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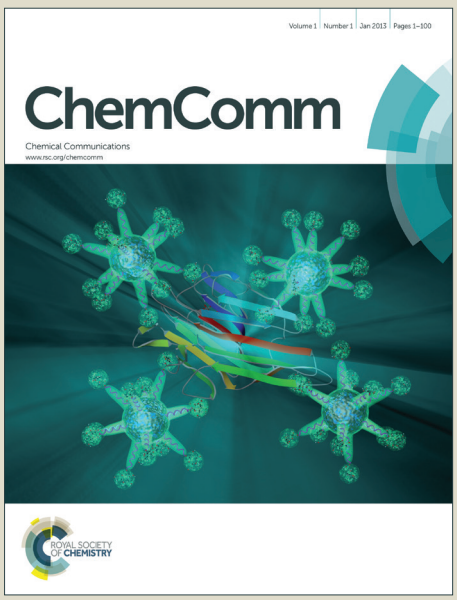

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A Metal-Free Dyotropic-Like Rearrangements of 2-Oxa Allylic Alcohols in the Presence of Organoboronic Acids

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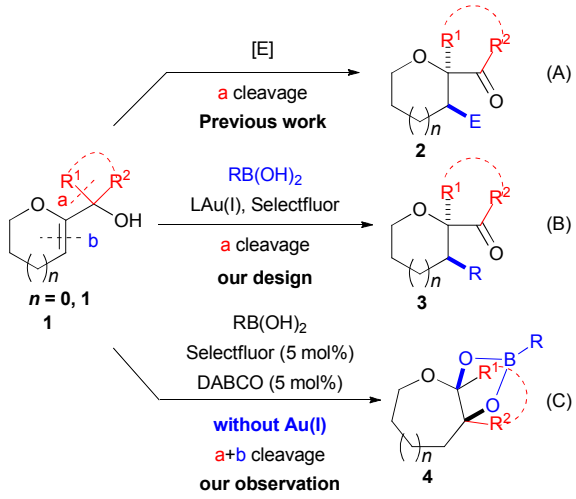
The first example of dyotropic-like rearrangement of 2-oxa allylic alcohols in the presence of catalytic amounts of Selectfluor and DABCO was reported, which provide a facile access to organoboronates. This reaction represents an unprecedented dyotropic rearrangement consisting of cleavage of two vicinal bonds (one C-C bond and one C=C bond).

Dyotropic rearrangements,[1] originally defined as reactions in which "two σ-bonds simultaneously migrate intramolecularly", have emerged as standard tools for the construction of organic and organometallic molecules with interesting properties, which were first introduced by M. T. Reetz in 1972.[2] Moreover, this unique rearrangement is often the single entry to facile access to complex target molecules. For example, the Wagner-Meerwein-type I dyotropic rearrangements of lactones, consisting of one C-C bond and one C-O bond migration, which has been proved to be an efficient and practical method for synthesis of lactones.[1,3] Recently, Yang, Luo, Tang, and their co-workers[3e] have successfully employed the Wagner-Meerwein-type dyotropic rearrangements of lactones in the enantioselective total synthesis of xanthanolide, a natural product with a wide range of biological activities.[4] On the other hand, as Fernández[1] pointed out in *Chemical Reviews* "the search for new dyotropic transformations in general continues unabated". Moreover, migration of two vicinal C-C bonds (most cases, one C-C and one C-X) have been considered as a highly synthetically useful but extremely challenging, thus, novel strategy is therefore highly desirable to address this issue.

2-Oxa allylic alcohols[5-7] with their salient features of simple structure, easy availability, have received much attention in past years. The groups of Paquette[5] and Tu[6] have done seminal work in this field. All these reactions related to 2-oxa allylic alcohols share a common process, that is, semipinacol rearrangement,[8] rapidly furnishing monocyclic, or spirocyclic ketones **2** (Scheme 1A). It is noteworthy that in these semipinacol rearrangements, only one C-C bond cleavage (a cleavage) takes place and the C=C double bond does not break. During the course of our efforts to develop gold-catalyzed oxidative cross-coupling reaction[9e] and expedient routes to spirocyclic ketones,[10] we envisaged that a gold-catalyzed tandem reaction of 2-oxa allylic alcohols with organoboronic acids consisting of the semipinacol rearrangement and oxidative cross coupling[9] might occur in the presence of oxidant (Selectfluor), which would provide a facile route to monocyclic or spirocyclic ketones **3** (Scheme 1B).

