OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Ni-Catalyzed Cycloisomerization between 3-Phenoxy Acrylic Acid Derivatives and Alkynes via Intramolecular Cleavage and Formation of the C−O Bond To Give 2,3-Disubstituted Benzofurans

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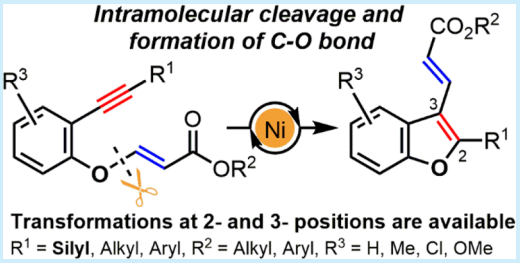
Supporting Information

ABSTRACT: Reactions based on transition-metal-catalyzed C−O bond cleavage have attracted much attention as a new synthetic method. Until now, several intermolecular reactions via C−O bond cleavage of aryl ethers, alkenyl ethers, esters, and others have been reported. Here we report an unprecedented C−O bond cleavage of 3-phenoxy acrylic acid derivatives, followed by intramolecular C−O bond formation with alkynes. This reaction gave 2,3-disubstituted benzofurans having useful functional groups—silyl substituents and acrylic acid derivatives—at the 2- and 3-positions, respectively. This report also described theoretical (DFT) insights into the mechanism.



Novel reactions based on transition-metal-catalyzed C−O bond cleavage have attracted much attention as a new synthetic method.[1] Until now, several intermolecular reactions via C−O bond cleavage of aryl ethers,[2,3] alkenyl ethers,[4] esters,[5,6] and others[7−9] have been reported (Scheme 1A). For example, many reactions of anisole derivatives (R^1 = Me) have been reported, and the C−O bond at the **a**-position is selectively cleaved by a transition metal catalyst.[2] In addition, many reactions using aryl aromatic esters (R^4 = aryl, R^5 = aryl) have been reported, and the C−O bond at the **c**-position is selectively cleaved.[5] Also, aryl carbamate (R^4 = NMe_2, R^5 = aryl) or aryl pivalate (R^4 = *t*Bu, R^5 = aryl) are known to cleave the **d**-position of the C−O bond.[6] In 2012, Tanaka reported the Rh-catalyzed intramolecular cyclization of naphthol-linked 1,6-enynes (Scheme 1B).[10a] This reaction proceeded via cleavage of the C(vinyl)−O bond followed by C(vinyl)−O bond formation with alkyne to give benzofuran derivatives, and there is no doubt

Scheme 1. C−O Bond Cleavage Reactions

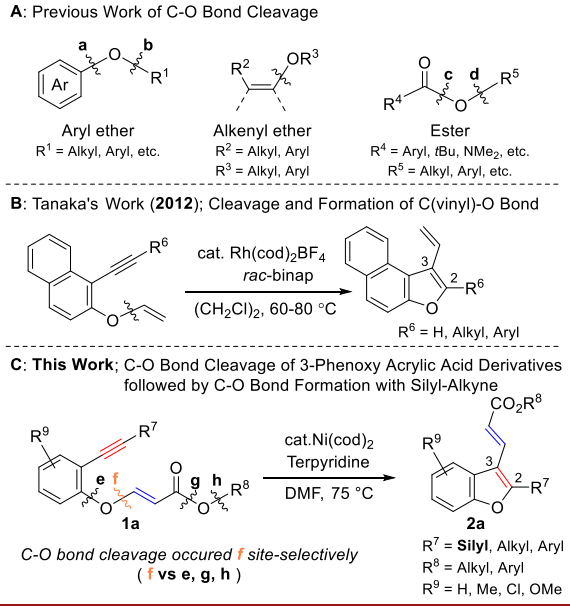
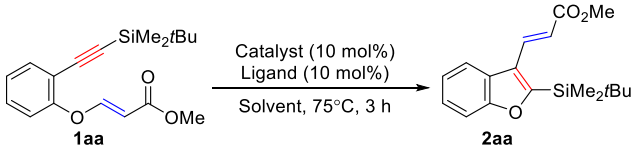


