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Two-Step One-Pot Synthesis of Benzoannulated Spiroacetals by Suzuki–Miyaura Coupling/Acid-Catalyzed Spiroacetalization

Alexey N. Butkevich,[†] Andrei Corbu,[†] Lieven Meerpoel,[‡] Ian Stansfield,[§] Patrick Angibaud,[§] Pascal Bonnet,[‡] and Janine Cossy*,[†]

Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10 rue Vauquelin, 75231 Paris Cedex 05, France, Janssen Research & Development, Division of Janssen-Cilag S.A., Oncology and Medicinal Chemistry, Campus de Maigremont, 27106 Val de Reuil, Cedex, France, and Janssen Research & Development, Division of Janssen Pharmaceutica N.V., Turnhoutsweg 30, 2340 Beerse, Belgium

janine.cossy@espci.fr

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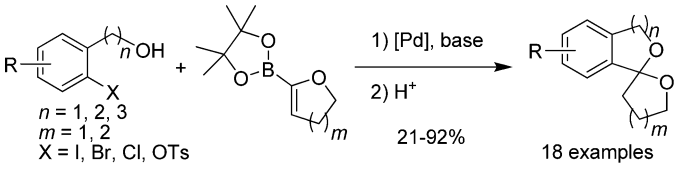
ABSTRACT



Substituted benzoannulated spiroacetals were prepared from (2-haloaryl)alkyl alcohols and dihydropyranyl or dihydrofuranyl pinacol boronates using a Suzuki–Miyaura coupling followed by an acid-catalyzed spirocyclization. Application of the reaction to a glycal boronate provides an approach to annulated spiroacetals in enantiopure form.

The spiroacetal ring system, in particular 1,6-dioxaspiro-[4.4]nonanes, 1,6-dioxaspiro[4.5]decanes, and 1,7-dioxaspiro-[5.5]undecanes, is present in a variety of natural products of different origins.[1] Several benzoannulated spiroacetals, such as rubromycins, heliquinomycin, papulacandin, paecilospirone, and berkelic acid, have demonstrated potent biological activity[2] and therefore remain attractive synthetic targets.

Spiroacetals have been prepared by acid-catalyzed cyclization of ω,ω'-dihydroxyketones,[3] 1,3-dipolar cycloaddition,[4] oxidative enolate coupling,[5] addition of 2-lithiofurans to phenylacetaldehydes followed by cyclization,[6] or an aromatic Pummerer-type reaction.[7] Metal-catalyzed (Ir, Rh, and Au) double hydroalkoxylation of disubstituted alkynes provides benzoannulated spiroacetals; however these reactions are rarely regioselective.[8] Several syntheses of

[†] ESPCI ParisTech.
[‡] Janssen Research & Development, Janssen Pharmaceutica N.V.
[§] Janssen Research & Development, Oncology and Medicinal Chemistry, Campus de Maigremont.

(1) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406–4440. Denmark, S. E.; Regens, C. S.; Kobayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2774–2776. Liu, G.; Wurst, J. M.; Tan, D. S. *Org. Lett.* **2009**, *11*, 3670–3673.

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(5) Lindsey, C. C.; Wu, K. L.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2365–2367.

(6) Qin, D.; Ren, R. X.; Siu, T.; Zheng, C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4709–4713.

(7) Akai, S.; Kakiguchi, K.; Nakamura, Y.; Kuriwaki, I.; Dohi, T.; Harada, S.; Kubo, O.; Morita, N.; Kita, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 7458–7461.

