

## RESEARCH ARTICLE

View Article Online

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Cite this: *Org. Chem. Front.*, 2018, **5**, 3129

Received 1st August 2018,  
Accepted 26th September 2018

DOI: 10.1039/c8qo00803e

rsc.li/frontiers-organic

# Electrochemical synthesis of 7-membered carbocycles through cascade 5-*exo-trig*/7-*endo-trig* radical cyclization†

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7-*endo-trig* cyclizations, especially for unhindered terminal alkenes, remain underdeveloped. We report herein an electrochemical synthesis of functionalized 7-membered carbocycles through a 5-*exo-trig*/7-*endo-trig* radical cyclization cascade. The first cyclization step of the cascade process forms a 5-membered ring with *trans*-disposition of the radical center and the remaining alkene. This *trans* configuration forces the 6-heptenyl radical to undergo regioselective 7-*endo* cyclization.

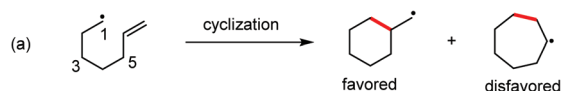
## Introduction

Radical cyclization reactions have become an indispensable tool for the synthesis of cyclic structures.<sup>1</sup> Among these reactions, those that form 7-membered carbocycles remain rare. The 6-heptenyl radicals usually undergo preferentially 6-*exo-trig* cyclization over the 7-*endo-trig* alternative (Scheme 1a) and the 7-octenyl radicals frequently form a mixture of 7- and 8-membered rings because of the competing 7-*exo*- and 8-*endo-trig* processes.<sup>2</sup> Several strategies have been developed to reverse the general preference of the 6-heptenyl radicals to favor the 7-*endo* mode of cyclization by introducing substituents at positions 1, 5, or 6 to increase the steric hindrance for the 6-*exo-trig* process (Scheme 1b and c).<sup>3</sup> Alternatively, annealing a *trans*-fused 5-membered ring has been found to be effective for reversing the 6-*exo*/7-*endo* selectivity even for a monosubstituted alkene (Scheme 1d).<sup>4</sup>

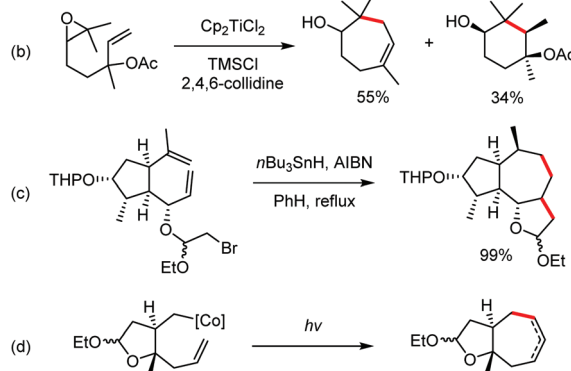
The promiscuous radical species can participate in various transformations including dimerization, H-atom abstraction, fragmentation, addition to  $\pi$  systems, *etc.*<sup>5</sup> To channel these reactive species toward cyclization reactions, it is important to control the rate of radical formation. Organic electrochemistry, which is an enabling and innately sustainable tool for organic synthesis, has been attracting increasing interest from synthetic chemists.<sup>6</sup> The electron transfer on the electrode can be

controlled easily through adjusting the electric current or electrode potential. Hence, the rate of radical formation under electrochemical conditions can be fine-tuned conveniently. In this area, we have reported electrochemical methods for the generation of nitrogen-centered radicals (NCRs) from N-H precursors, enabling the development of several cascade radical cyclization reactions.<sup>7</sup> Building on these studies, we report

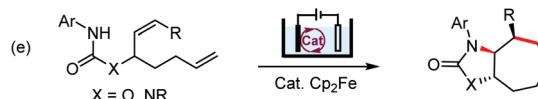
### Cyclization of 6-heptenyl radical



### Synthetic methods based on 7-*endo-trig* radical cyclization reactions



### Electrochemically enabled 5-*exo-trig*/7-*endo-trig* radical cascade (this work)



Scheme 1 7-*endo-trig* radical cyclization reactions.

