

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2018, 5, 3129

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

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Accepted 26th September 2018

DOI: 10.1039/c8qo00803e

rsc.li/frontiers-organic

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.

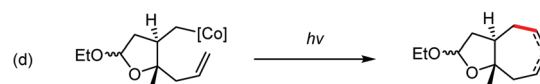
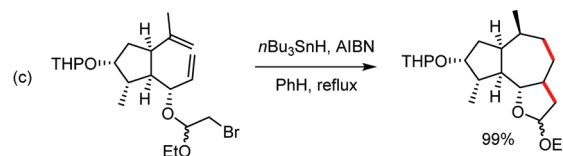
Introduction

Radical cyclization reactions have become an indispensable tool for the synthesis of cyclic structures.¹ 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.² 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).³ 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).⁴

The promiscuous radical species can participate in various transformations including dimerization, H-atom abstraction, fragmentation, addition to π systems, *etc.*⁵ 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.⁶ 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.⁷ Building on these studies, we report

Cyclization of 6-heptenyl radical

Synthetic methods based on 7-*endo-trig* radical cyclization reactionsElectrochemically 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

herein an electrochemically enabled 5-*exo-trig*/7-*endo-trig* cascade radical cyclization for the stereoselective preparation of functionalized 7-membered carbocycles.

Results and discussion

Our studies had begun by optimizing the electrolysis conditions for the cyclization of carbamate **1** that contained a di-substituted *cis*-alkene and a monosubstituted alkene. The *cis*-alkene was important to ensure a stereoselective 5-*exo-trig* cyclization for the carbamate.^{7a} Our previously developed reaction conditions^{7a} for alkene hydroamidation were also effective for this cascade cyclization. Hence the electrolysis was conducted in a three-necked round bottomed flask using a reticulated vitreous carbon (RVC) anode, a Pt plate cathode, and a constant current of 5 mA. The reaction employed ferrocene (Cp₂Fe)⁸ as the catalyst, Na₂CO₃ as the basic additive, and 1,4-cyclohexadiene (1,4-CHD) as the reducing reagent (Table 1). Under these conditions, the bicyclic 7-membered ring product **2** was formed stereoselectively in 60% yield along with 9% of monocyclized product **3**. Attempts to increase the yield of **2** by reducing the amount of 1,4-CHD (entries 2–4), changing the solvent system (entries 5–9), or varying the amount of basic additive (entries 10 and 11) failed.

We then investigated the reaction scope (Scheme 2). The internal alkene could be substituted with primary (**4**) or secondary (**5**) alkyl groups, but not a bulky *t*Bu group (**6**) probably because of the increased difficulty for the formation of the 7-membered ring.⁹ The cyclization reaction was compatible with *N*-phenyl groups bearing substituents with diverse elec-



Scheme 2 Scope of substrates. Reaction conditions: Undivided cell, substrate (0.2 mmol), THF (5 mL), MeOH (1 mL), argon, 2.0–3.0 h. ^aYield of the isolated product.

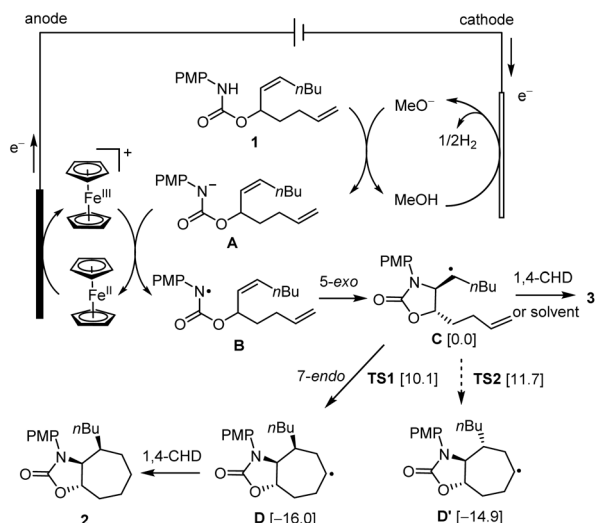
Table 1 Optimization of the reaction conditions^a

Entry	Deviation from the standard conditions	Yield ^b [%]	
		2	3
1	None	60 ^c	9
2	1,4-CHD (3 equiv.)	45	13
3	1,4-CHD (1 equiv.)	50	8
4 ^d	No 1,4-CHD	37 ^c	18 ^c
5	ClCH ₂ CH ₂ Cl/MeOH (5 : 1)	60	6
6	<i>t</i> BuOMe/MeOH (5 : 1)	35	18
7	1,4-Dioxane/MeOH (5 : 1)	47	16
8 ^d	PhCl/MeOH (5 : 1)	40	16
9	MeCN/THF (5 : 1)	54	7
10	0.5 equiv. of Na ₂ CO ₃	57	11
11	No Na ₂ CO ₃	44	19

^aUndivided cell, RVC anode ($j \cong 0.06$ mA cm⁻²), Pt cathode, **1a** (0.2 mmol), *n*Bu₄NBF₄ (0.1 M), MeOH (1 mL), THF (5 mL), reflux, argon, 2 h, 1.9 F mol⁻¹. ^bDetermined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard. ^cIsolated yield. ^dReaction for 2.5 h. PMP = *p*-methoxyphenyl.

tronic properties at the *para* position, including H (**7**), Me (**8**), halogens (F, Cl, Br; **9–11**), CF₃ (**12**) and CN (**13**). The structure of **12** was further confirmed by single crystal X-ray analysis. A *meta*-substituted *N*-phenyl group was also tolerated (**14**). Besides carbamates, urea type substrates bearing at the linking nitrogen atom a Me, Ph, or PMP group were also cyclized stereoselectively under the standard conditions to give cycloheptane-fused 2-imidazolones (**15–17**). The 7-membered ring formation was sensitive to the steric hindrance of the alkene distal to the reacting nitrogen atom as evidenced by the formation of monocyclized compound **18** as the only identifiable product in 62% yield from a substrate bearing two internal alkenes.

A possible mechanism for the electro-synthesis is proposed based on the results of this work and those of previously reported (Scheme 3).^{7a} When charge is passed through the cell, Cp₂Fe loses one electron to the anode to afford Cp₂Fe⁺. Meanwhile, the solvent MeOH is reduced at the cathode to afford methoxide (MeO⁻) and H₂. The base generated at the cathode deprotonates substrate **1** to give its conjugate base **A**. The anodically generated Cp₂Fe⁺ oxidizes **A** through single-electron transfer (SET) to regenerate Cp₂Fe and form NCR **B**.^{10–12} The latter radical undergoes stereoselective 5-*exo-trig* cyclization to give carbon-centered radical species **C**.^{7a} This



Scheme 3 Proposed mechanism. The numbers in the brackets are DFT (UB3LYP/6-31G*) calculated Gibbs free energies (kcal mol^{-1}) 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.^{2a} 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-

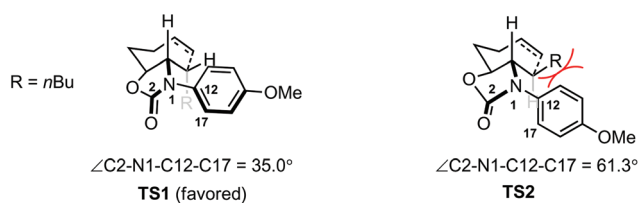


Fig. 1 Computed transition states for the cyclization of radical C.

gation of the PMP group with the lone pair of the nitrogen atom as evidenced by a much larger dihedral angle of $\angle\text{C2-N1-C12-C17}$ 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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