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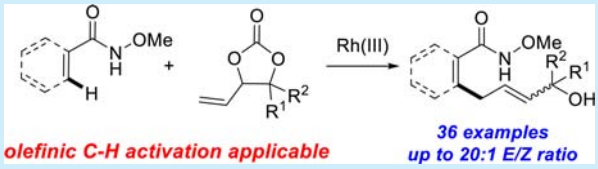
Mild Rhodium(III)-Catalyzed C−H Allylation with 4-Vinyl-1,3-dioxolan-2-ones: Direct and Stereoselective Synthesis of (*E*)-Allylic Alcohols

Shang-Shi Zhang, Jia-Qiang Wu, Ye-Xing Lao, Xu-Ge Liu, Yao Liu, Wen-Xin Lv, Dong-Hang Tan, Yao-Fu Zeng, and Honggen Wang*

School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

Supporting Information

ABSTRACT: A rhodium(III)-catalyzed C−H direct allylation reaction with 4-vinyl-1,3-dioxolan-2-ones has been developed. The reaction provides a facile and stereoselective access to substituted-(*E*)-allylic alcohols under mild and redox-neutral reaction conditions. Olefinic C−H activation is applicable, giving multi-functionalized skipped dienes in good yields. Minimal double-bond migration was observed.



Allylic alcohols are undoubtedly among the most synthetically useful building blocks in organic synthesis.[1] Therefore, the incorporation of an allylic alcohol functional group into a molecule is of great value. In addition, allyl arenes and skipped dienes are pervasive structural elements in biologically active compounds, as displayed by natural product lobatamide A,[2] antifilarial agent corallopyronin A,[3] the bacterial RNA-polymerase inhibitor ripostatin A,[4] and the well-known omega-3-acid ethyl ester (Figure 1). Reported methods for accessing allyl

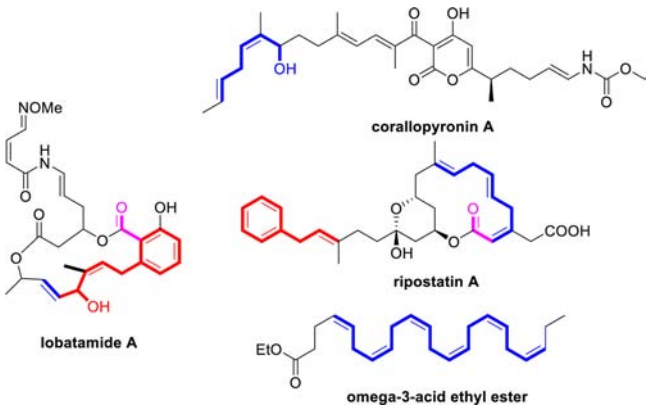
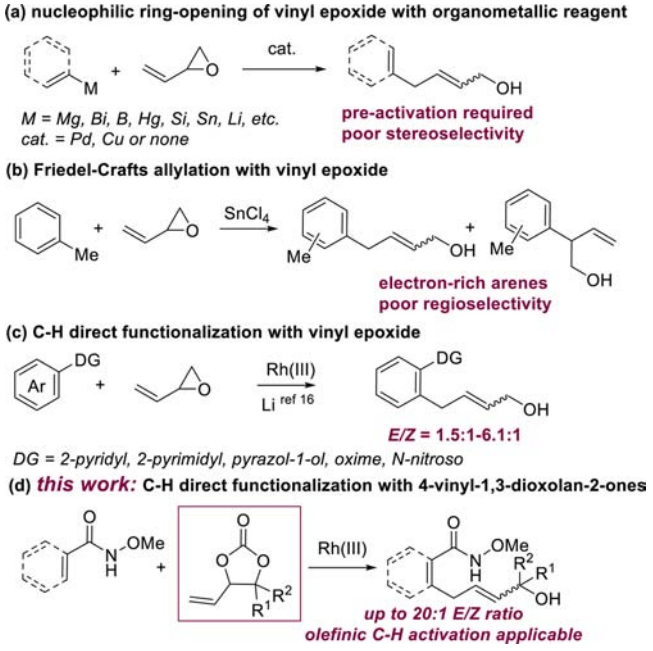


Figure 1. Allyl arenes (in red) and skipped dienes (in blue) in biologically active compounds.

