Natural Products Inspired [3 + 2] Cycloaddition Enables Efficient Syntheses of Lignans

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ABSTRACT

Mimicking biosynthetic pathways of hongkonoids led to the development of a new Cu(I)-catalyzed [3 + 2] cycloaddition of α-hydroxyketone and β-keto enol ethers, affording chiral tetrahydrofuran acetals in a highly diastereoselective manner and 100% atom economy. Computational studies on the mechanism disclosed a concerted but asynchronous Michael addition/aldol reaction. Of the same importance, this methodology provides a practical biomimetic approach for one-step construction of the dibenzylbutyrolactol lignan backbone starting from two phenyl propane derivatives, opening up a powerful new approach for lignan synthesis, which is showcased by succinct total syntheses of two biologically important aryltetralin-type lignans, β-apopicropodophyllin and cycloolivil. Given the mild and operationally simple conditions, the developed chemistry might have a promising prospect in potential industrial applications.

INTRODUCTION

Natural product (NP) research has historically given enormous momentum to the advancement of organic chemistry,[1] which not only provides a valuable source of inspiration and fuel to the total synthesis community,[2] but also is regarded as a significant breeding ground for new synthetic methodologies.[3] In our previous work, hongkonoids (e.g. hongkonoid A), a unique class of ascorbylated diterpenoids, have been isolated from *Dysoxylum hongkongense* (Figure 1A).[4] From the standpoint of biogenetical analysis, hongkonoids might be derived from L-dehydroascorbic acid and a phytane-type diterpenoid through the formation of 3-hydroxy tetrahydrofuran (THF) between the α-hydroxyketone unit of the former and the trisubstituted alkene of the latter via a [3 + 2]-cycloaddition. Inspired by the biosynthesis, we therefore hypothesized that a novel [3 + 2]-cycloaddition methodology between an α-hydroxyketone and alkene could be developed for the construction of 3-hydroxy THF rings (Figure 1A). Within the realm of NPs, 3-hydroxy THF rings are ubiquitous in polyketides,[5] alkaloids,[6] terpenoids,[7] lignans,[8] etc (Figure 1B). Previously, stereoselective syntheses of multisubstituted chiral THF rings have been extensively investigated.[9] In particular, two literature examples employing α-hydroxyketone derivatives and functionalized alkenes as substrates for the synthesis of 3-hydroxy THF derivatives have been reported (Figure 1C), including a Lewis-acid mediated formal [3 + 2] cycloaddition strategy developed by Angle and co-workers,[10] and a chiral amine-promoted asymmetric domino reaction reported by Carrillo and co-workers.[11] However, these methods are usually limited to certain activated substrates. Hence, a general and straightforward approach that expands rapid access to NPs bearing 3-hydroxy THF rings would be desirable.

Transition metal catalysts are widely used to mediate formal cycloadditions through coordination to unsaturated moieties.[12] Given the potential coordinating capability with alkene and α-hydroxyketone, a transition-metal-catalyzed strategy was thus applied to the [3 + 2] reaction. By leveraging highly electrophilic β-keto enol ethers[13] as the two-carbon

alkene synthons instead, we developed a highly diastereoselective Cu(I)-catalyzed [3 + 2] cycloaddition for preparation of hydroxylated THF acetals (Figure 1D).

