

Fe-Catalyzed Selective Formal Insertion of Diazo Compounds into C(sp)–C(sp³) Bonds of Propargyl Alcohols: Access to Alkyne-Substituted All-Carbon Quaternary Centers

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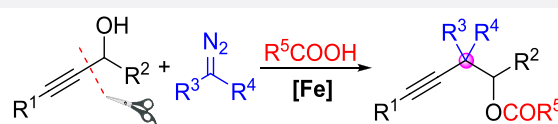
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ABSTRACT: The construction of all-carbon quaternary centers, especially those containing an alkyne-substituted framework, represents an important challenge in organic synthesis. Here we present a novel Fe-catalyzed selective formal insertion of diazo compounds into C(sp)–C(sp³) bonds of propargyl alcohols under mild conditions that enables the streamlined construction of alkyne-substituted all-carbon quaternary centers. This unique strategy starts with in situ generation of an ester group in the presence of carboxylic acids, followed by insertion of metal-carbene into C(sp)–C(sp³) bonds, which may open up a new reaction mode for exploring metal-carbene insertion into acyclic C–C bonds.



- ✓ The first one-carbon insertion into C(sp)–C(sp³) bonds
- ✓ Multicomponent assembly of alkyne-substituted all-carbon quaternary centers
- ✓ Mild reaction conditions and up to 40 examples

1. INTRODUCTION

All-carbon quaternary centers have rigidity and structural diversity and are key structural units in many natural products, pharmaceuticals, as well as biologically active molecules.^{1–7} Hence, the construction of all-carbon quaternary centers is quite attractive for organic synthetic chemists; structures containing alkyne-substituted framework are versatile intermediates and basic structural motifs in organic transformations.^{8,9} The most common method for obtaining alkyne-substituted all-carbon quaternary centers is through the whole assembly of alkynyl groups into other substrates (Figure 1a), such as Sonogashira coupling,^{10–12} electrophilic alkylation,^{13–16} enantioselective conjugate alkylation,^{17–19} and so on.^{20,21} Major obstacles to these aforementioned transformations include dimerization of terminal alkynes, reliance on functionalized precursors, and the β -H elimination of branched tertiary alkyl units. In this case, as an alternative strategy to solve these problems, we questioned whether a specific protocol could be realized through selective cleavage of C(sp)–C(sp³) bonds of internal alkynes and subsequent insertion of carbon sources to construct alkyne-substituted all-carbon quaternary centers (Figure 1b).^{22–25}

The selective cleavage of inherently inert C–C bonds and subsequent functionalization are considered as a formidable synthetic challenge due to the thermodynamic stability and kinetic inertness of C–C bonds.^{26–30} Nonetheless, significant advances have been made over the past decades, specifically in the insertion of diazo compounds into C–C bonds. In these transformations, acid or base can promote homologation of diazo compounds with ketones, which insert into C–C bonds

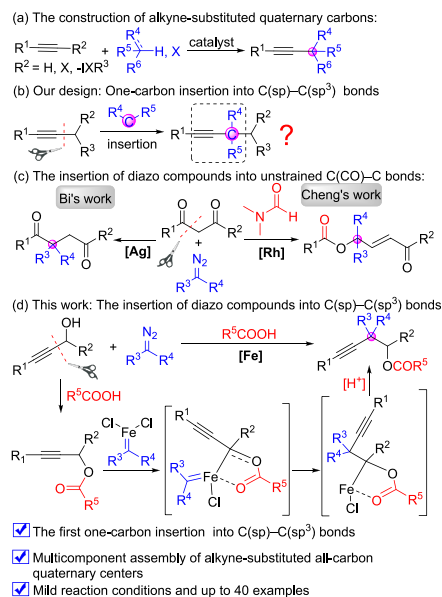


Figure 1. Construction of alkyne-substituted all-carbon quaternary centers and the insertion of diazo compounds into C–C bonds.

