Stereoselective Radical Cyclization Cascades Triggered by Addition of Diverse Radicals to Alkynes To Construct 6(5)−6−5 Fused Rings

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Supporting Information

ABSTRACT: Cascade radical cyclization of alkynyl ketones with various carbon- and heteroatom-centered radical precursors via a sequential radical addition/1,5-H radical shift/5-exo-trig/radical cyclization process was realized for the first time. This method provides a strategically novel and step-economical protocol for diversity-oriented synthesis of a wide range of carbocyclic and heterocyclic 6(5)−6−5 fused ring systems with three contiguous stereocenters, including a quaternary carbon in high yields with excellent chemo- and diastereoselectivity.

Complex carbon- or heteroatom-containing n−6−5 fused ring systems (n = 5 or 6) with multiple stereocenters are privileged structural motifs found in natural products and pharmaceutical compounds with important biological properties (Figure 1). For example, pycnanthuquinones A−C display antihyperglycemic activity in mice.1 (−)-Epipodophyllotoxin represents the aglycon of the potent clinical antitumor drugs etoposide and teniposide for the treatment of small cell lung cancer and Kaposi’s sarcoma.2 Therefore, considerable efforts have been devoted to the development of new and simple methods for the construction of such fused tricyclic frameworks.3 Although significant progress has been made, some crucial and challenging issues are far from being fully addressed, such as limited product scope, step-economy and starting material accessibility, and achievement of high degrees of stereocontrol in these stereocenter-abundant systems. Development of a new and efficient protocol for diversity-oriented synthesis of functionally, skeletally, and stereochmically diverse tricyclic scaffolds is highly desired.

Ingenious design and applications of radical cascade cyclizations have emerged as a powerful strategy to construct complex molecular scaffolds.4 Note that several cascade cyclizations have been efficiently applied to the total synthesis of complex natural products, such as schularisine A,5a barbiturates,5b and ophiobolin sesterterpene.5c However, addition of carbon- and heteroatom-centered radicals to unactivated alkynes is an especially attractive approach for the direct functionalization of alkynes as the alkyne is an easily accessible building block.6 In this context, initiated by pioneering works of Heiba and Dessau,7d Curran,7e−g Renaud,7h−j and others, the tandem H atom translocation/cyclization process triggered by vinyl radical intermediates8 has attracted considerable attention for constructing a wide range of five-membered rings. Inspired by these seminal works and driven by our continued interest in the area of radical chemistry,9 we envisioned that such inherently high-energy σ-type vinyl radicals,8 which could be in situ generated from addition of a variety of radicals to unactivated alkynes, would provide a driving force to undergo cascade 1,5-H radical shift/5-exo-trig/radical cyclization process (Scheme 1).

Herein, we report a new, efficient, and general cascade radical cyclization protocol for diversity-oriented synthesis of carbocyclic and heterocyclic fused tricyclic frameworks with three contiguous stereocenters, including a quaternary carbon from readily available alkynyl ketones, in which three new carbon−carbon bonds and two rings are simultaneously formed in a cascade process in high yields with excellent chemo- and diastereoselectivity.
diastereoselectivity. In the context of a diversity-oriented synthesis of fused tricyclic frameworks, the current protocol displays some exceptional advantages. (1) Functional group diversity: a variety of carbon- and heteroatom-centered radical sources, including trifluoromethyl, difluoromethyl, perfluoralkyl, and sulfonyl radical, are compatible. (2) Skeleton diversity: various carbocyclic and heterocyclic 6(5)−6−5 fused ring systems are easily collected. (3) Efficient control of chemoselectivity and diastereoselectivity of multiple stereocenters is realized under mild synthetic conditions from easily available acyclic precursors. Selective incorporation of a CF3 group into drug molecules may lead to significant improvement in the drug’s pharmacokinetic properties, binding selectivity, and metabolic stability. We began our investigation by exploring a radical tri-solvent effect of up to 14:1 with 73% yield. Furthermore, an obvious use of DBN resulted in a significantly increased diastereoselectivity. Most importantly, a CF3 group bearing a methyl group proved to be a suitable substrate, giving 3p in 50% yield along with 20% recovery of 1p. The structure and relative configuration of 3l were further confirmed by X-ray crystallographic analysis (Scheme 3).

To expand the synthetic utility of this methodology, we next focused on other more sterically hindered alkynyl 1,3-dicarbonyl substrates, which would offer a novel and promising method to synthesize cyclopenta[b]hydronaphthalenes with three contiguous stereocenters including a quaternary carbon (Scheme 4).

