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Dealkenylative Alkynylation Using Catalytic Fe^{II} and Vitamin C

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Abstract

In this paper, we report the synthesis of alkyl-tethered alkynes through ozone-mediated and Fe^{II}-catalyzed dealkenylative alkynylation of unactivated alkenes in the presence of alkynyl sulfones. This one-pot reaction, which employs a combination of a catalytic Fe^{II} salt and L-ascorbic acid, proceeds under mild conditions with good efficiency, high stereoselectivity, and broad functional group compatibility. In contrast to our previous Fe^{II}-mediated reductive fragmentation of α-methoxyhydroperoxides, the Fe^{II}-catalyzed process was devised through a thorough kinetic analysis of the multiple competing radical (redox) pathways. We highlight the potential of this dealkenylative alkynylation through multiple post-synthetic transformations and late-stage diversifications of complex molecules, including natural products and pharmaceuticals.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c05980.
Full experimental procedures and analytical data (^{1}H, ^{13}C, and ^{19}F NMR, HRMS) for new compounds (PDF)

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.2c05980

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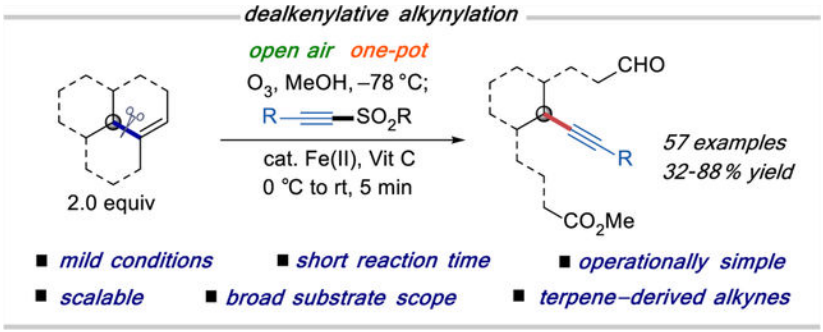

INTRODUCTION

Alkenes are seemingly ubiquitous in natural products and industrial chemicals. In fact, olefins are the second most frequently encountered functional group in natural products (39.85%).[1] Although many synthetic transformations using alkenes rely on functionalization of their C(sp^2)–C(sp^2) π-bonds, generalized methods for functionalizing vicinal alkene C(sp^2)–C(sp^3) linkages remain elusive. Recently, we reported a series of synthetic transformations in which a combination of O_3-mediated oxidation and stoichiometric Fe^{II}-mediated reductive fragmentation–radical capture allows functionalization of the seemingly inert C(sp^2)–C(sp^3) σ-bonds of feedstock olefins.[2] These transformations include hydrodealkenylations,[2b] thiylations,[2c] oxodealkenylations,[2d] and alkenylations.[2e] The net result is replacement of the alkene C(sp^3)–C(sp^2) bond with C(sp^3)–H, C(sp^3)–S, C(sp^3)–O, C=O, and C(sp^3)–C(sp^2) bonds. Our successes with these dealkenylative processes prompted us to investigate alkynyl radical donors[3] as suitable substitution partners, thereby forging C(sp^3)–C(sp) linkages, with consideration of the importance of chiral alkyl-substituted alkynes in drugs and pharmaceuticals (Figure 1A). Alkynes are highly versatile functional groups in chemical synthesis and commonly encountered as structural motifs in natural products, bioactive molecules, and organic materials.[4] Apart from serving as intermediates for a diverse series of transformations,[5] they find broad applications in the fossil fuel industry,[6] materials science,[7] and pharamceuticals.[8] Moreover, aliphatic terminal alkynes are used widely as tags in selective bioconjugation[9] and play a privileged role in Raman imaging spectroscopy.[10]

Over the past decade, the alkynylation of alkyl radicals using functionalized alkyne donors has emerged as an attractive route for the formation of C(sp^3)–C(sp) bonds under mild conditions.[3] Various methods, including thermal activation, transition metal catalysis, and photocatalytic approaches, have been used to generate suitable radicals (Figure 1B). In this context, alkynylative alkene difunctionalization (path **a**),[11] hydroalkynylation (**b**),[12] deconstructive cross-couplings (**c**),[13–15] and 1,5-hydrogen atom transfer (**d**)[16] have been the most common and successful strategies. Notably, some of these methods require functionalized carboxylic acid or amine derivatives.[13f,15] Despite these impressive advances, there is room for the development of other, more general, alkynylation strategies, particularly involving feedstock materials and earth-abundant metal catalysts. To the best of our knowledge, deconstructive strategies for the direct transfer of alkyne groups to the "inert" C(sp^2)–C(sp^3) σ-bonds of alkenes have not been described previously. When

using terpenes and terpenoids, members of Nature's chiral pool, as precursors to alkyl radicals, this strategy would allow the synthesis and post-functionalization of a new class of terpenoid-tethered enantiopure alkynes. We suspected that dealkenylative alkynylation might occur through the following mechanism. The Fe^{II}-mediated one-electron reduction of the hydroperoxide **A**, generated through Criegee ozonolysis[17] of the alkene **1** in MeOH, would afford the alkoxyl radical **B** together with an Fe^{III} complex (Figure 1C). The intermediate **B** would undergo β-scission to yield the alkyl radical **C**, which would then react with the alkynyl radical donor through α-addition to give the intermediate **D**, which, upon β-elimination, would afford the desired product **2**.

