[3 + 2] Cycloaddition of α-Aryl-α-diazoacetates with Terminal Alkynes via the Cooperative Catalysis of Palladium and Acid

Hongyu Guo, Sheng Zhang,* Xiaoqiang Yu, Xiujuan Feng, Yoshinori Yamamoto, and Ming Bao*

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ABSTRACT: Palladium and acid cooperative catalysis is presented as a strategy for the [3 + 2] cycloaddition of acceptor/donor-type diazo compounds with terminal alkynes. The [3 + 2] cycloaddition of α-aryl-α-diazoacetates with terminal alkynes proceeded smoothly to produce 2,3,5-trisubstituted furans with high yields. This synthesis method provided a direct and efficient pathway to prepare furan ring-containing organosilane and organoboron reagents. Synthetically valuable functional groups such as chloro and bromo atoms, methoxycarbonyl, and carbonyl remained intact during the [3 + 2] cycloaddition reaction.
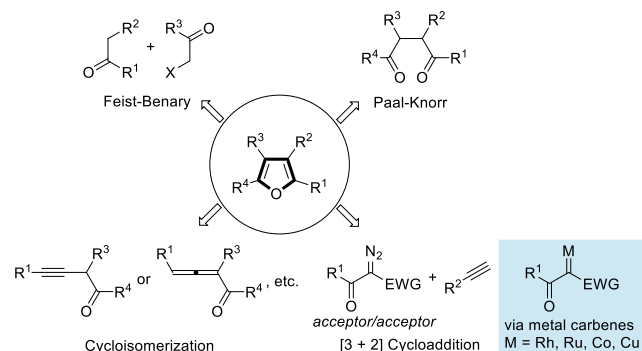
First general method for furan synthesis using acceptor/donor-type diazo compounds

KEYWORDS: *[3 + 2] cyclization, α-aryl-α-diazoester, terminal alkyne, cooperative catalysis, palladium*
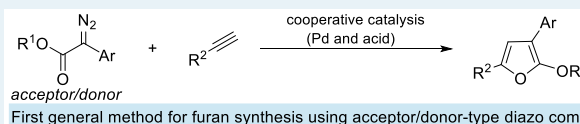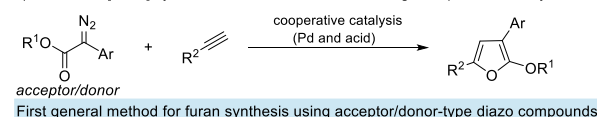
Multisubstituted furan moieties are found in diverse biologically active natural products,[1] pharmaceuticals,[2] and functional materials.[3] Over the past years, many approaches for constructing furan derivatives have been established.[4] These methods include the Paal−Knorr synthesis,[5] the Feist−Benary synthesis,[6] the cycloisomerization of carbonyl-containing alkyne or allene derivatives,[7] and the [3 + 2] cycloaddition of terminal alkynes with diazo compounds (Scheme 1a).[8] These methods have been proven to be very beneficial for synthesizing multisubstituted furans, but some drawbacks include the inability to produce furans with high flexibility regarding their substitution manner and difficulty in synthesizing furans containing sensitive functional groups.

Thus, developing a convenient and efficient method of synthesizing multisubstituted furan derivatives remains highly desirable.
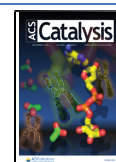
Among the above-mentioned well-known methods, the fourth one, namely, the [3 + 2] cycloaddition of terminal alkynes with diazo compounds, is considered to be a highly convenient and versatile method to access multisubstituted furans. However, diazo compounds are usually required to link two electron-withdrawing groups on the α-position; that is, acceptor/acceptor-type diazo compounds are usually required for successful [3 + 2] cycloaddition reaction. Very few studies have reported on the [3 + 2] cycloaddition of α-aryl-α-diazoacetates, i.e., acceptor/donor-type diazo compounds with terminal alkynes, which produces 2-alkoxy-3-aryl-5-aryl (or alkyl) furan derivatives.[9,10] The reason may be the weak reactivity of acceptor/donor-type metal carbene intermediates in electrophilic addition reaction with alkynes. In the course of our study on developing a new method for the synthesis of heteroaromatic compounds using alkynes as starting materials,[11] we succeeded in the [3 + 2] cycloaddition of acceptor/donor-type diazo compounds with terminal alkynes via palladium and acid cooperative catalysis (Scheme 1b). The obtained 2-alkoxyfurans could be directly used as the precursors to derive various butenolide products. The results are described in this paper.

