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Preference of 4-*exo* Ring Closure in Copper-Catalyzed Intramolecular Coupling of Vinyl Bromides with Alcohols

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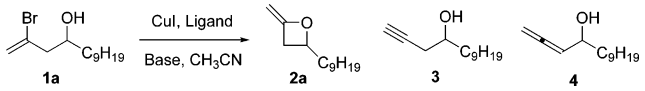
The copper-catalyzed formation of C−X (X = N, O, S, etc.) bonds has been successfully developed during the past few years.[1] With the intramolecular Ullmann coupling (IUC) as the strategy, the preparation of many medium- and even large-sized heterocycles can be achieved.[2] However, reports on the synthesis of strained heterocycles such as four-membered rings are rare with this IUC strategy.[3] In fact, this problem seems universal in transition-metal-catalyzed intramolecular coupling processes. We report here that the uncommon 4-*exo* ring closure in the copper-catalyzed intramolecular O-vinylation of γ-bromohomoallylic alcohols is not only an efficient process leading to the convenient synthesis of 2-methyleneoxetanes but also fundamentally preferred over other modes (5-*exo*, 6-*exo*, and 6-*endo*) of cyclization. Moreover, this unique selectivity is different from that of the corresponding palladium-catalyzed processes.

2-Methyleneoxetanes are biologically interesting and promising synthetic intermediates due to their unique combination of functionalities.[4] Unfortunately, there is a scarcity of methods for their preparation.[5] Owing to our interest in copper-catalyzed intramolecular vinylation,[3a,6] we envisioned that these compounds might be synthesized via Cu(I)-catalyzed O-vinylation of γ-bromohomoallylic alcohols. Thus, we explored this possibility with the use of **1a** as the model substrate, and the reactions were carried out in refluxing acetonitrile with the catalysis of CuI. The results are summarized in Table 1. Our initial screening on the ligands showed that 1,10-phenanthrolines (**E** and **F**) afforded the expected product **2a** in high yields, while other typical ligands (**A**−**D**) gave mainly alkyne **3** via direct elimination of HBr (entries 1−5, Table 1). 1,-10-Phenanthroline **F** was particularly effective, and the product **2a** was achieved in almost quantitative yield under mild conditions (entry 5, Table 1). We next examined the effect of base on the coupling reaction. Cs_2CO_3 turned out to be better than K_3PO_4 or K_2CO_3, while the organic base DABCO was ineffective (entries 5−8, Table 1). When NaO^{t}Bu was employed, **3** was obtained in almost quantitative yield within 10 min, which gradually isomerized to allene **4** (entry 9, Table 1). This observation also supported the oxidative addition mechanism of O-vinylation by excluding the elimination−addition mechanism (via the intermediacy of **3** or **4**).

With the optimized conditions in hand (10 mol % of CuI, 20 mol % of **E**, 200 mol % of Cs_2CO_3 in refluxing CH_3CN), we then examined the generality of this methodology. The results are listed in Table 2. The primary, secondary, and even tertiary alcohols all served as good substrates for the 4-*exo* ring closure (**2b**−**e**). Substrates with various substitutions afforded the expected products in good to excellent yields. A number of functional groups, such as −OH and −OBz, were well-tolerated (**2h**−**n**). Moreover, the configuration of the C=C double bond was nicely retained as evidenced by the reactions of **1f** and **1g**. As a comparison, the chloro analogue of **1a** remained inert under the optimized conditions. The results also indicated that the reactivity of alcohols decreases in the order of aliphatic > allylic > benzylic (**2h**−**j**), in accordance with the literature observations,[8a] while 1, 2, and 3° alcohols are of similar rates.[8b] The substitution on the C=C bond (**1f** and **1g**) discourages the cyclization, and the reactions had to be conducted at higher temperatures (dioxane, reflux).