RESULTS AND DISCUSSION

To put this idea into practice, we performed a preliminary investigation of the reaction conditions by reacting (−)-isopulegol (**1a**) as a model alkene with various alkynyl donors in the presence of stoichiometric Fe^{II}, as we had used previously for dealkenylative alkenylation (Table 1).[2e] Among the range of structurally diverse alkynyl radicophiles that we tested, including the bromoalkyne **3**,[12b,18] phenylpropiolic acid (**4**),[19] the (phenylethynyl)sulfone **5a**,[20] and the alkynyl triflone **6**,[21] we found that the sulfone **5a** performed the best, providing the desired alkyne **2aa** in 76% yield and 85:15 dr (Table 1a, bars 1–7). A slight increase in the yield of **2aa** and a lower diastereoselectivity occurred when changing the alkyne radical acceptor to (phenylethynyl)benziodoxolone (**7**)[22] under otherwise identical conditions (Table 1a, bars 8 and 9). The stereoselectivity, however, was poor (57:43 dr), presumably because of the lower steric bias resulting from the C–I bond (2.0 Å) being longer than the C–S bond (1.7 Å)[23] of the sulfone **5a**. Nevertheless, similar to our observations with the dealkenylative alkenylation, our attempts at radical alkynylation were mired by the formation of unavoidable byproducts: the ketone **2a′** (48%), the dimer **2a″** (14%), and the alkene **2a‴** (6%) (bars 1, 3, 4, 6, and 8).

One of the advantages of our dealkenylative strategy is the rapid generation of alkyl radicals through the reductive fragmentation of α-alkoxyhydroperoxides. The rate constant (k_1) for the bimolecular Fe^{II}-mediated decomposition of the hydroperoxide **A** to the oxyradical **B** is 1.2×10^7 M^{-1} s^{-1} (at 298 K)[24] and that (k_2) for the unimolecular β-scission of the oxyradical to the alkyl radical **C** is 6.2×10^8 s^{-1} (at 298 K) (Scheme 1).[25] Other than (our desired) addition to the radicophiles, the alkyl radical **C** can undergo oxidation, disproportion, and/or recombination to give side products, such as the alkene **E**, the alkane **F**, and the dimer **G**. No noticeable byproducts were observed during hydrodealkenylation or aminoxylation, even when using stoichiometric Fe^{II} salts, because the rate constants for 1, 2, and 3° radicals abstracting a hydrogen atom from benzenethiol are 1.3, 1.0, and 1.4×10^8 M^{-1} s^{-1}, respectively (at 298 K),[26] and the rate constants for (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) trapping of *n*-nonyl and *tert*-butyl radicals are 1.2×10^9 and 7.6×10^8 M^{-1} s^{-1}, respectively (at 298 K).[27] These rate constants are comparable with the rates of the side reactions of the alkyl radical **C**, resulting in very speedy reactions (1–2 min) for our hydrodealkenylation and dealkenylative aminoxylation, with negligible side products (see the Supporting Information for a detailed discussion). We made a critical observation when we diverged from trapping the alkyl radical **C** with a hydrogen-atom

donor (thiol) or a stable aminoxyl radical to using a disulfide or nitroolefin. Not only did we have to increase the number of equivalents of the radicophile (1.5 equiv of thiol or TEMPO to 3.0 equiv of disulfide), but also we had to use the radical trap, the nitroolefin, as the limiting reagent (with up to 3.0 equiv of alkene) to maintain a high yield of the products and minimize the formation of the side products. The rate constants for the additions of the alkyl radical to the respective radicophiles for dealkenylative alkenylation and alkynylation are approximately 7.6 and 1.8×10^5 M^{-1} s^{-1}, respectively.[28] These rate constants are lower than those for Fe^{III}-mediated oxidation of the radical **C** to the alkene **E** ($k_{ox} < 4.0 \times 10^9$ M^{-1} s^{-1}),[29] for disproportion of a pair of alkyl radicals **C** to the alkene **E** and the alkane **F** ($k_d = 1.8 \times 10^8$ M^{-1} s^{-1}),[30] and for combination of a pair of alkyl radicals **C** to the dimer **G** ($k_r = 1.7 \times 10^8$ M^{-1} s^{-1}).[29,30] The major byproduct ketone **H** can be formed either through Fe^{II}-mediated overreduction of the alkoxy radical **B** to the alkoxide or through abstraction of a hydrogen atom ($>1.2 \times 10^6$ M^{-1} s^{-1})[31] and hydrolysis.

Mechanistically, radical disproportion and combination could be minimized, relative to the reaction with the alkynyl sulfone, if the relative concentration of the intermediate radical **C** could be lowered. Furthermore, the formation of the ketone **H** and the alkene **E** would be inhibited if the concentrations of both the Fe^{II} and Fe^{III} species were to be decreased. Thus, we were encouraged to devise conditions employing a catalytic amount of Fe^{II} (to decrease the concentration of alkyl radicals at any given moment) and recycle oxidized Fe^{III} back to Fe^{II} (to decrease the concentrations of both species in lockstep). Thus, we performed our model reaction using a catalytic quantity of the Fe^{II} salt and a series of stoichiometric reductants (Table 1b). We were delighted to find that using L-ascorbic acid (vitamin C) as the stoichiometric reductant (2.0 equiv) and catalytic $FeSO_4 \cdot 7H_2O$ (20 mol %) increased the yield of the alkynylated product from 76 to 93% while decreasing the formation of the byproduct ketone (27%), alkene (7%), and dimer (trace amount) (Table 1b, bars 1 and 2). Cu(I) salts, known to facilitate the decomposition of hydroperoxides,[32] delivered the desired product **2a**, albeit in lower 73% yield (bars 3 and 4). Additional efforts at optimizing the reaction conditions using different stoichiometric reductants failed to offer better results (Table 1b, bars 5–13); see Table S1 in the Supporting Information for details. Reactions of ascorbate with Fe and Cu are central to metal-mediated antioxidant chemistry, and it is known to react overwhelmingly with the oxidized forms, Fe^{III} and Cu^{II}, of these metals.[33a] Vitamin C can donate one electron to regenerate Fe^{II} and Cu^{I} from Fe^{III} and Cu^{II}, respectively.[33,33b] Ultimately, this catalytic redox-based dealkenylative radical chemistry allowed us to employ readily available natural products (e.g., terpenes and terpenoids) as starting materials to streamline the chemical synthesis of terpene-derived chiral alkynes.