Initially, the [3 + 2] cycloaddition reaction of methyl 2-diazo-2-phenylacetate (**1a**) with phenylacetylene (**2a**) was

Scheme 1. Methods for Synthesizing Furan Derivatives

a) Well-known methods for synthesis of furan derivatives

Feist-Benary

Paal-Knorr

Cycloisomerization

[3 + 2] Cycloaddition

via metal carbenes
M = Rh, Ru, Co, Cu

b) This work: [3 + 2] cycloaddition of diazoacetates through cooperative catalysis

cooperative catalysis
(Pd and acid)

First general method for furan synthesis using acceptor/donor-type diazo compounds

selected to investigate the reaction conditions (Table 1). Even though the starting material **1a** completely disappeared, the

Table 1. Screening of Reaction Conditions[a]

entry	ligand	acid	solvent	yield (%)[b]
1	$^tBuPPh_2$	none	THF	ND[c]
2	$^tBuPPh_2$	PivOH	THF	ND[c]
3	$^tBuPPh_2$	TsOH·H$_2$O	THF	ND[c]
4	$^tBuPPh_2$	HCl in dioxane	THF	ND[d]
5	$^tBuPPh_2$	HCl·NEt$_3$	THF	25[e]
6	$^tBuPPh_2$	HBr·NEt$_3$	THF	62
7	PPh$_3$	HBr·NEt$_3$	THF	20
8	PCy$_3$	HBr·NEt$_3$	THF	18
9	P(p-FC$_6$H$_4$)$_3$	HBr·NEt$_3$	THF	6
10	P(p-MeOC$_6$H$_4$)$_3$	HBr·NEt$_3$	THF	50
11	$^tBuPPh_2$	HBr·NEt$_3$/FeBr$_3$	THF	78
12	$^tBuPPh_2$	HBr·NEt$_3$/FeBr$_3$	DCM	66
13	$^tBuPPh_2$	HBr·NEt$_3$/FeBr$_3$	toluene	77
14	$^tBuPPh_2$	HBr·NEt$_3$/FeBr$_3$	dioxane	76
15[f]	$^tBuPPh_2$	HBr·NEt$_3$/FeBr$_3$	THF	79
16[g]	$^tBuPPh_2$	HBr·NEt$_3$/FeBr$_3$	THF	80
17	$^tBuPPh_2$	FeBr$_3$	THF	45
18[g,h]	$^tBuPPh_2$	HBr·NEt$_3$/FeBr$_3$	THF	NR[i]
19[g,j]	$^tBuPPh_2$	HBr·NEt$_3$/FeBr$_3$	THF	82

