Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2021, **12**, 1311

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 7th October 2020
Accepted 20th November 2020

DOI: 10.1039/d0sc05556e

rsc.li/chemical-science

Cu-catalyzed hydroxycyclopropanol ring-opening cyclization to tetrahydrofurans and tetrahydropyrans: short total syntheses of hyperiones†

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Tetrahydrofurans (THFs) and tetrahydropyrans (THPs) are important core scaffolds frequently found in many molecules of medicinal importance. Herein, we report a novel copper-catalyzed hydroxycyclopropanol ring-opening cyclization methodology to synthesize di- or tri-substituted THFs and THPs. In this reaction, a strained C–C bond was cleaved and a new Csp^3–O bond was formed to produce the aforementioned O-heterocycles. The new THF synthesis features a broad substrate scope, scalability, and good functional-group tolerability. It enabled us to complete the shortest enantioselective syntheses of hyperiones A and B (3 and 4 steps, respectively), which is significantly shorter than the previously reported two total syntheses (≥10 steps).

Introduction

O-Heterocycles, particularly tetrahydrofurans (THFs) and tetrahydropyrans (THPs) are privileged scaffolds in bioactive natural products[1] and lifesaving drug molecules.[2] For example, THF-containing macrolide amphidinolide C1 (**1**, Fig. 1) has demonstrated potent inhibition activity against cancer cell proliferation.[3] Eribulin features three THFs and three THPs in its backbone and is an FDA-approved drug for treating various cancers.[4] Sofosbuvir, a nucleoside analog, is a pricy, but effective medication to treat hepatitis C.[5] Due to the importance of THFs and THPs in natural products, human medicines, and other fields, many synthetic strategies and methodologies have been developed for their syntheses.[6] Regardless of the recent advances, achieving high stereoselectivity *via* a ring forming process in preparing disubstituted or polysubstituted THFs and THPs still remains a synthetic challenge.[7] One commonly used ring closing strategy for THF and THP synthesis is *via* an intramolecular C–O bond formation. Intramolecular nucleophilic substitution *via* a 5 or 6-*exo-tet* cyclization process (*cf.* **5** → **4**) falls into this category.[6d–g] Related transition metal, electrophilic reagent (such as I_2 or PhSeCl) or radical promoted additions to the activated π-systems including olefins, alkynes, and allenes have been developed as well.[6h–o] A transition metal-catalyzed direct Csp^3–O ring closure is deemed an attractive strategy (*cf.* **6** → **4**), but poses significant challenges. When metalloalkyl species are involved, β-H elimination is always a potential problem, not to mention the difficulties involved in generating such metalloalkyl species. Furthermore, both the metalloalkyl species and the tethered alcohols are nucleophilic, therefore, an external oxidant is needed.

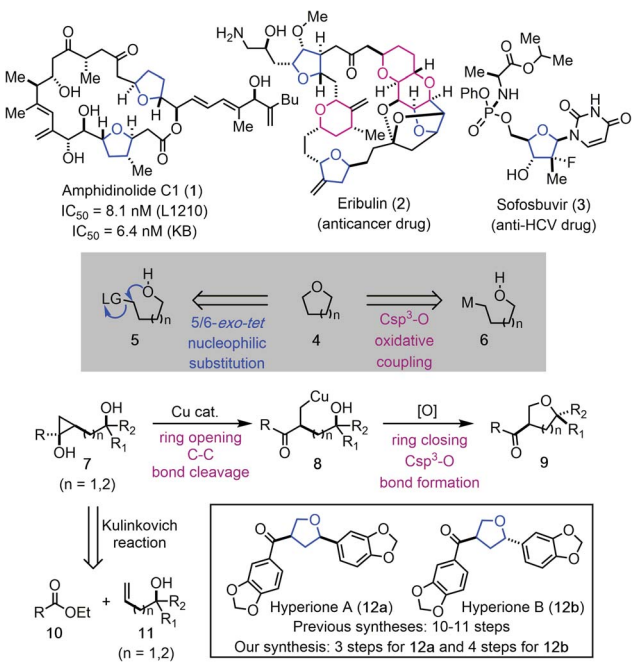

Fig. 1 THFs and THPs in natural products and drugs and our synthetic strategy.