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through a carbene-free process.³¹ Notably, transition metals with diazo compounds are able to form energetic carbenoids that can formally insert into the C–C bonds, producing homologues plus one carbon.³² This one-carbon insertion strategy not only allows selective cleavage of inert C–C bonds but also forms functionally all-carbon quaternary centers.^{33,34}

However, the strained system is commonly required as it can provide a pivotal thermodynamic driving force through strain release.^{35–39} In 2018, Bi and co-workers reported the first Ag-catalyzed one-carbon insertion into the unstrained C(CO)–C bonds of 1,3-dicarbonyl compounds using diazoes (the left of Figure 1c).^{40,41} Subsequently, Cheng's group developed an unparalleled Rh-catalyzed multicomponent assembly reaction of 1,3-diones, diazoesters, and *N,N*-dimethylformamide via insertion of O–C(sp³)–C(sp²) into unstrained C(CO)–C bonds (the right of Figure 1c).⁴² These two extremely rare examples successfully realized the insertion of diazoes into acyclic C–C bonds, but the range of substrates were limited to 1,3-dicarbonyl species. Moreover, to the best of our knowledge, the insertion of diazo-derived metal-carbene into C(sp)–C(sp³) bonds of internal alkynes is still unknown.^{43–46}

Inspired by Fe-catalyzed carbene transfer/insertion reactions,^{47–52} we envision the use of iron catalyst to mediate C–C bond insertion for the construction of important alkyne-substituted all-carbon quaternary centers. Herein, we present a novel Fe-catalyzed selective formal one-carbon insertion of α -diazoacetates into C(sp)–C(sp³) bonds of propargyl alcohols in the presence of carboxylic acids, providing a convenient route for the formation of alkyne-substituted all-carbon quaternary centers (Figure 1d). This transformation starts with in situ generation of ester groups by esterification of propargyl alcohol with carboxylic acid, avoiding the limitation of the ketone group, followed by insertion of diazo metal-carbene into the C(sp)–C(sp³) bond in the presence of FeCl₃ and carboxylic acid.

2. RESULTS AND DISCUSSION

Reaction Development. We commenced our investigation by using propargyl alcohol **1a** and α -diazoacetate **2a** (**Caution!** Diazo compound is a flammable as well as explosive substance; thus all manipulations should be performed on the practical scale) as the model substrates (Table 1). After extensive evaluation, 20 mol % of FeCl₃ as the catalyst and 10.0 equiv of HOAc as the additive and reaction partner in EtOAc under the argon (Ar) atmosphere at room temperature (r.t.) proved to be the optimal conditions, and afford the desired product **3a** in 88% isolated yield (entry 1). The target product **3a** was not detected without FeCl₃ or HOAc, indicating the importance of FeCl₃ and HOAc for this one-carbon insertion reaction (entries 2–3). Whether HOAc only plays as a source of ester group remains a question that deserves to be explored later. Subsequently, a series of iron catalysts like FeCl₂, FeBr₃, Fe(acac)₃, and Fe(NO₃)₃ were examined, but only FeCl₂ and FeBr₃ promoted the reaction in satisfactory yields (entries 4–7). Notably, copper or silver salt was not a suitable catalyst for this transformation (entries 8–9). Finally, reducing the loading of FeCl₃ resulted in a slight decrease in the yield of **3a** (entry 10).

Next, to emphasize the reproducibility of the transformation, we examined the reaction-condition-based sensitivity assessment (for details, see the Supporting Information).^{53,54} The radar diagram of sensitivity assessment (Figure 2) demonstrated that this reaction features low sensitivity, having

Table 1. Optimization of the Reaction Conditions^a

entry	variations from standard conditions	yield ^b
1	None	88%
2	No FeCl ₃	N.D. ^c
3	No HOAc	N.D. ^c
4	FeCl ₂ instead of FeCl ₃	71%
5	FeBr ₃ instead of FeCl ₃	81%
6	Fe(acac) ₃ instead of FeCl ₃	11%
7	Fe(NO ₃) ₃ instead of FeCl ₃	7%
8	CuBr instead of FeCl ₃	6%
9	AgOAc instead of FeCl ₃	10%
10	10 mol % of FeCl ₃	72%

^aReaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv), FeCl₃ (20 mol %), HOAc (10.0 equiv), and EtOAc (2.0 mL) at r.t. under Ar for 8 h. The d.r. of **3a** was about 9:1. ^bIsolated yields. ^cN.D. = Not detected.