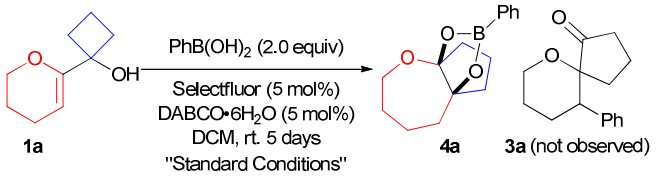


Scheme 1. Two different rearrangements of 2-oxa allylic alcohols

We started to test our hypothesis with the use of 2-oxa allylic alcohol **1a** and $PhB(OH)_2$ (2 equivalents) as the model substrates. To our surprise, the reaction did not give the desired coupling product spirocyclic ketone **3a**, but an unexpected product tricyclic organoboronate **4a** in 77% yield, when the reaction was subjected to Ph_3PAuCl (5 mol%) and Selectfluor (2.0 eq.) in CH_2Cl_2 (Table 1, entry 1). The structure of product was confirmed by the single-crystal X-ray diffraction analysis of **4m** (see SI).[11] This reaction involved a rarely reported dyotropic-like rearrangement between the vicinal C-C bond and C=C bond, leading to unprecedented two ring expansions of 2-oxa allylic alcohols. Considering the fact that organoboronates are not only important building blocks,[12,13] but also striking molecular frames,[12] with biological activities,[14] as well as probes in chemical biology[15], this unprecedented reaction is worthy to further study. Herein, we wish to report this unexpected dyotropic rearrangement of C-C bond and C=C bond (a + b cleavages) in the tandem reaction of 2-oxa allylic alcohols with organoboronic acids

(Scheme 1C). Further control experiments indicated that gold(I) complex itself may not promote the reaction in the absence of either Selectfluor or DABCO (Table 1, entries 1-3 vs. 8). After many attempts, we are pleased to find that 91% isolated yield could be obtained, when the reaction was carried out in DCM with the use of 2.0 equivalents of $PhB(OH)_2$, in the presence of 5 mol% of Selectfluor and 5 mol% of DABCO·$6H_2O$ (Standard Conditions, Table 1, entry 15). The replacement of DABCO with other bases such as K_2CO_3, Et_3N and DBU also led to lower yields (Table 1, entries 9-11). Without Selectfluor and/or DABCO·$6H_2O$ would result in much lower yields (Table 1, entries 12-14). Gratifyingly, the loading of $PhB(OH)_2$ could be reduced to 1.2 equivalents under the standard conditions without loss the efficiency (Table 1, entry 16). The reaction could be faster and be complete in 3 days in DCM at reflux, but resulted in much lower yield (Table 1, entry 17).

Table 1. Screening reaction conditions.

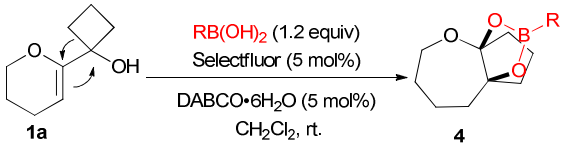


Entry	Change from 'Standard Conditions'	Yield(%)[a]
1[b]	PPh_3PAuCl, Selectfluor (2 eq.), no DABCO	77
2[b]	PPh_3PAuCl, no Selectfluor and DABCO	51
3[b]	PPh_3PAuCl, no Selectfluor	(70)
4	No Selectfluor and DABCO, $CHCl_3$	38
5	No Selectfluor and DABCO, 1, 2-DCE	35
6	No Selectfluor and DABCO, toluene	trace
7	No Selectfluor and DABCO, CH_3CN	trace
8	Selectfluor (2 eq.), no DABCO	66
9	K_2CO_3 instead of DABCO	40
10	Et_3N instead of DABCO	61
11	DBU instead of DABCO	74
12	No Selectfluor and DABCO, 9 days	52
13	No DABCO	61
14	No Selectfluor	16
15	None	93(91)
16	None, 1.2 eq. of $PhB(OH)_2$	93(91)
17	None, 1.2 eq. of $PhB(OH)_2$, reflux, 3 days	(75)

[a] NMR yield analysis using CH_2Br_2 as the internal reference, the number in parenthesis is the isolated yield. [b] 5 mol% of Ph_3PAuCl.