arenes or skipped dienes bearing a hydroxyl group at the allylic position generally necessitate the use of preactivated starting materials. For instance, the nucleophilic ring-opening of vinyl epoxide with a variety of organometallic reagents has been well established (Scheme 1a).[5] Nevertheless, the instability and/or toxicity of the corresponding organometallic reagents, associated with the usually observed poor stereoselectivities in the formation of mixtures of *E*/*Z* isomers, might hamper their

Scheme 1. Different Strategies toward Allyl Arenes or Skipped Dienes Bearing an Allylic Hydroxyl Group



synthetic applications. A Friedel−Crafts-type allylation with vinyl epoxide was also documented (Scheme 1b).[6] However, this reaction is only applicable to electron-rich arenes. Besides, low regioselectivity and overreaction are unaddressed issues.

In recent years, transition-metal-catalyzed C−H activation reaction has provided an attractive and straightforward method for the construction of C−C and C−heteroatom bonds.[7] Thus,

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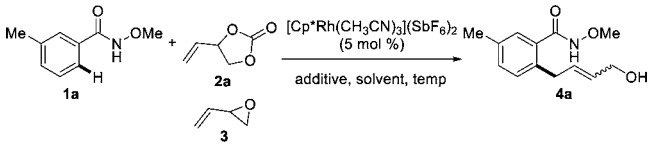
the direct C−H allylation has been achieved under the catalysis of various metals such as Rh(III),[8,9] Ir(I),[10] Ni,[11] Ru,[12] Re,[13] Pd,[14] and Cu.[15] Very recently, the group of Li reported an elegant Rh(III)-catalyzed C−C coupling of arenes with vinyl epoxide for the synthesis of allylic alcohols under the assistance of 2-pyridyl, 2-pyrimidyl, pyrazol-1-ol, oxime, and *N*-nitroso directing groups (Scheme 1c).[16] Unfortunately, in their reactions, low stereoselectivities (up to 6.1:1) were observed. In addition, no examples on the allylation of benzoic acid derivatives were reported. Given the widespread occurrence of carboxyl groups in functional molecules, for instance, in lobatamides A and ripostatin A (Figure 1, in pink), and their easily transformable ability to other functional groups, it would be highly interesting to develop a method for the elaboration of benzoic acid derivatives. Herein, we disclose our realization of a highly chemo- and stereoselective Rh(III)-catalyzed C−H allylation of benzamides with 4-vinyl-1,3-dioxolan-2-ones. The utilization of 4-vinyl-1,3-dioxolan-2-ones as coupling partners is key to success (vide infra).[17] Various substituted vinyl-1,3-dioxolan-2-ones were successfully applied. Importantly, this method is applicable to olefinic C−H activation reaction, generating skipped dienes functionalized with an allylic hydroxyl group.

We initiated our investigation by using *N*-methoxy-3-methylbenzamide **1a** as a substrate. We first tested the feasibility of the desired reaction under Li's conditions (3 mol % of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$, 1.2 equiv of **3**, 1.0 equiv of PivOH in $ClCH_2CH_2Cl$, rt).[16] However, no desired product was obtained (Table 1, entry 1). After extensive studies, we were able to determine that the commercially available 4-vinyl-1,3-dioxolan-2-one **2a** is a highly reactive coupling partner, providing

Table 1. Reaction Optimization[a]



entry	solvent	2a/3	additive (1 equiv)	yield (%)
1	$ClCH_2CH_2Cl$	**3**	PivOH	0[b]
2	MeOH	**2a**	CsOAc	45[c,d]
3	EtOH	**2a**	CsOAc	50[c,d]
4	CH_3CN	**2a**	CsOAc	59[c,d]
5	$ClCH_2CH_2Cl$	**2a**	CsOAc	45[c,d]
6	toluene	**2a**	CsOAc	55[c,d]
7	**CF_3CH_2OH**	**2a**	**CsOAc**	**81**[d]
8	CF_3CH_2OH	**2a**	K_2CO_3	57[d]
9	CF_3CH_2OH	**2a**	PivOH	0
10	CF_3CH_2OH	**2a**	K_2CO_3/PivOH	74[c,d,e]
11	CF_3CH_2OH	**2a**	Cs_2CO_3/PivOH	65[c,d,e]
12	CF_3CH_2OH	**2a**	CsOAc	76[c,d,f]
13	CF_3CH_2OH	**2a**	CsOAc	79[c,d,g]
14	CF_3CH_2OH	**2a**	CsOAc	0[h]
15	CF_3CH_2OH	**3**	CsOAc	18[c]
16	CF_3CH_2OH	**2a**	CsOAc	75[d,i]