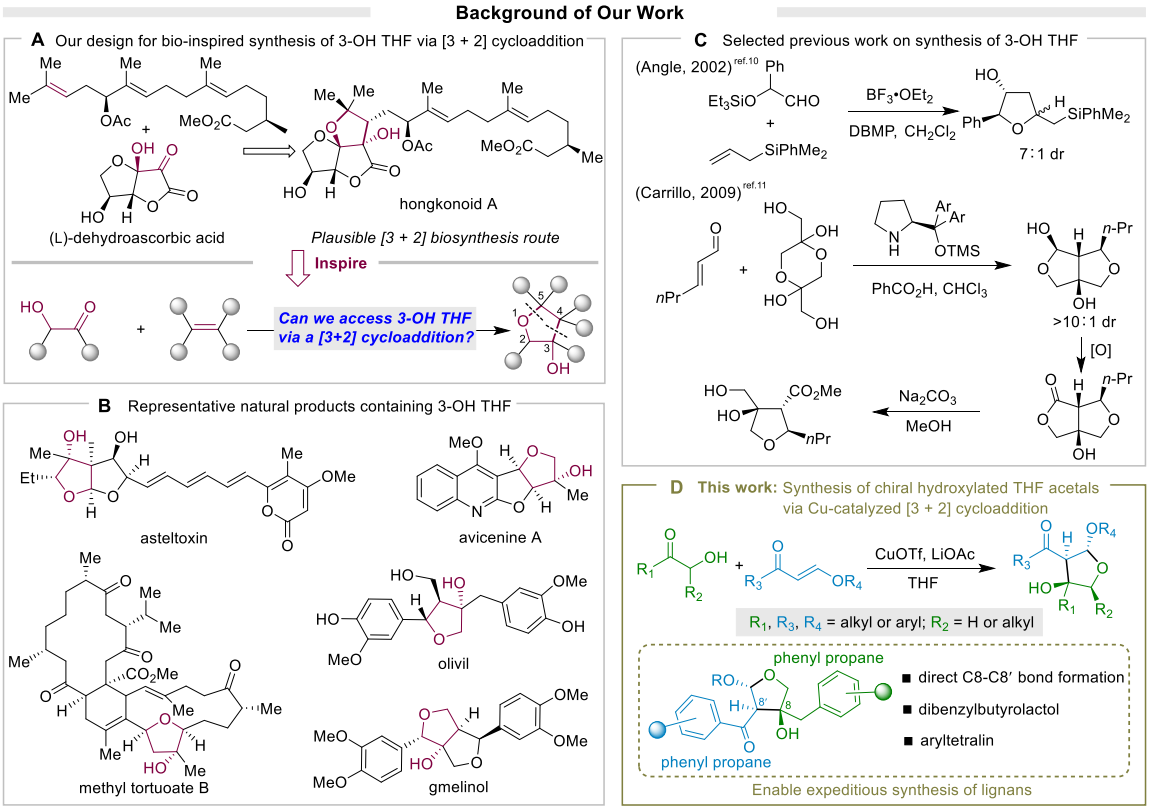


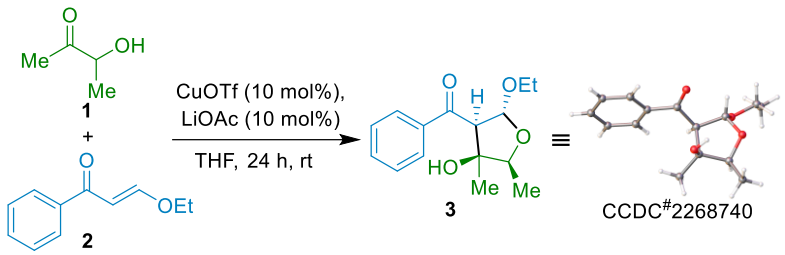
Figure 1. Discovery of Cu(I)-catalyzed [3 + 2] cycloaddition of α-hydroxyketone and β-keto enol ethers for the construction of functionalized THF acetals.

Lignans represent an important class of pharmacologically active NPs.[14] Although lignan synthesis has been extensively studied, the supply of lignans still depends largely on plant extraction.[15] More efficient synthetic approaches toward commercial lignan synthesis thus remain desirable. Noticeably, the developed chemistry allows an expeditious entry to dibenzylbutyrolactol lignan scaffolds via a direct C8–C8′ coupling strategy comparable to lignan biosynthetic process between two phenyl propane derivatives (Figure 1D). The utility of this transformation is demonstrated by concise total syntheses of two aryltetralin-type lignans, β-apopicropodophyllin (**53**) and cycloolivil (**54**). Herein, we

report our findings on the developed methodology, alongside the mechanism study and its application on lignan synthesis.

RESULTS AND DISCUSSION

Table 1. Optimization of Reaction Conditions[a]



entry	deviation from standard conditions	yield (%)[b]
1	none	80 (89)
2	without [Cu]	n.d.
3	without LiOAc	64
4	MeCN instead of THF	44 (75)
5	HFIP instead of THF	17
6	DCM instead of THF	53 (88)
7	MTBE instead of THF	56 (80)
8	DME instead of THF	66 (77)
9	DMF instead of THF	23
10	$Cu(OTf)_2$ instead of CuOTf	68 (82)
11	CuCl instead of CuOTf	66 (74)
12	CuBr instead of CuOTf	73 (84)
13	CuI instead of CuOTf	46 (95)

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), cuprous triflate (10 mol %), lithium acetate (10 mol %), THF (1 mL), rt, 24 h; [b]Yields of isolated products. The yields in parentheses are those obtained based on recovery of starting materials. Abbreviations: THF = tetrahydrofuran; HFIP = hexafluoroisopropanol; DCM = dichloromethane; MTBE = methyl *tert*-butyl ether; DME = 1,2-dimethoxyehtane; DMF = *N*,*N*-dimethylformamide; n.d. = not detected.