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), Pd(OAc)$_2$ (3 mol %), ligand (6 mol %), Brønsted acid (1.0 equiv), and FeBr$_3$ (5 mol %) in solvent (3 mL) at 80 °C under a nitrogen atmosphere for 12 h. [b]Isolated yield. [c]The desired product was not detected; the starting materials decomposed. [d]The desired product was not detected; an α-chlorinated byproduct, methyl 2-chloro-2-phenyl-acetate, was obtained in 79% yield. [e]Methyl 2-chloro-2-phenylacetate was obtained in 4% yield. [f]20 mol % of HBr·NEt$_3$ was used. [g]5 mol % of HBr·NEt$_3$ was used. [h]The reaction was performed without Pd(OAc)$_2$. [i]No reaction was found; the starting materials were recovered. [j]The reaction was performed for 2 h.
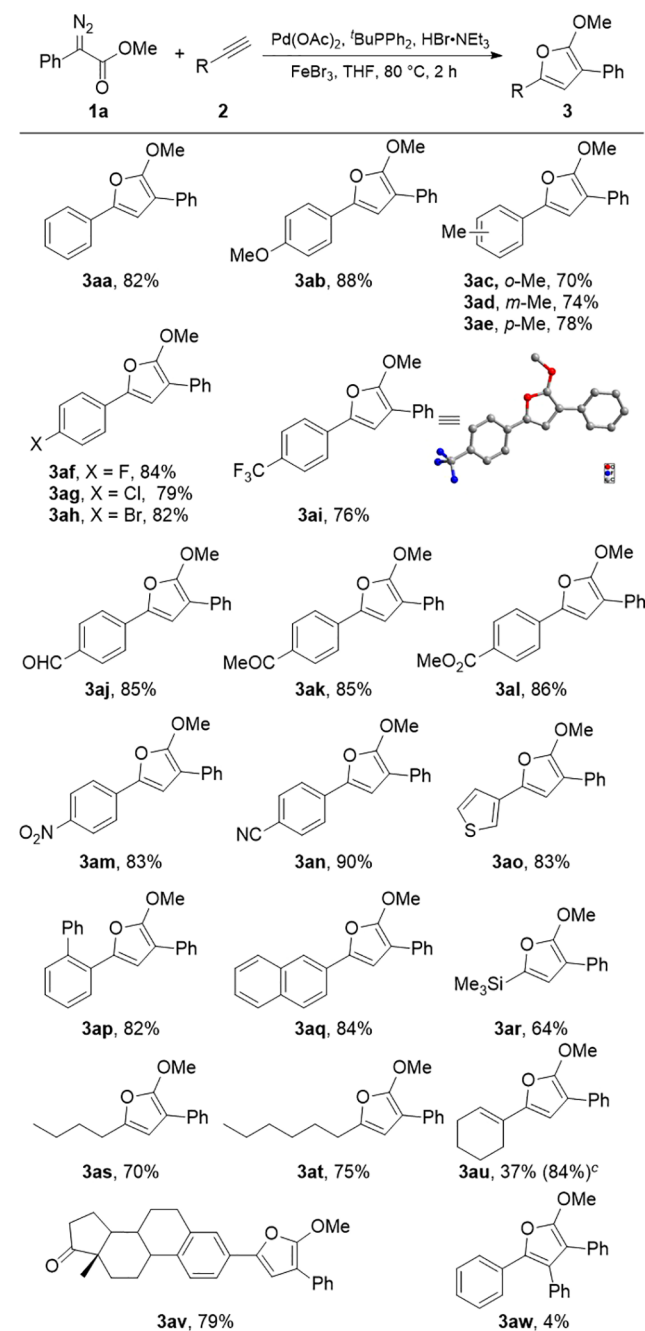
desired product 2-methoxy-3,5-diphenylfuran (**3aa**) did not form when the model reaction was carried out in tetrahydrofuran (THF) at 80 °C using Pd(OAc)$_2$ and $^tBuPPh_2$ as a precatalyst and a ligand, respectively (entry 1).

We speculated that an appropriate acid including Brønsted acid and Lewis acid may be required to enhance the electrophilicity of the palladium–carbene intermediate.[12] Then, the Brønsted acid was screened under the same conditions as used in entry 1, and the same result was obtained when the Brønsted acids pivalic acid (PivOH) and p-toluenesulfonic acid monohydrate (TsOH·H$_2$O) were examined (entries 2 and 3). However, instead of the desired product **3aa**, an α-chlorinated byproduct (i.e., methyl 2-chloro-2-phenylacetate) was obtained in 79% yield when HCl (4 M in dioxane) was tested (entry 4). The formation of product **3aa** was eventually detected (25%) along with 2-chloro-2-phenyl-acetate (4%) in the presence of HCl·NEt$_3$ (entry 5). The **3aa** yield dramatically increased to 62% when HCl·NEt$_3$ was changed to HBr·NEt$_3$ (entry 6). The ligands were subsequently screened using HBr·NEt$_3$ in THF. Among the phosphine ligands [$^tBuPPh_2$, PPh$_3$, PCy$_3$, P(p-FC$_6$H$_4$)$_3$, and P(p-OMeC$_6$H$_4$)$_3$] examined, $^tBuPPh_2$ proved to be the best

