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Synthesis of complex oxygenated heterocycles*

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Abstract: Versatile and chemoselective preparation of substituted oxygenated heterocycles is described. Highly diastereoselective metal-catalyzed syntheses of *trans*-2,6- and *cis*-2,6-disubstituted tetrahydropyrans (THPs) are presented, along with an easy one-pot access to various ring size benzoannulated spiroketals.

Keywords: heterocyclic chemistry; spiroketals; tetrahydropyrans.

INTRODUCTION

A number of natural and non-natural biologically relevant products incorporate in their structure *cis*- and/or *trans*-2,6-disubstituted tetrahydropyrans **I** (THPs), substituted spiroketals **II**, or benzoannulated spiroketals **III** (Fig. 1). Because of the ubiquity of these motifs, the development of efficient tactics and methods to access THPs and spiroketals is of high importance.

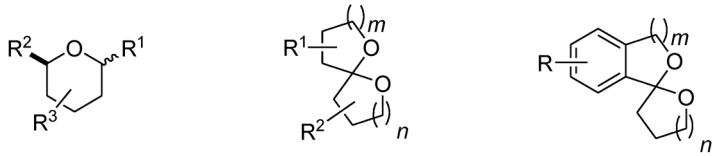

Fig. 1

SYNTHESIS OF 2,6-DISUBSTITUTED TETRAHYDROPYRANS

Among the substituted THPs, *trans*-2,6- and *cis*-2,6-disubstituted THPs are two abundant classes that can be found in a diversity of bioactive natural products such as leucascandrolide (antitumoral agent) [1] or non-natural products such as dapagliflozin (SGLT-2 inhibitor) [2] (Fig. 2).

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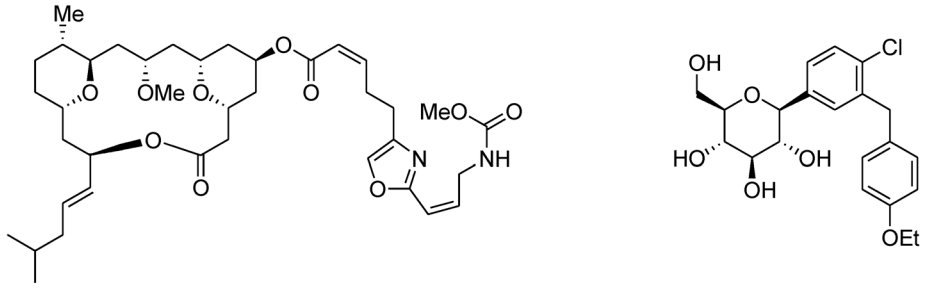
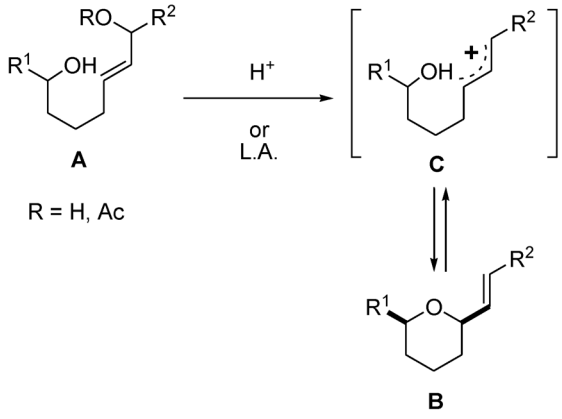


Fig. 2

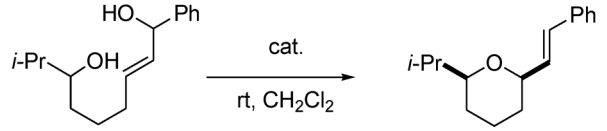
Various methods are currently available to access *cis*-2,6-disubstituted THPs either by forming a C–C bond or a C–O bond, and these methods have been extensively reviewed [3]. For our part, we were attracted by metal-catalyzed heterocyclization of δ-hydroxy alkenes **A**, bearing an allylic leaving group (OH or OAc). Metal catalysts based on palladium [3c,4] or gold [5] have been used to achieve the cyclization of monoallylic diol derivatives such as **A**. For each metal, a good diastereoselectivity was observed in favor of the *cis*-2,6-disubstituted THP. However, gold catalysts are expensive, and palladium is not eco-friendly. Due to these considerations, we tried to use cheap and nontoxic catalysts such as Brønsted or Lewis acids to achieve the synthesis of THPs. By using such catalysts, a delocalized carbocation **C** would be generated from **A** and trapped intramolecularly by the hydroxyl group to produce, under thermodynamic conditions, *cis*-2,6-disubstituted THPs (Scheme 1).