[a] **1a** (0.2 mmol), **2a**, or **3** (0.24 mmol), additive (1.0 equiv), [Rh^{III}] (5 mol %), solvent (1.0 mL), 0 °C, 12 h, isolated yields. [b] [Rh^{III}] (3 mol %), rt. [c] ^1H NMR yield. [d] E/Z > 20:1 was observed, determined by ^1H NMR. [e] Carbonate (1.1 equiv) and PivOH (30 mol %). [f] [Rh^{III}] (2 mol %) was used. [g] $[Cp^*RhCl_2]_2$ (2.5 mmol %) was used. [h] No rhodium was used. [i] Gram-scale reaction: **1a** (7.0 mmol), **2a** (8.4 mmol), CsOAc (7.0 mmol), [Rh^{III}] (2 mol %), CF_3CH_2OH (35.0 mL), 12 h, 1.23 g of **4a** was isolated.

allylic alcohol **4a** in 45% yield in the presence of CsOAc as additive in MeOH at 0 °C (entry 2). Screening of different solvents revealed CF_3CH_2OH to be the best (entries 2−7), giving **4a** in 81% isolated yield with excellent stereoselectivity (E/Z > 20:1). It should be noted that no double-bond migration isomers of **4a** were detected probably due to the rather mild reaction conditions. Substitution of CsOAc with K_2CO_3 gave a diminished yield (entry 8). The use of PivOH as additive shut down the reactivity completely (entry 9). It has been shown that the combined use of an insoluble carbonate base and a catalytic amount of soluble base is beneficial for C−H activations.[18] Indeed, in our cases, the use of K_2CO_3/PivOH or Cs_2CO_3/PivOH as additive provided better yields (entries 10 and 11 vs entry 8), but not better than CsOAc (entry 7). The lowering of catalyst loading from 5 to 2 mol % resulted in a slightly lower yield of 76% (entry 12). $[Cp^*RhCl_2]_2$ (2.5 mmol %) also showed good reactivity (79%, entry 13). A control experiment showed that rhodium is essential for the reactivity as its absence resulted in no reaction (entry 14). The efficacy of 2-vinyloxirane **3** as coupling partner was reexamined under the optimized conditions (entry 15). The reaction led to complex reaction products with the isolation of **4a** in only 18% yield. Notably, the reaction is easy to handle as no special exclusion of air and moisture is needed. A 7 mmol scale reaction was conducted with 2 mol % rhodium catalyst to give 1.23 g of **4a** in 75% yield, demonstrating the reaction is practical (entry 16).

With the optimized reaction condition established (Table 1, entry 7), we next explored the scope of this method. Gratifyingly, the reaction was compatible with a variety of commonly encountered functional groups such as fluoro (**4n**), chloro (**4b** and **4l**), bromo (**4c** and **4t**), iodo (**4d**), methoxyl (**4i** and **4s**), trifluoromethyl (**4g**), nitro (**4k** and **4o**), ester (**4e** and **4u**), amino (**4f**), and cyano (**4r**), giving the corresponding products in generally good-to-excellent yields (Scheme 2). With *meta*-substituted substrates, reactions at the less hindered position were exclusively observed (**4a−k**). Importantly, *ortho*-substituents did not hamper the reactivities (**4l−o**) with one exception compound **4p**. We suspected the oxygen atom of the methoxyl group together with the carbonyl group might act as a bidentate ligand, thereby directing the rhodium catalyst far away from the desired C−H bond. Not surprisingly, the reaction of *para*-substituted benzamide derivatives also gave significant amounts of diallylation products due to the remarkably high reactivities of the monoallylation products (**4q−u**). Fortunately, the separation of the mono- and diallylation products could be easily realized by using flash column chromatography. The reaction was also applicable to electron-rich heterocycles such as thiophene (**4w**), furan (**4x**), and indole (**4y**). The reaction of furan occurred exclusively at the α position. We also explored the feasibility of an olefinic C−H activation for the synthesis of skipped dienes. To our delight, the reaction of acrylic acid derivatives bearing a methyl or phenyl substituent at the α position both delivered the desired products in good yields with excellent stereoselectivities (**5a** and **5b**). Furthermore, the cyclic olefinic substrates also underwent reaction smoothly (**5c** and **5d**). Other benzamide derivatives such as *N*-propylbenzamide **6**, *N*,*N*-diisopropylbenzamide **7**, and Weinreb amide *N*-methoxy-*N*-methylbenzamide **8** showed no reactivities under the standard reaction conditions.