With the optimized reaction conditions in hand, we subjected a series of alkenes, including terpenes, terpenoids, and their derivatives, to dealkenylative alkynylation with (phenylethynyl)sulfonylbenzene (**5a**), affording a diverse range of substituted alkynes **2aa–2zk** (Scheme 2). The (−)-isopulegol-derived methyl ether **1b** afforded the product **2b** in 62% yield. Other monoterpenoids, including *trans*-(+)-dihydrocarvone (**1c**), (−)-dihydrocarveol (**1d**), *cis*-(+)-limonene oxide (**1e**), and (−)-limonene-1,2-diol (**1f**), were also suitable substrates, furnishing their corresponding alkyne products **2c–2f** in yields of 57–85%, with good to moderate diastereoselectivities. Apparently, the epoxide in *cis*-(+)-limonene

oxide (**1e**) was opened diastereoselectively to give the *trans*-methoxy alcohol **2e**. We found that the stereoselectivity of the radical addition was influenced by a combination of torsional and steric strains induced by the substituents at the α-, β-, and γ-positions of the alkene substrates.[34] The dealkenylative cleavage of the sesquiterpenoid (+)-nootkatone (**1g**) cleanly gave the single diastereoisomeric alkynylated product 2g in 50% yield. The biologically active triterpenoid betulin (**1h**) was also a competent partner, generating the expected product **2h** in a moderate yield of 45% as a single diastereoisomer. The bicyclic hydroxy ketone **1i** provided its corresponding product **2i** in 86% yield, with excellent diastereoselectivity (13:1 dr). The carvone-derived diol **1j** gave the ester **2j** in excellent yield. Notably, the primary OH group in the diol **1j** underwent intramolecular trapping of the Criegee intermediate during ozonolysis, producing the acetylated product **2j**. Moreover, the reaction of the bridged bicyclic alkene **1l** also worked well, providing the single diastereoisomer **2l**, albeit in a slightly low yield (41%), presumably because of a known complication of bridged carbon radicals.[35] The alkene derived from (−)-perillyl alcohol **1m** also reacted smoothly to afford the product **2m** in 59% yield, with exclusive diastereoselectivity. Caprolactones are employed widely as monomers for polymer synthesis.[36] We found that the alkene unit of the *trans*-(+)-dihydrocarvonederived lactone **1n** gave the alkynylated product **2n** in 50% yield, establishing a route toward biorenewable terpenoid-based caprolactone alkynes. The primary radical precursors **1o** and **1p** from α-ionone and (−)-sclareol, respectively, were also compatible, providing their fragmented products **2o** (66%) and **2p** (62%), respectively.

We also tested the reactivities of other readily accessible simple alkenes. As expected, isopropenylcyclohexane provided the alkynylated product **2q** in excellent yield. Primary, secondary, and tertiary alkyl radicals all engaged efficiently in the dealkenylative alkynylation, generating their corresponding products in moderate to good yields (**2r–2z**, 43–63%). Interestingly, the benzylic radical precursor **1za** did not deliver the desired product **2za** under our standard reaction conditions (see the Supporting Information for other incompatible substrates). We were delighted to find that methylenecycloalkanes and cycloalkenes were competent substrates, providing corresponding methyl esters (**2zb–2zg**) and alkynyl aldehydes (**2zh–2zj**), respectively. Methylenecyclohexane (**1zb**) and *N*-Boc-4-methylenepiperidine (**1zc**) gave the alkynylated esters **2zb** (62%) and **2zc** (65%), respectively. The fragmented coupling of methyleneadamantane (**1zd**) generated the phenylalkynyl ester **2zd** exclusively as a single diastereoisomer in 61% yield. Upon fragmentation, the naturally occurring terpenes camphene (**1ze**) and sabinene (**1zf**) generated their corresponding esters **2ze** (67%) and **2zf** (59%), respectively. The cyclohexene **1zh** and the cyclopentene **1zi** both proved amenable to dealkenylative alkynylation, affording their respective aldehydes in moderate yields. (+)-*p*-1-Menthene (**1zj**) reacted to generate the desired aldehyde **2zj** in 45% yield. The acyclic diterpene alcohol phytol **1zk**, which has been used as a precursor for the manufacture of synthetic forms of vitamins E and K_1, could also be alkynylated, giving **2zk** in 65% yield. Notably, a wide range of functional groups were tolerated under these reaction conditions, including hydroxyl, ketone, α,β-enone, β-hydroxy ketone, epoxide, ester, amide, enone, carbamate, and phthalimide units.

Using (−)-isopulegol (**1a**) as the radical precursor, we probed the scope of the alkynylsulfone[37] component (Scheme 3). Arylethynyl sulfones, containing either electron-donating or -withdrawing substituents, reacted smoothly, leading to the corresponding alkynes **2ab–2am** in moderate to good yields. For example, substituted benzene (**5b–5j**), pyridine (**5k**), thiophene (**5l**), naphthalene (**5n**), and phenanthroline (**5o**) units were well suited, giving their corresponding alkynylated products **2ab–2am** in yields of 42–83%. Notably, various functional groups, including siloxyl (**5h**), hydroxy (**5i**), halide (**5d**, **5g**, **5j**), and trifluoromethyl (**5f**) groups, were well tolerated. Alkyl- and silyl-substituted alkynyl sulfones engaged in the reaction smoothly, providing their internal alkynes (**2ap–2as**) in moderate yields (41–55%). We further demonstrated the utility of our methodology through the alkynylation of various complex bioactive compounds. For example, we synthesized drug-like alkynyl sulfones from complex substrates: dehydrocholic acid (a steroid), indomethacin (a nonsteroidal anti-inflammatory drug), and mestranol (a synthetic estradiol). Both the functionalized dehydrocholic acid (**5t**) and indomethacin (**5u**) proved to be suitable coupling partners for dealkenylative alkynylation, furnishing their products **2at** (55%) and **2au** (75%), respectively, in good yields. The sulfone derived from mestranol **5v** could also be alkynylated, giving **2av** in 36% yield.