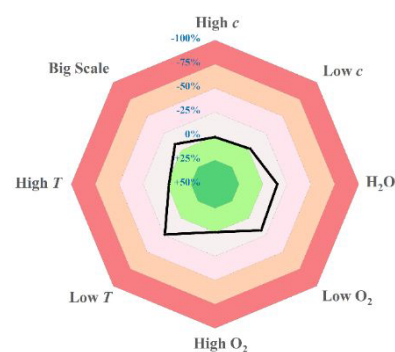
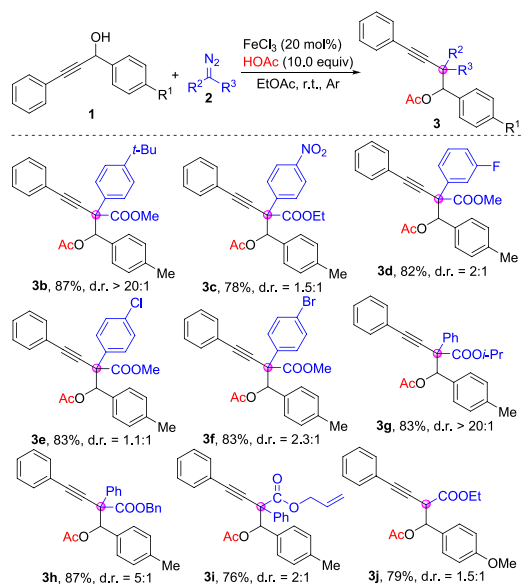


Figure 2. Sensitivity assessments.

outstanding reproducibility under various conditions. Moreover, this method can be scaled up to gram scale smoothly.

Substrate Scope of α -Diazoacetates. With the optimized reaction conditions in hand, we then proceed to investigate the scope of α -diazoacetates to explore the adaptability of this Fe-catalyzed selective formal one-carbon insertion, which was summed up in Scheme 1. To begin with, the effect of substituents on the aromatic ring of α -phenyldiazoacetates was examined. Gratifyingly, all electron-donating or electron-withdrawing groups on the aromatic ring, including *tert*-butyl (*t*-Bu), nitril, halide (F, Cl, and Br) groups, were well tolerated, providing the corresponding desired products (**3b–3f**) in good yields. Then, different ester moieties at the substituted α -aryldiazoacetates were surveyed. Varying the methyl at ester moieties to isopropyl (*i*-Pr), benzyl (Bn), and allyl moieties furnished the desired one-carbon insertion products (**3g–3i**) with slightly lower yields. Inspiringly, the one-carbon insertion reaction was also suitable for α -H diazoester (**3j**).

Substrate Scope of Propargyl Alcohols. The substrate scope of propargyl alcohols was next examined (Scheme 2). We were delighted to find that the Fe-catalyzed selective formal one-carbon insertion proceeded well with a wide range of propargyl alcohols, affording access to a diverse array of alkyne-substituted all-carbon quaternary centers. First, we set out to evaluate the effect of the neighboring hydroxyl position