To extend the scope of this transformation further, substituted vinyl-1,3-dioxolan-2-one **2** were synthesized and subjected to the reaction. We were pleased to find that the reaction occurred without difficulty regardless of an aromatic or aliphatic substituent at the fourth position (Scheme 3). However, the

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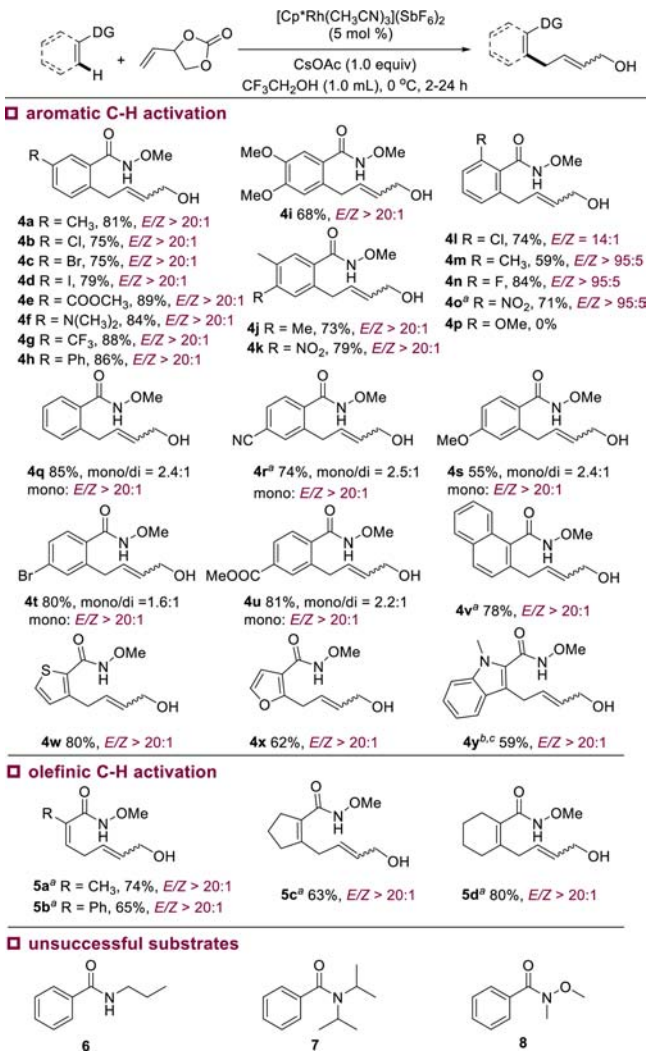
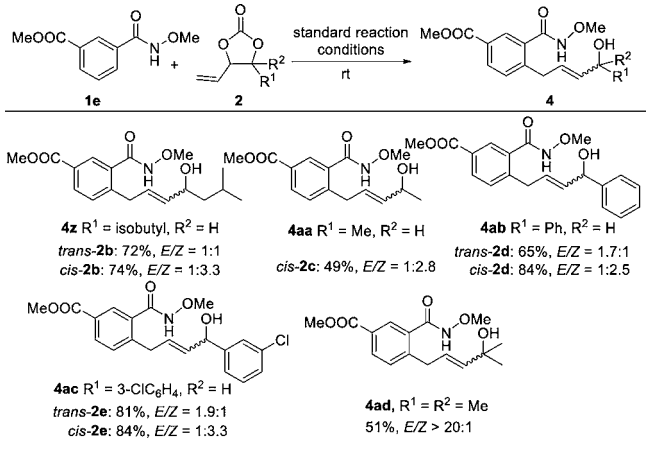
Scheme 2. Rhodium(III)-Catalyzed C−H Allylation Reactions with 4-Vinyl-1,3-dioxolan-2-one 2a