Optimization of the [3 + 2] Cycloaddition. Our foray into the envisioned [3 + 2] cycloaddition methodology started with a transition-metal catalyzed strategy, where α-

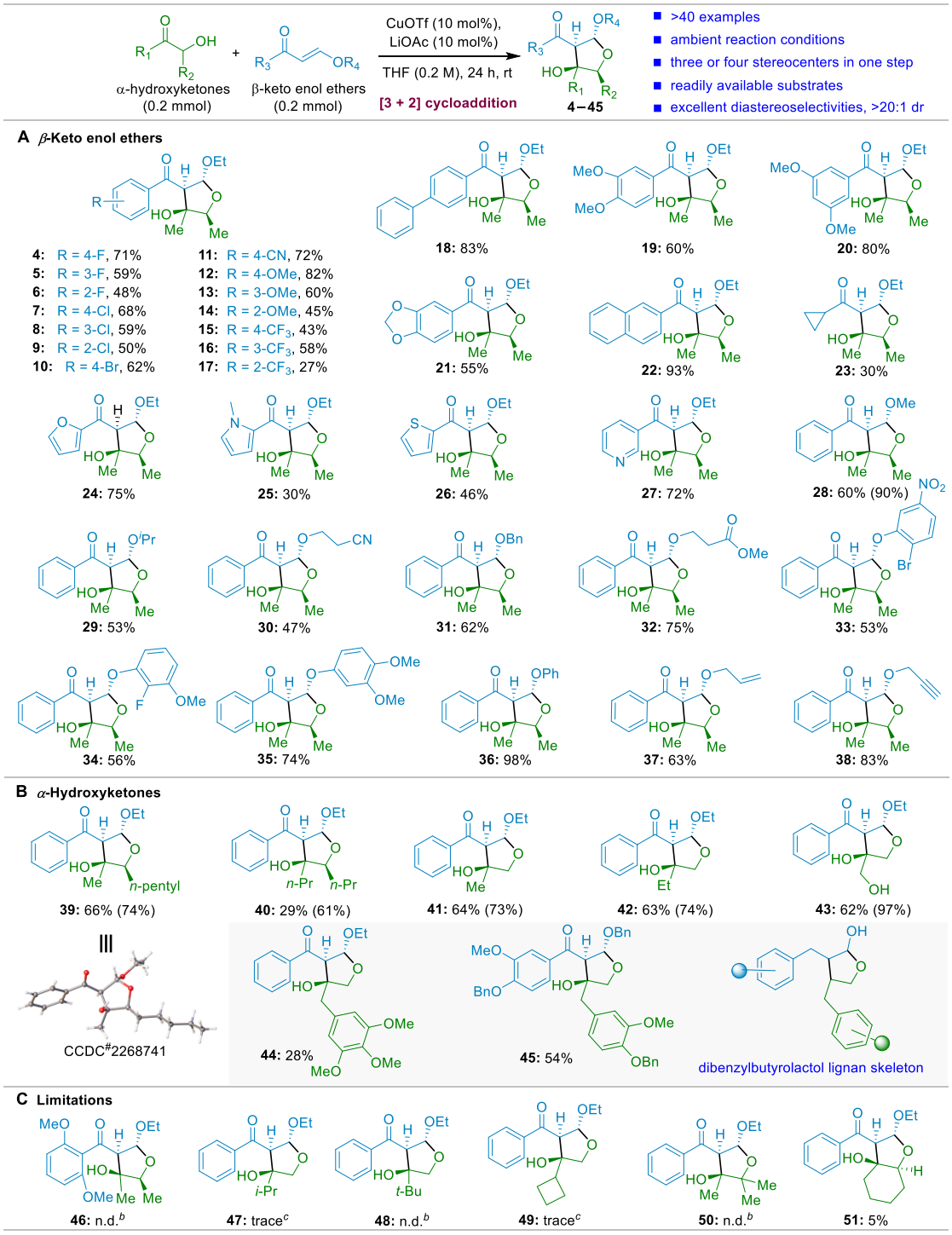
hydroxyketone (e.g. acetoin (**1**)) and conventional alkenes were used as substrates, which proved fruitless yet. To our delight, when *β*-keto enol ethers, e.g. (*E*)-3-ethoxy-1-phenylprop-2-en-1-one (**2**), served as the two-carbon alkene synthons instead in virtue of the strong electrophilicity,[13] the reactions were achieved with moderate to good diastereoselectivities to generate hydroxylated THF acetals under the catalysis of a variety of transition-metal salts, such as [Pd], [Rh], and [Cu] (see Supporting Information). Particularly, it was found that this reaction indeed proceeded readily with a combination of CuOTf (10 mol%) and LiOAc (10 mol%) in THF at room temperature for 24 h, yielding the desired cycloadduct **3** as a single diastereomer in 80% yield (89% yield based on recovery of starting materials) (Table 1). The copper catalyst proved essential to success of the reaction (entry 2). The base additive LiOAc was also important to this reaction, without which the isolated yield of **3** dropped to 64% (entry 3). The solvent effect was then investigated (entries 4–9). We found that reactions could proceed in most popular solvents. The use of polar protic solvents, e.g. HFIP, seemed unfavorable to the reaction, while ethers behaved better than other solvents. Finally, THF was established as the best solvent for this reaction. Screening other copper salts led to the discovery that Cu(II) was also effective in the catalysis (entry 10). Compared with CuOTf, other Cu(I) salts, including CuCl, CuBr, and CuI, all showed lower reactivities (entries 11–13).