Scheme 1. Substrate Scope with Regard to α -Diazoacetates^a

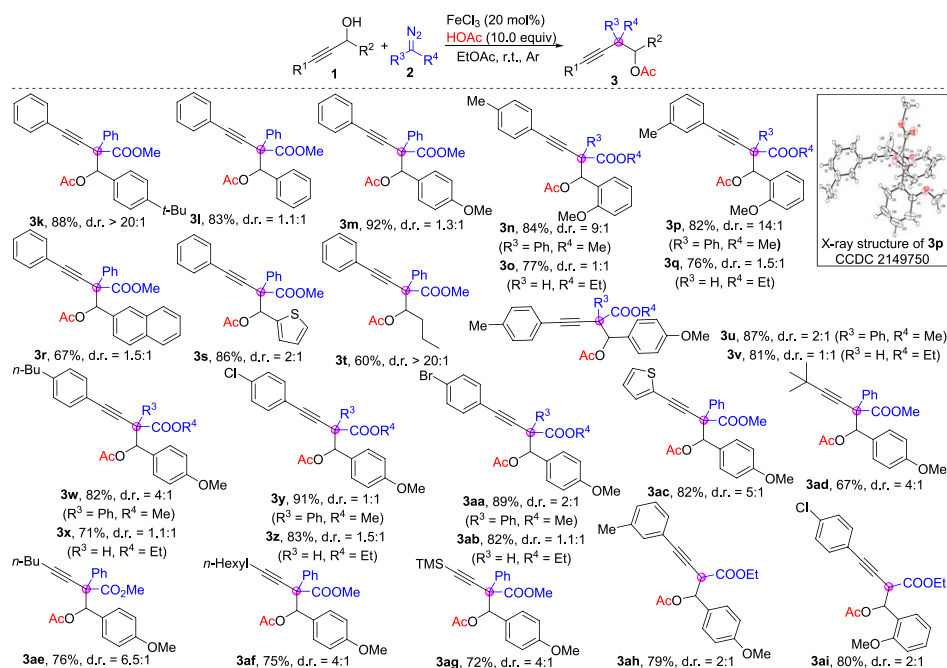
^aReaction conditions: 1 (0.2 mmol), 2 (2.0 equiv), FeCl₃ (20 mol %), HOAc (10.0 equiv), and EtOAc (2.0 mL) at r.t. under Ar for 8 h.

(R²) of the propargyl alcohols. When the substituents on the aryl group of R² were altered (3k–3r), the yields were kept at good to very good level. Importantly, the steric hindrance effect of the substrate was negligible, as demonstrated by the use of α -aryldiazoacetate or α -H diazoester as insertion partners (3n–3q). Moreover, the structure of product 3p was definitely confirmed by X-ray crystallography (CCDC 2149750). Substrates containing thienyl and alkyl were smoothly converted to the desired products 3s and 3t, respectively. Subsequently, we turned our attention to

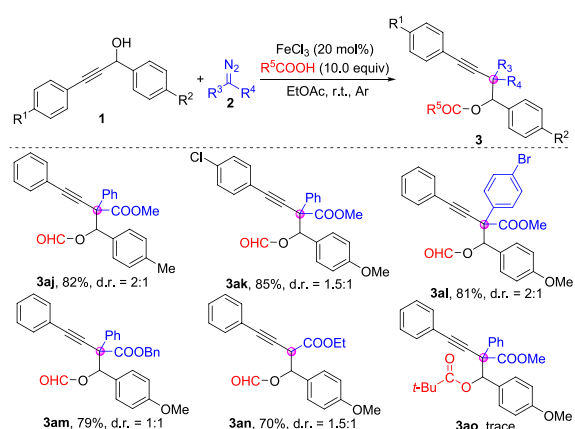
examining the substituents at the alkynyl position (R¹) of the propargyl alcohols. Several substituents, namely, Me, *n*-butyl (*n*-Bu), Cl, and Br, on the aromatic ring of R¹ were well tolerated (3u–3ab). In this, α -aryldiazoacetate was more efficient than α -H diazoester for this reaction under optimal conditions. Luckily, propargyl alcohol with thienyl was proved to be a suitable substrate, giving product 3ac in 82% yield. Aside from aromatic propargyl alcohols, a series of aliphatic substituted propargyl alcohols also gave the desired products 3ad–3af in slightly lower yields. Moreover, propargyl alcohol with trimethylsilyl (TMS) substituent at the alkynyl position was also easily transformed into the desired product 3ag in 72% yield. Finally, the reaction between propargyl alcohols with α -H diazoester could also be successfully converted to one-carbon insertion products 3ah–3ai in satisfactory yields.

Substrate Scope of Carboxylic Acids. Our attention then turned toward the development of one-carbon insertion based on other carboxylic acids (Scheme 3). We selected a few representative substrates to react with HCOOH (**Caution!** HCOOH is a corrosive and irritating liquid; contact with skin should be strictly avoided). Pleasingly, 1a readily took part in this reaction with HCOOH and gave the target product 3aj in 82% yield. Propargyl alcohol with Cl substituent was tolerated in this transformation (3ak). A variety of substituted α -diazoacetates were suitable partners and transformed into the corresponding products in moderate to good yields (3al–3an). Disappointingly, no desired product (3ao) could be generated when pivalic acid was employed as the acid source.