ligand (entries 7–10 vs 6). The combined use of the Brønsted acid HBr·NEt$_3$ and the Lewis acid FeBr$_3$[13] led to a further increase in yield of **3aa** (entry 11, 78%). The results obtained from the experiments of solvent screening indicated that the solvent did not significantly influence the reaction yield (entry 11 vs entries 12–14). Therefore, the solvent THF, with a boiling point lower than that of toluene and 1,4-dioxane, was employed as the reaction solvent. Almost no change in the **3aa** yield was observed with dramatically decreased HBr·NEt$_3$ loading to 20 mol % (entry 11 vs entry 15). Furthermore, almost the same high yield was observed again even with further decreased HBr·NEt$_3$ loading to 5 mol % (entry 16). When the Lewis acid catalyst FeBr$_3$ was used alone, only 45% yield was obtained (entry 17). A control experiment revealed the indispensable nature of Pd(OAc)$_2$ (entry 18). The target reaction was finally found to be completed within 2 h (entry 19).
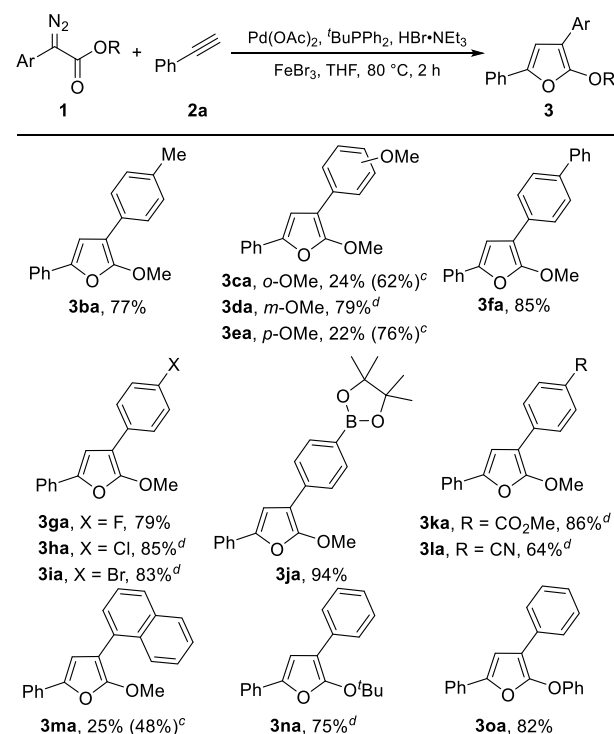
Under the optimum reaction conditions, substrate scope of the terminal alkynes was examined (Table 2). The reactions of the aryl acetylenes **2b**–**2e** bearing an electron-donating group [such as methoxy (MeO) or methyl (Me)] on para-, ortho-, or meta-positions proceeded as smoothly as **2a** to produce **3ab**–**3ae** in high to good yields (70–88%). The alkyne substrates **2f**–**2n** linking various electron-withdrawing groups (such as halogen atoms, CF$_3$, CHO, MeCO, MeO$_2$C, NO$_2$, and CN) on para-positions were subsequently investigated. The corresponding furan products **3af**–**3an** were obtained in high to excellent yields (76–90%). These results suggested that the electron property of the substituent did not exert an obvious effect on the reactivity of aryl acetylenes. Notably, the Cl and Br atoms substituted on the benzene rings of alkynes **2g**–**2h** were retained in the products **3ag**–**3ah**. No dehalogenation occurred at all, revealing that late-stage derivatization may produce additional valuable compounds. The structure of **3ai** was characterized by X-ray crystallography. Moreover, the 3-ethynylthiophene (**2o**), a sulfur-atom-containing alkyne substrate, was also demonstrated to be suitable for the current reaction after continuously investigating the substrate scope (**3ao**, 83%). No poisoning of the Pd catalyst was observed. As expected, the reactions of ortho-phenyl phenylacetylene (**2p**) and 2-ethynylnaphthalene (**2q**) proceeded smoothly to produce **3ap** and **3aq** in 82 and 84% yields, respectively. The furan product **3ar**, which can be used as a coupling partner in the Hiyama reaction,[14] was obtained in 64% yield when trimethylsilyl acetylene (**2r**) was examined. Subsequently, we investigated the reactivities of aliphatic alkyne substrates hex-1-yne (**2s**), oct-1-yne (**2t**), and 1-ethynylcyclo-hex-1-ene (**2u**) under the optimum reaction conditions. Products **3as** and **3at** were obtained in 70 and 75% yields, respectively. However, the pure product **3au** was obtained in only 37% yield owing to an unknown byproduct that cannot be easily removed. The estrone structure unit containing trisubstituted furan **3av** was isolated in 79% yield under the optimum reaction conditions, indicating that the current method can be applied in the postmodification of medicinally relevant molecules. Only a trace amount of the tetrasubstituted furan **3aw** was isolated when 1,2-diphenylacetylene (**2w**), an internal alkyne substrate, was finally tested. The reason was attributed to the steric hindrance caused by two phenyl groups.

