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Catalyst-Enabled Chemodivergent Construction of Alkynyl- and Vinyl-Substituted Diarylmethanes from *p*-Quinone Methides and Alkynes

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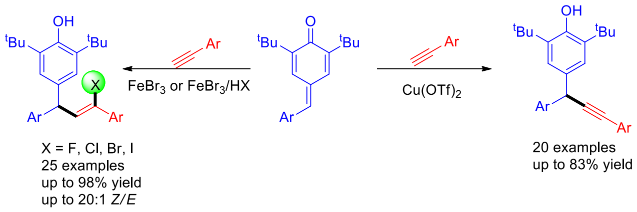
Supporting Information

ABSTRACT: Here, a catalyst-controlled chemodivergent 1,6-addition of *p*-quinone methides with alkynes was developed, affording diverse alkynyl- and vinyl-substituted diarymethanes. In this transformation, copper catalyzed the direct 1,6-addition of *p*-QMs with alkynes, while iron promoted the three components reaction of *p*-QMs, alkynes, and halogens from iron salts or added HX acid. The salient features of this transformation include completely controllable chemoselectivity, mild conditions, inexpensive catalysts, and good substrates scopes.



The development of efficient methodologies to selectively construct diverse compound libraries is highly important in modern organic synthesis.[1] In this context, divergent synthesis of diverse products from the same starting materials by tuning the reaction conditions such as temperature, pressure, solvent, catalyst, and so on attracts more and more attention but poses considerable challenges.[2] Diaryl or polyarylmethane compounds are important structural units in many natural products and bioactive molecules (Figure 1). For example, DAMNIs and DABOs were expected to suppress HIV-1 and antagonists of the thyroid hormone receptor.[3] Thus, the development of efficient and diverse methods to access diaryl and polyarylmethane compounds is highly desirable.

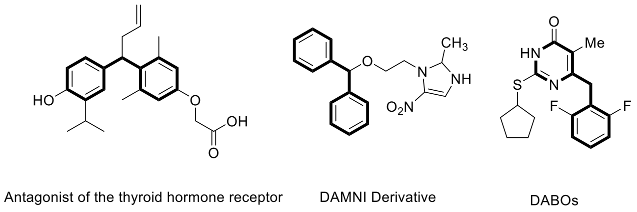


Figure 1. Bioactive molecules containing diarymethanes.

Recently, *p*-quinone methides (*p*-QMs) have been proven to be an important Michael acceptor to obtain diaryl and polyarylmethane compounds via 1,6-conjugated addition and related cycloaddition. In the past decade, a series of efficient catalytic systems including metal catalysts and organocatalysts have been established for the reactions of *p*-QMs with a wide range of nucleophiles.[4−8] Recently, Fan,[5a−c] Jørgensen,[5d] Enders,[5e] Deng,[5f] Lin and Yao,[5g] Zhao,[5h] and others have explored a lot of 1,6-conjugate addition reactions of *p*-QMs with C(sp^3) nucleophiles, such as malonates, aldehydes, oxindoles, and glycine Schiff base.[5] Liao,[6a] Sun,[6b] Anand,[6c] Fan,[6d] our group,[6e,f] Wu,[6g] Lin, and Yao[6h] have reported a few examples of 1,6-conjugate addition reactions with C(sp^2) nucleophiles including aromatic rings and alkenes.[6] However, to the best of our knowledge, there is only one example for the 1,6-addition of *p*-QMs with C(sp) nucleophiles. Very recently, Anand reported a *N*-heterocyclic carbene (NHC)-catalyzed 1,6-conjugate addition of *p*-QMs with TMSCN for access to α,α'-diarylated nitriles.[7] However, alkynes, which are known as versatile building blocks and important intermediates for compounds of value in biochemistry and material science, have not yet been explored for the nucleophilic addition to *p*-QMs. Although there are few reactions of *p*-QMs with alkynes, alkynyl normally serve as electrophiles. Lin and co-workers discovered a cascade three-component iodoazidation of *p*-quinone methides to construct spiro[4.5]deca-6,9-dien-8-ones (Scheme 1a).[9a] The same group reported a silver-catalyzed cascade 1,6-addition/5-*exo-dig* cyclization reaction between *p*-quinone methides and propargyl malonates (Scheme 1b).[9b] The Shi group disclosed base-catalyzed [4 + 2] cycloaddition of *o*-hydroxyphenyl-substituted *p*-quinone methides with ynones or benzyne (Scheme 1c).[9c] During the course of our ongoing studies on *p*-QMs[6e,f] and alkyne chemistry,[10] we wondered whether terminal alkynes could