Scope of the [3 + 2] Cycloaddition. Encouraged by the optimization results, the scope and generality of the [3 + 2] cycloaddition reaction were then evaluated. Using the developed protocol, the reaction between a wide range of *α*-hydroxyketones and *β*-keto enol ethers with different R_3 and R_4 substituents were examined. As shown in Table 2, all the products could be obtained with excellent diastereoselectivities (>20:1 dr). First, we conducted the reactions of acetoin (**1**) with *β*-ethoxy enones bearing different keto groups. Compound **1** could work well with *β*-ethoxy enones incorporating substituted phenyl groups to afford the corresponding hydroxylated THF acetals in moderate to good yields. An array of electron-donating or -withdrawing functionalities on the phenyl rings such as

fluoro (**4**–**6**), chloro (**7**–**9**), bromo (**10**), nitrile (**11**), methoxy (**12**–**14**), trifluoromethyl (**15**–**17**), and phenyl (**18**) groups were left unperturbed. Compared with *meta*- and *para*-substituted substrates, *ortho*-substituted ones generally furnish the corresponding products (**6**, **9**, **14**, and **17**) in lower yields, and di-*ortho*-substituted ones even failed to undergo the reaction (**46**), indicating that the steric hindrance has a great impact on the transformation. In addition, 3,5- or 4,5-substituted phenyl rings (**19**–**21**) were also compatible under the standard conditions. Notably, an excellent yield (93%) was obtained when the naphthyl substrate (**22**) was employed as the reaction partner. However, the presence of alkyl ketones would disfavor the reaction, as exemplified by the much lower reaction yield for the cyclopropyl substrate (**23**). Heterocycles are among the most prevalent structural motifs in bioactive leads.[16] Gratifyingly, it was found that heteroaromatic groups could also be introduced to the products in decent yields (**24**–**27**). We then investigated the reaction scope of acetoin (**1**) with β-keto enol ethers bearing different R_4 groups. Pleasingly, alkyl, aryl, allyl, and propargyl substrates could all react with **1** successfully to afford the corresponding THF acetals (**28**–**38**) in moderate to excellent yields. Particularly, phenol THF acetal **36** could be produced in almost quantitative yield, suggesting that the phenol ether was the most reactive substrate.

Next, we investigated the reactivity of α-hydroxyketones (Table 2). The results showed that a range of primary and secondary α-hydroxyketones could well take part in the reaction to generate the corresponding THF acetals (**39**–**45**). Significantly, compounds **44** and **45** possessing characteristic dibenzylbutyrolactol lignan backbones[14] were achieved by a strategy involving a direct C8–C8′ bond formation of two phenyl propane units, which is highly comparable to the biosynthesis processes of lignans.[17] However, the steric hindrance around the keto and hydroxy groups could extremely influence the reactions, as evidenced by the nonproductive isopropyl (**47**), *tert*-butyl (**48**), and cyclobutyl (**49**) substrates and tertiary α-hydroxy ketone (**50**). Additionally, compound **51** was produced only in a trace amount, showcasing the low reactivity of cyclic α-hydroxyketones.

