ORGANIC LETTERS
2013
Vol. 15, No. 10
2482–2485

Metal-Controlled Cycloaddition of 2-Alkynyl-1,4-benzoquinones and Styrenyl Systems: Lewis Acid versus π Acid

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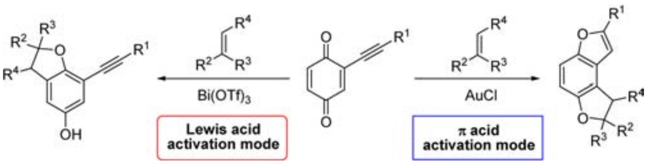
Received April 7, 2013

ABSTRACT



Metal-controlled cycloaddition of 2-alkynyl-1,4-benzoquinones and electron-rich styrenyl systems were investigated. The density functional theory (DFT) calculations revealed that the regioselectivity of the cycloaddition results from the different activation modes of Bi(OTf)$_3$ and AuCl.

Cycloaddition between 1,4-benzoquinones and alkenes is a valuable transformation in organic synthesis.[1] It has become a classical and commonly used approach to prepare various dihydrobenzofurans[2] and indoles.[3] For substituted 1,4-benzoquinones, regiocontrolled cycloaddition is essential to make this reaction practically useful. The Engler group investigated the reaction of alkoxy-1,4-benzoquinones and styrenes.[4] They found that the regioselectivity depends on the nature and the number of equivalents of Lewis acid used as promoters. Bidentate binding of the Lewis acid to the C-1 carbonyl group and the C-2 alkoxy oxygen or monodentate binding of the Lewis acid to the C-4 carbonyl group leads to different cycloaddition products.

Recently, we have directed our focus to the synthetic application of the dearomatization of 2-alkynyl phenols and 2-alkynyl anilines.[5] We found that the oxidation of 2-(2-phenylethynyl)phenol with 2 equiv of PhI(OAc)$_2$ in methanol formed 2-(2-phenylethynyl)-1,4-benzoquinone **1a**.[6] Since there are multiple reaction sites in the structure of 2-alkynyl-1,4-benzoquinones, we were interested in the regioselectivity of their cycloaddition with alkenes. The reaction might be promoted via various ways and form three cycloaddition products **3**, **4**, and **5** (Scheme 1). When a Lewis acid was employed, it might coordinate with

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10.1021/ol400956h

the C-1 or the C-4 carbonyl group via a monodentate mode (intermediates **I** and **II**). The Lewis acid might also coordinate with the C-1 carbonyl group and the C-2 triple bond via a bidentate mode (intermediate **III**). When a π acid was used, it might coordinate with the C-2 triple bond via a monodentate mode (intermediate **IV**). This activation might induce the nucleophilic attack of the C-1 carbonyl oxygen on the electron-deficient triple bond to generate an oxonium ion (intermediate **V**) or a carbocation (intermediate **VI**).[7]

To begin our study, we chose 4-methoxystyrene as the reaction partner of 2-(2-phenylethynyl)-1,4-benzoquinone to evaluate the catalytic activities of various metal salts. The reactions were conducted in acetonitrile at room temperature in the presence of 0.1 equiv of catalyst, and representative results are shown in Table 1. The generation of compound **3aa** was observed when gold(I) salts were used (Table 1, entries 1−3). Compound **3aa** was isolated in a 33% yield from the reaction using gold(I) chloride as the catalyst.[8] In(III), Fe(III), Ru(III), Pt(II), Cu(II), and Bi(III) salts exhibited different catalytic activities in the formation of product **5aa**, and $Bi(OTf)_3$ was the best catalyst. The formation of compound **4aa** was not observed in all reactions.