We conducted standard control experiments to provide additional evidence for a radical pathway for this reaction (Scheme 4). The addition of 1.5 equiv of TEMPO, a radical scavenger, under our standard conditions, inhibited the alkynylation of **1a** with **5c**, yielding only 21% of the alkynylation product, accompanied by the alkyl-TEMPO adduct in 62% yield (5:1 dr). In addition, we employed (+)-3-carene (**9a**) in a radical clock experiment. When subjected to the standard dealkenylative alkynylation process, we isolated the ring-opened product **10a** in 52% yield, consistent with radical-induced ring opening of the transient cyclopropylcarbinyl radical, occurring with a rate constant of $1.2 \times 10^8\ s^{-1}$.

We performed the reaction of (−)-isopulegol (**1a**) and (phenylethynyl)sulfonylbenzene (**5a**) on a 20 mmol scale to exemplify its practicability and scalability. Under the standard conditions, we isolated the alkynylated product **2aa** in 75% yield (Scheme 5A). The feasibility and operational simplicity of converting alkenes into synthetically versatile alkynes through this O_3-mediated/Fe^{II}-catalytic system encouraged us to explore further chemical manipulations of the alkynylation products (Scheme 5B). Treatment of **2ar** with ammonium fluoride removed the trimethylsilyl (TMS) group to afford the terminal alkyne **11** (95%), which we then subjected to Cucatalyzed Huisgen [3 + 2] cycloaddition, producing the triazole **12** and 1,2-oxazole **13** in 68 and 75% yield, respectively.[38] Hydroboration of **11** with pinacolborane (HBPin) in the presence of Schwartz's reagent led to the vinylboronate ester **14**.[39] Furthermore, alkyne **11** could also undergo an annulation reaction to give the indole **15** in excellent yield.[40] Oxidative cleavage of the TMS-alkynylated products **2ar**/**16** under Ru/periodate conditions gave direct access to the chiral carboxylic acids **17** (75%) and **18** (51%), respectively.[37b] Furthermore, the TMS-substituted alkyne **16**, upon simple hydroboration/oxidation, furnished the carboxylic acid **19**.[41] Hydrogenation of **2aa** afforded the enantiopure phenethylated product **20** in almost quantitative yield. The Au-catalyzed and acid-mediated hydration of **2aa** enabled an atom-economical synthesis of the (−)-isopulegol-derived phenone **21** in excellent yield

(78%). γ-Alkynyl alcohols are valuable intermediates in organic synthesis, participating in a wide range of cascade cyclizations. Treatment of the alkynol **2aa** with salicylaldehyde in the presence of TMSOTf gave the tetrahydrofuranochromene **22** (75%) through a cascade hydroalkoxylation–formal [4 + 2] cycloaddition.[42] A novel cascade reaction forming the (−)-isopulegol-derived alkoxyquinoline **23** was achieved in 58% yield when using 1.2 equiv of *o*-azidobenzaldehyde and TMSOTf in CH_2Cl_2 at room temperature. The mechanism of this reaction involved a Lewis acid-promoted oxonium ion-driven carboamination of the alkyne.[43] Furthermore, the alkynol **2aa** was readily transformed into the tetrahydroquinoline **24** in excellent yield (85%) upon treatment with (*E*)-1-(4-methoxyphenyl)-*N*-phenylmethanimine. This reaction proceeded through a Au-catalyzed hydroalkoxylation/Povarov cascade.[44]