Scheme 1

To verify this hypothesis, compound **1** was prepared and then treated with Brønsted acids such as AcOH, CSA, PTSA, and TfOH. Among these acids, TfOH turned out to be the best one as **2** was isolated in 99 % yield with a dr of 97/3 in favor of *cis*-**2**. In addition, different Lewis acids were tested, such as $InCl_3$, $TiCl_4$, and $FeCl_3{\cdot}6H_2O$, and the iron salt was found to be the best catalyst in terms of yield and diastereoselectivity (dr = 97/3) (Table 1).

Table 1

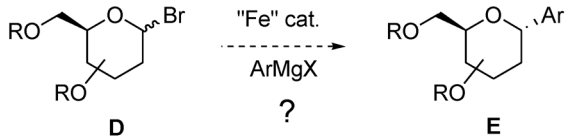


1 **2**

Entry	Cat. (mol %)	Time (h)	Yield (dr)
1	AcOH (10 mol %)	24	no conversion
2	CSA (5 mol %)	48	71 % (57/43)
3	PTSA.H_2O (5 mol %)	48	77 % (96/4)
4	TfOH (5 mol %)	3	99 % (97/3)
5	$InCl_3$ (5 mol %)	48	76 % (92/8)
6	$TiCl_4$ (5 mol %)	96	87 % (76/24)
7	$FeCl_3 \cdot H_2O$ (5 mol %)	2	66 % (97/3)

As $FeCl_3 \cdot 6H_2O$ is very cheap, eco-friendly, and easier to handle than TfOH, $FeCl_3 \cdot 6H_2O$ was selected to study the scope of the reaction which was extended to δ-hydroxy allylic alcohols **3–8** (Table 2) [6]. *Cis*-2,6-THPs **9–14** were obtained in good yields and with good diastereoselectivities. Various groups were tolerated at the allylic position such as phenyl, mesityl, as well as alkyl groups. In the latter case, longer reaction times were required in order to obtain THPs (Table 2, entry 4). The geometry of the double bond (Table 2, entry 2) as well as the position of the hydroxyl groups of the allylic alcohols did not affect the outcome of the reaction, as **10** and **11** were obtained in good yields and diastereomeric excesses (Table 2, entries 2 and 3). Furthermore, the reaction is chemoselective as hydroxyl and ester groups were tolerated (Table 2, entries 5 and 6).