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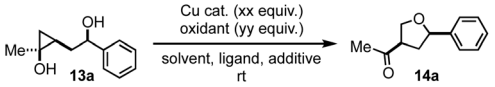
† Electronic supplementary information (ESI) available. CCDC 1996070. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0sc05556e

Our continued interest in cyclopropanol ring-opening cross coupling reactions made us wonder if metalloalkyl species such as **6** could be generated from a cyclopropanol precursor (*cf.* **7** → **8**, Fig. 1). Cyclopropanols are highly strained molecules and can be readily prepared *via* the Kulinkovich reaction, the Simmons–Smith reaction, and other protocols.[8] Despite of their intrinsic ring strain, cyclopropanols are bench stable and can be stored for months or years. Meanwhile, their strain offers unusual reactivity. Synthetic chemists have been harnessing this reactivity and developed a variety of cyclopropanol ring-opening reactions to install different functional groups such as aryl, alkynyl, alkenyl, acyl, activated alkyl, halogen, nitrile, azide, amine, and others at the β-position of carbonyl compounds.[9] We have developed palladium-catalyzed hydroxycyclopropanol ring-opening carbonylative lactonization to facilitate total syntheses of complex natural products.[10] Meanwhile, we developed a series of copper-catalyzed cyclopropanol ring-opening trifluoromethylation, trifluoromethylthioation, amination, and alkylation with activated alkyl electrophiles.[11] However, cyclopropanol ring-opening β-oxygenation *via* a transition metal-catalyzed Csp^3–O cross coupling reaction has not been realized. Our experience in this area taught us that copper-homoenolates derived from cyclopropanol ring opening are less prone to β-H elimination in comparison to the corresponding palladium intermediates. We wondered the possibility of trapping the copper-homoenolate derived from a cyclopropanol with an alcohol *via* an oxidative cross coupling process. If such process happens in an intramolecular fashion, it would lead to valuable O-heterocycles such as THFs and THPs (*cf.* **7** → **8** → **9**). It would also represent one of the very few methods to rearrange strained molecules to O-heterocycles.[12] This method would offer several advantages. First, the starting material can be convergently assembled from readily available ester **10** and (bis)homoallylic alcohol **11** by using the diastereoselective cyclopropanol synthesis method developed by Cha and co-workers.[13] Second, the stereochemistry of the THF or THP products would rely on the stereochemistry of **7** not the ring forming process. Third, the intramolecular process may enable the Csp^3–O bond formation of sterically hindered tertiary alcohols. Fourth, the product would be equipped with an aryl or alkyl ketone for further elaboration. Meanwhile, several challenges lie in the proposed cyclopropanol ring-opening cyclization process. First, for unsymmetrical cyclopropanol such as **7**, competitive ring-opening processes exist. Metal-mediated ring opening is required to ensure selective cleavage of the less substituted C–C bond and radical-mediated ring opening needs to be suppressed to avoid the cleavage of the more substituted C–C bond and formation of a more stable radical. Second, once intermediate **8** is formed, reductive elimination to form the Csp^3–O bond should be facilitated before the copper-homoenolate decomposes to an enone or other byproducts. Third, a proper oxidant needs to be identified which could promote the catalytic cycle without oxidizing the tethered alcohol or promoting undesired radical cyclopropanol ring-opening processes. Herein, we report the details of our efforts in realizing such a copper-catalyzed cyclopropanol ring-opening cyclization to synthesize substituted THFs or THPs and its application in the shortest total syntheses of natural products hyperiones A (**12a**, 3 steps) and B (**12b**, 4 steps).

Results and discussion

Our investigation started with hydroxycyclopropanol **13a**, which was prepared from ethyl acetate and 1-phenylbut-3-en-1-ol using the method developed by Cha and co-workers.[13] To prove the concept, we first explored the use of stoichiometric Cu(II) salt and were delightful to discover that desired *cis* 3-methylketone-5-phenyl substituted THF product **14a** was obtained in 42% or 35% yield when 2.0 equiv. of $Cu(OTf)_2$ or $Cu(OAc)_2$ were used, respectively (entry 1 and 2, Table 1). Encouraged by these results, we started to evaluate different oxidants to render the Cu(II) salt catalytic. Both oxygen (entry 3) and 1,4-benzoquinone (BQ, entry 5) were effective oxidants when 0.1 equiv. of $Cu(OTf)_2$ was used, but *t*BuOOH failed the task (entry 4). Cu(I) salt such as CuBr was less efficient than $Cu(OTf)_2$ (entry 6). Solvent evaluation revealed that toluene was better than 1,2-dichloroethane (DCE), dichloromethane (DCM), benzene, and others. Molecule sieves were not necessary. Interestingly, commonly used phenanthroline (entry 10) and bathophenanthroline (entry 11) ligands for copper-catalyzed reactions completely inhibited the transformation. Further reducing the amount of BQ led to significantly decreased yield. We then explored several commercially available BQ derivatives including *p*-xyloquinone (entry 13), 2,6-dimethyl BQ (entry 15), methyl BQ (entry 16), and 1,4-naphthoquinone

