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Cycloisomerization between Aryl Enol Ether and Silylalkynes under Ruthenium Hydride Catalysis: Synthesis of 2,3-Disubstituted Benzofurans

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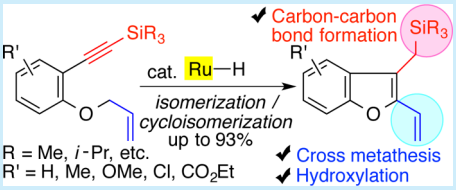
Supporting Information

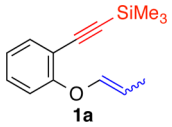
ABSTRACT: Metal-catalyzed cycloisomerization reactions of 1,*n*-enynes have become conceptually and chemically attractive processes in the search for atom economy, which is a key subject of current research. However, metal-catalyzed cycloisomerization between aryl enol ether and silylalkynes has not been developed. The ruthenium hydride complex catalyzed cycloisomerization between aryl enol ether and silylalkynes is reported to give benzofurans having useful functional groups, vinyl and trimethylsilylmethyl, on the 2- and 3-positions, respectively.



Transition-metal-catalyzed cycloisomerization[1] is an atom-economical method for the construction of complex carbocyclic and heterocyclic frameworks,[2] as, in cycloisomerizations, all atoms contained in the starting material are retained in the final product. Hence, cycloisomerizations have received much attention as perfect atom-efficient chemical transformations.

Enol ethers have been widely used in not only polymer synthesis but also organic synthesis owing to their electron-rich double bonds.[3] Although reactions[4] of silyl enol ethers and alkyl enol ethers have been greatly reported, reactions of aryl enol ethers, a type of enol ether, have been limited to arylation with Grignard reagents,[5] radical or nitrative cyclizations,[6] and alkylation via C−H bond activation.[7] Recently, several groups reported transition-metal-catalyzed reactions of aryl enol ethers to give oxygen-containing heterocycles. The Tanaka group reported a rhodium-catalyzed enantioselective Alder−ene reaction of 2-ethynylphenyl vinyl ether to give dihydrobenzofuran.[8] Moreover, the Liu group reported gold-catalyzed cyclization of 2-ethynylphenyl vinyl ether with external nucleophiles to give benzo[*b*]oxepine.[9] The Lin group reported ruthenium-catalyzed[10] cyclization of 2-ethynylphenyl vinyl ether to give benzoxepine.[11] In addition, the Li group reported copper-catalyzed [2 + 2 + 1] annulation of 2-ethynylphenyl vinyl ether with *α*-carbonyl alkyl bromides through C−Br/C−H functionalization to give tricyclic heterocycles.[12] The Fürstner group reported a bond-making/bond-breaking cascade cycloisomerization/cross-coupling reaction of 2-ethynylphenyl vinyl ether with Grignard reagents.[13] All of these reactions are organometallic-catalyzed reactions between aryl enol ethers and alkynes, which has a proton or carbon. Here, we report an unprecedented ruthenium hydride catalyzed cycloisomerization of aryl enol ether and silylalkynes to yield 2,3-disubstituted benzofurans having useful functional groups, vinyl and trimethylsilylmethyl, on the 2- and 3-positions, respectively. Benzofuran is present in numerous bioactive natural products as well as pharmaceuticals and polymers.[14] This method is suitable to synthesize a key intermediate for abexinostat, a broad-spectrum hydroxamic acid-based inhibitor of histone deacetylase (HDAC) with potential antineoplastic activity.

We envisioned that an unprecedented cycloisomerization of aryl enol ether and silylalkynes would be suitable methodology to give substituted benzofurans. We prepared 2-(trimethylsilyl)-ethynylphenyl vinyl ethers (**1a**) (Figure 1) and attempted a variety of reaction conditions using conventional catalysts.[8−13] However, we could obtain only a trace amount of the expected benzofuran at most. We then treated **1a** with not only commercially available ruthenium hydrides, such as RuHCl(CO) $(PPh_3)_3$ and $RuH_2(CO)$ $(PPh_3)_3$, but also ruthenium hydride **A**[15] with a nitrogen-containing heterocyclic carbene (NHC) ligand under various conditions (Figure 2 and Scheme 1). When **1a** was treated with 5 mol % of RuHCl(CO) $(PPh_3)_3$ or $RuH_2(CO)$ $(PPh_3)_3$ in refluxing *p*-xylene, the expected benzofuran **2a** was obtained in low yields. The same reaction, using a ruthenium hydride species **A** generated from the Grubbs catalyst second generation **II** (Scheme 1), yielded the corresponding 3-[(trimethylsilyl)methyl]-2-vinylbenzofuran **2a** in 84% yield (Scheme 2). Compound **2a** could be a useful synthon because it has a good functional group for further chemical transformations on both the 2- and 3-positions of benzofuran. Before examining these chemical transformations,



1a

Figure 1. 2-(Trimethylsilyl)ethynylphenyl vinyl ethers **1a**.