CONCLUSIONS

In summary, we have developed an efficient dealkenylative alkynylation of feedstock olefins, using O_3, vitamin C, and a catalytic Fe^{II} salt as reagents, providing access to a variety of synthetically useful functionalized alkynes under mild conditions. To minimize the extent of possible side reactions, the Fe^{II}-catalyzed reductive fragmentation of the α-alkoxyhydroperoxides was designed with a thorough kinetic analysis of the multiple competing radical (redox) pathways. Using this simple protocol, members of Nature's chiral pool, including terpenes and terpenoids, could be employed as sources of radicals that are enantiopure for the synthesis of new classes of terpenoid-tethered chiral alkynes. Furthermore, we demonstrated the synthetic utility of the product alkynes through various post-alkynylation transformations. A wide range of cascade cyclizations furnished polycyclic natural product-like scaffolds, expanding the practicality of this method. The virtues of this reaction include the mild conditions; broad substrate scope; engagement of (hetero)aryl, alkyl, and silyl alkynes; and superb functional group compatibility. We anticipate that dealkenylative alkynylation will harness the untapped reactivity of abundant feedstock materials and renewable natural products, thereby facilitating the production of seemingly challenging synthetic intermediates for the functionalization of biomedically relevant molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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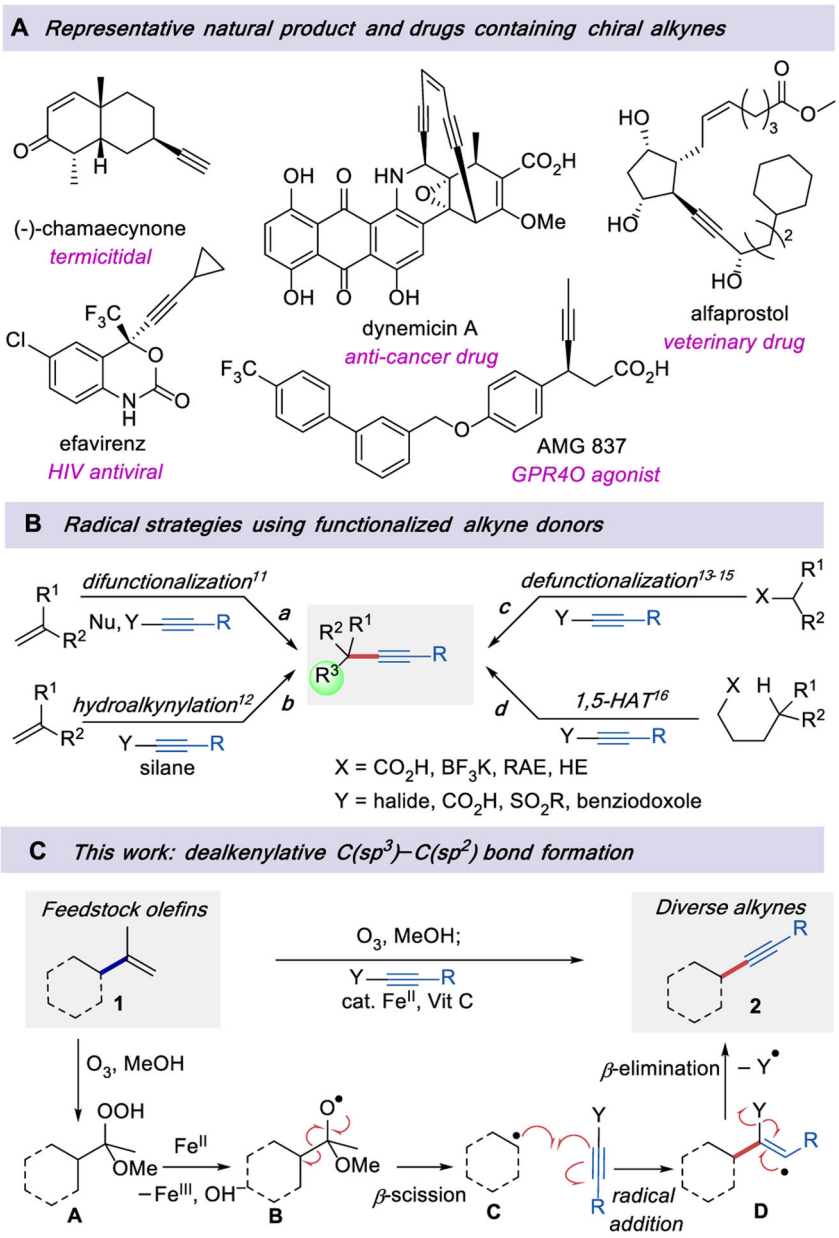
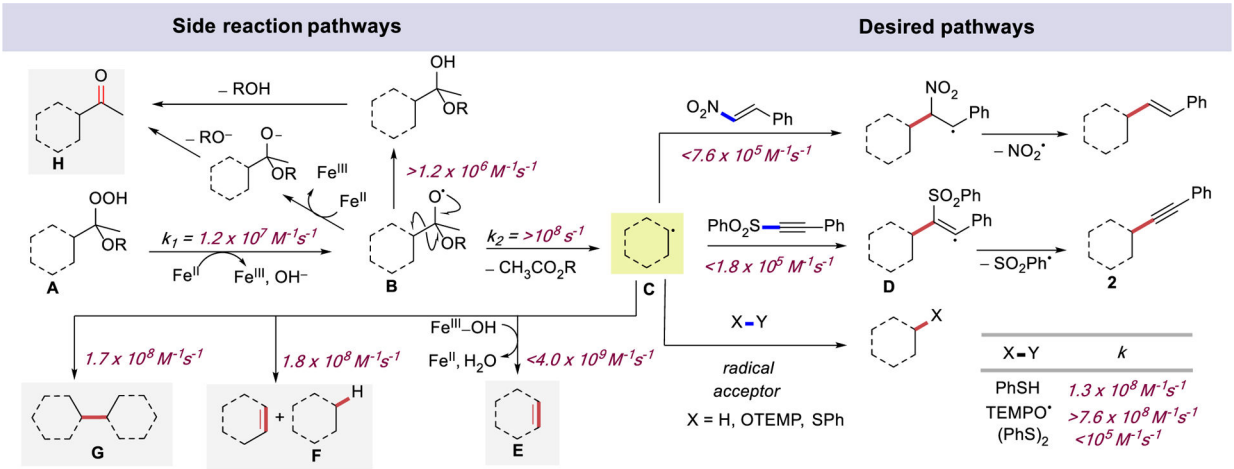
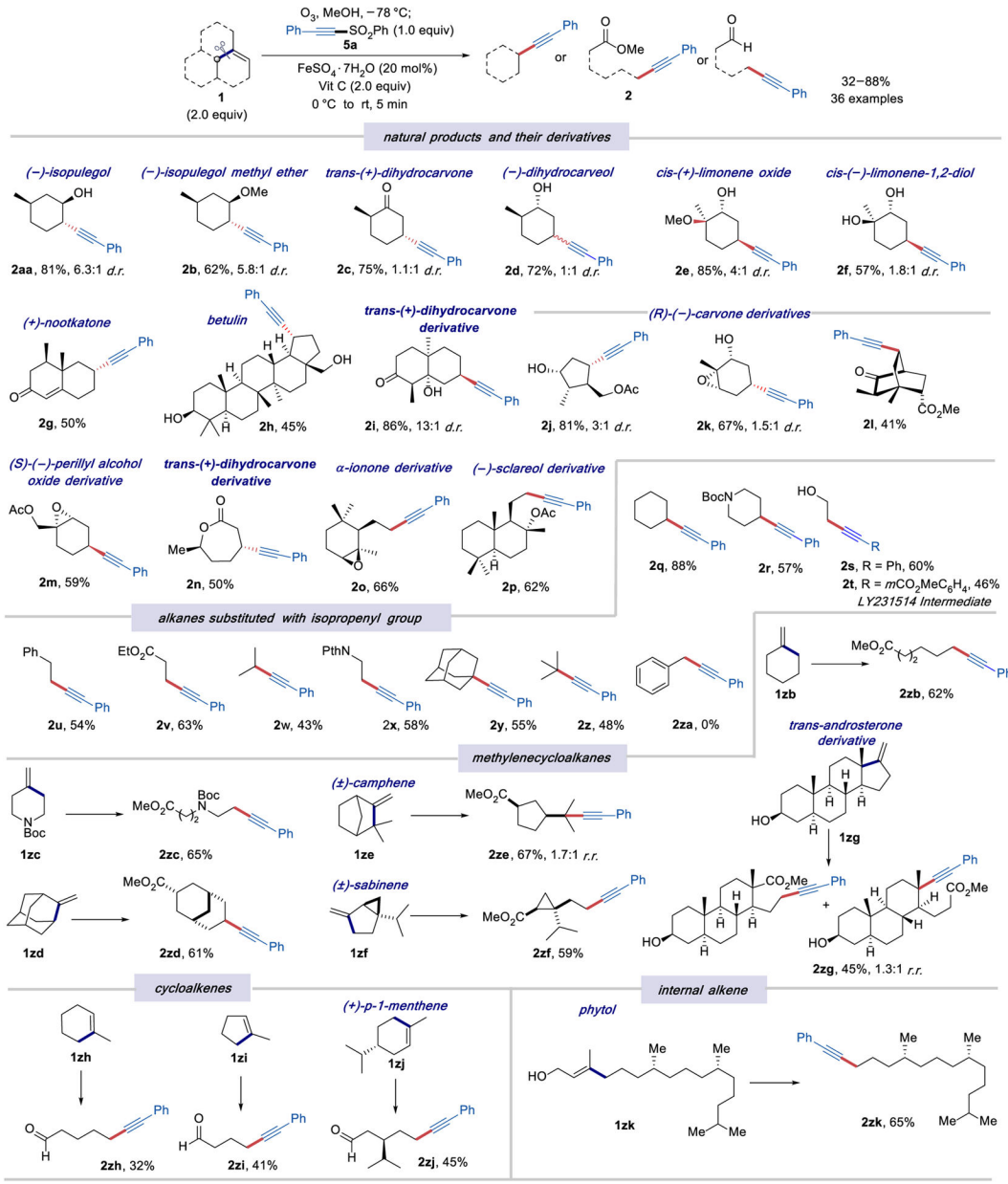