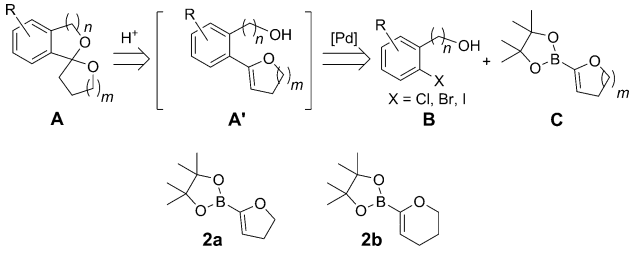
(8) Fugami, K.; Hagiwara, N.; Okeda, T.; Kosugi, M. *Chem. Lett.* **1998**, 81–82. Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437–5440. Messerle, B. A.; Vuong, K. Q. *Organometallics* **2007**, *26*, 3031–3040. Zhang, Y.; Xue, J.; Xin, Z.; Xie, Z.; Li, Y. *Synlett* **2008**, *2008*, 940–944. Selvaratnam, S.; Ho, J. H. H.; Huleatt, P. B.; Messerle, B. A.; Chai, C. L. L. *Tetrahedron Lett.* **2009**, *50*, 1125–1127. Ho, J. H. H.; Hodgson, R.; Wagler, J.; Messerle, B. A. *Dalton Trans.* **2010**, *39*, 4062–4069. Ho, J. H. H.; Choy, S. W. S.; Macgregor, S. A.; Messerle, B. A. *Organometallics* **2011**, *30*, 5978–5984.

10.1021/ol302088w

benzoannulated spiroacetals have relied on a Pd-catalyzed cross-coupling between aryl halides and stannylated dihydropyrans or dihydropyranyl silanols leading to 6-aryl-3,4-dihydro-2*H*-pyrans. These pyrans underwent spirocyclization with a side chain at the C-2 position of the aryl group when reacted with an electrophilic epoxidation reagent, such as DMDO or *m*-CPBA.[9] Recently, the treatment of 6-(ω-hydroxyalkyl)-3,4-dihydro-2*H*-pyrans and related dihydrofurans and tetrahydrooxepins with binaphthol-phosphoric acids[10a] or binaphthol-derived iminodiphosphoric acids[10b] has been reported to lead to optically active spiroacetals.

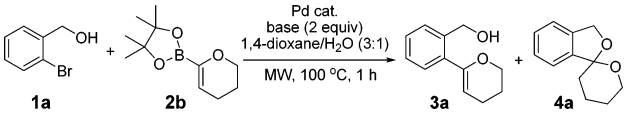
Due to the known toxicity and persistence of organostannanes, and as the preparation of silanols has to be realized in several steps, we have planned to access benzoannulated spiroacetals **A** in an efficient convergent manner from the corresponding (2-haloaryl)alkyl alcohols **B** and pinacol boronates **C**, employing a one-pot Suzuki–Miyaura coupling/acid-catalyzed spiroacetalization approach (Scheme 1).

Scheme 1. Retrosynthetic Approach



In a test reaction, the starting boronate **2b**[11] was reacted with 2-bromobenzyl alcohol **1a** followed by an acidic treatment of the obtained intermediate **3a**. At first, different palladium catalysts and bases were tested in order to optimize the conditions of the Suzuki–Miyaura coupling. The reaction was carried out in 1,4-dioxane/H_2O (3:1) at 100 °C under microwave irradiation. Among the palladium catalysts and bases tested, Pd(dppf)Cl_2 (5 mol %) in the presence of Na_2CO_3 or NaOH (2 equiv) led to the highest yield of the coupling product **3a** (82%). The desired spiroacetal **4a** was also obtained in 6% yield, likely due to Lewis acid properties of the Pd catalyst (Table 1, entry 3). To achieve the complete transformation of **3a** into **4a**, *p*-TsOH (3 equiv) was added to the reaction mixture, leading directly to spiroacetal **4a** in 86% yield (Table 1, entry 4). The palladium catalyst loading could be successfully decreased to 2 mol %; however using smaller amounts of catalyst (0.5 mol %) resulted in a significantly lower yield of **4a** (Table 1, entry 5).

