Iron-catalyzed carboazidation of alkenes and alkynes

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Carboazidation of alkenes and alkynes holds the promise to construct valuable molecules directly from chemical feedstock therefore is significantly important. Although a few examples have been developed, there are still some unsolved problems and lack of universal methods for carboazidation of both alkenes and alkynes. Here we describe an iron-catalyzed rapid carboazidation of alkenes and alkynes, enabled by the oxidative radical relay precursor t-butyl perbenzoate. This strategy enjoys success with a broad scope of alkenes under mild conditions, and it can also work with aryl alkynes which are challenging substrates for carboazidation. A large number of diverse structures, including many kinds of amino acid precursors, fluoroalkylated vinyl azides, other specific organoazides, and 2H-azirines can be easily produced.
Alkynes, the basic building blocks of proteins are being used increasingly in bio-relevant modification of proteins and pharmaceutical applications. Development of more versatile methods to provide useful but synthetically challenging amino acid frameworks from chemical feedstocks is always highly desired. Carboazidation of alkenes and alkynes holds the promise to construct valuable molecules including amino acid precursors and has therefore attracted much attention recently. Although several carboazidations of alkenes have been developed by Huang, Renaud, Liu, Masson, Zhu, Jiao and Xu, there are some unsolved problems in this field. How to realize the carboazidation reaction using nontoxic, inexpensive and readily available reagents with a broad scope of olefins remains a question. In addition, the carboazidation of alkynes is even more challenging than carboazidation of alkenes. There is only one successful carboazidation of alkynes reported by Liu, which works for single carbon functionality, i.e., a trifluoromethyl group using Togni’s reagent. The reason for the lack of methods for carboazidation of alkynes might be attributed to the relative lower efficiency of incorporation of azide species compared to other competing reactions. The development of carboazidation of alkynes is even more challenging than carboazidation of alkenes (Fig. 1a). There is only one successful carboazidation of alkynes reported by Liu, which works for single carbon functionality, i.e., a trifluoromethyl group using Togni’s reagent (Fig. 1b). The reason for the lack of methods for carboazidation of alkynes might be attributed to the relative lower efficiency of incorporation of azide species compared to other competing reactions.

Results
Carboazidation of alkenes. We investigated the reaction parameters for carboazidation in the presence of TBPB and found that ferrous trifluoromethanesulfonate (Fe(OTf)2, ferrous triflate) is optimal (Fig. 2, see details in Supplementary Table 1 and Supplementary Figures 2–4), delivering the corresponding product 3 in 89% yield at rt with DME (dimethoxyethane) as the solvent and azidotrimethylsilane (TMSN3) as the azidation reagent. Possible by-products 4, 4', and 4'' were not observed.

With the optimized conditions in hand, we studied the scope of the reaction with alkyl iodides (Fig. 3 and Supplementary Figures 5–34). Fluoroalkyl iodides were examined first and the corresponding fluoroalkyl-azidation products (5–10) were obtained in high yields. The reaction of styrene with iodoacetoneitrile proceeds smoothly, affording the corresponding product (11) in 86% yield. Reactions with ethyl iodoacetates affords products (12–14) with the yield ranging from 71–85%. With 1-iodo-3,3-dimethylbutan-2-one the reaction delivers the azide (15) in 61% yield. Three electron rich alkyl iodides, i.e., 1-chloro-4-iodobutane, 1-iododecane and 2-iodobutane are not.
effective in this reaction as the direct azidation of alkyl iodides to form alkyl azides occurs. It should be noted that the reactions with perfluoroalkyl iodides are very fast, completing in 10 min in many cases.

Subsequently, we studied the substrate scope of olefins (Fig. 4 and Supplementary Figs. 35–189). As examples, α-azido esters (16–27 in Fig. 4a), β-azido esters (28–37 in Fig. 4b), γ-azido esters (38–63 in Fig. 4c), other azido acid derivatives (64–69 in Fig. 4d–g) and organoazides (70–75 in Fig. 4h) were obtained. The functional group compatibility of this reaction is good: a series of functional groups, such as halogen, ester, carboxylic acid (69), and free hydroxyl group (74) are tolerated under the reaction conditions. Both terminal and internal alkenes (28–37, 58, and 65) are compatible with the reaction. The carboazidation reactions of 1-oc-tene with iodomethane and iodobutane are not successful under the reaction conditions.

To highlight the synthetic applications, 8, 19 and 78 were reduced to amine 76, amino acid 77 and pyrrolidinone 79, respectively (Fig. 5 and Supplementary Figs. 190–199).

**Carboazidation of alkynes.** Vinyl azides (1-azidoalkynes) are versatile building blocks in organic synthesis and have been used in many transformations to synthesize bioactive alkaloids and heterocycles. Although the carboazidation of alkynes can difunctionalize alkynes, affording 1-azidoalkynes which can be subsequently converted to 2H-azirines, reports of such efficient methods are rare, and accordingly, we studied the carboazidation of alkynes. After carefully screening the reaction conditions, Fe(OTf)3 was found to be the best catalyst, producing a carboazidation product (81) while avoiding the formation of the atom-transfer radical addition (ATRA) product (81’) (Fig. 6a, see details in Supplementary Table 2 and Supplementary Figs. 200–208). In view of the broad synthetic utilities of 2H-azirines, the conversion of vinyl azides to 2H-azirines was studied. It was found that compound 81 could be converted into a 2H-azirine (82) in toluene at 120 °C (Fig. 6b).