Table 1. Optimization of Reaction Conditions



entry	catalyst	ligand	solvent	yield (%)[a]
1	$Ni(cod)_2$	**L1**	DMF	92[b] (84)[c]
2	$Ni(cod)_2$	PCy_3	DMF	6
3	$Ni(cod)_2$	dppe	DMF	0
4	$Ni(cod)_2$	dcype	DMF	7
5	$Ni(cod)_2$	SIPr·HCl	DMF	6[d]
6	$Ni(cod)_2$	**L2**	DMF	17
7	$Ni(cod)_2$	**L3**	DMF	52
8	$Ni(cod)_2$	**L4**	DMF	38
9	$Ni(cod)_2$	**L1**	PhMe	<1
10	$Ni(cod)_2$	**L1**	THF	92
11	$NiBr_2$·glyme	**L1**	DMF	<1
12	$Ni(acac)_2$	**L1**	DMF	<1
13	$Ni(cod)_2$	**L1**	DMF	87[e]

Received: September 6, 2019

DOI: 10.1021/acs.orglett.9b03170
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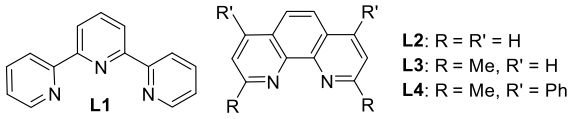
Table 1. continued

entry	catalyst	ligand	solvent	yield (%)[a]
14	$PtCl_2$	none	DMF	0
15	$Rh(cod)BF_4$	(*rac*)-binap	DMF	0



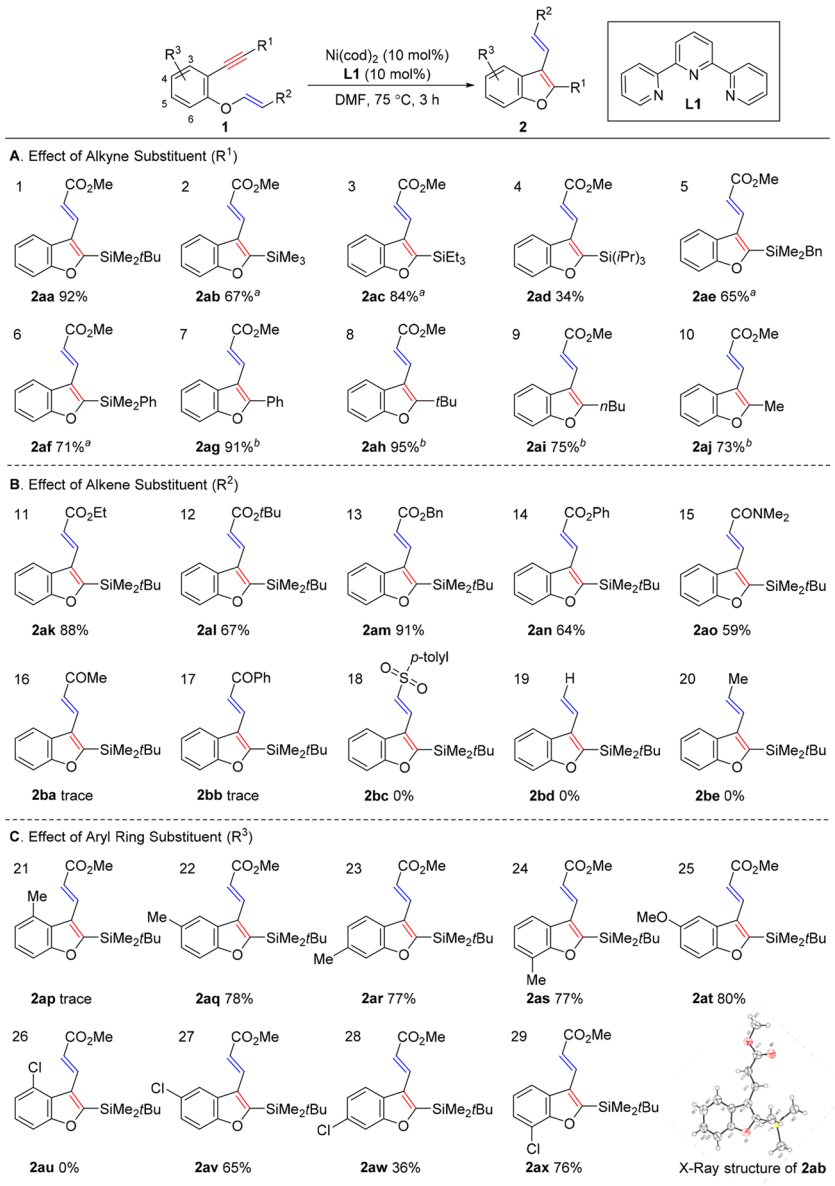
[a]Yields were determined by NMR using 1,3,5-trimethoxy-benzene as the internal standard. [b]Isolated yields. [c][$Ni(cod)_2$] (5 mol %), 6 h. [d]With NaO*t*Bu (20 mol %). [e]With 9,10-dihydroanthracene.