Table 2. Scope of the Cu(I)-catalyzed Diastereoselective [3 + 2] Cycloaddition of *α*-Hydroxyketones and *β*-Keto Enol Ethers[a]



[a]Yields of isolated products are indicated in each case. The yields in parentheses are those obtained based on recovery of starting materials. [b]n.d. = not detected. [c]Detected by LC-MS analysis.

Mechanistic Study of the [3 + 2] Cycloaddition Reaction. The high diastereoselectivities and good yields for the Cu(I)-catalyzed [3 + 2] reaction prompted us to study the mechanism. As shown in Figure 2, **36** was chosen as the model compound in calculations. The reaction starts with coordination of the substrate **36a** and the THF-coordinated 3-oxobutanolcopper(I) complex **1-Cu**, giving **IN1**, which is endergonic by 5.8 kcal/mol. Here **1-Cu** formed from (*R*)-3-hydroxybutan-2-one and Cu catalyst is the used model for one substrate and catalyst, and the chiral carbon in this species has a *R* configuration. Initially we hypothesized that the [3 + 2] reaction is a stepwise process involving intermolecular Michael addition of alkoxyl oxygen atom in **1-Cu** toward **36**, followed by intramolecular aldol reaction. But calculation suggested that this is a concerted but asynchronous process, where Michael addition is ahead of aldol reaction, as revealed by the most favored transition state **TS2-*Re***, in which the forming C-O bond length in the Michael process is 2.01 Å, while the C-C bond formation via expected aldol reaction is lagging behind, with the forming C-C bond length of 3.35 Å. IRC calculations supported this analysis and the results are depicted in Figure 2 to help us appreciate this concerted process. This transition state gives **IN3-*RRSR***. A competing transition state **TS2-*Si*** giving another stereoisomer **IN3-*RSRS*** is higher than **TS2-*Re*** by 6.1 kcal/mol, suggesting that the major product should be **IN3-*RRSR***. This is consistent with experimental observations. The preference of **TS2-*Re*** over **TS2-*Si*** can be understood by the *syn*-pentane repulsion between the methyl and the phenoxy group in the latter transition state. Several other transition state such as **TS2-*Si*** and two open Michael addition transition states **TS4-*Re*** and **TS4-*Si*** (see Supporting Information), which are followed by aldol reaction, are disfavored and some of them given in Figure 2. **TS4-*Si*** is also disfavored against **TS2-*Re*** by 2.7 kcal/mol, which may be attributed to the lack of secondary interaction which appeared in **TS2**. Several other pathways, *e.g.,* Michael additions to *cis*-phenoxyenone have also been investigated and are not favored (see Supporting Information). The final step of the [3 + 2] reaction is ligand exchange reaction between **IN3-*RRSR*** and (*R*)-3-hydroxybutan-2-one.