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Scheme 1. Reactions of *p*-QMs with Alkynes

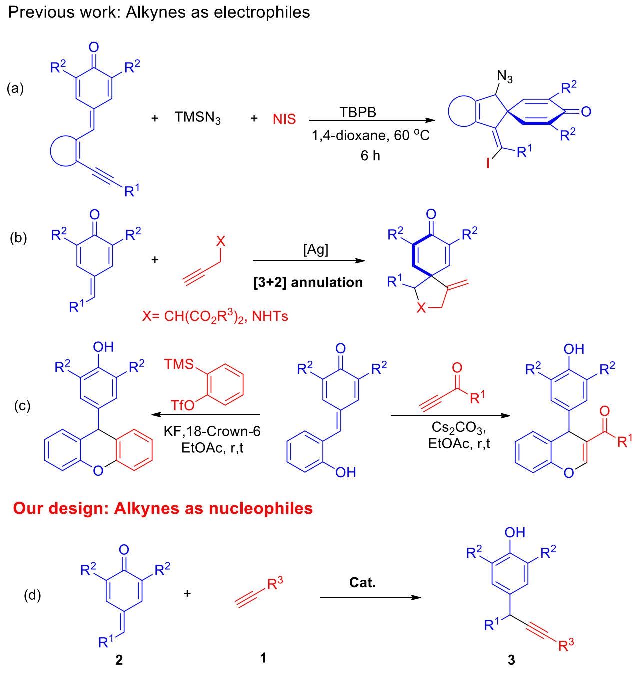
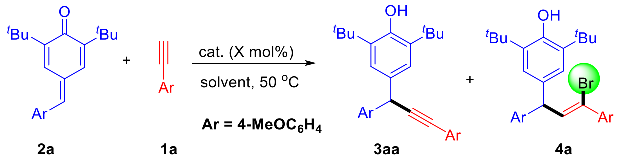


Table 1. Optimization of Reaction Conditions^{a}



entry	cat. (X)	solvent	3aa yield (%)^{b}	4a yield (%)^{b}
1	In(OTf)$_3$ (10)	Toluene	69	0
2	Bi(OTf)$_3$ (10)	Toluene	41	0
3^{c}	Cu(OTf)$_2$ (10)	Toluene	80	0
4^{c}	CuOTf·0.5C$_6$H$_6$ (10)	Toluene	70	0
5^{c}	Cu(OTf)$_2$ (10)	CH$_3$CN	trace	0
6^{c}	Cu(OTf)$_2$ (10)	DMF	0	0
7^{c}	Cu(OTf)$_2$ (10)	dioxane	46	0
8^{c}	Cu(OTf)$_2$ (10)	THF	0	0
9	Fe(OTf)$_3$ (10)	Toluene	0	0
10	FeBr$_3$ (40)	Toluene	0	76
11	FeBr$_3$ (40)	THF	0	trace
12	FeBr$_3$ (40)	dioxane	0	58
13^{d}	HBr (200)	Toluene	0	77
14^{e}	FeBr$_3$ (5)	Toluene	0	86

^{a}Unless otherwise noted, all reactions were carried out with **2a** (0.2 mmol), **1a** (0.4 mmol), Cat (X mol %) in solvent (2 mL) at 50 °C for 6–24 h. ^{b}Isolated yield. ^{c}60 °C. ^{d}2 equiv of HBr was added at room temperature for 24 h. ^{e}FeBr$_3$ (5 mol %) and HBr (2.0 equiv) were added at room temperature for 3 h.

serve as C(sp) nucleophiles via 1,6-addition of *p*-QMs (Scheme 1d).