Mechanistic Investigation. To obtain more information about the reaction pathway of the described transformation, several additional experiments were conducted (Scheme 4). The one-carbon insertion proceeded smoothly when 2,2,6,6-tetramethylpiperidinoxy (TEMPO) or butylated hydroxytoluene (BHT) was introduced into the reaction system, suggesting that the radical pathway may not be involved in

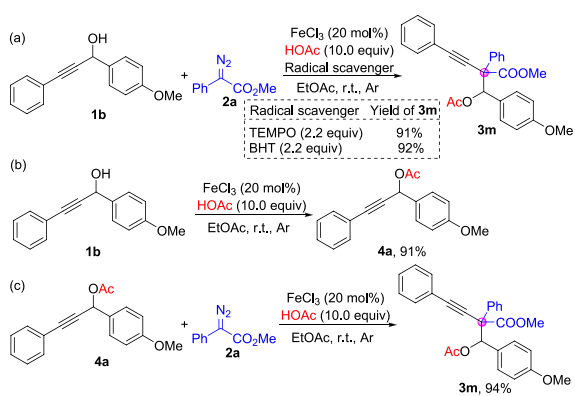
Scheme 2. Substrate Scope with Regard to Propargyl Alcohols^a

^aReaction conditions: 1 (0.2 mmol), 2 (2.0 equiv), FeCl₃ (20 mol %), HOAc (10.0 equiv), and EtOAc (2.0 mL) at r.t. under Ar for 8 h.

Scheme 3. Substrate Scope with Regard to Carboxylic Acids^a

^aReaction conditions: **1** (0.2 mmol), **2** (2.0 equiv), FeCl₃ (20 mol %), HOAc (10.0 equiv), and EtOAc (2.0 mL) at r.t. under Ar for 8 h.

Scheme 4. Mechanistic Studies



this reaction (Scheme 4a). The role of HOAc in this reaction was investigated next. The **1b** could be converted to propargyl ester **4a** under standard conditions in the absence of diazo substrate, which confirmed the presence of an esterification process (Scheme 4b). Next, propargyl ester **4a** was treated with **2a** under the standard reaction conditions; the desired product **3m** was obtained in 94% yield (Scheme 4c). This result demonstrated the significant role of the ester group introduced by esterification reaction with carboxylic acid.

Then, the correlation between the yield of **3m** and the amount of HOAc was investigated by the use of **1b** or **4a** as the reaction partner (Figure 3). As shown in the red curve (**1b** as the reaction partner), the yield of **3m** increased slowly and then rapidly with the increase of HOAc concentration, which was probably due to the initial involvement of esterification reaction before 5.0 equiv of HOAc. As presented in the blue curve (**4a** as the reaction partner), 7% of **3m** was still detected when no HOAc was in the reaction system, but the yield of **3m** increased rapidly with the increase of HOAc concentration. In addition, it is noteworthy that the yield of **3m** approached the maximum when 7.0 equiv of HOAc was added. These results suggested that HOAc not only acted as a source of the ester group to initiate this multicomponent reaction but also promoted diazo metal-carbene insertion into the C(sp)–C(sp³) bond of propargyl alcohol.

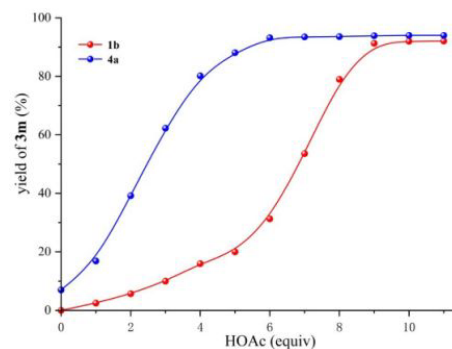


Figure 3. Correlation between the yield of **3m** and the amount of HOAc.