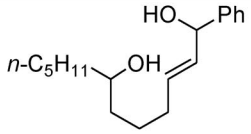
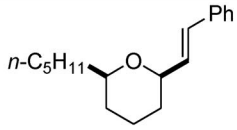
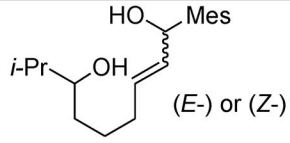
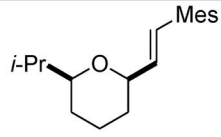
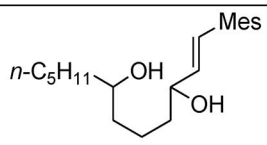
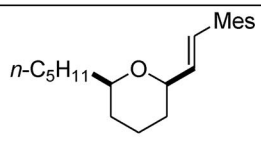
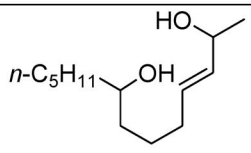
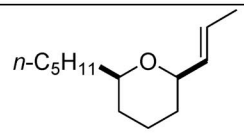
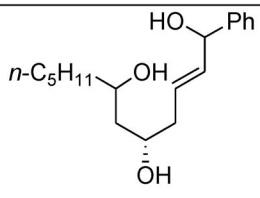
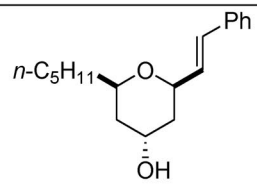
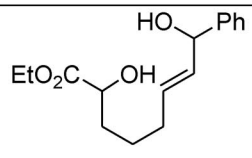
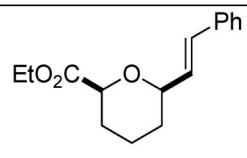
We focused next on an easy stereoselective synthesis of *trans*-2,6-disubstituted THPs and, more particularly, α-*C*-arylglycosides as these compounds might be good candidates as inhibitors of carbohydrate processing enzymes [7]. Although numerous methods exist to prepare *C*-glycosides, metal-catalyzed cross-coupling between 1-halogeno glycosides and organometallics represents a powerful tool. However, the major drawback of such a coupling is a β-H elimination and/or a β-elimination of the C2 substituent that leads to a glucal. In addition, in most cases, a diastereomeric mixture in favor of the β-*C*-glycosides is obtained [8]. The precedents of metal-catalyzed cross-coupling yielding only α-epimers are very rare, and the stereoselectivity depends strongly on the nature of the glycoside and on the reaction conditions. α-*C*-Alkylglycosides can also be obtained from α-*C*-anomeric glycosyl radicals. As it was previously demonstrated that a radical pathway can intervene during iron-catalyzed cross-coupling between Grignard reagents and secondary alkyl halides [9], and as this coupling is chemoselective, a coupling reaction between an aryl Grignard reagent and α-bromo glycosides **D** using iron catalysts was envisioned to obtain α-*C*-arylglycosides **E** (Scheme 2).



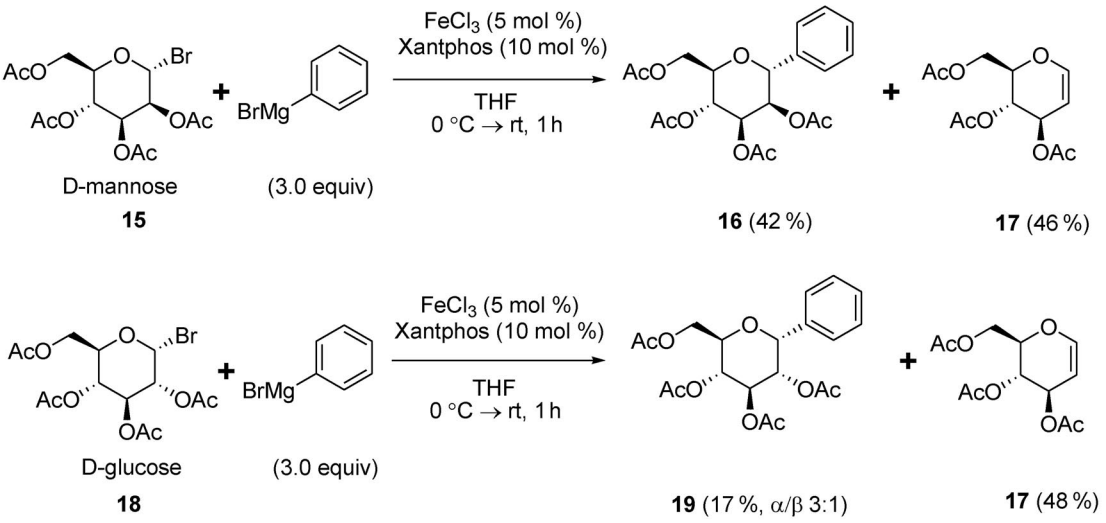
D **E**

Scheme 2

Table 2

entry	starting material	cyclized product	time (h)	(yield, dr)
1	 **3**	 **9**	1	(99 %, 98/2)
2	 **4**	 **10**	1	(82-96 %, 94/6)
3	 **5**	 **11**	1	(88 %, 95/5)
4	 **6**	 **12**	24	(82 %, 97/3)
5	 **7**	 **13**	3	(99 %, 93/7)
6	 **8**	 **14**	48	(99 %, 90/10)