To validate this hypothesis, we initiated our investigation using aryl acetylene **1a** and *p*-QM **2a** as the model substrates. The selected results of conditional optimization are summarized in Table 1. The desired product alkynyl-substituted diarylmethane **3aa** was isolated in 69% yield at 50 °C with the catalysis of 10 mol % of In(OTf)$_3$ in toluene for 48 h (Table 1, entry 1). Because of this promising result, we then investigated several Lewis acids including Bi(OTf)$_3$ and Cu(OTf)$_2$ (Table 1, entries 2 and 3 and Table S1), among which Cu(OTf)$_2$ was found to be the best catalyst, delivering 80% isolated yield at 60 °C. Cu(I) can also catalyze this reaction, but the yield is lower than Cu(II) (Table 1, entry 4). Solvent screening showed that acetonitrile, DMF, dioxane, and THF cannot improve the isolated yield (Table 1, entries 5–8). Unfortunately, no enantioselectivity was obtained after several chiral ligands such as Box and PyBox were tried (for more details, see Table S1, entries 14–17). To our surprise, Fe(OTf)$_3$ could not catalyze the reaction of *p*-QM **2a** with terminal alkyne **1a** (Table 1, entry 9). When FeBr$_3$ was added in this reaction, a new product **4a** via three-component reaction involving alkyne, *p*-QMs, and bromine was obtained. After further careful screening, the catalytic system involving 5 mol % of FeBr$_3$ and 2 equiv of HBr showed the best catalytic activity, and **4a** was obtained in 86% yield after 3 h at room temperature (Table 1, entry 14). This result indicated that iron was an efficient catalyst for this three-component reaction.

With the optimized reaction conditions for the synthesis of alkynyl-substituted diarylmethanes in hand (Table 1, entry 3), we then investigated the substrate scope of various *p*-QMs **2** and alkynes **1**. As shown in Figure 2, diverse substituents on *p*-QMs **2** are tolerable in this reaction. The reaction of *p*-QMs **2** with an electron-donating group and H affords the corresponding products **3aa**–**3ag** in 70–82% yield. The *p*-QMs involving naphthyl and electron-withdrawing groups (F, CN) on phenyl were suitable for this transformation (**3ah**–**3ai**). Gratifyingly, the reaction of *p*-QMs with an alkyl group (**2k**) and alkyne **1a** proceeds smoothly, affording the corresponding product **3ak** in 71% yield. In the case of alkynes, this conjugated 1,6-addition tolerated various substituents on the phenyl ring close to alkynyl, such as H (**3ba**), electron-donating methyl (**3ca**), ethoxyl (**3da**), and electron-withdrawing halo (**3ea**–**3ga**) at the *para* position, delivering the corresponding products in good yields (65–78%). It was noteworthy that alkynes with heteroaryl and ferrocenyl derived alkynes were also suitable substrates for this transformation (**3ha**–**3ia**). In addition, the enyne substituted diarylmethane **3ja** can also be obtained via this approach. However, aliphatic alkyne (1-octyne) was not suitable in this transformation, affording messy products. We also synthesized TMS-substituted *p*-QM **2l**. Unfortunately, only 41% ketone from hydrolysis of alkyne **1a** was isolated after the reaction of **2l** and **1a** under the standard conditions.