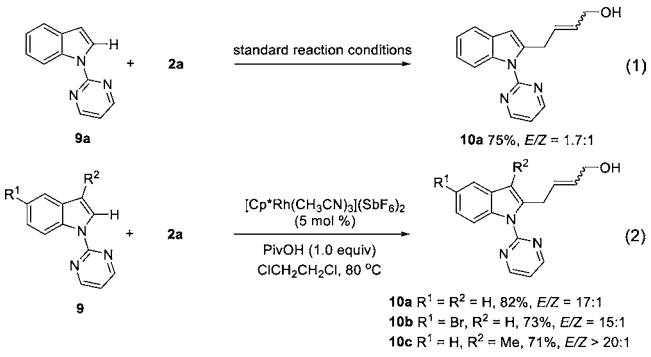
[a]At 30 °C. [b]At 80 °C. [c]DCE was used as solvent.

Scheme 3. Substrate Scope on the Use of Substituted Vinyl-1,3-dioxolan-2-one 2



E/*Z* ratio varies depending on the stereochemistry of the coupling partner. Thus, with *trans*-substituted vinyl-1,3-dioxolan-2-one **2**, the reactions slightly favored the formation of the *E* isomer. On the other hand, the *cis*-substituted **2** gave the *Z* isomer preferentially, probably because of the steric issues leading to selective facial coordination of the alkene to the metal in the reaction mechanism (vide infra). 4,4-Dimethyl-substituted **2** delivered the corresponding product in moderate yield, but with excellent stereoselectivity (**4ad**).

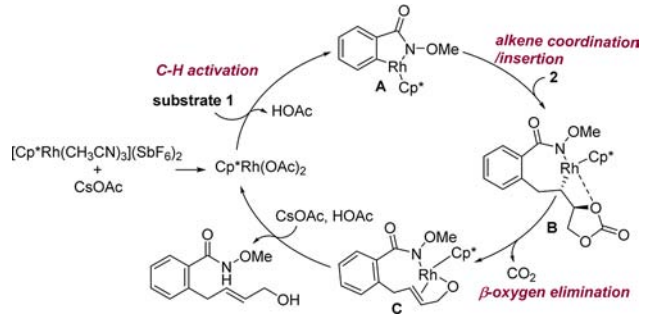
The allylation of indoles bearing a pyrimidine directing group were extensively explored in Li's work.[16] Disappointingly, when **9a** was reacted with **2a** under our standard reaction conditions, a low *E*/*Z* ratio of 1.7:1 was also observed (eq 1). Interestingly,



however, by using a modified conditions of Li's,[16] the stereoselectivities were improved significantly to 15−20:1 (vs 1.8−4.2:1 in Li's work) (eq 2). A 3-methyl group was well tolerated (**10c**).

On the basis of literature precedent,[8a−f] a tentative mechanism was proposed for this transformation (Scheme 4). The active

Scheme 4. Mechanistic Rationale



catalyst $Cp^*Rh(OAc)_2$ is generated by a ligand exchange from $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ with CsOAc. C−H activation takes place under the assistance of the directing group to give a rhodacycle **A**. The coordination of the alkene **2** to the metal is followed by a migratory insertion to generate intermediate **B**. The π-facial-selectivity of this step, which might be greatly influenced by the substituent of **2**, determines the *E*/*Z* ratio of the final product. Subsequently, a β-oxygen elimination occurs to form the new double bond bearing an allylic hydroxyl group while releasing one molecule of CO_2. The resulting allylic alcohol **4** is then released with the concurrent regeneration of the rhodium catalyst.

In summary, by using vinyl-1,3-dioxolan-2-one **2** as a novel coupling partner, we have developed a rhodium(III)-catalyzed C−H allylation reaction for the synthesis of functionalized allylic alcohols. The reaction is applicable to both aromatic and olefinic substrates, giving allylarenes and skipped dienes, respectively, in good to excellent yields. While unsubstituted vinyl-1,3-dioxolan-2-one was used, excellent *E*/*Z* ratios were observed. The reaction

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proceeded under rather mild reaction conditions and is very easy to handle. Broad substrate scope and good functional group tolerance were found. A gram-scale reaction was performed to showcase the practicability of this transformation. Given the great importance of allylic alcohols in bioactive compounds and synthetically valuable building blocks, we anticipate this method will find applications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wanghg3@mail.sysu.edu.cn.

Notes

The authors declare no competing financial interest.

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