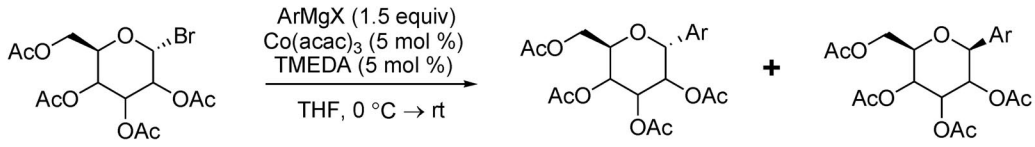
The first α-bromo glycoside investigated was *O*-acetyl α-bromo-D-mannose **15**. After extensive screening, the best conditions found for the cross-coupling of **15** with PhMgBr involved the use of 3 equiv of PhMgBr, Xantphos (10 mol %), $FeCl_3$ (5 mol %) in THF. At full conversion of **15**, *C*-α-phenylglycoside **16** was isolated in 42 % yield and glucal **17** was formed in 46 % yield. When the same conditions were applied to *O*-acetyl-α-bromo-D-glucose **18**, α-*C*-phenylglycoside **19** was formed in only 17 % yield with an α/β ratio of 3/1, and the major product isolated was glucal **17** (48 %) (Scheme 3).



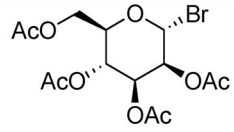
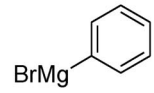
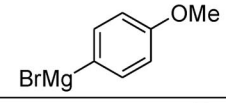
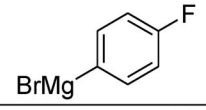
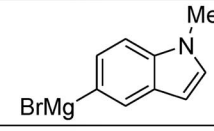
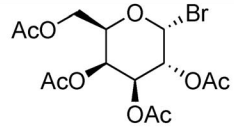
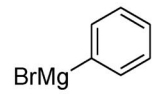
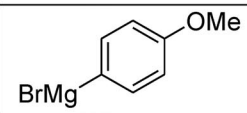
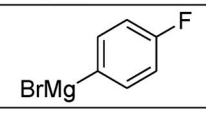
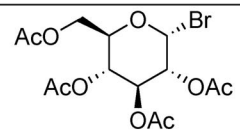
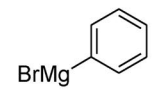
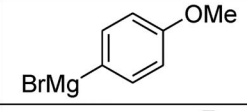
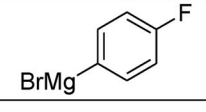
Scheme 3

Interestingly, both products **16** and **19** were obtained as α-isomers, and an anomeric carbon-centered radical could be formed during the oxidative addition of a low-valent iron intermediate into the C1–Br bond. As our optimization of an iron catalyst to decrease the amount of glucal **17** failed, we had to explore a new catalytic system and we turned our attention to a cobalt-centered catalytic system. Indeed, cobalt catalysts were reported to achieve the cross-coupling between aryl Grignard reagents and secondary alkyl halides. These catalytic systems are compatible with substrates bearing a β-hydrogen or a β-alkoxy substituent, and the cross-coupling was reported to proceed through a radical pathway [10]. The cobalt-catalyzed coupling of *O*-acetyl-α-bromo-D-mannose **15** with PhMgBr was examined, and among the different cobalt salts and ligands tested, $Co(acac)_3$ (5 mol %), tetramethylethylenediamine (TMEDA) (5 mol %) in tetrahydrofuran (THF) from 0 °C to rt, proved to be the best conditions. Under these conditions, **15** was transformed into **16** in 76 % yield when treated with PhMgBr (1.5 equiv), and no traces of glucal **17** were detected by gas chromatography/mass spectrometry (GC/MS). The reaction is general as electron-rich or electron-poor aryl Grignard reagents can be used providing similar yields of the coupling products (Table 3, entries 1–3). The cross-coupling was also possible with indole Grignard derivatives (Table 3, entry 4). With α-bromo galactose derivatives **20** (Table 3, entries 5–7), the cross-coupling was diastereoselective as only the α-isomer was formed. With 1-bromo-*O*-acetyl-glucose **18**, low diastereoselectivities were obtained (α/β ratio of 2:1 to 3:1) (Table 3, entries 8–10) [11].