Having successfully achieved the Cu-catalyzed 1,6-addition of *p*-QMs with alkynes, we then examined the substrate scope of iron-promoted three-component bromoalkenylation. There are two catalytic conditions: In conditions A, 40 mol % of FeBr$_3$ was added as the catalyst and bromine source. In conditions B, the amount of FeBr$_3$ decreased to 5 mol %, and 2 equiv of HBr was added as bromine source. We first examined the substrate scope of *p*-QMs. In conditions A, it was found that *p*-QMs bearing electron-donating R^1 groups at different positions of the phenyl ring could generate products **4** in moderate yields (52%–85%) and good to excellent *Z*/*E* selectivity (Figure 3, **4a**–**4i**). If the phenyl ring of *p*-QM was replaced by *tert*-butyl, the reaction could afford the corresponding product **3ak** in 67% yield and 5:1 stereoselectivity. Then a variety of alkynes were tested. 4-

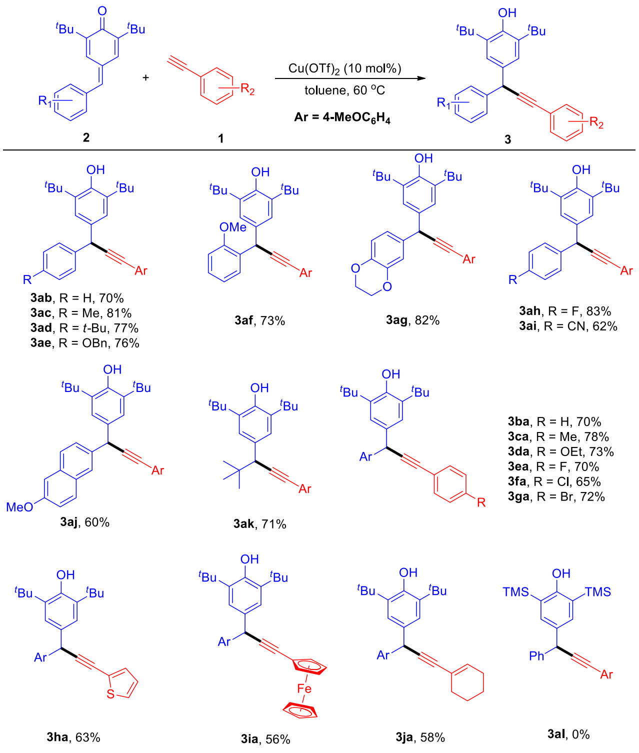


Figure 2. Copper-catalyzed 1,6-additions of p-QMs with terminal alkynes. Unless otherwise noted, all reactions were carried out with **2** (0.2 mmol), **1** (0.4 mmol), and Cu(OTf)$_2$ (10 mol %) in toluene (2 mL) for 6−24 h.