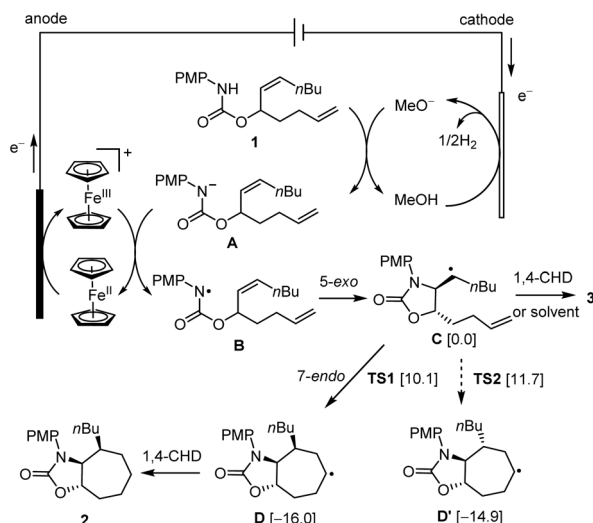
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† Electronic supplementary information (ESI) available. CCDC 1823050. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8qo00803e





**Scheme 3** Proposed mechanism. The numbers in the brackets are DFT (UB3LYP/6-31G\*) calculated Gibbs free energies (kcal mol<sup>-1</sup>) in the gas phase. Energies of D, D', TS1 and TS2 are relative to C.

radical abstracts a H-atom from 1,4-CHD or the solvent molecules to give monocyclized compound 3, or undergoes 7-*endo-trig* cyclization with the remaining terminal alkene to give the bicyclic radical intermediate D. The reduction of radical D via H-atom transfer affords the final 7-membered ring product 2. The 6-heptenyl radical bearing a monosubstituted alkene usually cyclizes preferentially in a 6-*exo* fashion instead of 7-*endo*.<sup>2a</sup> The *trans* disposition of the C-centered radical and the alkene in intermediate C is critical in channelling the cyclization to the 7-*endo* pathway. The alternative 6-*exo-trig* cyclization is probably inhibited by the high ring strain because of the *trans*-fusion of the forming bicyclic ring system.

Density functional theory (DFT) calculations were carried out to shed light on the origin of the stereochemistry of the 7-membered ring formation. The results suggested that the 7-*endo-trig* cyclization to form intermediate D with 3,4-*cis* stereochemistry was kinetically and thermodynamically favored over the alternative 3,4-*trans* stereochemistry as shown for D' (Scheme 3). Analysis of the computed transition states TS1 and TS2 for the two cyclization pathways revealed that the steric repulsion between the PMP group and the *n*Bu group in TS2 is probably responsible for the unfavorable formation of D' (Fig. 1). To reduce the steric repulsion, the PMP group in TS2 rotates away from the *n*Bu group leading to reduced conju-

gation of the PMP group with the lone pair of the nitrogen atom as evidenced by a much larger dihedral angle of  $\angle C2-N1-C12-C17$  for TS2 (61.3°) compared with TS1 (35.0°).

## Conclusions

In summary, we have developed a catalytic radical cascade cyclization reaction featuring a 7-*endo-trig* cyclization of an unhindered monosubstituted alkene. These reactions provide efficient and stereoselective access to functionalized 7-membered carbocyclic compounds.

## Conflicts of interest

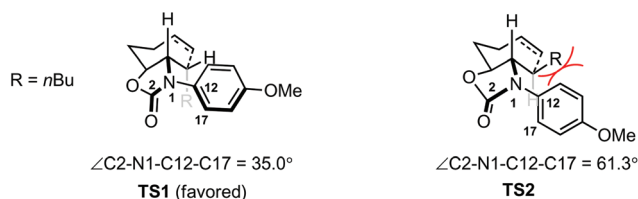
There are no conflicts to declare.

## Acknowledgements

This work was supported by the National Natural Science Foundation of China (21672178) and the Ministry of Science and Technology (2016YFA0204100).

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**Fig. 1** Computed transition states for the cyclization of radical C.

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