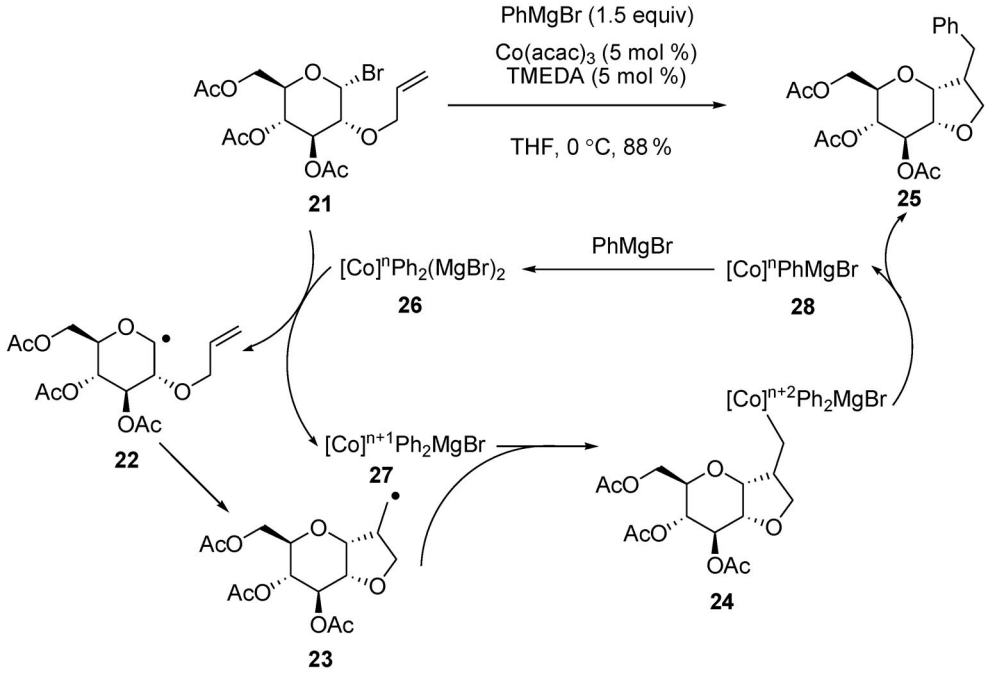
Table 3



15, 18, 20 α–isomer β-isomer

entry	substrate	ArMgX	yield	α/β
1	 **15**		76 %	>9/1
2	**15**		70 %	>9/1
3	**15**		88 %	>9/1
4	**15**		53 %	>9/1
5	 **20**		61 %	>9/1
6	**20**		82 %	>9/1
7	**20**		75 %	>9/1
8	 **18**		96 %	3/1
9	**18**		88 %	2.4/1
10	**18**		81 %	2/1

To verify if a radical pathway is operational in the cobalt-catalyzed cross-coupling of 1-bromo glycosides, the reaction of **21** with PhMgBr was examined (Scheme 4). As expected, when **21** was treated with PhMgBr (1.5 equiv) in the presence of $Co(acac)_3$ (5 mol %)/TMEDA (5 mol %) in THF at 0 °C and then the reaction was warmed to rt, **25** was isolated in 88 % yield. This product results from the formation of the anomeric radical **22**, which cyclizes to **23** according to a 5-*exo*-trig process. This radical intermediate reacts with the cobalt species **27**, yielding intermediate **24**, which leads to **25** after reductive elimination [11].



Scheme 4

SYNTHESIS OF SPIROKETALS

Spiroketals **II** and **III** (Fig. 1) appear in a wide range of naturally occurring substances isolated from a variety of sources such as bacteria, fungi, plants, insects, and marine organisms [12]. These spiroketals have demonstrated potent biological activity, for example, antitumor properties in the case of bistramide A [13], (spiroketal **II**), and berkelic acid [14] (benzoannulated spiroketals **III**) (Fig. 3).