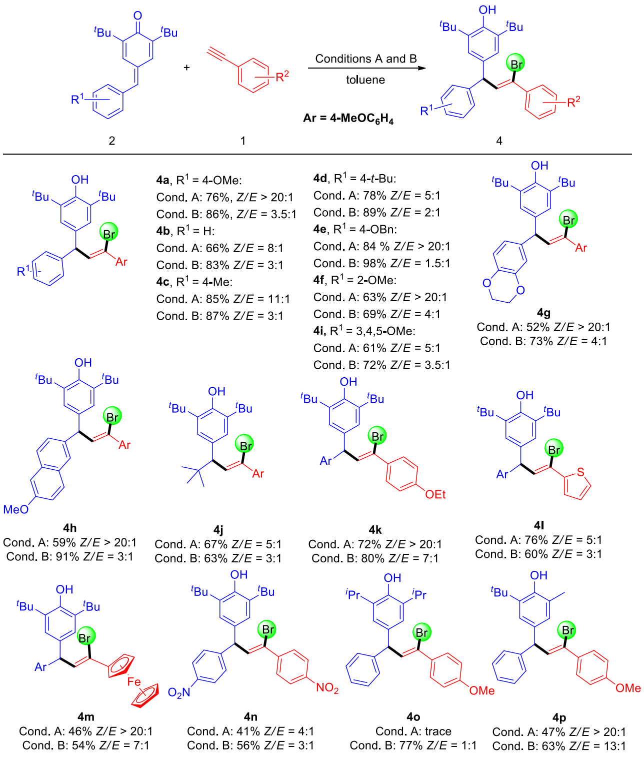


Figure 3. FeBr$_3$-mediated bromoalkenylation of *p*-QMs. Conditions A: **2** (0.2 mmol), **1** (0.4 mmol), and 40 mol % of FeBr$_3$ were added in toluene (2 mL) at 50 °C for 6−12 h. Conditions B: **2** (0.2 mmol), **1** (0.4 mmol), HBr (2 equiv), and 5 mol % of FeBr$_3$ was added in toluene (2 mL) at room temperature for 3−8 h. Total yield of two isolated isomers. *Z*/*E* ratios were determined by ^{1}H NMR.

Ethoxyphenylacetylene gave the corresponding products **4k** in good yield (72%) with excellent selectivity (>20:1). Furthermore, the alkynes involving heteroaryl and ferrocenyl were also suitable for this transformation (**4i−4m**). However, the electron-withdrawing group (−NO$_2$) on alkynes lowered the yield and selectivity (**4n**). Compared with conditions A, the reaction temperature in conditions B was lowered to room temperature, and the yield of **4** was higher with the decreasing *Z*/*E* selectivities (**4a−4n**). Unfortunately, the reaction of the *p*-QM with isopropyl instead of *tert*-butyl could not give the corresponding product in conditions A. However, the product **4o** could be obtained in 77% yield with 1:1 *Z*/*E* selectivity under conditions B. The *p*-QM with methyl on phenol was also suitable for this transformation and gave the product **4p** under conditions A and B. Similarly, both aliphatic alkyne- and TMS-substituted *p*-QM **2l** were still not compatible in these two conditions. In addition, the reaction of internal alkyne does not work (for more details, see Table S6).

To further broaden the substrate scope of the reaction, we wondered if other halogens (F, Cl, I) can also be involved in the reaction. When HCl was used instead of HBr, the reaction also worked smoothly to afford the corresponding chloro-substituted olefin product **5a**. However, the yield of chloro olefin is lower than that yield of brominated olefin, which might be attributed to the lower nucleophilicity of chloride than that of bromide. We then examined the substrate scope of this chloroalkylation reaction of alkynes. As shown in Figure 4, when the substituent on the phenyl ring of *p*-QMs was an electron-donating group, it gave the corresponding chloroolefins **5a−5d** in 50−67% yield. It seemed that the position of the substituents had little influence on the reaction, while the *Z*/*E* ratio of the corresponding chloroolefin product had a huge impact. Methoxy at the *para* position of the phenyl ring of *p*-QMs gave an excellent *Z*/*E* ratio (**5a**, *Z*/*E* = 12:1), but when the phenyl ring of *p*-QM was replaced by naphthyl, *Z*/*E* of **5d** was reduced to 1:1. When the