The scope of the acceptor/donor-type diazo substrates was then examined utilizing **2a** as the reaction partner (Table 3). The reaction of diazo substrate **1b** having a Me group on the para-position of the benzene ring proceeded as smoothly as **1a**

Table 2. Scope of Terminal Alkynes[a,b]

3aa, 82% **3ab**, 88% **3ac**, o-Me, 70% / **3ad**, m-Me, 74% / **3ae**, p-Me, 78%

3af, X = F, 84% / **3ag**, X = Cl, 79% / **3ah**, X = Br, 82% **3ai**, 76%

3aj, 85% **3ak**, 85% **3al**, 86%

3am, 83% **3an**, 90% **3ao**, 83%

3ap, 82% **3aq**, 84% **3ar**, 64%

3as, 70% **3at**, 75% **3au**, 37% (84%)[c]

3av, 79% **3aw**, 4%

[a]Reaction conditions: **1a** (0.55 mmol), **2** (0.5 mmol), Pd(OAc)$_2$ (3 mol %), ^{t}BuPPh$_2$ (6 mol %), NEt$_3$·HBr (5 mol %), and FeBr$_3$ (5 mol %) in THF (3 mL) at 80 °C under a nitrogen atmosphere for 2 h. [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy with CH$_2$Br$_2$ as an internal standard.

to afford **3ba** in 77% yield. However, the MeO-substituted analogues **1c** and **1e** produced **3ca** and **3ea** in relatively low yields under the optimum reaction conditions due to their inherent instability. The reactions of diazo substrates **1c** and **1e** required the combined use of HBr·NEt$_3$ (1.0 equiv) and PhB(OH)$_2$ (1.0 equiv) to offer the furan products **3ca** and **3ce** in relatively high yields (62 and 76%, respectively; details in the Supporting Information). The reaction of **1d** required a long time to complete, furnishing the furan product **3da** in 79% yield. The *para*-phenyl-substituted substrate **1f** smoothly

Table 3. Scope of α-Aryl-α-diazoacetates[a,b]

3ba, 77% **3ca**, o-OMe, 24% (62%)[c] / **3da**, m-OMe, 79%[d] / **3ea**, p-OMe, 22% (76%)[c] **3fa**, 85%

3ga, X = F, 79% / **3ha**, X = Cl, 85%[d] / **3ia**, X = Br, 83%[d] **3ja**, 94% **3ka**, R = CO$_2$Me, 86%[d] / **3la**, R = CN, 64%[d]

3ma, 25% (48%)[c] **3na**, 75%[d] **3oa**, 82%

[a]Reaction conditions: **1** (0.55 mmol), **2a** (0.5 mmol), Pd(OAc)$_2$ (3 mol %), ^{t}BuPPh$_2$ (6 mol %), HBr·NEt$_3$ (5 mol %), and FeBr$_3$ (5 mol %) in THF (3 mL) at 80 °C under a nitrogen atmosphere for 2 h. [b]Isolated yield. [c]The reaction was performed with the combined use of HBr·NEt$_3$ (1.0 equiv) and PhB(OH)$_2$ (1.0 equiv). [d]The reaction was conducted for 3 h.

underwent the [3 + 2] cycloaddition to give product **3fa** in 85% yield. Interestingly, the *para*-fluoro-substituted substrate **1g** exhibited reactivity relatively higher than that of the *para*-chloro- and bromo-substituted substrates **1h** and **1i**. Substrate **1g** was found to be consumed completely within 2 h, providing furan product **3ga** in 79% yield. The furan products **3ha** and **3ia** were isolated in 85 and 83% yields, respectively, when the reactions of **1h** and **1i** were carried out for 3 h. Notably, the furan-moiety-containing arylboron compound **3ja**, which can be used for functional material synthesis by the Suzuki reaction,[15] was obtained in excellent yield (94%). This result further proved the utility of the present method in organic synthesis. Reactions of the diazo substrates **1k** and **1l** bearing an electron-withdrawing group CO$_2$Me or CN on the *para*-position of the benzene ring were completed within 3 h to furnish **3ka** and **3la** in 86 and 64% yields, respectively. Although the diazo substrate **1m** completely disappeared within 2 h, the furan product **3ma** was isolated in only 25% yield. The **3ma** yield was finally increased to only 48% by the combined use of HBr·NEt$_3$ (1.0 equiv) and PhB(OH)$_2$ (1.0 equiv). The reason was ascribed to the steric hindrance caused by the naphthalene ring. Diazo substrates *tert*-butyl 2-diazo-2-phenylacetate (**1n**) and phenyl 2-diazo-2-phenylacetate (**1o**) were suitable for the current [3 + 2] cycloaddition reaction, providing **3na** and **3oa** in 75 and 82% yields, respectively. Other types of diazo substrates, such as alkyl/acceptor diazo ester **1s**, H/acceptor diazo ester **1t**, and acceptor/acceptor diazo ester **1u**, were also investigated. However, the desired

products were not detected; the starting materials were decomposed (for details, see the Supporting Information).