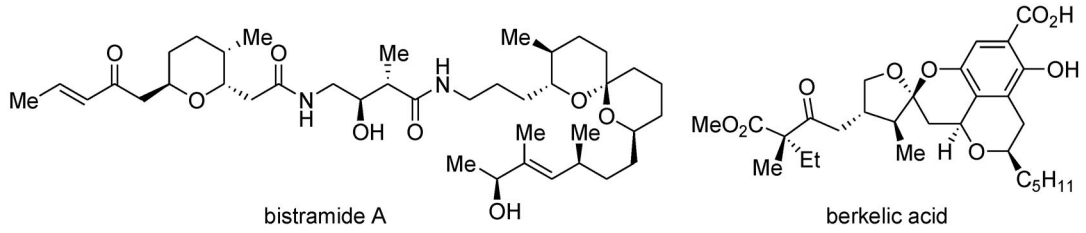
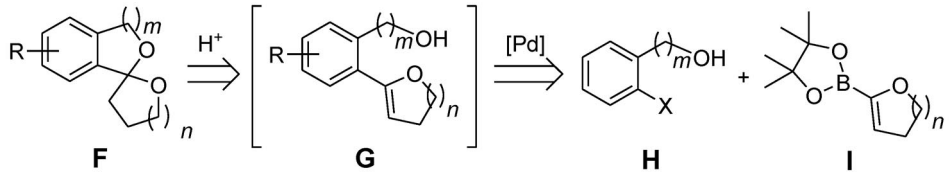


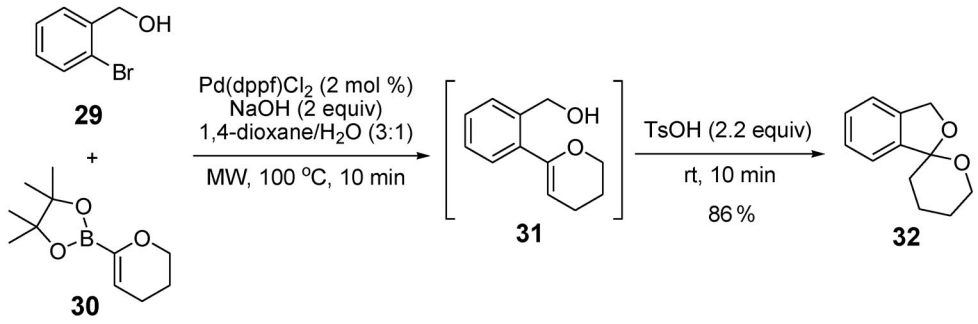
Fig. 3

A large number of methods have been developed to access spiroketals [15], however, these approaches are often linear and not regioselective [16]. Several preparations of benzoannnulated spiroketals have relied on a Pd-catalyzed cross-coupling between aryl halides and stannylated dihydropyrans or dihydropyranyl silanols, followed by a spirocyclization with a side chain at the *ortho*-position of the aromatic ring upon reaction with an electrophilic epoxidation reagent [17]. Recently, the synthesis of optically active spiroketals has been achieved by the treatment of 6-(ω-hydroxyalkyl)-3,4-dihydro-2*H*-pyrans with catalytic amounts of optically active acids [18]. Due to the known toxicity of organostannanes and the poor availability and complex preparation of silanols, we have planned a convergent access to benzoannulated spiroketals **F** from the corresponding pinacol boronates **I** and (2-haloaryl)alkyl alcohols **H** via intermediate **G**, employing a one-pot Suzuki–Miyaura coupling/acid-catalyzed spiroketalization (Scheme 5).