that this reaction is useful in organic synthesis. However, applicable substrates for this reaction are limited to 1,6-enyne compounds with unsubstituted vinyl ether and simple alkynes having H, alkyl, or aryl. Therefore, the substituents of benzofuran derivatives are automatically limited to H or the alkyl or aryl group at the 2-position or vinyl at the 3-position, respectively, and further chemical transformations of products are rather difficult. Against this research background, here we report an unprecedented C−O bond cleavage of 3-phenoxy acrylic acid derivatives, followed by intramolecular C−O bond formation with silyl-alkynes (Scheme 1C).

In this reaction, 2,3-disubstituted benzofurans, which are present in numerous bioactive natural products and pharmaceuticals,[11] were obtained, and all atoms contained in the starting material were retained in the final product. Moreover, these products have a useful substituent (ex. silyl) and an acrylic acid derivative at the 2- and 3-positions, respectively. The mechanism of this reaction was proposed by DFT calculations (Scheme 3).

We prepared substrate **1aa** and subjected it to several reaction conditions (Table 1). As a result, when using $Ni(cod)_2$ and terpyridine (**L1**) as a ligand in DMF, the desired benzofuran (**2aa**) was obtained in 92% yield (entry 1). Instead of **L1**, phosphine ligands (PCy_3, dppe, dcype) or *N*-heterocyclic carbene ligands (SIPr·HCl) were used; however, the reaction

Table 2. Substrate Scope and Limitations



[a]Reactions were run in THF. [b]Reactions were run at 120 °C.

DOI: 10.1021/acs.orglett.9b03170
Org. Lett. XXXX, XXX, XXX−XXX

hardly progressed (entries 2−5). When other nitrogen-containing ligands (**L2**, **L3**, **L4**) were used, **2aa** was obtained in 17%, 52%, and 38% yields, respectively (entries 6−8). When PhMe was used as solvent instead of DMF, or when $NiBr_2$·glyme or $Ni(acac)_2$ was used as a Ni source instead of $Ni(cod)_2$, the reaction did not proceed (entries 9, 11, and 12). In the control experiment with 9,10-dihydroanthracene (entry 13), we knew that this reaction did not proceed via radical species. Also, when transition metal catalysts with the property of a π-Lewis acid were used, the formation of **2aa** was not observed (entries 14 and 15).

The substrate scope and limitations of this reaction are summarized in Table 2.