Table 1 Reaction condition optimization



Entry	Reaction conditions	Yield[a]
1	$Cu(OTf)_2$ (2.0), DCE, M.S., 24 h	42%
2	$Cu(OAc)_2$ (2.0), DCE, M.S., 24 h	35%
3	$Cu(OTf)_2$ (0.1), O_2, DCE, M.S., 12 h	41%
4	$Cu(OTf)_2$ (0.1), *t*BuOOH (2.0), DCE, M.S., 6 h	0%
5	$Cu(OTf)_2$ (0.1), BQ (2.0), DCE, M.S., 12 h	51%
6	CuBr (0.1), BQ (2.0), DCE, M.S., 12 h	27%
7	$Cu(OTf)_2$ (0.1), BQ (2.0), DCM, 4 h	67%
8	$Cu(OTf)_2$ (0.1), BQ (2.0), benzene, 4 h	57%
9	$Cu(OTf)_2$ (0.1), BQ (2.0), tol., 4 h	68%
10	$Cu(OTf)_2$ (0.1), BQ (2.0), L1 (0.2 equiv.), tol., 4 h	0%
11	$Cu(OTf)_2$ (0.1), BQ (2.0), L2 (0.2 equiv.), tol., 4 h	0%
12	$Cu(OTf)_2$ (0.1), BQ (0.5), O_2 (balloon), tol., 4 h	65%
13	**$Cu(OTf)_2$ (0.1), *p*-xyloquinone (2.0), tol., 4 h**	**76[b,c]%**
14	**$Cu(OTf)_2$ (0.1), *p*-xyloquinone (0.5), O_2 (balloon), tol., 4 h**	**75%**
15	$Cu(OTf)_2$ (0.1), 2,6-dimethyl BQ (2.0), tol., 4 h	70%
16	$Cu(OTf)_2$ (0.1), methyl BQ (2.0), tol., 4 h	74%
17	$Cu(OTf)_2$ (0.1), 1,4-naphthoquinone (2.0), tol., 4 h	62%
18	$Cu(OTf)_2$ (0.1), tol., 16 h	6%

[a] Isolated yield. [b] 73% yield for gram scale. [c] 92% ee when **14a** was prepared from the corresponding enantioenriched homoallylic alcohol with 92% ee; L1: phenanthroline; L2: bathophenanthroline; DCE: 1,2-dichloroethane; BQ: 1,4-benzoquinone; M.S.: molecular sieve.

(entry 17) and identified *p*-xyloquinone as the superior one. Notably, a combination of BQ (0.5 equiv., entry 12) or *p*-xyloquinone (0.5 equiv., entry 14) with oxygen (balloon) gave similar results to the use of 2.0 equiv. of BQ or *p*-xyloquinone. For the convenience of operations, we decided to use a single oxidant, *p*-xyloquinone, for the substrate scope investigations. Additionally, when the reaction was conducted at gram-scale, 73% yield of **14a** was obtained. Compound **14a** could also be produced in enantioenriched form (92% ee) from the corresponding enantioenriched homoallylic alcohol (92% ee).