Scheme 1. Cycloaddition of 2-Alkynyl-1,4-benzoquinones and Electron-Rich Alkenes

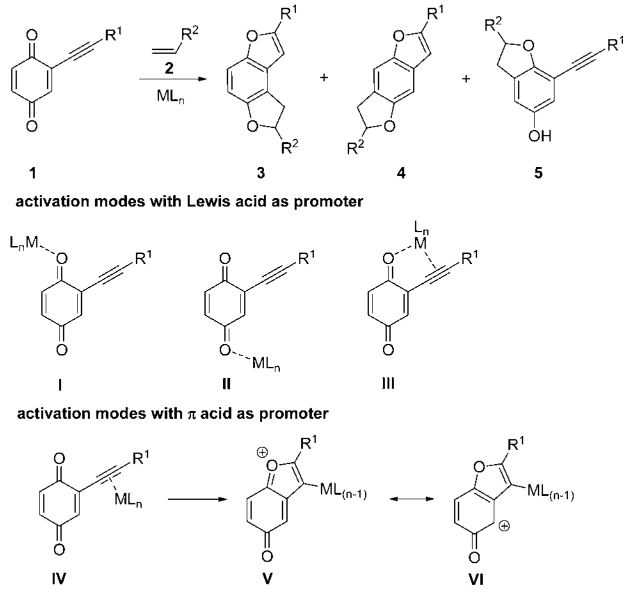
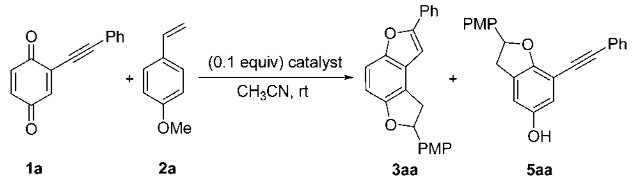


Table 1. Evaluation of Metal Salts[a]



entry	catalyst	**3aa** (%)[b]	**5aa** (%)[b]
1	$Ph_3PAuOTf$	<5	0
2	$Ph_3PAuSbF_6$	17	0
3	AuCl	33	0
4	$AuCl_3$	0	0
5	$Pd(OAc)_2$	0	0
6	$PdCl_2(CH_3CN)_2$	0	0
7	AgOTf	0	0
8	$Rh(PPh_3)_3Cl$	0	0
9	$Co(acac)_3$	<5	0
10	CuCl	0	0
11	$TiCl_4$	0	0
12	$InCl_3$	0	12
13	$FeCl_3$	0	63
14	$RuCl_3$	0	56
15	$PtCl_2$	0	65
16	$CuCl_2$	0	28
17	$Cu(OTf)_2$	0	58
18	$Bi(OTf)_3$	0	66
19	$Zn(OTf)_2$	0	0
20	$Fe(OTf)_2$	0	0
21	$Ni(OTf)_2$	0	0
22	$Yb(OTf)_3$	0	0
23	$Dy(OTf)_3$	0	0

[a] General reaction conditions: Reactions performed on 0.2 mmol scale using 2 equiv of **2a**, 10 mol % catalyst in CH_3CN (2 mL) at 25 °C. [b] Reported yields are of the isolated product based on compound **1a**.

To gain more insight into the reaction regioselectivity, the B3LYP density functional theory (DFT) calculations were performed with the Gaussian 09 package using the 6-31+G(d,p) basis set for the main group atoms and the LANL2DZ basis set for Au and Bi atoms.[9] The other calculation details were provided in the Supporting Information. The condensed Fukui function, introduced in the DFT by Parr and Yang,[10] is the most important local

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reactivity index. It has become a valuable tool to deal with the site selectivity in a wide range of organic reactions.[11] For the nucleophilic attack of the atom site k of the molecule, the condensed Fukui function is defined as the following equation in terms of the atomic charges:[9]

$$f_k^+ = q_k(N) - q_k(N+1)$$

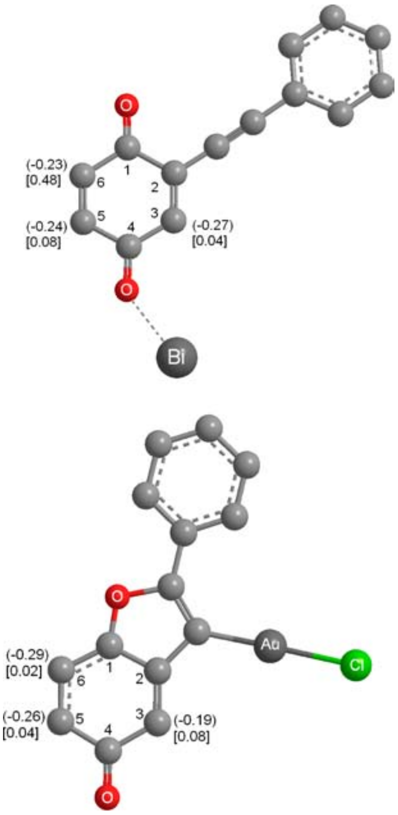

Figure 1. Optimized structures of intermediate **II** with Bi(III) as the catalyst (top) and intermediate **V** with Au(I) as the catalyst (bottom). The numbers in parentheses are the NBO charges on atoms, and the numbers in square brackets are the condensed Fukui functions. For clarity, the counterion (trifluoromethanesulfonate anion) is omitted for the Bi(III) catalyst.