Using the best reaction conditions (Table 1, entry 1), we next examined the effect of alkyne substituents (Table 2A). Having a silyl group on the alkyne, $SiMe_3$, $SiEt_3$, $Si(iPr)_3$, $SiMe_2Bn$, and $SiMe_2Ph$, derivatives **1ab**−**1af** gave the corresponding cyclized products **2ab**−**2af** in 67%, 84%, 34%, 65%, and 71% yields, respectively. When using substrate **1ab**, not only **2ab**[12] but also the desilylated products were obtained in 67% and 17% yields, respectively, together with lower yields of TIPS product **2ad**, probably due to steric hindrance. Derivatives with aryl or alkyl groups on the alkyne, i.e., phenyl derivative **1ag**, *tert*-butyl derivative **1ah**, *n*-butyl derivative **1ai**, and methyl derivative **1aj**, were converted well to **2ag**, **2ah**, **2ai**, and **2aj** in yields of 91%, 95%, 75%, and 73%, respectively. However, the substrate with a terminal alkyne could not take part in this reaction, resulting in a complex mixture.

The effects of substituents on the alkene are summarized in Table 2B. Ethyl ester derivative **1ak**, *tert*-butyl ester derivative **1al**, benzyl ester derivative **1am**, phenyl ester derivative **1an**, and dimethyl amide derivative **1ao** gave the corresponding cyclized products **2ak**−**2ao** in 88%, 67%, 91%, 64%, and 59% yields, respectively. However, the substrates having ketone on the alkene (**1ba**, **1bb**) did not take part in this reaction very well,[13] and substrates having sulfone, hydrogen, or methyl on the alkene (**1bc**−**1be**) were not changed at all. These results suggest that the carbonyl group on the alkene is important for the progress of this cyclization.

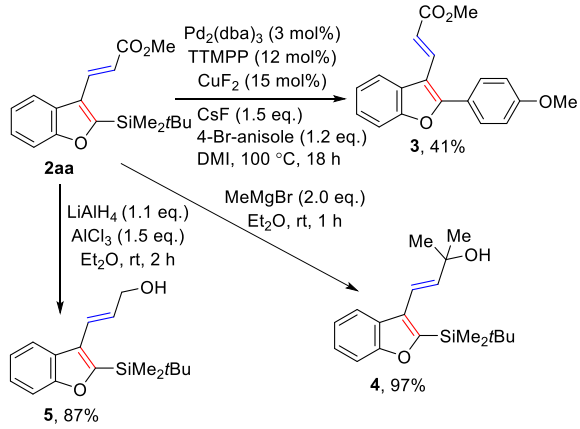
Table 2C summarizes the substituent effects on the aromatic ring. Compounds **1aq**−**1at** and **1av**−**1ax**, which have a substituent at the 4-, 5-, or 6-position, were converted to the corresponding cyclized products **2aq**−**2at** and **2av**−**2ax**, respectively, in good yields. However, substrates **1ap** and **1au**, with a substituent at the 3-position, were almost unchanged, probably due to their steric hindrance toward cyclization.

Chemical transformations of **2aa** were possible (Scheme 2). For example, the $SiMe_2tBu$ at the 2-position of benzofuran **2aa** was converted to the corresponding 2-aryl derivative **3** in 41% yield by Hiyama cross coupling[14] with 4-bromoanisole. Also, the acrylic acid methyl ester at the 3-position of **2aa** was converted to the corresponding allyl alcohol derivatives **4** or **5** via reaction with MeMgBr or $LiAlH_4/AlCl_3$ in high yields. These results have shown that **2aa**, efficiently prepared by our cycloisomerization between silylalkynes and 3-phenoxy acrylic acid derivatives, may serve as a good synthon.