Table 1. Optimization of the Reaction Conditions

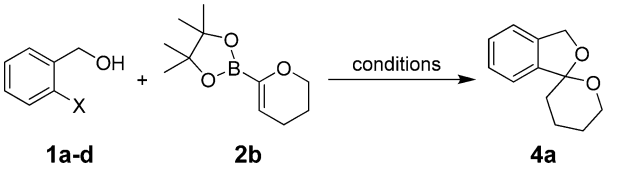


entry	Pd cat. (mol %)	base	yield **3a**	yield **4a**
1	$Pd(PPh_3)_4$ (5)	Na_2CO_3	67%	–
2	$Pd(MeCN)_2Cl_2$ (5) PCy_3 (10)	Na_2CO_3	64%	3%
3	Pd(dppf)Cl_2 (5)	Na_2CO_3	82%	6%
4[a]	Pd(dppf)Cl_2 (2)	NaOH	–	86%[b]
5[a]	Pd(dppf)Cl_2 (0.5)	NaOH	–	58%[b]

[a] Reaction time 10 min. [b] Yield of **4a** after cyclization with TsOH (3 equiv) for 10 min at rt.

Spiroacetals of type **A** were prepared from various (2-haloaryl)alkyl alcohols **B**, such as iodide **1b**, chloride **1c**, and tosylate **1d**, by using the conditions reported in Table 2.

Table 2. Scope of the Leaving Group[a]



entry	X, **1**	cond	yield **4a**
1	Br, **1a**	A	86%
2	I, **1b**	A	92%
3	Cl, **1c**	A	0%
4	Cl, **1c**	B	84%
5	OTs, **1d**	A or B	0%
6	OTs, **1d**	C	21%

[a] **Conditions A**: Pd(dppf)Cl_2 (2 mol %), NaOH (2 equiv), 1,4-dioxane/H_2O (3:1), MW, 100 °C, 10 min, then TsOH·H_2O (2.2 equiv), rt, 10 min. **Conditions B**: $Pd(MeCN)_2Cl_2$ (3 mol %), XPhos (6 mol %), NaOH (2 equiv), 1,4-dioxane/H_2O (3:1), MW, 100 °C, 10 min, then TsOH·H_2O (2.2 equiv), rt, 10 min. **Conditions C**: $Pd(OAc)_2$ (2 mol %), BrettPhos (4 mol %), K_3PO_4 (3 equiv), *t*-BuOH, MW, 110 °C, 2 h, then TsOH·H_2O (5.5 equiv), rt (monitored by TLC).

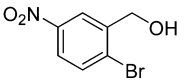
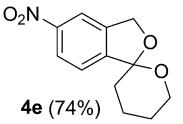
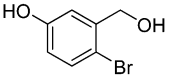
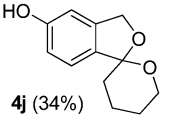
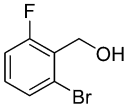
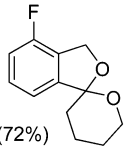
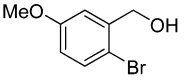
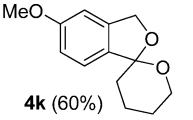
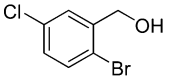
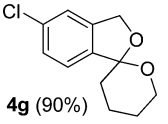
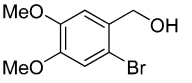
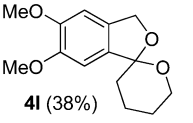
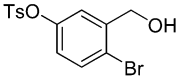
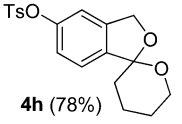
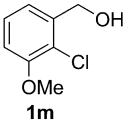
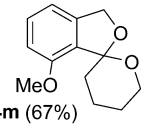
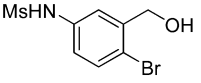
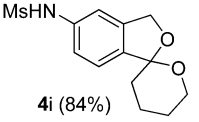
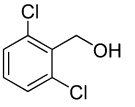
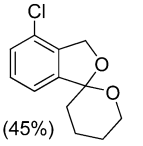
2-Iodobenzyl alcohol **1b** was converted to **4a** in 92% yield under conditions A (Table 2, entry 2), while 2-chlorobenzyl alcohol **1c** was not reactive and required a more active catalytic system, $Pd(MeCN)_2Cl_2$ (3 mol %)/XPhos (6 mol %), to produce **4a** in 84% yield after acid-catalyzed cyclization (conditions B, Table 2, entry 4). The cross-coupling with 2-(hydroxymethyl)phenyl tosylate **1d** was