Proposed Mechanism. Based on the density functional theory (DFT) calculations (for details, see the Supporting Information) and literature precedents,^{20,47,49,55,56} we propose a possible reaction pathway (Figure 4). Initially, in the

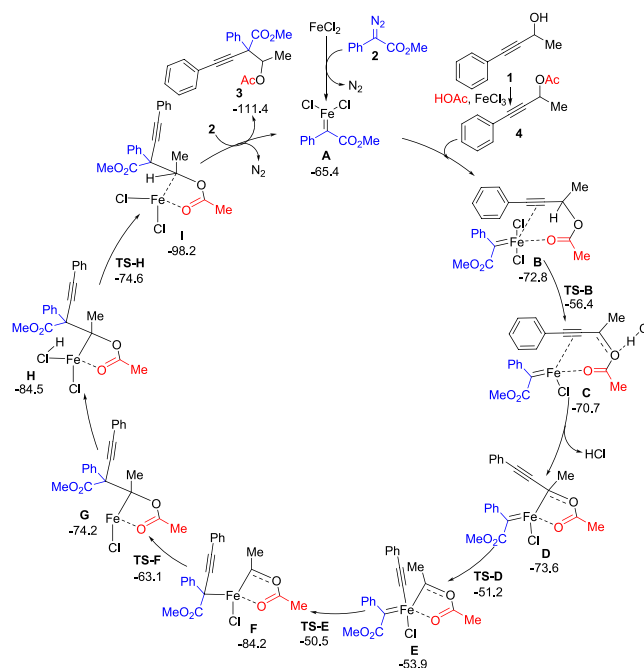


Figure 4. Plausible reaction mechanism with DFT calculations.

presence of Lewis acid FeCl₃, esterification product **4** is in situ formed from the propargyl alcohol **1** with HOAc. In parallel, Fe³⁺ catalyst can be reduced to Fe²⁺ by the diazo compound. Subsequently, the Fe²⁺ complex attacks the negatively charged diazo compound **2**, leading to the formation of iron carbene complex **A** after irreversible removal of N₂. Then, the coordination of **A** with **4** gives complex **B**. Afterward, intermediate **B** is first deprotonated from the carbon atom adjacent to the ester group under the assistance of a Cl⁻ anion along with release of the HCl molecule to give intermediate **D**, which undergoes a migration of the alkynyl group to the iron catalyst through the transition state TS-D followed by reduction elimination (TS-E) to generate species **F**. Next, the tertiary carbon atom attacks the carbonyl carbon through TS-F to yield intermediate **G**. Finally, intermediate **G** undergoes a protonation process with the assistance of the previous step releasing HCl or HOAc in this reaction system to

afford the desired product. Notably, the activation barrier is 23.1 kcal/mol for this pathway, so these computational results are consistent with the experimental observations in the Fe-catalyzed insertion reactions.

3. CONCLUSION

In conclusion, we have developed a novel Fe-catalyzed selective formal one-carbon insertion of C(sp)–C(sp³) bonds between propargyl alcohols and α -diazoacetates using carboxylic acids under mild conditions. This approach starts with in situ generation of an ester group, followed by the insertion of diazo metal-carbene into the C(sp)–C(sp³) bond, which enables the convenient construction of alkyne-substituted all-carbon quaternary centers. Controlled experiments demonstrated that carboxylic acid not only serves as a source of ester group to initiate this multicomponent reaction, but also promotes diazo metal-carbene insertion into the C(sp)–C(sp³) bond. Notably, this unique strategy represents the first example of C(sp)–C(sp³) bond cleavage and subsequent functionalization for the assembly of alkyne-substituted all-carbon quaternary centers through the metal-carbene insertion process, which potentially pioneer a new reaction mode for exploring metal-carbene insertion into acyclic C–C bonds. Further studies on the other types of diazo metal-carbene insertion and asymmetric catalysis are currently investigated in our laboratory.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscentsci.2c00204>.

Synthetic procedures, sensitivity assessments, compound characterization (copies of ¹H, ¹³C, and ¹⁹F NMR spectra), density functional theory calculations, and additional data (PDF)

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Notes

The authors declare no competing financial interest.

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