With these conditions identified, we studied the substrate scope regarding alkyl iodides and alkynes. The results are shown in Fig. 7 and Supplementary Figs. 209–283. Fluoroalkyl iodides and aryl alkynes react well in these transformations. Reaction of 1-iododecane with ethynylbenzene does not deliver the desired product. As an example, reaction of 1-octyne delivers only the ATRA product (107) in 42% yield.

To highlight the synthetic applications of this method further, vinyl azides and 2H-azirines were converted to 108, 109 and 110 in high yields (Fig. 8 and Supplementary Figs. 284–295). The geometry of vinyl azides was confirmed by X-ray crystallographic analysis of product 109 (see details in Supplementary Figure 1 and Supplementary Table 3).

**Discussion**

In summary, we have developed a carboazidation of alkenes and alkynes enabled by TBPB. This key transformation has been successfully used to afford various valuable structural skeletons, including many amino acid precursors, vinyl azides and 2H-azirines. It is noteworthy that this carboazidation works for both alkenes and alkynes with multiple carbon functionalities.

**Methods**

**Typical procedure for carboazidation of alkenes.** Fe(OTf)3 (9 mg, 0.025 mmol) was added to a dried Schlenk tube equipped with a magnetic bar. This tube was then flushed with N2 gas (3 times) and an N2 atmosphere was maintained using an N2 balloon. A thoroughly mixed solution of alkene (0.5 mmol), alkyl iodide (0.65–1.5 mmol), TMSN3 (0.7–1.7 mmol) and TBPB (0.75–1.75 mmol) in DME (2 mL) was added to the catalyst by syringe and the mixture was stirred vigorously for 3–120 min at the appropriate temperature. After completion of the reaction, judged by TLC, the solvent was evaporated and the residue was purified by flash chromatography on silica gel using petroleum ether and EtOAc to give the corresponding product.
**Fig. 4** Scope of alkenes. **a** Synthesis of α-azido esters. **b** Synthesis of β-azido esters. **c** Synthesis of γ-azido esters. **d** Synthesis of α,γ-azido esters. **e** Synthesis of an α,β-azido ester. **f** Synthesis of an αβ,γ-azido ester. **g** Synthesis of an azido acid. **h** Synthesis of other organoazides. General reaction conditions: Fe(OTf)₂ (5 mol%), 1 (0.5 mmol), 2 (0.65–1.0 mmol), TMSN₃ (1.0 mmol), TBPB (1.0 mmol) in DME (2 mL) at rt under an N₂ atmosphere. Isolated yields. dr values were determined by ¹H NMR.
Fig. 5 Applications of carboazidation products. a Reduction to amine. b Reduction to α-amino acid. c Cyclization to pyrrolidinones

Fig. 6 Carboazidation of alkynes. a Optimized reaction conditions. b Cascade transformation of vinyl azide to 2H-azirine

Fig. 7 Substrate scope of carboazidation of alkynes and further transformation to 2H-azirines. General reaction conditions: Fe(OTf)$_3$ (0.025 mmol), alkyne (0.5 mmol), RI (0.75 mmol), TMSN$_3$ (1.0 mmol), TBPB (1.0 mmol) in DME (2 mL) at rt for 5–20 min and then in toluene at 120 °C for 10 min under an N$_2$ atmosphere. Isolated yields.
Typical procedure for carboazidation of alkynes. Fe(OTf)₃ (12.7 mg, 0.025 mmol) was added to a dried Schlenk tube equipped with a magnetic bar. Then this tube was flushed with N₂ (3 times) and an N₂ atmosphere was maintained using an N₂ balloon. A thoroughly mixed solution of alkyne (0.5 mmol), R₂ (0.75 mmol), TMSN₃ (1.0 mmol) and TBPB (1.0 mmol) in DME (2 mL) was added to the catalyst by syringe and the mixture was stirred vigorously for 5–20 min at rt. After completion of the reaction, judged by TLC, the volatile compounds were removed by pump and the residue was dissolved in toluene (3 mL). The resulting mixture was then stirred at 120°C for 10 min. The solvent was then evaporated and the residue was purified by flash chromatography on silica gel using petroleum ether and EtOAc to give the corresponding product.

Data availability
Detailed experimental procedures and characterization of compounds can be found in the Supplementary Information. The X-ray crystallographic coordinates obtained free of charge from The Cambridge Crystallographic Data Centre via CCDC (109: CCDC 1864994). These data could be found in the Supplementary Information. The X-ray crystallographic coordinates of peroxides and alkenes with copper salts. J. Am. Chem. Soc. 105, 1862–1872 (1983).

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Author contributions
H.X., N.R., and W.I. performed the synthetic experiments and analyzed the experimental data. H.B. directed the investigations and prepared the manuscript. H.X., M.-F.C., X.Z., J.-H.S., and Y.L. contributed to the discussion and preparation of the manuscript.

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