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Stereo-selective synthesis of *cis*-alkenes/halo-alkenes by reaction of diphenylmethane with ethynylbenzenes via sp³ C–H bond activation promoted by iron salts

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With the emergence of the concepts of 'atom economy' and 'green chemistry', great efforts have been made to use cheap and environmentally benign metals¹⁻³ and to develop C–H activation reactions⁴ recently. The cross dehydrogenative coupling (CDC) between two different C-H bonds to form C-C bond has been known as one of the most efficient and straightforward methodologies for organic framework construction.⁵ As the metal with the biggest reserve on the earth and low toxicity, iron has been the research hotspot for many years⁶ and indeed, iron exhibited comparatively good catalytic ability in many reactions. With the development of research, some special properties have also been found for iron catalyzed reactions. The Mao group reported a specific cis/trans isomerism of the target products in the cross-coupling reaction of vinvl bromides or chlorides with imidazoles catalyzed by iron in 2009.⁷ In 2010 our research group reported the synthesis of substituted 1-halo-1,4-pentadiene derivatives by the reaction of 1,3-diphenylpropenes with ethynylbenzenes promoted by iron salts,⁸ which specifically formed *cis*-alkenes after dehalogenative hydrogenation. Moreover, our reaction was also a convenient, efficient, and simple way to synthesize alkenyl halides if FeX₃ was used as a promoter.

cis-Alkenes have long intrigued organic chemists because they are motifs of many natural products (Scheme 1),⁹ and usually

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ABSTRACT

A stereo-selective reaction for the synthesis of *cis*-alkenes/halo-alkenes from diphenylmethane and ethynylbenzenes was developed in the presence of iron(III) bromide or chloride. Alkenyl bromides/chlorides were obtained in comparatively good yields in chlorobenzene under mild reaction conditions. © 2012 Elsevier Ltd. All rights reserved.

> served as substrates or intermediates in countless transformations.¹⁰ It is a great challenge to synthesize large groups substituted *cis*-alkenes in organic synthesis.¹¹ The general synthesis methodologies of cis-alkenes are the hydrogenative reduction of the acetylenes with special transition metal catalysts which are usually expensive and poisonous, cis-eliminations in the gas phase,¹² carbometallation of alkynes,¹³ McMurry coupling,¹⁴ Witting-Peterson reaction, and Horner-Wadsworth-Emmons Olefination. In 2010, Wang reported a reaction to synthesize alkenyl bromides and chlorides from diphenylmethanol and ethynylbenzene,¹⁵ and their method actually was *cis*-alkenes selective if their products were debrominated. But no methodology directly using diphenylmethane and ethynylbenzene as starting substrates via CDC reaction was reported. Herein we report a new reaction using diphenylmethane derivatives as substrates, in order to develop a stereo-selective and convenient path to get *cis*-alkenes.

> Firstly diphenylmethane (**1a**) and ethynylbenzene (**2a**) were chosen as standard substrates under a dry nitrogen atmosphere, and the results are summarized in Table 1. Benzoquinone (BQ) was firstly used as the oxidant and dichloroethane (DCE) was used as a solvent, but no desired product was detected in spite of screening the reaction temperature (Table 1, entries 1–3) or solvents (Table 1, entry 4). When 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used as the oxidant instead of BQ, a comparatively good yield was obtained (Table 1, entry 6). According to NMR and thereafter debromination of the product **3l** (Scheme 2), the



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Scheme 1. Several natural products with motifs of *cis*-alkenes.

Table 1Optimization of the reaction conditions^a



Entry	Metal (equiv)	Oxidant	Solv.	Temp (°C)	Yield ^b (%)
1	FeCl ₃ (1.0)	BQ	DCE	80	ND
2	FeCl ₃ (1.0)	BQ	DCE	110	ND
3	FeCl ₃ (1.0)	BQ	DCE	120	ND
4	FeCl ₃ (1.0)	BQ	C ₆ H ₅ Cl	120	ND
5	FeCl ₃ (1.0)	DDQ	DCE	120	Trace
6	FeCl ₃ (1.0)	DDQ	C ₆ H ₅ Cl	120	63
7	FeBr ₃ (1.0)	DDQ	C ₆ H ₅ Cl	120	Trace
8	FeBr ₃ (1.0)	DDQ	C ₆ H ₅ Cl	50	64
9	FeBr ₃ (1.0)	DDQ	DMF	50	ND
10	FeBr ₃ (1.0)	DDQ	PhNO ₂	50	ND
11	FeBr ₃ (1.0)	DDQ	CH ₃ NO ₂	50	17
12	FeBr ₃ (1.0)	DDQ	DCE	50	14
13	FeBr ₃ (1.0)	DDQ	Ethykene glycol diethylether	50	ND
14	FeBr ₃ (1.0)	t-BuOOBu-t	C ₆ H ₅ Cl	50	ND
15	FeBr ₃ (1.0)	PhI(OAc) ₂	C ₆ H ₅ Cl	50	ND
16	FeBr ₃ (0.1)	DDQ	C ₆ H ₅ Cl	50	28
17 ^c	FeBr ₃ (1.0)	DDQ	C ₆ H ₅ Cl	50	Trace

^a Unless otherwise specified, the reaction was carried out using 0.5 mmol of **1a**, 0.6 mmol of **2a**, 2.0 mL of solvent, and 0.6 mmol of oxidant under an atmosphere of dry nitrogen.