(9) Denmark, S.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221–3224. Wurst, J. M.; Liu, G.; Tan, D. S. *J. Am. Chem. Soc.* **2011**, *133*, 7916–7925. Potuzak, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc.* **2005**, *127*, 13796–13797. Dubois, E.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1990**, 1191–1192. Elsley, D. A.; MacLeod, D.; Miller, J. A.; Quayle, P.; Davies, G. M. *Tetrahedron Lett.* **1992**, *33*, 409–412.

(10) (a) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074–8077. (b) Čorić, I.; List, B. *Nature* **2012**, *483*, 315–319.

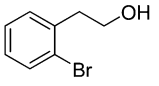
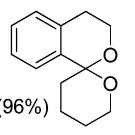
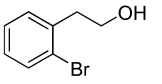
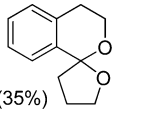
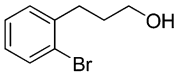
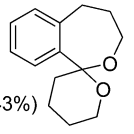
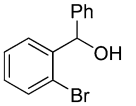
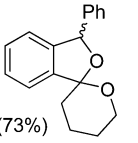
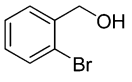
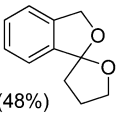
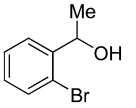
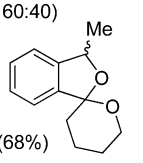
(11) Boronate **2b** was prepared on a multigram scale by metalation of 3,4-dihydro-2*H*-pyran with the *n*-BuLi/*t*-BuOK system followed by treatment with trimethyl borate, pinacol, and acetic acid (see Supporting Information).

Table 3. Substitution of the Aromatic Ring: Scope and Limitations[a]

entry	ArX, **1e-n**	cond	product (yield)	entry	ArX, **1e-n**	cond	product (yield)
1	 **1e**	A	 **4e** (74%)	6	 **1j**	A	 **4j** (34%)
2	 **1f**	A	 **4f** (72%)	7	 **1k**	A	 **4k** (60%)
3	 **1g**	A	 **4g** (90%)	8	 **1l**	B	 **4l** (38%)
4	 **1h**	A	 **4h** (78%)	9	 **1m**	C	 **4m** (67%)
5	 **1i**	A	 **4i** (84%)	10	 **1n**	C	 **4n** (45%)

[a] **Conditions A:** $Pd(dppf)Cl_2$ (2 mol %), NaOH (2 equiv), 1,4-dioxane/H_2O (3:1), MW, 100 °C, 10 min, then $TsOH \cdot H_2O$ (2.2 equiv), rt, 10 min. **Conditions B:** $Pd(PPh_3)_2Cl_2$ (5 mol %), Na_2CO_3 (2 equiv), 2,2,2-trifluoroethanol, MW, 100 °C, 1 h. **Conditions C:** $Pd(MeCN)_2Cl_2$ (3 mol %), XPhos (6 mol %), NaOH (2 equiv), 1,4-dioxane/H_2O (3:1), MW, 100 °C, 10 min, then $TsOH \cdot H_2O$ (2.2 equiv), rt, 10 min.

Table 4. Side Chain and Cycle Size Variation[a]

entry	ArBr, **1**	boronate	product (yield) (dr)	entry	ArBr, **1**	boronate	product (yield) (dr)
1	 **1o**	**2b**	 **4o** (96%)	4	 **1o**	**2a**	 **4r** (35%)
2	 **1p**	**2b**	 **4p** (43%)	5	 **1s**	**2b**	 **4s** (73%) (dr = 60:40)
3	 **1a**	**2a**	 **4q** (48%)	6	 **1t**	**2b**	 **4t** (68%) (dr = 60:40)

[a] Conditions: $Pd(dppf)Cl_2$ (2 mol %), NaOH (2 equiv), 1,4-dioxane/H_2O (3:1), MW, 100 °C, 10 min, then $TsOH \cdot H_2O$ (2.2 equiv), rt, 10 min.