Figure 1.

(A) Representative chiral alkyne natural products and biologically active drugs. (B) Known radical strategies for functionalized alkynes (RAE = redox-active ester; HE = Hantzsch ester). (C) Proposed dealkenylative alkynylation.

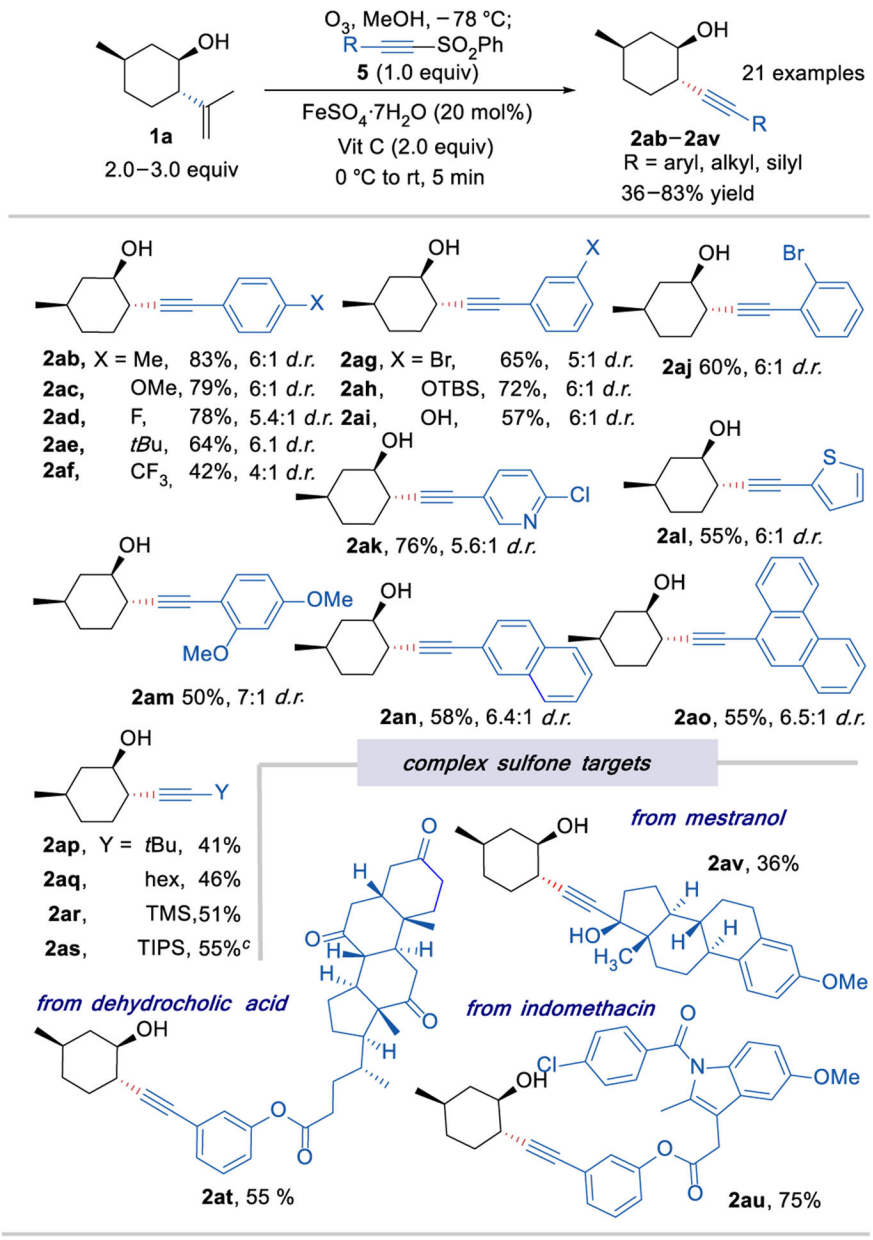


Scheme 1.
Key Reaction Pathways and Reaction Rates



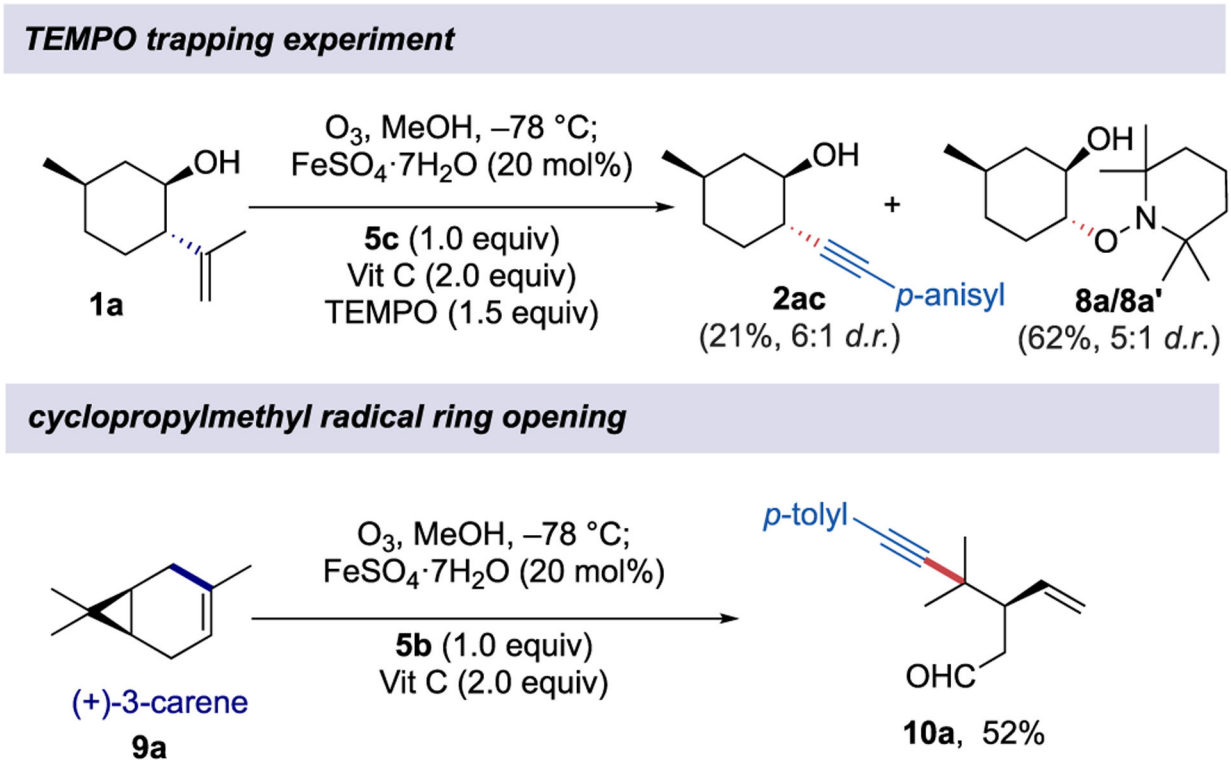
Scheme 2. Scope of Alkene Substrates[a,b,c]

[a]Reaction conditions: alkene (1.0 mmol), MeOH (0.025 M with respect to **1**), ozone (until the reaction solution turns pale blue), (ethynylsulfonyl)benzene (**5a**, 0.5 mmol), $FeSO_4{\cdot}7H_2O$ (0.1 mmol), L-ascorbic acid (1.0 mmol), 0 °C, 5 min. [b]Isolated yield. [c]Unless otherwise stated, the dr was calculated from the ^1H NMR spectrum of the crude product or from the isolated yields of the major and minor isomers.