We then prepared a collection of hydroxycyclopropanols and evaluated them under the optimized reaction conditions (Tables 2 and 3). In general, the reaction has a broad substrate scope for the synthesis of substituted THFs. A good functional group tolerability was observed as well. For example, 3-methylketone-5-aryl substituted THFs can be prepared (**14a–i**). Both electron rich and electron deficient aryl groups worked effectively (**14a–g**). Heteroaryl groups such as pyrrole (**14f**), thiophene (**14h**), and indole (**14i**) were tolerated, but not furan. The aryl groups can also be switched to alkyl groups such as bulky *tert*-butyl group (**14j**) and TBS-ether containing alkyl groups (**14k** and **14l**). All of these cases led to the formation of 3-methylketone-5-aryl/alkyl substituted THFs with *cis* stereochemistry, which are otherwise difficult to synthesize. Notably, tertiary alcohols are suitable substrates as well (**14m–p**). Higher reaction yields were obtained for these tertiary alcohols, which indicates a Thorpe–Ingold effect to facilitate the Csp^3–O ring closing process despite the steric hindrance of the tertiary alcohols. Additionally, hydroxycyclopropanols derived from different esters can be used to deliver products with different substituents on the resulting ketones (**14q–v**). Again, both aryl and alkyl groups are tolerated.

We then tried to expand the established reaction conditions for the syntheses of THFs to THPs, but were less successful in this direction (Table 3). For the cases of cyclopropanols of type **15**, which are derived from the Kulinkovich reaction between ethyl acetate and the corresponding bishomoallylic alcohols, while we were able to obtain the desired THP products **16a–16d**, the yields were significantly lower than the corresponding THF cases. In addition to the desired THP products, for each case, we observed the formation of cyclopropanol ring-opening protonation product (*cf.* **17a–d**). The isolation of **17a–d** as the major products suggests a radical cyclopropane C–C bond cleavage mode to break the more substituted C–C bond. The resulting secondary radical intermediate was then quenched or underwent hydrogen atom transfer (HAT) process to give side products **17a–d** in the end. Notably, when an inseparable epimeric mixture of **15a** (R_1, R_2 = H, Ph or Ph, H) was used, the formation of **16a** with a 3,6-*trans* stereochemistry was observed, but not the one with a 3,6-*cis* stereochemistry, which indicates that the ring-opening cyclization process is sensitive to the stereochemistry of the tether secondary alcohol.

To provide insights about the reaction mechanism of the copper-catalyzed cyclopropanol ring-opening intramolecular Csp^3–O cross coupling reaction, a series of experiments were conducted. First, $Cu(OTf)_2$ catalyst is essential for the cyclopropanol ring opening as well as the THF or THP ring closure. Without $Cu(OTf)_2$, 95% of the starting material **13a** was recovered without any **14a** formation. Interestingly, when **13a′**, the epimer of **13a**, was used, desired THF product **14a′** with *trans* stereochemistry was produced in 30% yield together with 9% of **18** and 44% of enone **19a** (Fig. 2). The formation of enone **19a** as the major product from **13a′** indicates again that the stereochemistry of the secondary alcohol of **13a** or **13a′** plays an important role in determining the cyclopropanol ring-opening pathways, which will be discussed in the proposed catalytic

Table 2 Substrate scope for the tetrahydrofuran synthesis

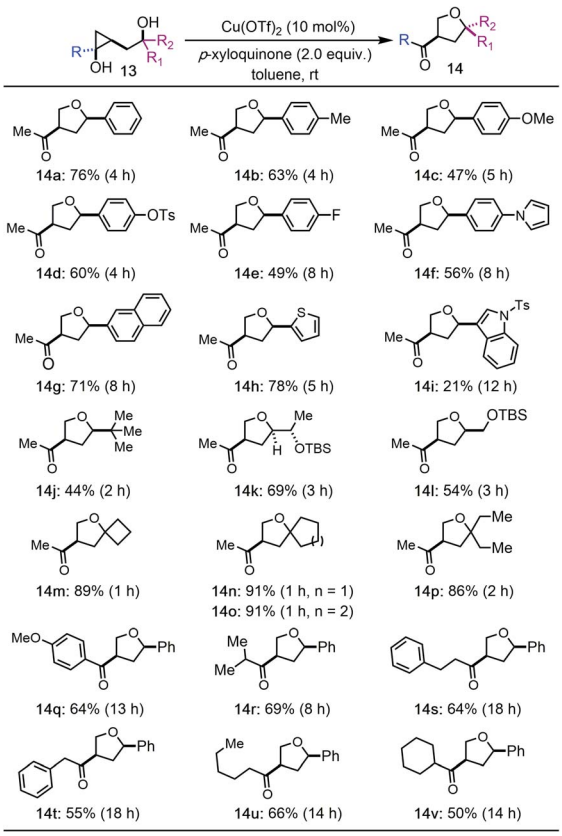
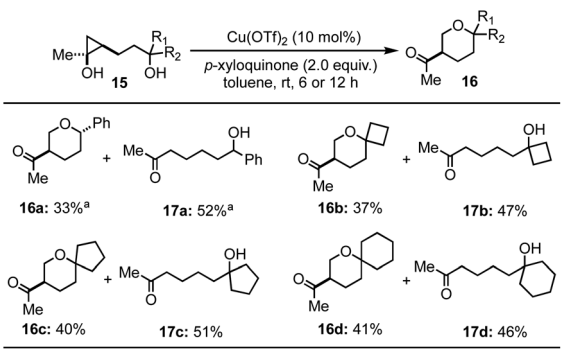