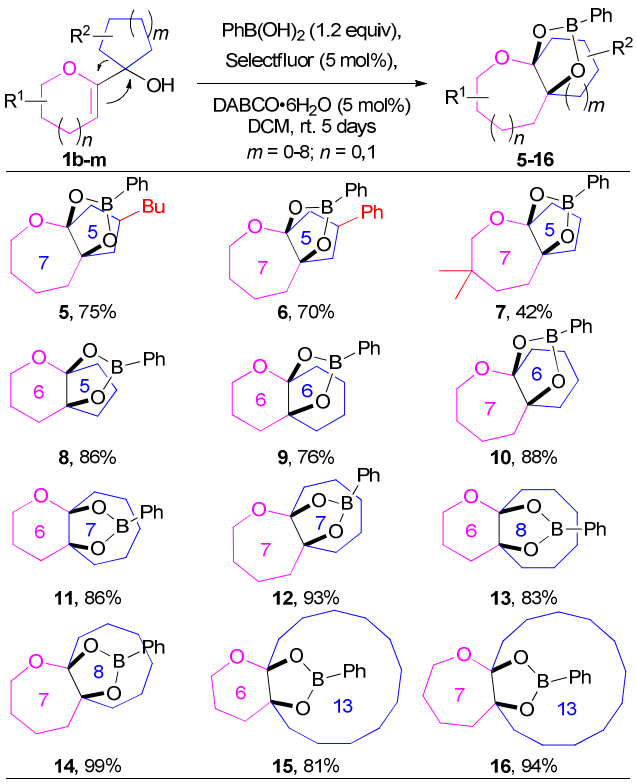
With the optimal conditions (Table 1, entry 16) in hand, we next turn to examine the scope of organoboronic acid (Table 2). Gratifyingly, the scope of organoboronic acid is very general, and the reactions of different arylboronic acids work well to afford the corresponding products in good yields. The reaction of *ortho*-methylphenylboronic acid with **1a** requires longer time and gives relatively lower yield (**4b**, 67%) than those *meta*- or *para*-substituted ones (**4c**, 85%, **4d**, 83%, and **4e**, 84%), indicating that the steric hindrance of the *ortho*-position may bring some negative effect. Both electron-donating group such as methyl and electron-withdrawing group such as ester could be well tolerated, leading to the desired products **4f** and **4k**, in 70% and 71% isolated yields, respectively. Notably, different halogen atoms such as fluoro-, chloro-, bromo-, and iodo- could be well compatible with the reaction conditions, furnishing the desired tricyclic boronates **4g-4j** in 78–88% yields (Table 2, entries 6-9). These halo-substituents could provide further opportunity for functional group transformation. Besides the substituted phenylboronic acids, other arylboronic acids such as 1-naphthylboronic acid (**4l**, Table 2, entry 11), 2-naphthylboronic acid (**4m**, Table 2, entry 12) as well as furan-2-ylboronic acid (**4n**, Table 2, entry 13), and alkylboronic acid such as *n*-butylboronic acid (**4o**, Table 2, entry 14) could be used to produce the corresponding tricyclic organoboronates in 53-84% yields, indicating that the scope of organoboronic acids is extremely general.

Table 2. Examination of the scope of organoboronic acids

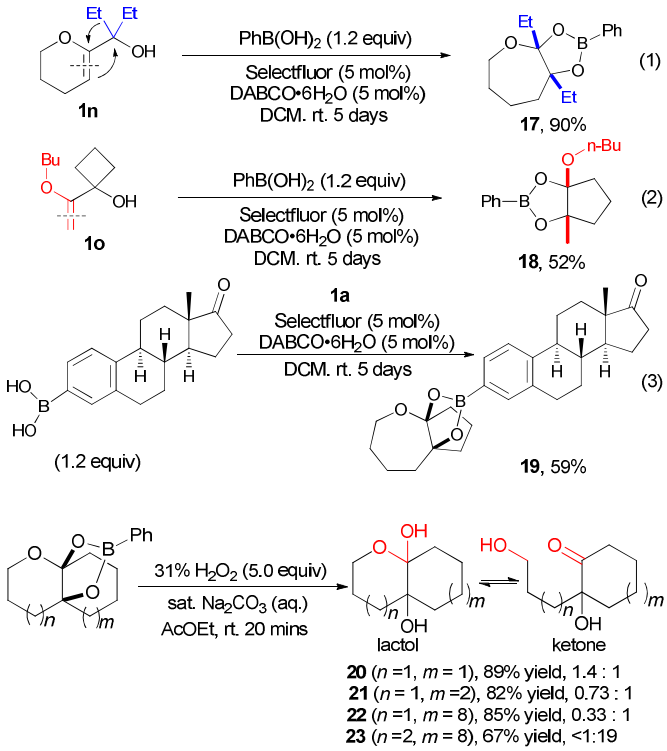


Entry	$RB(OH)_2$	Time (d)	**4**, Isolated Yield
1	2-$MeC_6H_4B(OH)_2$	6	**4b**, 67%
2	3-$MeC_6H_4B(OH)_2$	5	**4c**, 85%
3	4-$MeC_6H_4B(OH)_2$	5	**4d**, 83%
4	3,5-$Me_2C_6H_3B(OH)_2$	5	**4e**, 84%
5	4-$MeOC_6H_4B(OH)_2$	7	**4f**, 70%
6	4-$FC_6H_4B(OH)_2$	5	**4g**, 85%
7	4-$ClC_6H_4B(OH)_2$	5	**4h**, 87%
8	4-$BrC_6H_4B(OH)_2$	5	**4i**, 78%
9	4-$IC_6H_4B(OH)_2$	5	**4j**, 88%
10	4-$EtO_2CC_6H_4B(OH)_2$	5	**4k**, 71%
11	1-NaphthylB$(OH)_2$	5	**4l**, 78%
12	2-NaphthylB$(OH)_2$	5	**4m**, 84%
13	2-furyl boronic acid	5	**4n**, 53%
14	*n*BuB$(OH)_2$	5	**4o**, 71%