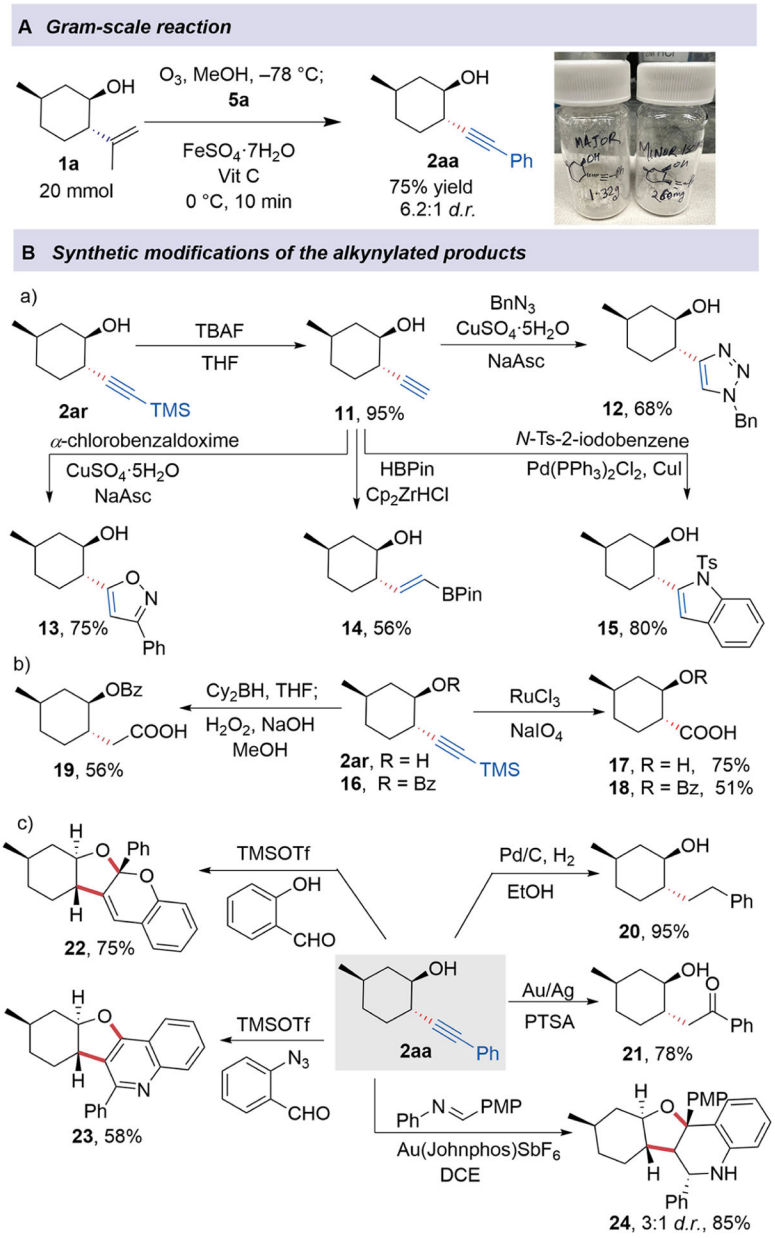


Scheme 3. Scope of Benzenesulfonyl Alkyne Substrates[a,b,c]

[a]Standard conditions: alkene **1a** (1.00 mmol), MeOH (0.025 M with respect to **1a**), ozone, alkynylsulfone **5** (0.5 mmol), $FeSO_4·7H_2O$ (0.1 mmol), L-ascorbic acid (1.0 mmol), 0 °C, 5 min. [b]Isolated yield. [c]NMR spectral yield.



Scheme 4.
Reactions Performed to Verify the Intermediacy of Alkyl Radicals

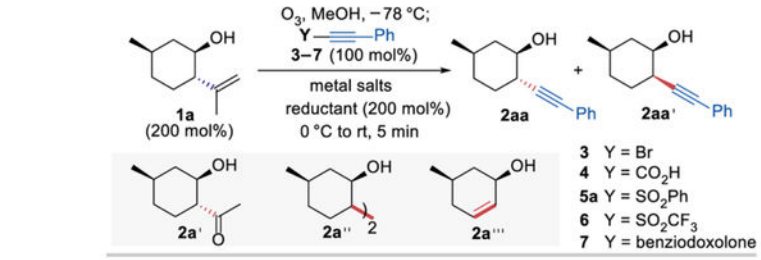


Scheme 5. Synthetic Utility of Dealkenylative Alkynylation[a]

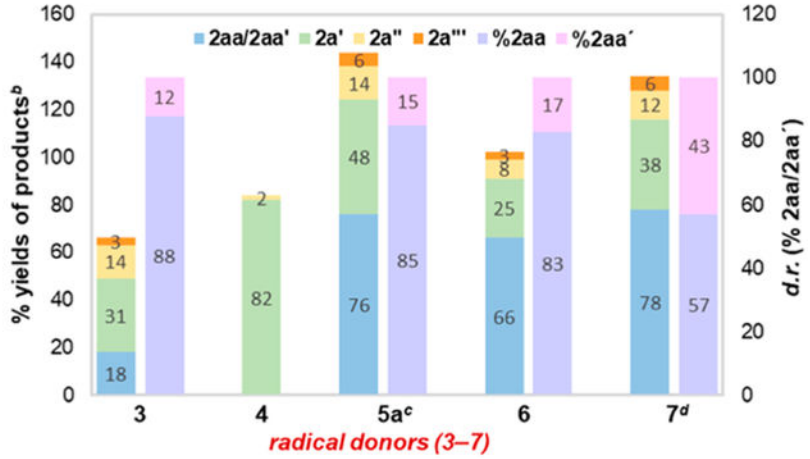
[a]All yields are isolated yields. See the Supporting Information for experimental details.

Table 1.

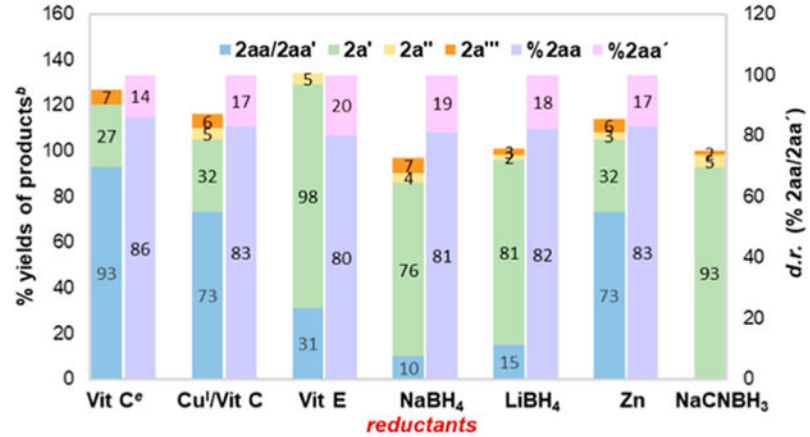
Optimization of Dealkenylative Alkynylation[a,b]



a. Screening of alkynyl donors using stoichiometric Fe^{II} salt



b. Screening of reductants using catalytic Fe^{II} and Cu^{I} salts



J Am Chem Soc. Author manuscript; available in PMC 2023 August 17.

[a] Reaction performed on a 0.05 mmol scale.

[b] Yield determined using ^{1}H NMR spectroscopy with 1-chloro-2,4-dinitrobenzene as the internal standard.

[c] Isolated yield was 72%.

[d] Isolated yield was 73%.

[e] Isolated yield was 81%. See the Supporting Information for detailed procedures.