For the $Bi(OTf)_3$ catalyzed reaction, we could not locate the stable structure of intermediate **III** or **IV**. The optimization led to the monodentate mode structure **I** due to the apparent Lewis acid character of the Bi(III) salt. However, this optimized structure is unstable by 3.18 kcal/mol compared with the most favored intermediate **II** (Figure 1, top). Although the funan-like intermediate **V** was located as well, the relative energy from intermediate **II** is 9.16 kcal/mol, which means that intermediate **V** is very unstable. Meanwhile, the computational results indicated that the most stable intermediate for the AuCl catalyzed reaction is the funan-like intermediate **V** (Figure 1, bottom). It is more stable by more than 20 kcal/mol than the other four intermediates. This result is in line with the concept of a carbophile π acid. That is to say, the different favored activation modes for $Bi(OTf)_3$ and AuCl result inherently from the nature of the metal salts: $Bi(OTf)_3$ acts as a Lewis acid, and AuCl acts as a π acid.

On the basis of the NBO (natural bond orbital) analysis of the intermediate **V** in the AuCl catalyzed reaction (Table 2), the C-3 position is more positively charged (−0.19) compared to the C-5 (−0.26) and the C-6 (−0.29) position. The condensed Fukui function also predicts that the nucleophilic attack will occur at the C-3 position. At the same time, the NBO analysis and the condensed Fukui function of the intermediate **II** in the $Bi(OTf)_3$ catalyzed reaction reveal that there is a preference at the C-6 position for the nucleophilic attack. These results are in good agreement with the experimental results.

Additionally, all the [3 + 2] cycloaddition transition states for the $Bi(OTf)_3$ or the AuCl catalyzed reaction were located. The potential energy surfaces indicate that both reactions can proceed with reasonable activation barriers. The $Bi(OTf)_3$ catalyzed reaction features a highly asynchronous concerted pathway. The AuCl catalyzed reaction proceeds in a stepwise pathway. For the $Bi(OTf)_3$ catalyzed reaction, the real catalytic species is not clear. $Bi(OTf)_2^+$ is also a possible catalytic species for this reaction.[12]

After various solvents, temperatures, and ratios of reagents were screened, the optimal reaction conditions were established. Compared with the $Bi(OTf)_3$ catalyzed reaction (the optimized conditions: 0.1 equiv of $Bi(OTf)_3$, CH_3CN, 0 °C, 3 h), a higher reaction temperature (50 °C) and a longer reaction time (10 h) with THF as solvent were required for the AuCl catalyzed reaction. With the optimized reaction conditions in hand, the reaction scope was investigated (Table 3). Notably, all reactions were regioselective under the conditions **A** or **B**. A variety of electron-rich styrenyl systems were found to be suitable cycloaddition partners. For example, when 1-methoxy-4-(prop-1-en-2-yl)benzene **2e** was used, the AuCl catalyzed reaction produced product **3ae** in a 71% yield, and the $Bi(OTf)_3$ catalyzed reaction provided product **5ae** in an almost quantitative yield. When styrene or 4-methylstyrene was used, no reaction was observed under the standard conditions. 2-Alkynyl-1,4-benzoquinones bearing an electron-rich or -poor aryl group, a *tert*-butyl or a *n*-butyl group, a cyclopropyl group, or a hydrogen atom were readily accommodated in both transformations. When substrate **1i** bearing a TMS group was employed, the reactions were complex, and no desired products were isolated. The structures of products were confirmed by single-crystal diffraction analysis of compounds **3ee** and **5ee**.