^b Isolated yield based on the amount of diphenylmethane consumed.

^c The reaction was carried out in open air atmosphere.



Scheme 2. Debromination of 3l. Reaction conditions: (1) 0.35 mmol of 3l, 1.1 mmol of BuLi, 4 mL of dry THF, -78 °C, under an atmosphere of dry nitrogen; (2) 15 mL of H₂O, rt.

configuration of the products was determined. The major isomer was the desired *cis*-alkene. This was in accordance with our previous result. The minor product was the double bond shifted product (**4a**). Very little *trans*-alkene (**3a**') was detected. In consideration of the common adhibition of bromine compound in organic reactions for the better leaving ability of bromine atom, FeBr₃ was applied to the reaction while no desired product was detected at 120 °C (Table 1, entry 7). Considering the FeBr₃ may be more active than FeCl₃, the reaction temperature was lowed to 50 °C when FeBr₃ was used, then a good yield was received (Table 1, entry 8). Then solvents such as DMF, PhNO₂, CH₃NO₂, DCE, and ethylene glycol diethylether were screened (Table 1, entries 9–13), and chlorobenzene was the preferable solvent in this condition. Moreover, t-BuOOBu-t or PhI(OAc)₂ was tested as the oxidant. However, they were unsuitable to this system. When the amount of FeBr₃ was reduced to 0.1 equiv, the desired product was only obtained in 28% yield. If the reaction was performed in air, acetophenone was collected together with much starting material.

With the optimized reaction conditions established (Table 1, entry 8), the generality and efficiency of the DDQ-mediated oxidative cross-coupling reaction between various diphenylmethane derivatives and different ethynylbenzenes were explored. The

Table 2

Cross-dehydrogenative coupling of various alkynes and diphenylmethane derivatives^a



3f:4f (6:1)

Table 2 (continued)



(continued on next page)

Table 2 (continued)



^a 0.5 mmol of **1**, 0.6 mmol of **2**, 2.0 mL of C₆H₅Cl, and 0.6 mmol of DDQ, 50 °C, 24 h.

^b Based on diphenylmethane.

^c 0.5 mmol of **1**, 0.6 mmol of **2**, 2.0 mL of C₆H₅Cl, and 0.6 mmol of DDQ, 50 °C, 16 h.

^d 0.5 mmol of **1**, 0.6 mmol of **2**, 2.0 mL of C₆H₅Cl, and 0.6 mmol of DDQ, 10 °C, 12 h.



Scheme 3. Proposed Mechanism.

results were outlined in Table 2. The reaction was sensitive to electronic changes both on the phenyl group of the alkyne and methane. Ethynylbenzene with an electronic-withdrawing group reacted well with the diphenylmethane under the standard reaction conditions (Table 2, entries 3, 5, 7, 10, and 12), whereas the low yield of o-trifluoromethylphenylacetylene (Table 2, entries 4, 8, and 11) was attributed to the relatively insensitive to the reaction conditions. Little desired product was obtained when ethynylbenzenes with electron-donating groups such as methyl, ethyl and propyl were used until intense electron-donating groups were attached to the phenyl group of diphenylmethane (Table 2, entries 13-15). 4,4'-dimethoxydiphenylmethane reacted well with ethynylbenzenes with both electron-donating groups and electronwithdrawing groups. This implied that the reaction may start from the oxidation of methylene of the diphenylmethane. In most cases if no electron-withdrawing groups on product no isomer 4 was formed. Aliphatic alkynes such as *n*-octyne and heterocyclic alkynes like 2-acetylenefuran and 2-acetylenepyrrole were not amenable to this system.

A possible mechanism for the FeX₃-promoted addition of diphenylmethane to aromatic alkyne is shown in Scheme 3. First, the methylene of diphenylmethane was oxidized by DDQ to form a conjugated intermediate **A**,^{5a} and promoted by iron(III) the bromide anion attacked the ethynylbenzene (**2a**) followed by C–C bond formation with intermediate **A** to give the desired product **3a**,^{16a} and **3a** may be rearranged to **4a** in the acidic conditions.

In summary, we have successfully obtained stereoselective alkenyl halides from the reaction of diphenylmethane and aromatic alkyne promoted by FeBr₃ or FeCl₃. The *cis*-configuration of the alkenes was confirmed after debromination even if there were two big groups in the same side. Further investigations of the application of this kind of iron salt in organic reactions are underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012. 05.083.

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