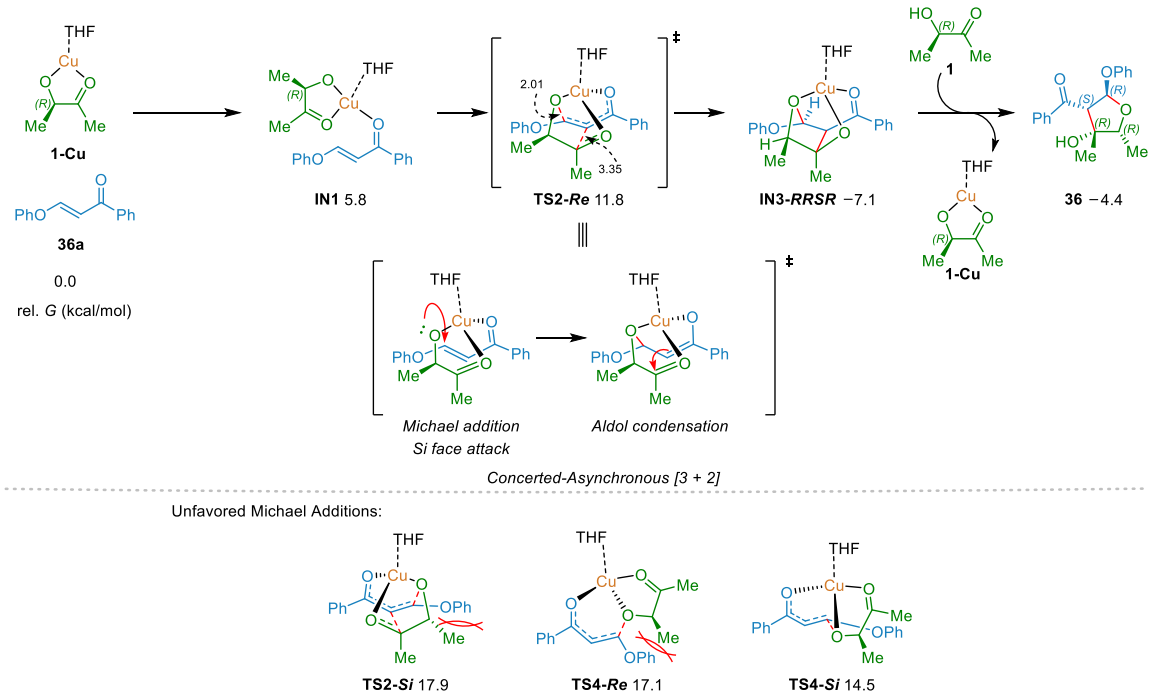


Figure 2. The most favored reaction pathway for the [3 + 2] reaction and some disfavored transition states computation carried out at ωB97M-V/def2-QZVPP/SMD(THF)//PBE0-D4/def2-TZVP(-f)/CPCM(THF) level. Geometric parameters of **TS2-*Re*** are given in angstrom.

The overall activation free energy of this [3 + 2] reaction is 14.5 kcal/mol in the model system (11.8 kcal/mol comes from **36** to **TS2-*Re*** while 2.7 kcal/mol is for ligand exchange from **IN3-*RRSR*** to **36**), which is lower than the expected value for a room temperature reaction. We reasoned that there are some resting states that could be more stable and consequently higher activation free energy than 14.5 kcal/mol is required to realize this [3 + 2] reaction.

Application of the [3 + 2] Cycloaddition to Lignan Synthesis. As mentioned above, dibenzylbutyrolactol lignan scaffolds could be constructed in a single step by utilizing the developed [3 + 2] cycloaddition method. It was envisaged that these dibenzylbutyrolactol lignan scaffolds could be further converted to a wider range of lignans, such as aryltetralin-type lignans, an important class of secondary metabolites with antiviral, antibacterial, and

antineoplastic properties.[18] Among them, particularly, podophyllotoxin (**52**) (Figure 3) and its derivatives have triggered intense studies owing to the remarkable anticancer potential, culminating in the approval of two clinically commonly used anticancer drugs, etoposide and teniposide.[19] To demonstrate the practicability of this methodology, we herein report the concise syntheses of two aryltetralin-type lignans, *β*-apopicropodophyllin (**53**)[20] and cycloolivil (**54**)[21] (Figure 3).

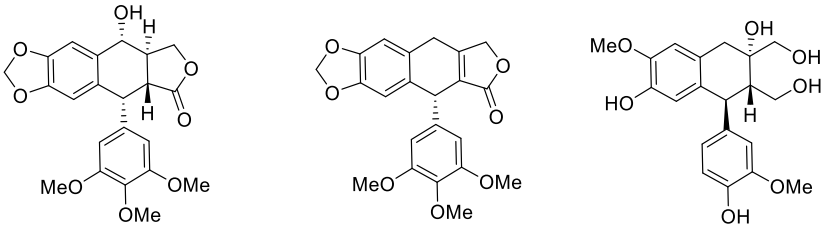


Figure 3. The structures of (−)-podophyllotoxin (**52**), (+)-*β*-apopicropodophyllin (**53**), and (+)-cycloolivil (**54**).