Table 3 Substrate scope for tetrahydropyran synthesis



[a] A 1 : 1 mixture of diastereomers was used as starting material.

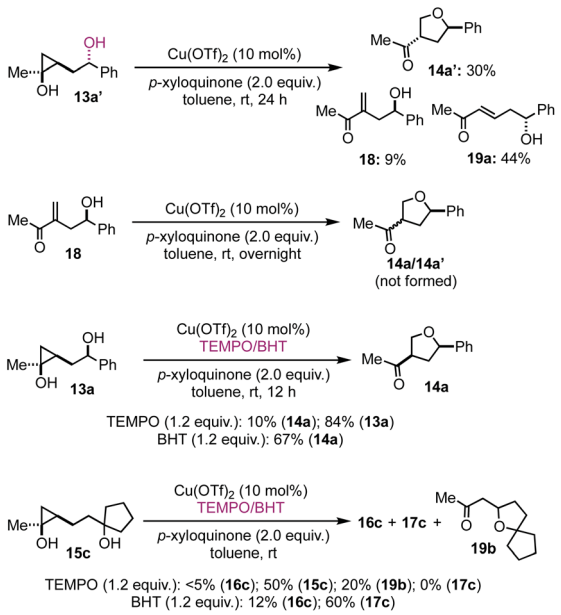


Fig. 2 Mechanistic studies.

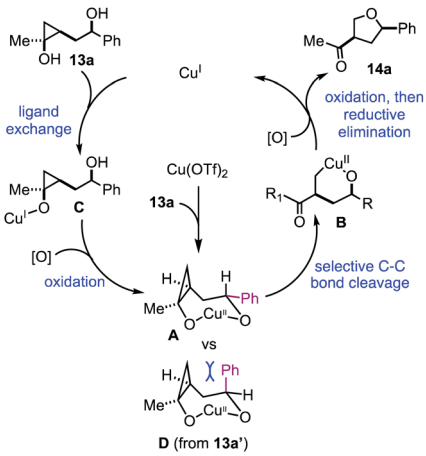
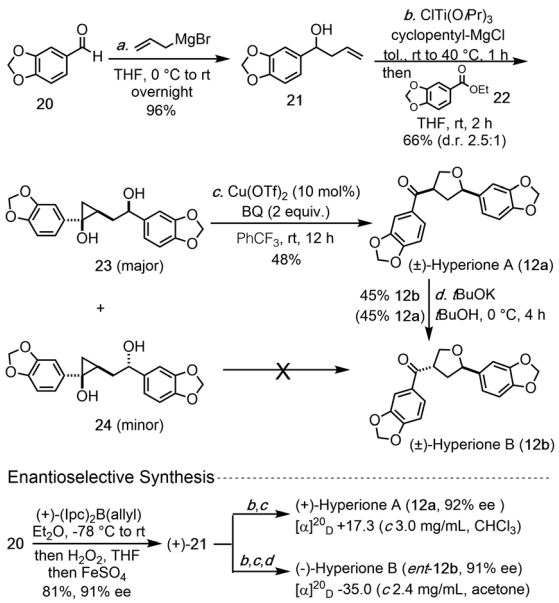


Fig. 3 Proposed reaction mechanism.

