively). Surprisingly, a higher temperature did not give an improved result (Table 2, entry 3, 100 °C, 2 h, 80% yield).

With the optimized conditions in hand, we decided to explore the scope of this ene-type substitution reaction. The substrate scope of FeCl<sub>3</sub>·6H<sub>2</sub>O catalyzed process of 1,1-diphenylethylene **1a** with propargylic alcohol **2** is shown in Table 3. A wide range of propargylic alcohol bearing an electron-donating group or electron-withdrawing group at the  $R^1$  position, as well as 
 Table 1
 Investigation of catalysts<sup>a</sup>

Entry         Catalyst         Yield (%           1         FeCl <sub>3</sub> 74           2         FeCl <sub>3</sub> ·6H <sub>2</sub> O         77           3         FeBr <sub>3</sub> 56           4         Fe <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> ·H <sub>2</sub> O <sup>c</sup> 5         Fe(acac) <sub>3</sub> <sup>c</sup> 6         Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O         52           7         FeCl <sub>2</sub> 15           8         Fe2Pr         c	1a	Ph 2a	CH <sub>3</sub> CN, 80 °C 2 h	Ph Ph 3a //
1 $FeCl_3$ 74         2 $FeCl_3 \cdot 6H_2O$ 77         3 $FeBr_3$ 56         4 $Fe_2(SO_4)_3 \cdot H_2O$ $-e^c$ 5 $Fe(acac)_3$ $-e^c$ 6 $Fe(NO_3)_3 \cdot 9H_2O$ 52         7 $FeCl_2$ 15         8 $FePr$ $e^c$	Entry	Catalys	Yield (%) <sup>b</sup>	
$6$ $1 \in B_1^\circ$ $-e^\circ$ $9$ $Fe(OAc)_2$ $-e^\circ$ $10$ $Fe(BF_4)_2 \cdot 6H_2O$ $51$ $11$ $FeSO_4 \cdot 7H_2O$ $-e^\circ$ $12$ $Fe(CIO_4)_2 \cdot H_2O$ $24$ $13$ $FeS$ $-e^\circ$ $14$ $CuCl_2$ $-e^\circ$ $16$ $AgOAc$ $-e^\circ$	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16	FeCl <sub>3</sub> FeCl <sub>3</sub> ·6 FeBr <sub>3</sub> Fe <sub>2</sub> (SO Fe(acaa Fe(NO FeCl <sub>2</sub> FeBr <sub>2</sub> Fe(OA Fe(BF <sub>4</sub> FeSO <sub>4</sub> · Fe(ClO FeS CuCl <sub>2</sub> CuCl AgOAd	$H_2O$ $h_{4})_3 \cdot H_2O$ $c)_3$ $g)_3 \cdot 9H_2O$ $c)_2$ $b)_2 \cdot 6H_2O$ $7H_2O$ $7H_2O$ $0_{4})_2 \cdot H_2O$	$ \begin{array}{c} 74 \\ 77 \\ 56 \\^{c} \\ 52 \\ 15 \\^{c} \\ 51 \\^{c} \\ 24 \\^{c} \\^{c$

<sup>*a*</sup> Reaction conditions: 1,1-diphenylethylene **1a** (0.24 mmol, 1.2 equiv.), 1-phenylprop-2-yn-1-ol **2a** (0.2 mmol, 1.0 equiv.), 10 mol% catalyst, 80 °C, MeCN (1.0 mL), 2 h. <sup>*b*</sup> Yield of isolated product after column chromatography. <sup>*c*</sup> <10% yield.

 Table 2
 Optimization of other parameters<sup>a</sup>

Ph Ph 1a	+ Ph 2a	FeCl <sub>3</sub> · 6H <sub>2</sub> O (10 mol%) Solvent, 80 °C 2 h	Ph Ph 3a
Entry <sup>a</sup>	$T/^{\circ}C$	Solvent	Yield (%) <sup>b</sup>
1 2 3 4 5 6 7 8 9 10 11 12 13	80 80 100 60 25 80 80 80 80 80 80 80 80 80	DCE CH <sub>3</sub> CN CH <sub>3</sub> CN CH <sub>3</sub> CN CH <sub>3</sub> CN Toluene EtOAc CH <sub>3</sub> NO <sub>2</sub> PhCF <sub>3</sub> 1,4-Dioxane THF MeOH DMSO	74 77 80 70 58 29 62 70 54 -c -c

<sup>*a*</sup> Unless specified, see the Experimental section for reaction conditions. <sup>*b*</sup> Yield of isolated product after column chromatography. <sup>*c*</sup> <10% yield.

naphthalene ring, and heterocyclic thiophene ring provided the desired complexes **3a–w** in moderate to high yields (Table 3, **3a–r**, 44–90% yield). In addition, this process tolerated an  $R^2$  group as well as the  $R^1$  group (Table 3, **3t–w**, 44–81% yield). It is noteworthy that alkenyl group could be applied to the  $R^1$  position (Table 3, **3s**, 70% yield).

Extension of substrate scope was examined using various symmetric and asymmetric 1,1-diphenylethylenes **2b–d** (Table 4). Moderate to excellent yields were obtained within 11 h (Table 4, 57–98%). Notably, asymmetric 1,1-diphenylethylene provided a

#### Table 3 Scope of propargylic alcohols



 Table 4
 Scope of diarylethylenes



good yield (Table 4, 3d', 75%), but with poor regioselectivity ( $Z/E \sim 1:1$ ). In addition, heterocyclic ring functionalized propargylic alcohol **2** also reacted with 1,1-diphenylethylenes and afforded the desired product in moderate yield (Table 4, 3b' and 3c').

Our postulated reaction pathways are summarized in Scheme 2. In the initial step,  $FeCl_3$  triggers the dehydroxylation of propargylic alcohol **2a** to form the intermediary propargyl cation **A** which is in equilibrium with the corresponding  $sp^2$ -hybridized allenylium cation **B**. The subsequent ene-type nucleophilic addition of 1,1diphenylethylene **1a** to allenylium cation **B** leads to an intermediate **C**. Finally, intermediate **C** undergoes a dehydrogenation step to offer a diarylalkenyl propargylic complex **3a**. The configuration of the new products was determined by analogy with the X-ray crystal structure of a suitable single crystal (Table 4, product **3p**) (See Supporting Information†).<sup>10</sup>



Scheme 2 Proposed catalytic cycle.

#### Conclusions

In summary, we have documented here a Fe-catalyzed reaction of propargylic alcohols with 1,1-diaryl alkenes. The propargylation of propargylic alcohols with 1,1-diaryl alkenes in the presence of FeCl<sub>3</sub>·6H<sub>2</sub>O enabled us to trigger an ene-type substitution process to furnish a diarylalkenyl propargylic complex framework in moderate to high chemical yields (43–98%). Studies directed to clarify the functionalities of these compounds as well as the extension of this strategy to other substrates is currently underway.

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