Table 1. Optimization of Reaction Conditions in the Synthesis of **2a**



1a **2a** **3** **4**

entry[a]	ligand[b]	base	yield of **2a** (%)[c]	yield of **3** (%)[c]
1		Cs_2CO_3	0	85
2	**A**−**C**	Cs_2CO_3	0	∼60
3	**D**	Cs_2CO_3	14	32
4	**E**	Cs_2CO_3	71	0
5	**F**	Cs_2CO_3	98	0
6	**F**	K_2CO_3	54	0
7	**F**	K_3PO_4	58	0
8	**F**	DABCO	0	0
9	**F**	NaO^{t}Bu	0	98[d]
10	**F**		0	0

[a] Reaction conditions: **1a** (0.3 mmol), CuI (0.03 mmol), ligand (0.06 mmol), base (0.6 mmol), CH_3CN (3 mL), reflux, 8 h. [b] **A**: *N*,*N*′-Dimethylethylenediamine; **B**: 2-aminopyridine; **C**: L-proline; **D**: 1,2-*trans*-bis(pyridin-2-ylmethylene)cyclohexane-1,2-diamine; **E**: 3,4,7,8-tetramethyl-1,10-phenanthroline; **F**: 1,10-phenanthroline. [c] Isolated yield based on **1a**. [d] The reaction time was 10 min.

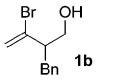
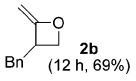
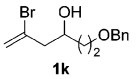
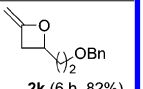
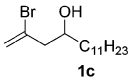
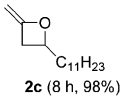
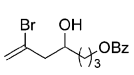
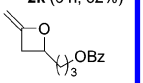
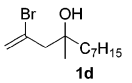
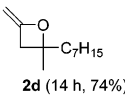
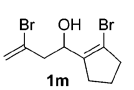
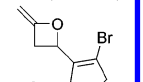
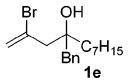
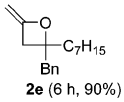
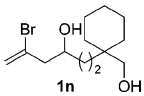
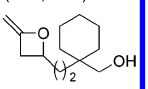
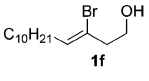
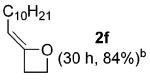
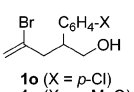
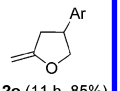
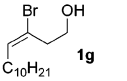
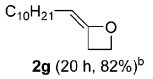
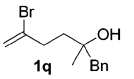
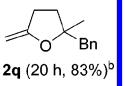
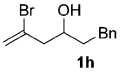
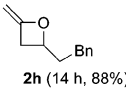
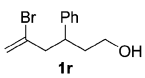
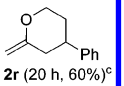
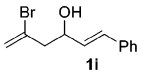
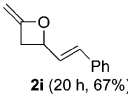
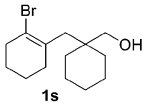
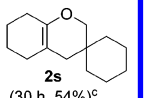
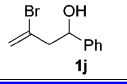
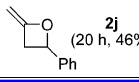
The above methodology was then successfully extended to other modes of cyclization. The IUC in 5-*exo* (**2o**−**q**), 6-*exo* (**2r**), and even 6-*endo* (**2s**) modes proceeded smoothly under the optimized conditions (Table 2).

The ease of the 4-*exo* ring closure shown in Tables 1 and 2 prompted us to explore the competition among different modes of cyclization. Thus, the reactions of substrates **5a**−**g**, each having two possible IUC pathways, were performed (Table 3). We were surprised to find that, in all of the cases, oxetanes **6a**−**g** via 4-*exo* cyclization were the only detectable products whose structure was unambiguously established by 2D NMR experiments. These results clearly revealed that the 4-*exo* ring closure is fundamentally preferred over the 5-*exo* (entries 1−5, Table 3), 6-*exo* (entry 6, Table 3), and 6-*endo* (entry 7, Table 3) modes. To the best of our knowledge, these are the first examples in transition-metal-catalyzed chemistry describing the predominance of 4-*exo* cyclization.