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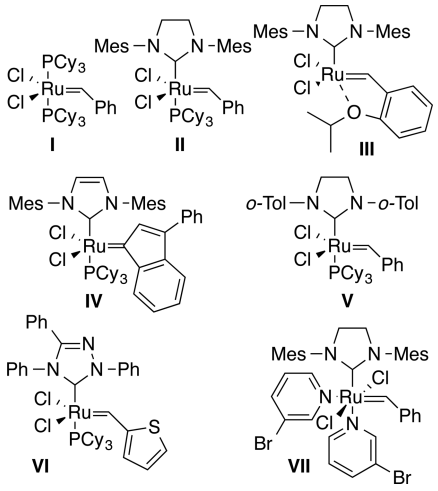
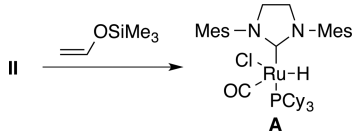
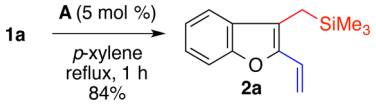


Figure 2. Ruthenium carbene catalysts **I**–**VII**.

Scheme 1. Ruthenium Hydride A with the NHC Ligand



Scheme 2. Cycloisomerization of 2-Ethynylphenyl Vinyl Ether 1a to give 2a

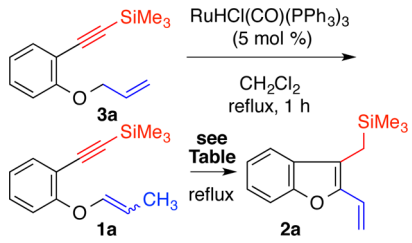


we decided to optimize reaction conditions for this cycloisomerization as a one-pot reaction from the precursor **3a** to **2a** through **1a**.

A solution of **3a** and RuHCl(CO) $(PPh_3)_3$ (5 mol %) in dichloromethane was refluxed for 1 h, and **3a** was converted to **1a**, quantitatively. Without purification, cycloisomerization of the obtained **1a** was examined using several catalysts and solvents (Table 1). As previously mentioned, when crude **1a** was treated with a commercially available ruthenium hydride,[16] **2a** was obtained in 38%, 15%, or 32% yields (two steps), respectively (Table 1, entries 1–3). In contrast, the same reaction, using a ruthenium hydride species **A** generated from the Grubbs catalyst second generation **II** (Scheme 2), yielded the corresponding 3-[(trimethylsilyl)methyl]-2-vinylbenzofuran **2a** in 84% yield (two steps) (Table 1, entry 4).[17] These results suggest that the NHC ligand on the ruthenium hydride species is important for this cycloisomerization to proceed. We determined that higher temperature, i.e., *p*-xylene refluxing temperature, was necessary for this cycloisomerization (Table 1, entries 5 and 6). Next, we examined several ruthenium carbene catalysts **III**–**VII** (Figure 2) and found that **II** and **III** are suitable precatalysts for this cycloisomerization (Table 1, entries 7–11). Control experiments using conventional catalysts for 1,6-enyne cycloisomerization failed to yield **2a** (Table 1, entries 12–15).

Based on these results, we next examined the effect of alkyne substituents (Table 2). Trialkylsilyl, $Si(i\text{-}Pr)_3$, $SiMe_2Bn$, and $SiMe_2Ph$, derivatives **3b**–**d** gave the corresponding cyclized products in 93%, 78%, and 76% yields, respectively; the yield difference is most likely the result of steric effects. Derivatives