Finally, allyl 2-diazo-2-phenylacetate (**1p**), cinnamyl 2-diazo-2-phenylacetate (**1q**), and 3-phenylpropargyl 2-diazo-2-phenyl-acetate (**1r**) were examined (Table 4). The [3 + 2]

## Table 4. Reactions of Allyl and Propagyl α-Aryl-α-diazoacetates with Phenylacetylene: Synthesis of Butenolides[a,b]

4pa, 76%   **4qa**, 81%[c]   **4ra**, 36%[d]
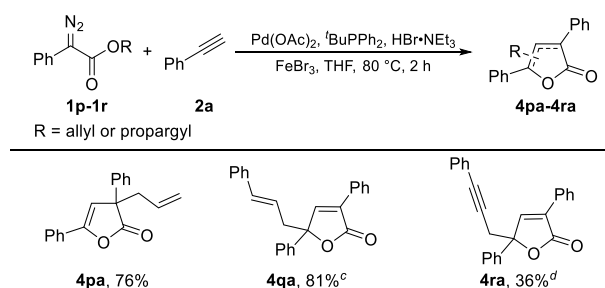
[a]Reaction conditions: **1p**−**1r** (0.55 mmol), **2a** (0.5 mmol), Pd(OAc)$_2$ (3 mol %), ^{t}BuPPh$_2$ (6 mol %), HBr·NEt$_3$ (5 mol %), and FeBr$_3$ (5 mol %) in THF (3 mL) at 80 °C under a nitrogen atmosphere for 2 h. [b]Isolated yield. [c]The reaction was carried out for 3 h. [d]The reaction was carried out for 12 h.

cycloaddition reaction of **1p** occurred and was followed by Claisen rearrangement reaction to afford an unexpected product, α-allylbutenolide **4pa**, in 76% yield.[16] Interestingly, the generated furan products successively underwent Claisen and Cope rearrangement reactions to produce the butenolides **4qa** and **4ra** in 81 and 36% yields, respectively, when the diazo substrates **1q** and **1r** were utilized. The force driving the Cope rearrangement reaction was considered to originate from the strong steric hindrance in the Claisen rearrangement product (details in the Supporting Information).

The transformation of the furan product **3an** was studied to further explore the practicability and utilization of our methodology (Scheme 2). As expected, the oxidative ring-

Scheme 2. Derivatization of Product 3an
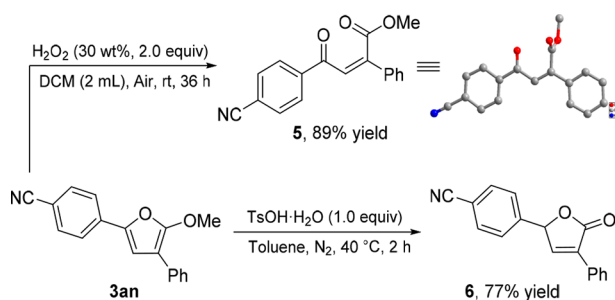
opening reaction of **3an** smoothly occurred in the presence of H$_2$O$_2$ to give the Z-type γ-carbonyl butenoate derivative **5** in 89% yield.[17] The structure of **5** was characterized by X-ray crystallography. In addition, the hydrolysis of **3an** also occurred smoothly to produce the butenolide product **6** in 77% yield.[18] Products **5** and **6** can be used to synthesize additional useful compounds.[19]

To gain insights into the mechanism underlying the [3 + 2] cycloaddition of acceptor/donor-type diazo compounds with terminal alkynes, some control experiments were conducted (Scheme 3). Product **3ab-*d*** was isolated in 73% yield with 89%