Scheme 3. Substrate Scope of Alkynyl Ketonesa,b

![Scheme 3](image)

**Scheme 3. Substrate Scope of Alkynyl Ketone**

**Scheme 4. Substrate Scope of Alkynyl 1,3-Dicarbonyla,b**

![Scheme 4](image)

**Scheme 4. Substrate Scope of Alkynyl 1,3-Dicarbonyl**

With the optimized conditions, we next investigated the substrate scope of alkynyl ketones with diverse substituents (Scheme 3). A variety of alkynyl aryl ketones, bearing either electron-donating groups (R = CH3, OMe) or electron-withdrawing groups (R = Br, Cl, CN, NO2) at the para position of the phenyl ring, reacted smoothly with 2a, affording 3b−3g in 66−88% yields with excellent diastereoselectivity. Substrate with meta-substituent (3-Br) in the phenyl ring gave two regioisomers, 3h and 3h′, in 85% yield with a regioselectivity of 3:1. This reaction shows excellent compatibility with disubstituted phenyl and heteroaromatic groups, yielding the 6−6−5 fused ring 3i and 5−6−5 fused ring 3j in 83 and 65% yields. Furthermore, substrates bearing other tethered groups, such as malononitrile- and oxygen-tethered 1k−1m, were also well-tolerated to give final products 3k−3m in 52−72% yields. Most importantly, 1n and 1o without any tether were also applicable to this process, affording 3n and 3o in 64 and 84% yields, respectively, even with only 10 mol % of DBN as the catalyst. Notably, internal alkyne 1p bearing a methyl group proved to be a suitable substrate, giving 3p in 50% yield along with 20% recovery of 1p. The structure and relative configuration of 3l were further confirmed by X-ray crystallographic analysis (Scheme 3).

After systematic optimization of different reaction parameters, we found that 1q with a 1,3-diketone group was efficiently converted to 3q in 61% yield with excellent diastereoselectivity with 10 mol % of TBD. A variety of functional groups including 1,3-diketone (1r) and β-ketone ester (1s,1t) were also compatible with the current system in the presence of TBD or DBN, affording 3r−3t in 55−65% yield with excellent diastereoselectivity. Most importantly, 1u with a diester-tethered...
group was also suitable, and 3u bearing densely multiple substituents was isolated in 89% yield.

We next extended other radical precursors. In recent years, visible-light-driven photooxidoreduction catalysis has become an eco-friendly and powerful tool for the generation of various radical species.11 As expected, reaction of 1c and 1e with p-toluenesulfonyl chloride (4) under visible light photooxidoreduction catalysis conditions12 delivered sulfonyl-containing fused rings in good yields with poor diastereoselectivity. Diastereoselectivity was significantly improved to >20:1 after in situ treatment of the reaction mixture with DBN at 60 °C for 6 h (Scheme 5). For

Scheme 5. Substrate Scope with Sulfonyl Chlorides

“Reaction conditions: 1 (0.2 mmol), 4 (0.4 mmol), Na2HPO4 (0.4 mmol), [Ir] = [Ir(dbmm)(ppy)2PF6 (1 mol %)], EA (4 mL), blue LED at rt for 12 h under argon.” Yield of isolated product. “The dr ratio was obtained when the crude mixture was further treated with DBN (1.2 mmol) at 60 °C for 6 h. Reaction conditions: 1 (0.2 mmol), 6 (0.4 mmol), Na2HPO4 (0.4 mmol), Ir(ppy)3 (1 mol %), EA (4 mL), blue LED at rt for 12 h under argon. Yield of isolated product.

sterically hindered alkynyl 1,3-dicarbonyl substrates 1u−1w, fused ring compounds 5u−5w were obtained in 62−73% yields with excellent diastereoselectivity under standard conditions without any organic base. The structure and relative configuration of 5u were further confirmed by X-ray crystallographic analysis (Scheme 5). Success of CF3 radical installation to generate 7c, 7u, and 7w in 63−73% yields with >20:1 dr achieved with perfluorobutanesulfonyl chloride (6)13 via extrusion of sulfur dioxide under similar reaction conditions demonstrates the utility of the present methodology to introduce a perfluoroalkyl group to fused ring systems via a radical process (Scheme 5).

To further expand this methodology and in light of the increasing importance of the difluoromethylene group (CF2) in drug and agrochemical design,13 we investigated the reaction of alkynyl ketones with EtO2CCF2I8 under the standard conditions, which enables the 1,5-H radical shift process, established by Renaud,7e−7h the origin of excellent diastereoselectivity observed in this reaction remains unclear and deserves further detailed studies. In conclusion, we have successfully developed the radical cyclization of easily available alkynyl ketones via a sequential 1,5-H radical shift/S-exo-trig/radical cyclization process triggered by radical trifluoromethylation, sulfonylation,
perfluoroalkylation, or difluoromethylation of alkenes. The reaction provides a new facile and straightforward approach for the diversity-oriented synthesis of carbocyclic and heterocyclic fused tricyclic frameworks with three contiguous stereocenters, including a quaternary carbon in high yields, with excellent chemo- and diastereoselectivity. To the best of our knowledge, this is the first example using in situ generated vinyl radicals as the key intermediate in cascade radical cyclizations for the construction of 6(5)−6−5 fused rings, which would provide a particularly advantageous alternative to the traditional tandem H atom translocation/cyclization process triggered by vinyl radicals.7

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02599.

Experimental procedures, characterization of all new compounds, Table S1, Schemes S1−S3 (PDF)

X-ray data for 3I (CIF)

X-ray data for 5u (CIF)

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### Notes

The authors declare no competing financial interest.

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