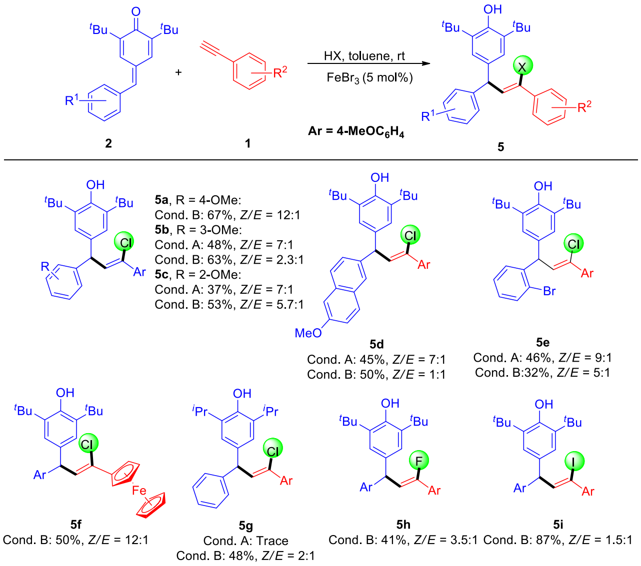


Figure 4. FeBr$_3$-mediated haloalkenylation of *p*-QMs. Conditions A: **2** (0.2 mmol), **1** (0.4 mmol), and 40 mol % of FeCl$_3$ was added in toluene (2 mL) at 50 °C for 6−12 h. Conditions B: **2** (0.2 mmol), **1** (0.4 mmol), HX (2 equiv), and 5 mol % of FeBr$_3$ were added in toluene (2 mL) at room temperature for 3−8 h. Total yield of two isolated isomers. *Z*/*E* were determined by ^{1}H NMR.

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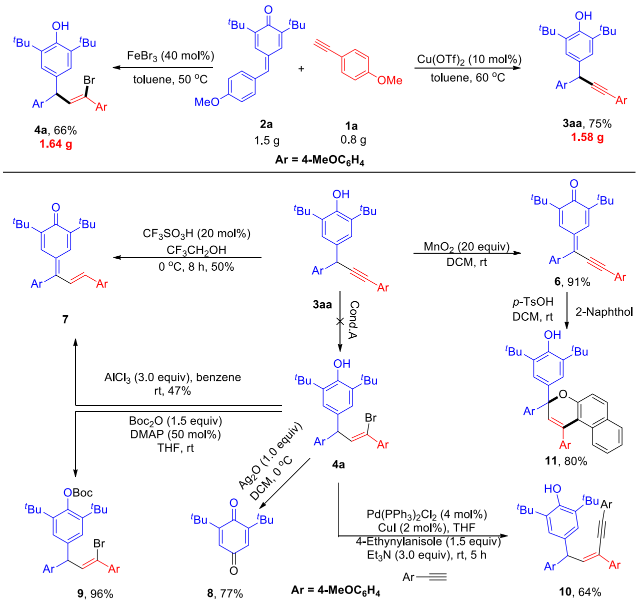
substituent in phenyl ring of *p*-QMs was an electron-withdrawing group, the yield of **5f** decreased to 32%. When the *tert*-butyl of *p*-QM was changed by isopropyl, the yield was 48% ($Z/E = 2{:}1$). Ferrocenylethyne gave the corresponding product **5f** in 50% yield and 12:1 Z/E ratio. In addition, the moderate Z/E ratios of **5b**−**5e** could be improved by using 40 mol % of $FeCl_3$ (conditions A) as promoter instead of HCl. Considering the commonality of halogenated hydrogen, we envisioned whether HF and HI could also react accordingly. As we hypothesized, fluorinated product **5h** was obtained in 41% yield ($Z/E = 3.5{:}1$) when HF (2 equiv) was added to the reaction with iron catalyst at room temperature for 48 h. Because the nucleophilicity of I is the highest in halogen, the corresponding iodo product **5i** was obtained in a yield of 87% ($Z/E = 1.5{:}1$).