Scheme 3. Control Experiments
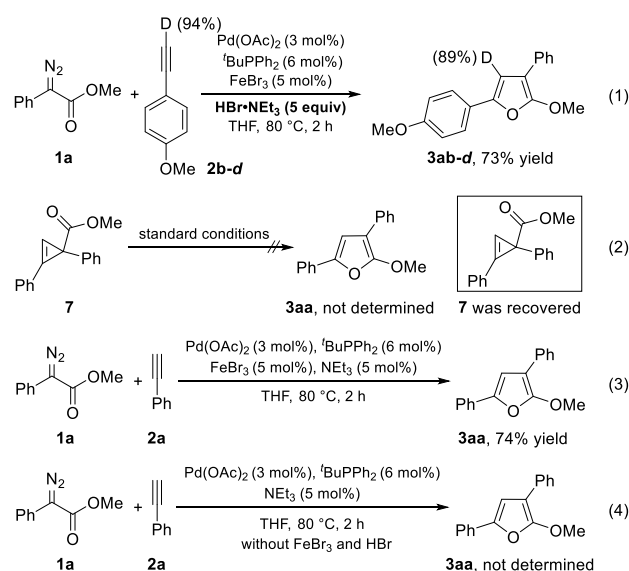
deuterium incorporation when the deuterium-labeled substrate **2b-*d*** was examined in the presence of excess Brønsted acid (5.0 equiv, eq 1). This result indicated that the formation of a metal acetylide intermediate was not involved in the target [3 + 2] cycloaddition.[20] No reaction was found when the cyclopropene **7** was examined under the standard conditions, suggesting that the target [3 + 2] cycloaddition did not proceed through [2 + 1] cycloaddition and the subsequent ring-opening rearrangement reaction (eq 2).[21] Compared with the yield of **3aa** shown in Table 1 (entry 17), increased yield was obtained by the combined use of FeBr$_3$ and NEt$_3$ (eq 3), which may be the reason why the target [3 + 2] cycloaddition required FeBr$_3$ and HBr·NEt$_3$ to provide a good yield (Table 1). HBr·NEt$_3$ acted as both the proton and Lewis base sources in the current cooperative catalysis. The role of NEt$_3$ is not clear at present; NEt$_3$ probably acted as a stabilizer or ligand for the zwitterion intermediate[22] and the palladium−carbene species (see Scheme 4).[23] No generation of product **3aa** was observed when the reaction of **1a** with **2a** was also performed in the absence of FeBr$_3$ or HBr, indicating that an acid catalyst is necessary for the target reaction to take place (eq 4 of Scheme 3). Subsequently, a kinetics study was conducted to estimate the efficiency of FeBr$_3$ and HBr (Figure 1; for details,
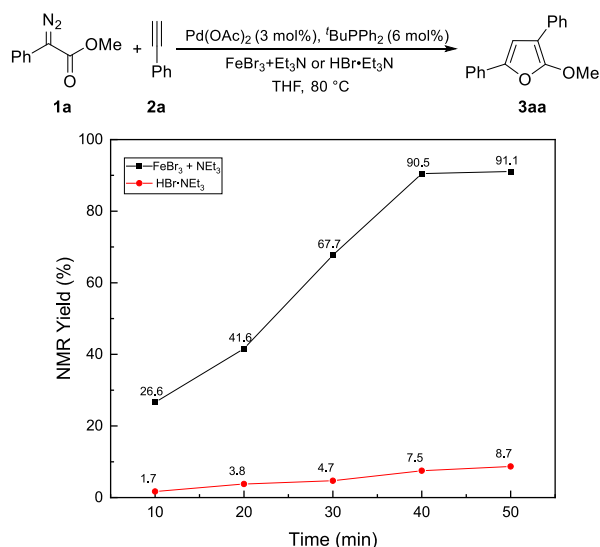
Scheme 4. Proposed Mechanism
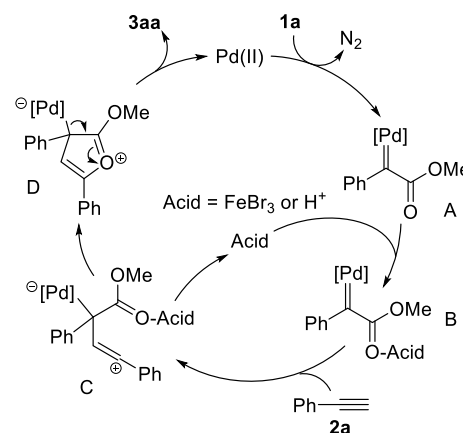
Figure 1. Kinetic study. The yield of product was determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

see the Supporting Information). The results obtained indicated that both FeBr$_3$ and HBr acted as catalyst for the target reaction, and the catalytic efficiency of FeBr$_3$ is higher than that of HBr.