In conclusion, we have developed a metal-controlled cycloaddition of 2-alkynyl-1,4-benzoquinones and electron-rich styrenyl systems. The density functional theory calculations revealed that the regioselectivity of the cycloaddition

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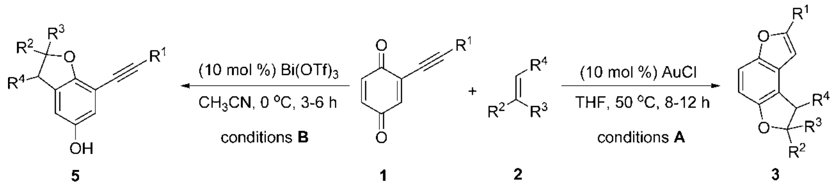
Table 2. NBO Charges Based on Electrostatic Potential and Condensed Fukui Function Calculation at B3LYP/6-31G(d)/LANL2DZ

			NBO charges			condensed Fukui functions				
entry	catalyst	intermediate	C-3	C-5	C-6	C-3	C-5	C-6	computationally preferred carbon	experimentally preferred carbon
1	AuCl	**V**	−0.19	−0.26	−0.29	0.08	0.04	0.02	C-3	C-3
2	$Bi(OTf)_3$	**II**	−0.27	−0.24	−0.23	0.04	0.08	0.48	C-6	C-6

Table 3. Reactions Scope Investigation[a]



entry	R^1	R^2	R^3	R^4	conditions A **3** (%)[b]	conditions B **5** (%)[b]
1	C_6H_5	4-$MeOC_6H_4$	H	H	**3aa** (45)	**5aa** (71)
2	C_6H_5	3,4-$(MeO)_2C_6H_3$	H	H	**3ab** (46)	**5ab** (92)
3	C_6H_5	C_6H_5	H	H	**3ac** (0)	**5ac** (0)
4	C_6H_5	4-MeC_6H_4	H	H	**3ad** (0)	**5ad** (0)
5	C_6H_5	4-$MeOC_6H_4$	Me	H	**3ae** (71)	**5ae** (99)
6	C_6H_5	4-MeC_6H_4	Me	H	**3af** (47)	**5af** (72)
7	C_6H_5	4-$MeOC_6H_4$	Et	H	**3ag** (41)	**5ag** (89)
8	C_6H_5	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	**3ah** (38)	**5ah** (90)
9	C_6H_5	4-$MeOC_6H_4$	Me	Me	**3ai** (30)	**5ai** (72)
10	C_6H_5	2-thiophene	Me	H	**3aj** (55)	**5aj** (78)
11	4-MeC_6H_4	4-$MeOC_6H_4$	Me	H	**3be** (55)	**5be** (88)
12	4-ClC_6H_4	4-$MeOC_6H_4$	Me	H	**3ce** (67)	**5ce** (91)
13	4-FC_6H_4	4-$MeOC_6H_4$	Me	H	**3de** (52)	**5de** (61)
14	cyclopropyl	4-$MeOC_6H_4$	Me	H	**3ee** (50)	**5ee** (65)
15	*t*-Bu	4-$MeOC_6H_4$	Me	H	**3fe** (76)	**5fe** (96)
16	*n*-Bu	4-$MeOC_6H_4$	Me	H	**3ge** (45)	**5ge** (81)
17	H	4-$MeOC_6H_4$	Me	H	**3he** (41)	**5he** (42)
18	TMS	4-$MeOC_6H_4$	Me	H	**3ie** (0)	**5ie** (0)
19	*t*-Bu	4-$MeOC_6H_4$	Et	H	**3fg** (63)	**5fg** (91)
20	*t*-Bu	4-$MeOC_6H_4$	4-$MeOC_6H_4$	H	**3fh** (65)	**5fh** (73)
21	*t*-Bu	4-$MeOC_6H_4$	Me	Me	**3fi** (81)	**5fi** (95)
22	*t*-Bu	2-thiophene	Me	H	**3fj** (65)	**5fj** (89)

[a] General reaction conditions: Reactions performed on 0.2 mmol scale using 3 equiv of **2** and 10 mol % catalyst. [b] Reported yields are of the isolated product based on compound **1**.

results from the different activation modes of $Bi(OTf)_3$ and AuCl. Current effort has also been made to extend its scope and possible synthetic applications, and these results will be reported in due course.

Acknowledgment. Financial support from National Natural Science Foundation of China (Nos. 21072033 and 21102019) is gratefully acknowledged.

Supporting Information Available. Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR of new compounds, X-ray diffraction structures, and crystallographic data of compounds **3ee** and **5ee** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.