Next, the reaction scope of this reaction was examined by variation of the component of 2-oxa allylic alcohols **1** (Scheme 2). From the results shown in Scheme 2, several points are noteworthy: (1) substituents on both rings of 2-oxa allylic alcohols are compatible, leading to the corresponding products such as **5**, **6**, and **7** in acceptable yields; (2) a series of 6/5, 7/5, 6/6, 7/6, 6/7, 7/7 bicyclical hemiketal derived organoboronates **5-12** could be well constructed and produced (Scheme 2); (3) to our delight, synthetically challenging medium-sized ring such as 8-membered ring could be well constructed in high yields (**13**, 83% and **14**, 99% yield); (4) large-sized ring synthesis is a long-standing synthetic challenge, we are glad to find that 13-membered ring could be well constructed and the corresponding organoboronates **15** and **16** were obtained in high yields. All these findings support that the ring-strain is not necessary at all to achieve double ring-expansions of both two rings. With the knowledge that the ring strain is not necessary, we then paid our attention on the reactions of 2-oxa allylic alcohols **1n** and **1o** with a single cyclic ring, both two reactions proceeded smoothly under the standard conditions, leading to the desired products **17** and **18**, in 90% and 52% isolated yields, respectively [Eqs. (1-2)]. The relative lower yield of compound **18** is due to its acid-sensitivity and easy decomposition during the purification process by column chromatography. The present reaction could be used for late-stage modification of natural products, for example, the reaction of estronylboronic acid with **1a** could afford compound **19** in 59% yield [Eq. (3)].



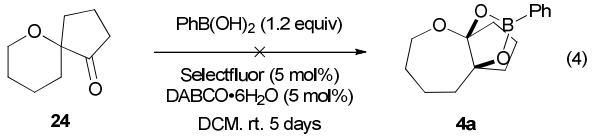
Scheme 2. Examination of the scope of 2-oxa allylic alcohols.



Scheme 3. Hydrolysis of the products.

Considering that bicyclic hemiketals (lactols) are frequently appeared skeletons in natural products,[16] we made efforts to hydrolysis of the products. When the organoboronates were subjected to the reaction mixture of aqueous 31% of H_2O_2 under basic conditions, lactols **20-23** with the corresponding hydroxyketone as an equilibrium mixture could be obtained in moderate to high yields (Scheme 3).[17] The equilibrium would favor the hydroxyketone as the predominant form with increasing either ring size of the two rings.

In order to gain insight of the mechanism, spirocyclic ketone **24** was prepared from **1a** according to the reported procedure.[6c] It was observed that no reaction occurred under standard conditions [Eq. (4)], indicating that the reaction might not proceed through the further transformation of spirocyclic ketone, the product from the semipinacol rearrangement of **1a**. A plausible mechanism that accounts for the formation of the dyotropic-like rearrangement product was proposed, which could be found in the supporting information.



In summary, we have demonstrated an unprecedented dyotropic-like rearrangement between two vicinal bonds (one C-C bond and one C=C bond) in the tandem reaction of 2-oxa allylic alcohols with organoboronic acids in the presence of catalytic amount of Selectfluor and DABCO under mild conditions, which provided a facile access to synthetic valuable bicyclic and tricyclic organoboronates. To the best of our knowledge, this reaction represents the first example of transformation of 2-oxa allylic alcohols consisting of two ring-expansions without requiring ring strain. The salient features of this transformation include simple and easy accessible substrates, metal-free, broad substrate scope, mild conditions, environmentally benign (only water as by-product) and easy further transformation to synthetic useful building blocks. Further studies including the mechanistic study and the synthetic applications are underway and will be reported in due course. We thank the 973 Programs (2011CB808600), National Natural Science Foundation of China (21372084), Changjiang Scholars and Innovative Research Team in University for financial support.

Notes and references

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Electronic Supplementary Information (ESI) available: experiment procedure, data and spectra of all new compounds, See DOI: 10.1039/c000000x/

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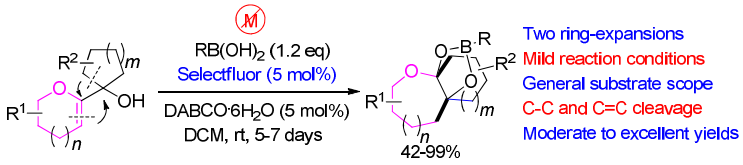

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