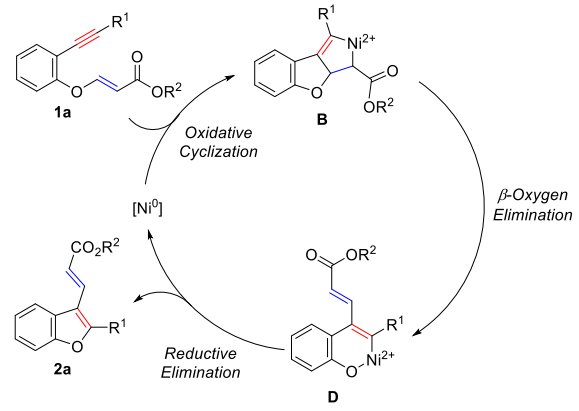
Finally, we performed DFT calculations of the stability of each intermediate expected to form in this reaction (Scheme S1).[15] Based on these calculations, the following mechanism is proposed (see Scheme 3).

First, the substrate is proposed to react with the Ni complex to form intermediate **A** (shown in Scheme S1 in SI) via oxidative addition of the C(vinyl)−O bond to the nickel complex or intermediate **B** via oxidative cyclization between the alkyne and the alkene. As a result of comparing the relative stabilities of

Scheme 2. Chemical Transformations



Scheme 3. Possible Reaction Pathway



intermediates **A** and **B**, intermediate **B** is expected to be more stable by 8.5 kcal/mol. Moreover, comparing the stabilities of intermediate **C** (shown in Scheme S1 in SI) formed by O−Ni insertion to the alkyne of intermediate **A** and intermediate **D** formed by C−Ni insertion to the alkyne of intermediate **A** or *β*-oxygen elimination of intermediate **B**, intermediate **D** is expected to be more stable by 9.8 kcal/mol. These results suggest that the mechanism via intermediate **B** and intermediate **D** is thermodynamically favored. The observations of the reaction mechanism by experiments are shown in the Supporting Information.

Although the substrates for this reaction have four possible C−O bonds that could be cleaved (see Scheme 1c, bonds e, f, g, and h), the rapid formation of stable nickelacycle **B** apparently outcompetes these other processes.

In conclusion, we developed the C−O bond cleavage of 3-phenoxy acrylic acid derivatives, followed by intramolecular C−O bond formation with alkyne. In this reaction, 2,3-disubstituted benzofurans **2a**, having a silyl substituent and an acrylic acid derivative at the 2- and 3-positions, respectively, are reported for the first time to our knowledge. Substituents at the 2- and 3-positions of compound **2aa** were able to convert to other substituents. The reaction mechanism was proposed by DFT calculations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03170.

Experimental procedures, computational details, and preparation of compounds (PDF)

DOI: 10.1021/acs.orglett.9b03170
Org. Lett. XXXX, XXX, XXX−XXX

NMR spectra of compounds (PDF)

Characterization data and X-ray structure analysis (PDF)

Accession Codes

CCDC 1948857 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was partially supported by a Grant-in-Aid from JSPS KAKENHI for Precisely Designed Catalysts with Customized Scaffolding (Grant No. JP 18H04260 and JP 15H05805), T15K149760, and T15KT00630, by Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Numbers JP18am0101084 and JP19am0101084. DFT calculations were performed with supercomputer at RCCS, Okazaki, Japan.

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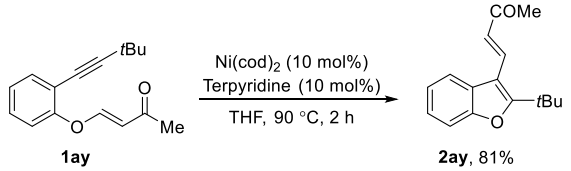
(12) The structure of **2ab** was determined by X-ray structure analysis.

(13) The reaction proceeded in 81% yield with the substrate **1ay** having a *t*Bu group on the alkyne and a ketone on the alkene. Products **2ba** and **2bb** are probably unstable.



1ay **2ay**, 81%

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(15) See Supporting Information.

DOI: 10.1021/acs.orglett.9b03170
Org. Lett. XXXX, XXX, XXX−XXX