Scheme 5

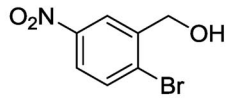
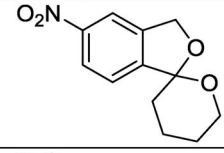
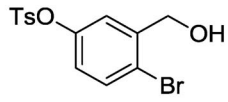
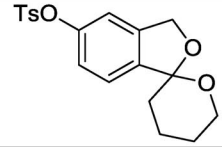
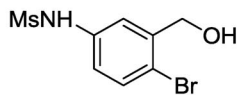
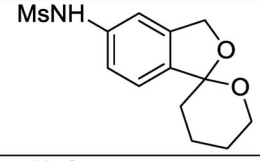
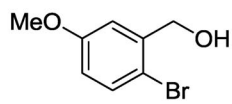
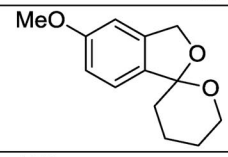
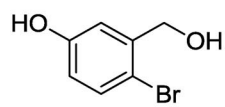
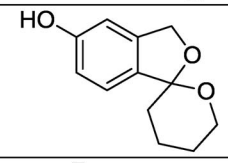
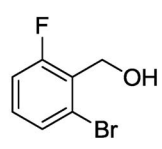
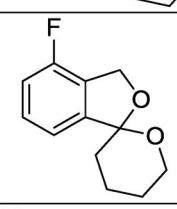
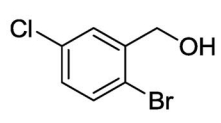
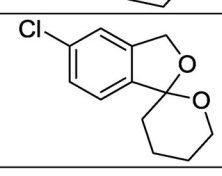
The test reaction was realized with 2-bromobenzyl alcohol **29** and boronate **30** (Scheme 6). Different palladium catalysts and bases were screened, and the best yield of the coupling product was obtained when Pd(dppf)Cl_2 (2 mol %) in the presence of NaOH (2 equiv) was used. Under these conditions, **31** was formed and, to achieve its transformation into **32**, *p*-toluenesulfonic acid (2.2 equiv) was added to the reaction mixture. Spiroketal **32** was then isolated in 86 % yield.



Scheme 6

The reaction is general, and the results are reported in Table 4. In this process, different functional groups on the aromatic ring can be tolerated, such as nitro, sulfonate, sulfonamide, hydroxyl, methoxyl groups and halides (F, Cl). Except for the hydroxy-substituted substrate (Table 4, entry 5), the yields of spiroketals are good to excellent (Table 4) [19].

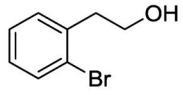
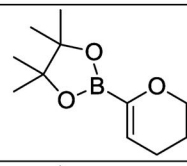
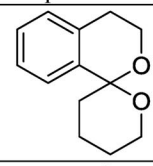
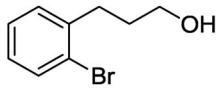
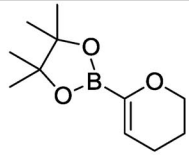
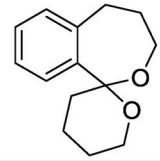
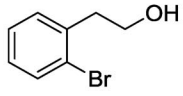
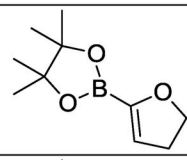
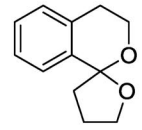
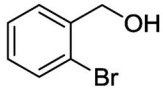
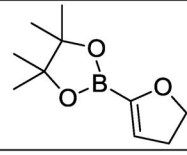
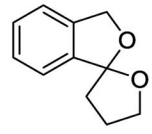
Table 4

Entry	Starting material	Spiroketal	Yield
1			74 %
2			78 %
3			84 %
4			60 %
5			34 %
6			72 %
7			90 %

Spirocycles with different ring size combinations were prepared using this method, such as benzoannulated [5,5]-, [5,6]-, [6,6]-, and [6,7]-spiroketals (Table 5).

In summary, we have developed rapid and convergent syntheses of THPs and benzoannulated spiroketals by using highly chemoselective processes: a cyclization of δ-hydroxyallyl alcohols induced by $FeCl_3 \cdot 6H_2O$, producing *cis*-2,6-disubstituted THPs; a radical coupling reaction between 1-halogeno glycosides and aryl Grignard reagents catalyzed by cobalt salts to produce *trans*-2,6-disubstituted THPs; and a one-pot Suzuki–Miyaura coupling/acid-catalyzed spiroketalization to obtain benzoannulated spiroketals. These versatile and chemoselective processes are potentially applicable to the synthesis of complex bioactive natural products.

Table 5

Entry	Starting material	Boronate	Spiroketal	Yield
1				96 %
2				43 %
3				35 %
4				48 %

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