β-Apopicropodophyllin (**53**) is a naturally occurring podophyllotoxin derivative.[20] Recently, its racemic form was found to show extraordinary and selective antiproliferative activity against the A2780 human ovarian cancer cell line (IC_{50} = 63.1 ± 6.7 nM).[22] Meyers and co-workers first reported the total synthesis of (+)-**53** based on a diastereoselective addition of aryllithium to a naphthalene-containing chiral oxazoline.[23] Recently, Kwon and co-workers achieved the concise synthesis of (±)-**53** through cationic cyclization of a well-designed trimethylsilylalkyne derivative.[24] Peng's group accomplished the synthesis of (+)-**53** using a Ni-catalyzed reductive tandem coupling strategy developed by their lab.[25]

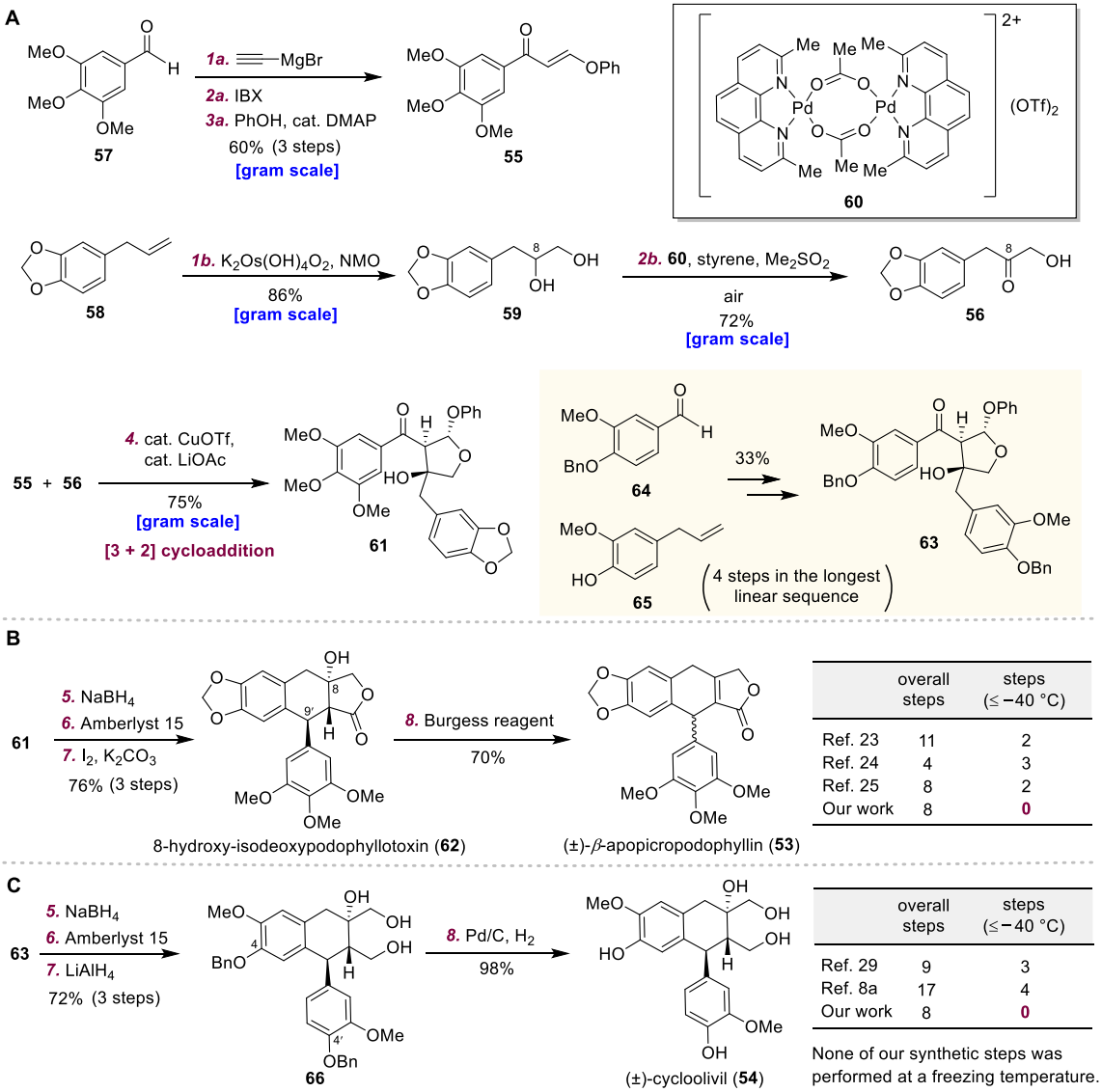
Our synthesis commenced with scalable preparation of two key precursors, *β*-keto enol ether **55** and *α*-hydroxyketone **56**, using 3,4,5-trimethoxy benzaldehyde (**57**) and safrole (**58**) as the starting materials, respectively (Scheme 1A). The addition reaction of **57** with the Grignard reagent, ethynylmagnesium bromide, was first performed. The propynol intermediate, without purification, was oxidized with IBX, and reacted with phenol through