cycle. Additionally, when compound **18** was subjected to the optimized reaction conditions, we didn't observe any **14a** or **14a′**, which rules out the formation of the THF ring *via* a Baldwin's rule disfavored 5-*endo-trig* oxa-Michael addition. Radical inhibitors such as TEMPO and BHT were explored as well. The formation of **14a** or **16c** was dramatically inhibited by the addition of 1.2 equiv. of TEMPO to the reaction mixture. Cyclopropanol **13a** or **15c** were recovered in 84% or 50% yield, respectively. For the case of **15c**, a new byproduct **19b** was isolated in 20% yield, which presumably came from a 5-*exo-trig* cyclization of the corresponding enone byproduct or direct trapping of a β alkyl carbocation with the tertiary alcohol. However, when BHT was used, desired THF product **14a** was still produced in 67% yield from **13a**. For the case of **15c**, the yield of THP product **16c** dropped from 40% to 12% and the yield of **17c** increased slight from 51% to 60%. The latter is likely due to the fact that BHT is a superb hydrogen atom donor, which could quickly quench the β alkyl radical derived from a radical cyclopropane ring opening process.

Based on the above experimental results, a plausible catalytic cycle was proposed in Fig. 3. $Cu(OTf)_2$ would enter the catalytic process by reacting with **13a** to form a 7-membered metallocycle intermediate (**A**). Once intermediate **A** is formed, selective cyclopropane ring opening would lead to copper-homoenolate **B**, which would be further oxidized by *p*-xyloquinone to the corresponding Cu(III) intermediate. Reductive elimination similar to the Chan–Lam process[14] would give product **14a** and generate a Cu(I) species, which would be the starting point for the rest of the catalytic cycles. This Cu(I) species would coordinate with substrate **13a** *via* a ligand exchange process to form alkoxy–Cu(I) intermediate **C**. In our previous studies,[11] we showed that Cu(I) salts were ineffective to promote cyclopropanol ring opening. Thus, intermediate **C** would be oxidized to a Cu(II) intermediate by *p*-xyloquinone. The secondary alcohol on the appended side chain would coordinate with the copper center to form the same 7-membered metallocycle **A** to continue the rest of the cycle (**A** → **B** → **14a**) and regenerate the Cu(I) species. When compound **13a** was used, intermediate **A** with the large phenyl group in the pseudo equatorial position would be formed. With compound **13a′**, intermediate **D** would be formed. The phenyl group of **D** would take the pseudo axial position and experience strong steric repulsion with the methylene group of the cyclopropane ring. Therefore, intermediate **D** would not be favored. When **15a** was used, the coordination of the secondary alcohol on the copper center would require an 8-membered ring formation, which is energetically undesirable. Overall, the stereochemistry of the secondary alcohol as well as its distance from the cyclopropanol are significant for which reaction pathway will occur. It enforces a strong directing effect on the reaction.



Scheme 1 Total syntheses of hyperiones.

We then began to apply the copper-catalyzed cyclopropanol ring-opening cyclization to prepare two THF-containing natural products, hyperiones A and B. Both of them were isolated from the leaves of *Hypericum chinense*,[15] an important herb medicine to treat fever, hepatitis, and sepsis. Hyperiones A and B are two norlignan natural products derived from the well-known dietary lignan sesamin or its epimer asarinin. In 2013, the groups of Barker[16] and Deska[17] independently reported their total syntheses of these two natural products. Barker's syntheses of hyperiones A and B involve 10 steps started from a known oxazolidinone, which can be prepared in one step from commercially available starting material. Their key THF ring formation is a low yielding acid-catalyzed cyclization (23%). The Deska syntheses require 10 steps and involves two enzymatic reactions and one Ag-catalyzed cycloisomerization to form a dihydrofuran ring which was reduced later.