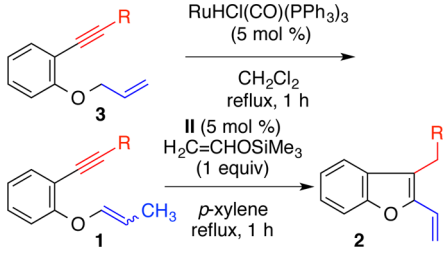
Table 1. Optimization of One-Pot Olefin Isomerization/Cycloisomerization



entry	cat. (5 mol %)	solvent	time(h)	**2a**, yield (%) (from **3a**)
1	$RuHCl(CO)(PPh_3)_3$	*p*-xylene	24	38
2	$RuH_2(CO)(PPh_3)_3$	*p*-xylene	48	15
3[a]	**I**	*p*-xylene	8	32
4[a]	**II**	*p*-xylene	1	84
5[a]	**II**	PhMe	4	55
6[a]	**II**	THF	4	0
7[a]	**III**	*p*-xylene	1	83
8[a]	**IV**	*p*-xylene	1	62
9[a]	**V**	*p*-xylene	1	trace
10[a]	**VI**	*p*-xylene	1	0
11[a]	**VII**	*p*-xylene	1	69
12	$RuClCp(PPh_3)_2$	*p*-xylene	1	0
13[b]	$[IrCl(cod)_2]_2$	*p*-xylene	1	0
14	$Pd(OAc)_2(PPh_3)_2$	*p*-xylene	1	0
15[c]	$[Rh(cod)_2BF_4]$	*p*-xylene	1	trace

[a]1 equiv of CH_2=CHOSiMe$_3$ was added. [b]25 mol % of AcOH was added. [c]5 mol % of (*rac*)-binap was added.

Table 2. Effect of Alkyne Substituent on Reaction Yield



entry	**3**	R	**2**, yield (%) (from **3**)
1	**3a**	$SiMe_3$	**2a**, 84
2	**3b**	$Si(i\text{-}Pr)_3$	**2b**, 93
3	**3c**	$SiMe_2Bn$	**2c**, 78
4	**3d**	$SiMe_2Ph$	**2d**, 76
5	**3e**	CH_3	**2e**, 39
6	**3f**	*t*-Bu	**2f**, 36
7	**3g**	CH_2OSiMe_2-*t*-Bu	**2g**, 28
8	**3h**	$CH(OEt)_2$	**2h**, 0
9	**3i**	Ph	**2i**, 0

with weaker electron-withdrawing groups on the alkyne, i.e., *tert*-butyl derivative **1f**, silyloxymethyl derivative **1g**, diethoxymethyl derivative **1h**, and phenyl derivative **1i**, did not take part in this reaction very well; **1h** and **1i** were unchanged, and **1e**, **1f**, and **1g** were converted to **2e**, **2f**, and **2g** in 39%, 36%, and 28% yields, respectively.

The effects of substituents on the benzene ring are summarized in Table 3; the data show the scope and limitation of this cycloisomerization. All of the substrates **3j**–**v** were subjected to the reaction conditions used in Table 1, entry 4 (Table 3). Compounds **1k**–**m**,**o**–**q**,**s**–**v**, which have a

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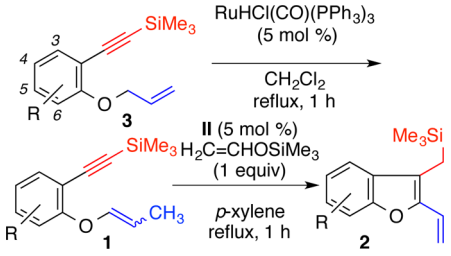
Table 3. Effect of Benzene Substituent on Reaction Yield



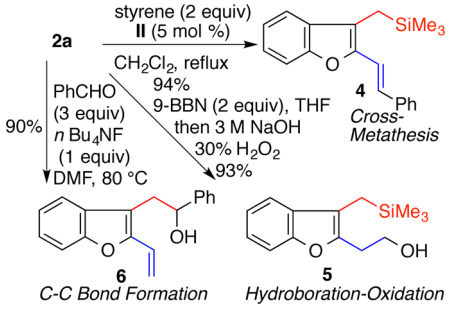
entry	3	R	2, yield (%) (from 3)
1	**3a**	H	**2a**, 84
2[a]	**3j**	3-Cl	**2j**, 45
3	**3k**	4-Cl	**2k**, 80
4[b]	**3l**	5-Cl	**2l**, 71
5[a]	**3m**	6-Cl	**2m**, 55
6[a]	**3n**	3-Me	**2n**, 54
7	**3o**	4-Me	**2o**, 75
8[a]	**3p**	5-Me	**2p**, 70
9	**3q**	6-Me	**2q**, 87
10[b]	**3r**	3-OMe	**2r**, 61
11	**3s**	4-OMe	**2s**, 84
12	**3t**	5-OMe	**2t**, 81
13	**3u**	6-OMe	**2u**, 74
14[b]	**3v**	4-CO_2Et	**2v**, 54[c]