Based on the experimental results and previous reports,[8f,13,24] a mechanism was proposed for the present cooperative catalytic [3 + 2] cycloaddition reaction (Scheme 4). First, diazo substrate **1a** reacted with palladium catalyst to generate the palladium–carbene species A, which was then activated by H$^+$ and/or FeBr$_3$ to form intermediate B. The carbon-atom-linking palladium in intermediate B became more positive, thereby easily undergoing electrophilic attack to alkyne substrate **2a** to produce intermediate C. Then, intermediate C cyclized to form furan product **3aa** through a cyclic zwitterion intermediate D and regenerated the catalytic species Pd(II).

The influence of substituents on the reaction rate was finally analyzed, and inverted V-shaped Hammett plots were observed for arylacetylenes and α-aryl-α-diazoacetates. For arylacetylenes, the electron-donating and electron-withdrawing substituents showed positive (ρ, +0.21) and negative (ρ, −0.12) slopes, respectively (Figure 2). The relatively low ρ values (+0.21 and −0.12) observed suggested that arylacetylene substrates were not involved in the rate-determining step in the reactions shown in Table 2.[25] Similar positive (ρ, +1.01) and negative (ρ, −1.07) linear Hammett correlations were observed for α-aryl-α-diazoacetates (Figure 3). The relatively high ρ values (+1.01 and −1.07) observed demonstrated that α-aryl-α-diazoacetate substrates were involved in the rate-determining steps and existing two different rate-determining steps (Table 3).[26] The formation of palladium–carbene intermediate and the electrophilic attack of an activated palladium–carbene intermediate to an alkyne might be the rate-determining steps.

In conclusion, we developed a general and straightforward method to synthesizing 2,3,5-trisubstituted furans using acceptor/donor-type diazo compounds as starting materials. The [3 + 2] cycloaddition of α-aryl-α-diazoacetates with terminal alkynes proceeded smoothly via palladium and acid cooperative catalysis, and the 2,3,5-trisubstituted furans were obtained in high to excellent yields. NEt$_3$ was considered to be
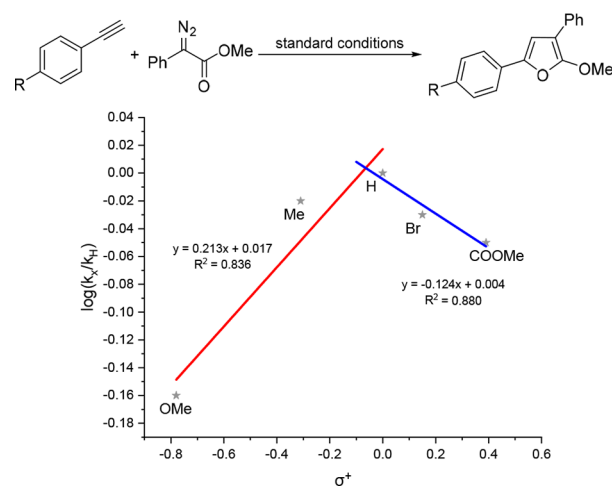

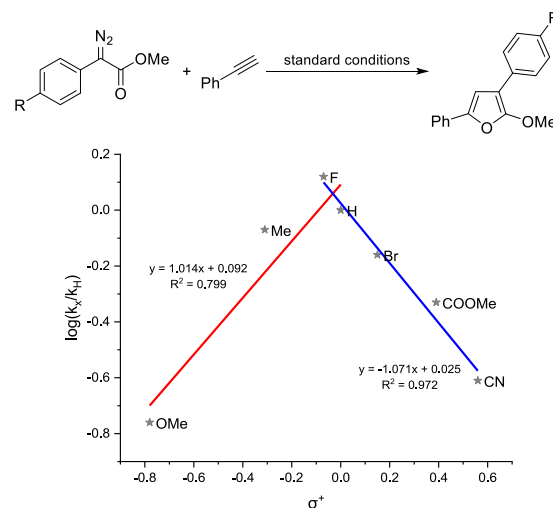**Figure 2.** Hammett plot for the reactions of *para*-substituted arylacetylenes.

Figure 3. Hammett plot for the reactions of *para*-substituted α-aryl-α-diazoacetates.

an efficient additive to improve the product yields. The good functional group tolerance, mild reaction conditions, and experimental simplicity enabled the current protocol to be highly useful for the preparation of multisubstituted furans.

■ ASSOCIATED CONTENT

ⓈI **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02533.

General considerations; materials and methods; optimization studies; experimental procedures; characterization data; ^{1}H, ^{13}C, IR, and mass spectra of new compounds; optical data of **3am** and **3an** (PDF)

Crystallographic data for **3ai** (CIF)

Crystallographic data for **5** (CIF)

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