The newly developed copper-catalyzed cyclopropanol ring-opening cyclization enabled us to complete the total synthesis of hyperione A in 3 steps and hyperione B in 4 steps (Scheme 1), which are significantly shorter than the reported ones. Our synthesis started with commercially available aldehyde **20**, which underwent Grignard 1,2-addition with allylMgBr to give known allylic alcohol **21** in 96% yield. Kulinkovich reaction between **21** and ester **22** gave a 2.5 : 1 separable mixture of cyclopropanols **23** and **24** in 66% total yield. Cyclopropanol **23** underwent the copper-catalyzed ring-opening cyclization smoothly to complete the total synthesis of hyperione A (**12a**) in only 3 steps, but cyclopropanol **24** failed to deliver hyperione B (**12b**) directly. Alternatively, *t*BuOK-promoted epimerization converted hyperione A to B in 45% yield with 45% of hyperione A recovered. Notably, for the conversion of **23** to **12a**, BQ is a better oxidant than *p*-xyloquinone and trifluorotoluene is superior to toluene as the solvent. Additionally, homoallylic alcohol **21** could be prepared in enantioenriched form (91% ee) by using an asymmetric 1,2-addition,[18] which eventually led to asymmetric total syntheses of (+)-hyperione A (**12a**, 92% ee) and (−)-hyperione B (*ent*-**12b**, 91% ee). The optical rotation of synthetic (+)-hyperione A is +17.3 (*c* 3.0 mg mL^{-1}, $CHCl_3$), same in sign and about an order magnitude smaller than the reported value for natural hyperione A (+195.6; *c* 0.045, $CHCl_3$).[15] Similar observation was reported by Barker *et al.* (−18.5; *c* 0.016, $CHCl_3$)[16] and Deska *et al.* (+19.2; *c* 0.045, $CHCl_3$).[17] The optical rotation of synthetic (−)-hyperione B is −35.0 (*c* 2.4 mg mL^{-1}, acetone), opposite in sign and similar in magnitude to the reported value for natural hyperione B.

As mentioned earlier, one advantage of the new THF/THP synthesis is that the product will be equipped with an aryl/alkyl ketone at the C3 position, which could be further functionalized to produce a variety of products. For example, the carbonyl group of **14a** could be easily converted to a gem difluoro group (*cf.* **25**, Scheme 2) upon the treatment with DAST.[19] Both **14a** and **16a** could undergo spirocyclization with aryl hydrazine **26** to afford **27** and **28** in 82% and 62% yield, respectively.[20] Additionally, methyl ketone **14a** could be converted to hydrazone **29**, whose structure was confirmed by X-ray analysis.[21] Hydrazone **29** could undergo a Pd-catalyzed cross coupling reaction with aryl bromide **30** to afford **31** in good yield.[22]

Conclusions

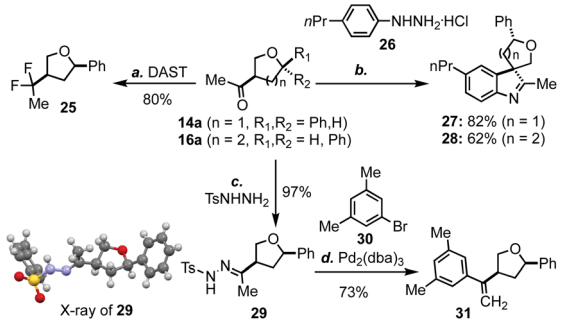
In summary, we developed a novel copper-catalyzed cyclopropanol ring-opening cyclization to synthesize O-heterocycles including THFs and THPs. The reaction has a broad substrate scope for synthesizing THFs. Its synthetic potential was demonstrated by a 3 or 4-step total synthesis of hyperione A or B, respectively, as well as the diversifications of the ketone containing THFs/THPs to more sophisticated products. Mechanistically, a selective C–C bond cleavage followed by an oxidative Csp^3–O bond formation occurred in the reaction process. The alcohol on the appended side chain functions not only as a nucleophile for the Csp^3–O bond formation, but also a directing group to guide the cyclopropane ring opening. This new method is conceptually different from all the other THF/THP synthesis and is expected to have broad application in facilitating the synthesis of natural products and other bioactive molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by NIH R35 GM128570 and NSF CAREER 1553820. We thank the NIH P30CA023168 for supporting shared NMR resources to Purdue Center for Cancer Research. The XRD data was collected on a new single crystal X-ray diffractometer supported by the NSF through the Major Research Instrumentation Program under Grant No. CHE 1625543.



Scheme 2 Synthetic applications. (a). DAST, CH_2Cl_2, reflux, 24 h, 80%; (b) **26**, AcOH, reflux, 6 h, 82% (**27**), 62% (**28**); (c) $TsNHNH_2$, MeOH, rt, overnight, 97%; (d) **30**, $Pd_2(dba)_3$ (1 mol%), Xphos (2 mol%), *t*BuOLi (2.2 equiv.), dioxane, reflux, 12 h, 73%.

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