a phenol-yne click reaction[26] to afford the first precursor **55** in 60% yield over 3 steps. The dihydroxylation of **58** smoothly produced the diol **59** in 86% yield. Selective aerobic oxidation of the secondary alcohol at C8 position catalyzed by Pd complex **60** gave the second desired precursor **56** in an appreciable yield (72%).[27] By following the developed protocol, subsequent [3 + 2] cycloaddition between **55** and **56** was achieved to produce the dibenzylbutyrolactol lignan-like intermediate **61** in 75% yield on gram scale, which was then subjected to reduction by sodium borohydride (Scheme 1B). Upon treatment with the acidic heterogeneous catalyst Amberlyst 15, a tandem process that involves removal of the phenyl group and acid-mediated cyclization was triggered. The crude product was then oxidized with iodine,[28] producing 8-hydroxy-isodeoxypodophyllotoxin (**62**) in a satisfactory yield (76% over 3 steps). Of note, compound **62** is a 9′-epimer of the aglycone of 3α-*O*-(β-D-glucopyranosyl)desoxypodophyllotoxin,[22] a recently reported lignan glycoside with strong antiproliferative activity. Dehydration of **62** with Burgess reagent yielded the target product (±)-β-apopicropodophyllin (**53**) in 70% yield.

Cycloolivil (**54**) is another commonly occurring aryltetralin-type lignan showing significant free radical scavenging activity.[21] Iwasaki and co-workers first accomplished the total synthesis of (±)-**54**, based on the stereoselective hydroxylation of α,β-dibenzyl-γ-butyrolactone.[29] Recently, the Hanessian group reported the first asymmetric synthesis of **54** through a combination of chemoenzymatic and biomimetic methods for systematic introduction of functional groups.[8a] Our synthesis initiated with preparation of the dibenzylbutyrolactol lignan-like intermediate **63**, which could be readily synthesized from benzylvanillin (**64**) and 4-allylguaiacol (**65**) in 33% yield via a longest linear sequence of 4 steps by following the similar synthetic procedure as for **61** (Scheme 1A). Subsequent reduction with sodium borohydride followed by an acid-mediated tandem process catalyzed by Amberlyst 15 proceeded smoothly to afford the crude product, which was reduced by lithium aluminum hydride, providing 4,4′-*O*-dibenzyl cycloolivil (**66**) in 72% yield over 3 steps. Finally, removal of the benzyl protection furnished the synthetic target

(±)-cycloolivil (**54**) (Scheme 1C).

Scheme 1. Concise Syntheses of (±)-*β*-Apopicropodophyllin (53) and (±)-Cycloolivil (54)



	overall steps	steps (≤ −40 °C)
Ref. 23	11	2
Ref. 24	4	3
Ref. 25	8	2
Our work	8	**0**

	overall steps	steps (≤ −40 °C)
Ref. 29	9	3
Ref. 8a	17	4
Our work	8	**0**

None of our synthetic steps was performed at a freezing temperature.

CONCLUSIONS

In conclusion, we have explored a highly diastereoselective Cu(I)-catalyzed [3 + 2] cycloaddition for fabrication of diverse THF acetals, inspired by the biosynthetic pathways of hongkonoids. This method permits formation of 3–4 stereocenters in one step, and shows

broad substrate scope and good atom economy. The mechanism of this [3 + 2] reaction revealed by calculation was shown to be a concerted but asynchronous Michael addition/aldol reaction. By applying the methodology, dibenzylbutyrolactol lignans can be readily accessed from two phenyl propane units. Further transformations allow expedient access to a wider range of lignans, such as the aryltetralin type. The total syntheses of bioactive aryltetralin lignans, *β*-apopicropodophyllin (**53**) and cycloolivil (**54**), have been achieved with a longest linear sequences of 8 steps in 24% and 23% overall yields, respectively. Compared with the reported ones, our synthetic routes avoid freezing reaction conditions, and thus are likely to be more suitable for commercial production. Given the mildness and practicability, this method might present an enticing prospect for industrial lignan production.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS publications website at https://XXX.

Accession Codes

CCDC 2268740 (**3**) and 2268741 (**39**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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