[a]10 mol % of **I** was employed. Reaction time was 8 h. [b]Reaction time was 3 h. [c]**2v** is an unstable compound.

substituent at the 4-, 5-, or 6-position, were converted to the cycloisomerized product **2** in good yields. However, **1j,n,r**, with a substituent at the 3-position, were respectively converted to **2j,n,r** in only 45%, 54%, and 61% yields (Table 3, entries 2, 6, and 10). There were sharp contrasts between 1,2,3-trisubstituted and 1,2,6-trisubstituted substrates, although both have substituents at the *ortho* position. These results suggest that some ruthenium hydride species react with the silylalkyne moiety faster than the vinyl ether moiety on **1** in this cycloisomerization (see the Supporting Information for the proposed mechanism).

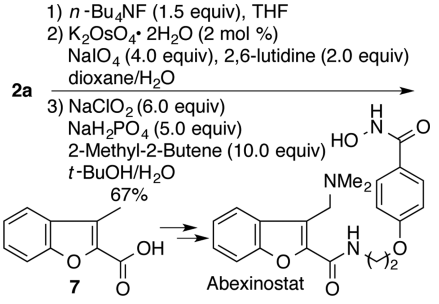
Chemical transformations of **2a** were possible (Scheme 3). For example, the vinyl group at the 2-position of benzofuran **2a**

Scheme 3. Chemical Transformations of 2a



was converted to the corresponding disubstituted alkene derivative **4** or the hydroxyethyl derivative **5** via cross-metathesis or hydroboration−oxidation in quantitative yields, respectively. The (trimethylsilyl)methyl group at the 3-position of **2a** reacted with benzaldehyde in the presence of fluoride ion, and the carbon−carbon bond-forming product **6** was obtained in 90% yield. These results have shown that **2a**, efficiently prepared by our cycloisomerization between silylalkyne and vinyl ether, may serve as a good synthon. Indeed, **2a** was efficiently converted to a key intermediate **7**[18] for abexinostat, a HDAC inhibitor with potential antineoplastic activity (Scheme 4).

Scheme 4. Synthesis of a Key Intermediate 7 for Abexinostat



Finally, we used NMR spectroscopy to obtain information on the active ruthenium species in this cycloisomerization.[19] We compared the ^{1}H and ^{31}P NMR spectra of catalysts (**II** and **A**) in *p*-xylene and the reaction mixture for the cycloisomerization. For catalyst **II**, we observed signals for the benzylidene proton at 19.7 ppm in the ^{1}H NMR spectrum and tricyclohexylphosphine at 29.8 ppm in the ^{31}P NMR spectrum. In the cycloisomerization reaction mixture spectra, new catalyst **A** peaks appeared within 10 min along with the cycloisomerized compound **2a** peaks, while with the ruthenium carbene catalyst **II** and **1a** peaks disappeared (Figure S1). These results and those of the control experiments shown in Table 3 suggest that this cycloisomerization proceeds via a ruthenium hydride **A**, and a plausible reaction mechanism is drawn in Scheme S1.

In conclusion, we developed a ruthenium hydride catalyzed cycloisomerization of **1**, having (trialkylsilyl)alkyne and arylvinyl ether moieties, to give 2,3-disubstituted benzofurans **2**, having vinyl and (trimethylsilyl)methyl groups on the 2- and 3-positions, respectively, for the first time to our knowledge. compound **2** is a useful synthon, and **2a** was efficiently converted to a key intermediate for abexinostat. This is also another example of a nonmetathesis reaction using a ruthenium carbene catalyst.[20] These reactions will be of interest because ruthenium carbene catalysts are widely used in functional molecular synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00985.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) In the presence of vinyloxytrimethylsilane **I** was converted to $RuHCl(CO)(PCy_3)_2$. See ref 15c.

(17) Although we tried a one-pot tandem sequence of double-bond isomerization and subsequent cycloisomerization under various conditions, the reaction was unsuccessful. For example, after a solution of **II** (5 mol %) and vinyloxytrimethylsilane (1 equiv) in *p*-xylene was heated at 40 °C for 10 min, **3a** was added, and the whole was refluxed for 1 h to give **2a** in 40% yield.

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