To further understand the unique selectivity in the above copper-catalyzed processes, we tried the possible Pd(0) catalysis in O-vinylation (Scheme 1, see also Supporting Information for details). Our efforts showed that, with $Pd(OAc)_2$ (5 mol %)/BINAP (7.5 mol %) as the catalyst and Cs_2CO_3 (2 equiv) as the base, compound **1q** underwent highly efficient cross-coupling (5-*exo*) in refluxing THF to give the product **2q** in 94% yield. However, under the same conditions, the primary alcohol **1o** gave only the β-hydride

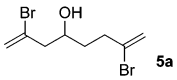
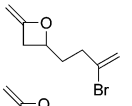
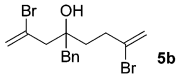
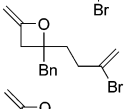
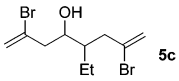
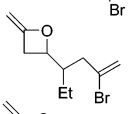
10.1021/ja072793w CCC: $37.00

Table 2. Intramolecular Coupling of Vinyl Bromides with Alcohols

substrate	product (time, yield[a])	substrate	product (time, yield[a])
 **1b**	 **2b** (12 h, 69%)	 **1k**	 **2k** (6 h, 82%)
 **1c**	 **2c** (8 h, 98%)	 **1l**	 **2l** (3 h, 86%)
 **1d**	 **2d** (14 h, 74%)	 **1m**	 **2m** (24 h, 60%)
 **1e**	 **2e** (6 h, 90%)	 **1n**	 **2n** (9 h, 85%)
 **1f**	 **2f** (30 h, 84%)[b]	 **1o** (X = *p*-Cl) **1p** (X = *p*-MeO)	 **2o** (11 h, 85%) **2p** (11 h, 86%)
 **1g**	 **2g** (20 h, 82%)[b]	 **1q**	 **2q** (20 h, 83%)[b]
 **1h**	 **2h** (14 h, 88%)	 **1r**	 **2r** (20 h, 60%)[c]
 **1i**	 **2i** (20 h, 67%)	 **1s**	 **2s** (30 h, 54%)[c]
 **1j**	 **2j** (20 h, 46%)		

[a] Isolated yield based on **1**. [b] The reaction was conducted in refluxing dioxane. [c] The reaction was conducted in refluxing toluene.

Table 3. Competition Experiments in the O-Vinylation of Alcohols

entry	substrate	time (h)	product	yield (%)[a]
1	 **5a**	5	 **6a**	60
2	 **5b**	4	 **6b**	82
3	 **5c**	10	 **6c**	80
4	**5d**	9	**6d**	82
5	**5e**	8	**6e**	83
6	**5f**	9	**6f**	76
7	**5g**	7	**6g**	79

[a] Isolated yield based on **5**.

elimination product **7** and no reaction occurred for **1a**. Moreover, the $Pd(OAc)_2$/BINAP-catalyzed reaction of **5b** in refluxing 1,2-dimethoxyethane gave the 5-*exo* cyclization product **8** rather than

Scheme 1. $Pd(OAc)_2$/BINAP-Catalyzed Intramolecular Coupling

[a, b] See text.

the 4-*exo* cyclization product **6b**, along with the formation of diene **9** via intramolecular Heck reaction.[9]

The above difference between Pd(0) and Cu(I) in O-vinylation is truly remarkable. While the Pd-catalyzed method is sensitive to substrate structures and suffers from the competing β-hydride elimination,[10] the Cu-catalyzed processes enjoy their generality to include a wide range of substrates. More importantly, the selectivity between 4-*exo* and 5-*exo* cyclization is completely reversed by switching the catalyst from Cu to Pd.

Although the reason for the preference of 4-*exo* cyclization in Cu(I)-catalyzed O-vinylation remains unclear, it might be possible that the Cu(I) coordinates to the alkoxide prior to its oxidative insertion into the C−Br bond. Furthermore, the transition state for 4-*exo* cyclization as a Cu-containing five-membered ring structure could be sterically more easily accessible and thermodynamically more stable than that of the corresponding 5-*exo*, 6-*exo*, or 6-*endo* cyclization. Presumably, the analogous Pd-containing five-membered ring might not be sterically favorable as Pd(0) is much larger in size than Cu(I). Further studies to elucidate the mechanism of this unusual preference and to understand the difference between Cu(I) and Pd(0) catalysis in O-vinylation are currently underway in our laboratory.

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Supporting Information Available: Typical procedures for the IUC of γ-bromohomoallylic alcohols and for the Pd(0)-catalyzed reactions, the characterizations of **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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