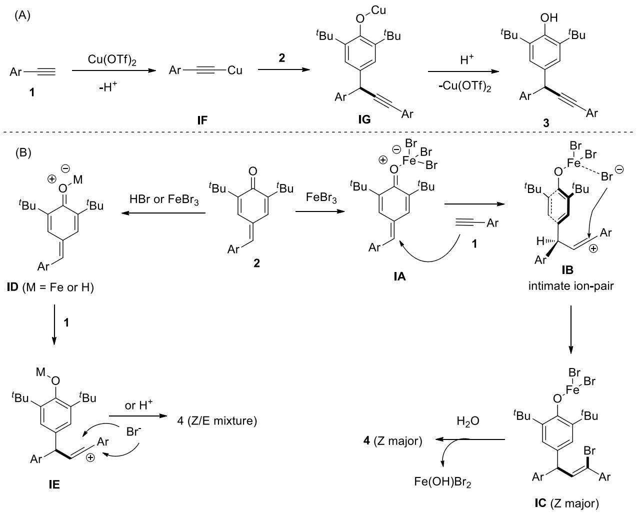
Furthermore, these two divergent reactions were easy to scale up. A gram-scale reaction of 1.5 g of **1a** and 0.8 g of **2a** was carried out under the standard conditions, furnishing 1.58 g of **3aa** in 75% isolated yield catalyzed by $Cu(OTf)_2$ and 1.64 g of **4a** in 66% isolated yield promoted by $FeBr_3$, respectively (Scheme 2). Moreover, to exhibit the synthetic application of these divergent reactions, several transformations of **3aa** and **4a** are shown in Scheme 2. Compound **3aa** can be oxidized by MnO_2 at room temperature, affording alkynyl *p*-QMs **6** in excellent yield. The alkynyl *p*-QMs **6** can be converted into spiro compound **11** in 80% yield via tandem 1,8-conjugated addition/6-endo trig cyclization. Under acidic conditions, **3aa** isomerized to vinyl *p*-QMs **7** in moderate yield. Compound **4a** could also deliver vinyl *p*-QMs **7** in 47% yield promoted by $AlCl_3$. Compound **4a** could be easily oxidized to quinone **8** by Ag_2O, and the protection of hydroxyl of **4a** was achieved in excellent yield. Various coupling reactions on alkenyls should be suitable for **4a**. For example, **10** can be obtained in 64% yield via Sonogashira coupling reaction of **4a** and terminal alkynes. However, **3aa** could not convert into **4a** under conditions A.

Scheme 2. Gram Scale-up and Transformation of Products



Based on the above results and previous studies, we considered that the Cu(II)-catalyzed 1,6-addition reaction is somehow similar to the known Cu(II)-catalyzed addition reaction of alkynes to unsaturated double bonds.[11] As illustrated in Scheme 3A, $Cu(OTf)_2$-activated terminal alkyne **1** resulted in the copper alkynylide bond intermediate **IF**,[11g] which then attacked *p*-QMs **2** to generate intermediate **IG**. After protonation and regeneration of the catalyst $Cu(OTf)_2$, product **3** was obtained. Two plausible pathways for the Fe-catalyzed three-component reaction are depicted in Scheme 3B. If HBr was absent in the reaction, $FeBr_3$-coordinated *p*-QMs **1** afforded the intermediate **IA**, which was attacked by the π electron of alkyne **2** to give the vinyl cation **IB**. Then intimate ion pair **IB** underwent the intramolecular type addition of bromide anion to generate intermediate **IC**, which posed a *Z* double bond. Finally, the hydrolysis of **IC** gave the product **4** with *Z* as the major isomer and released $Fe(OH)Br_2$ to promote the next transformation. Under conditions B, *p*-QMs **1** coordinated with Fe or protonation to afford the intermediate **ID**, which was attacked by the π electron of alkyne **2** to give the vinyl cation **IE**. Because a lot of Br^- was generated in solution, intermediate **IE** underwent the intermolecular addition of free bromide anion to afford the product **4** as a Z/E mixture.

Scheme 3. Proposed Mechanism



In summary, we have developed a novel catalyst-controlled chemodivergent reaction of *p*-quinone methides and alkynes. This protocol provides facile access to diverse substituted alkynyl- and vinyl-substituted diarylmethanes, which widely exist in many natural products and bioactive molecules. The salient features of this transformation include broad scope of substrates, inexpensive metal catalysts, controllable chemoselectivity, mild conditions, simple operation, easy gram-scale use, and diverse convenient transformations of the products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02810.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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