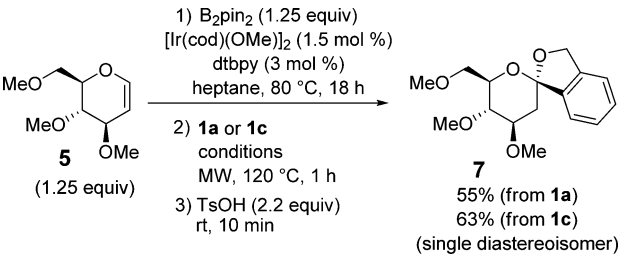
difficult to achieve and required an even more active catalyst (Pd(0)/BrettPhos)[12] (conditions C, Table 2, entry 6). Importantly, under conditions A, chloride and tosylate substituents present on the aromatic ring are tolerated and not involved in cross-coupling reactions. The results are summarized in Table 3.

Substituted 2-halobenzyl alcohols **1e**−**1n** were transformed into the corresponding spiroacetals **4e**−**4n** in moderate to excellent yields (38−90%). As can be concluded from the results, electron-withdrawing groups were generally well tolerated (Table 3, entries 1 and 4), while very electron-rich substrates suffered from diminished yields due to side reactions during the cyclization step. Alternative reaction conditions (conditions B) had to be employed to attain practical yields (Table 3, entry 8).

Benzoannulated [5,5]-, [5,6]-, [5,7]- and [6,6]-spiroacetals were successfully prepared under conditions A depending on the length of the hydroxyalkyl side chain of the aryl halide as well as on the ring size of the boronates **2a,b** (Table 4, entries 1−4). A diastereomeric ratio of 60:40 was observed when secondary benzyl alcohols **1s** and **1t** were used; however, the diastereomeric spiroacetals were found to interconvert rapidly in the presence of a catalytic amount of acid (Table 4, entries 5 and 6).

To demonstrate the applicability of our method to the synthesis of chiral spiroacetals, boronate ester **6**, prepared from trimethyl-D-glucal **5**,[13] was reacted with either **1a** or **1c** in the presence of a Pd catalyst and Na_2CO_3 as a base in anhydrous 1,4-dioxane or MeCN (use of NaOH in a 1,4-dioxane/water mixture resulted in complete protodeboronation of **6** to the starting glycal **5**). The product of this reaction was spiroacetal **7** as the anomerically stabilized diastereoisomer, isolated in 55−63% yield (Scheme 2).

Scheme 2. Preparation of 2-Deoxy-D-glucose-Derived Spiroacetal **7**[a]



[a] Conditions: $Pd(dppf)Cl_2$ (2 mol %), Na_2CO_3 (2 equiv), MeCN, **1a** *or* $Pd(MeCN)_2Cl_2$ (3 mol %), XPhos (6 mol %), Na_2CO_3 (2 equiv), 1,4-dioxane, **1c**.

In summary, we have developed a rapid convergent microwave-assisted synthesis of benzoannulated spiroacetals using a one-pot Suzuki−Miyaura coupling reaction/spiroacetalization. This versatile and chemoselective process is potentially applicable to the synthesis of complex biologically active natural products.

Acknowledgment. Janssen Pharmaceutica is gratefully acknowledged for financial support.

Supporting Information Available. Full experimental details and characterization data (^1H NMR, ^{13}C NMR, IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(12) (a) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954–3957. (b) Pd/XPhos-catalyzed Suzuki−Miyaura coupling of aryl tosylates has also been reported but was not successful in our case; see: Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.

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