JOC*Note*

$Ru_3(CO)_{12}$-Catalyzed Reactions of Catechols with Alkynes: An Atom-Economic Process for the Synthesis of 2,2-Disubstituted 1,3-Benzodioxoles from the Double Addition of the O−H Bond Across a Triple Bond

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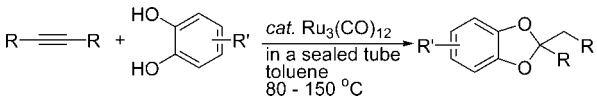


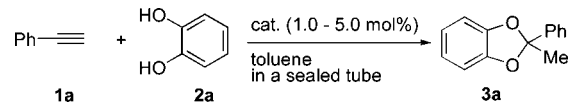
$Ru_3(CO)_{12}$ has been found to be the efficient catalyst for the addition reactions of catechols with both terminal and internal alkynes to selectively afford 2,2-disubstituted 1,3-benzodioxoles in good to high yields. The formation of 2,2-substituted 1,3-benzodioxoles results from the tandem addition of two O−H bonds of catechols to alkyne's triple bond.

1,3-Benzodioxoles are one of the important classes of heterocyclic compounds due to their existence in natural products such as piperine,[1] sesamol,[2] and justicidin[3] and having diverse biological activities.[4] The common synthetic methods for construction of 1,3-benzodioxoles are focused on the condensation of catechols with aldehydes or ketones in the presence of various acidic catalysts.[5]

Development of atom-economic reactions in organic synthesis is one of the important and challenging research areas. In continuation of our interest in transition metal-catalyzed activation of the O−H bond and its addition reaction to alkynes,[6] we have designed and investigated the cyclic addition reactions of catechols with alkynes to establish the efficient catalytic system for the synthesis of 2,2-disubstituted 1,3-benzodioxoles, which are expected to be promising starting materials to be converted to the related analogues of 1,3-benzodioxole-containing compounds for their biological studies.

To our knowledge, in very recent years, there is only one report on the cyclic addition of catechols with dimethyl acetylenedicarboxylate, which is an activated internal alkyne in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane).[7]

TABLE 1. Reaction of Phenylacetylene (1a) with Catechol (2a) under Different Conditions[a]



1a 2a 3a

entry	catalyst (mol %)	1a:2a	temp (°C)/time (h)	yield (%)[b]
1	$ReBr(CO)_5$ (5)	1.0	110/20	<5
2	$ReBr(CO)_5$ (5)	3.0	150/20	20
3	$Ru_3(CO)_{12}$ (5)	3.0	150/20	>99
4	$Ru_3(CO)_{12}$ (5)	1.2	120/12	>99
5	$Ru_3(CO)_{12}$ (2)	1.1	100/12	95
6	$Ru_3(CO)_{12}$ (2)	1.1	80/12	90 (84)

[a] Reactions were carried out with 1.0−3.0 mmol of **1a**, 1.0 mmol of **2a**, and 2−5 mol % of catalyst (relative to **2a**) in 1.0 mL of toluene in a sealed tube. [b] Yield according to GC based on the amount of **2a** used. The number in parentheses is isolated yield.

Table 1 shows the results of the reaction of phenylacetylene (**1a**) with catechol (**2a**) under different reaction conditions. Our initial attempts were directed toward the catalytic evaluation of $ReBr(CO)_5$ for the activation of the O−H bond of **2a** and its addition to alkyne, since our earlier work demonstrated that $ReBr(CO)_5$ was an efficient catalyst for the activation of the O−H bond of carboxylic acids and its addition to terminal alkynes.[6b,c] However, when a mixture of **1a** with an equimolar amount of **2a** was heated in toluene in the presence of $ReBr(CO)_5$ (5 mol%) at 110 °C for 20 h, only a trace amount of adduct was observed (entry 1). Increasing the reaction temperature to 150 °C and using an excess amount of **2a** (3 equiv) resulted in the formation of 2-methyl-2-phenyl-1,3-

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TABLE 2. $Ru_3(CO)_{12}$-Catalyzed Reaction of 2a with Alkynes[a]

entry	alkyne	temp (°C)	product		yield (%)[b]
1	Me—≡—Ph **1b**	100	*p*-tolyl, Me	**3b**	89
2	*n*-C_5H_{11}—≡ **1c**	100	*n*-C_5H_{11}, Me	**3c**	82
3	Ph—≡—Ph **1d**	150	Ph, Ph	**3d**	79
4	Et—≡—Et **1e**	150	Pr, Et	**3e**	83
5	Pr—≡—Pr **1f**	150	*n*-Bu, Pr	**3f**	94
6	*n*-Bu—≡—*n*-Bu **1g**	150	*n*-C_5H_{11}, *n*-Bu	**3g**	93
7	Ph—≡—Me **1h**	150	Et, Ph	**3h**	86
8	Ph—≡—Et **1i**	150	Pr, Ph	**3i**	14
			Ph, Et	**3i'**	63
9	Ph—≡—*n*-Bu **1j**	150	*n*-C_5H_{11}, Ph	**3j**	8
			Ph, *n*-C_4H_9	**3j'**	78
10	Ph—≡—COOMe **1k**	150	COOMe, Ph	**3k**	75

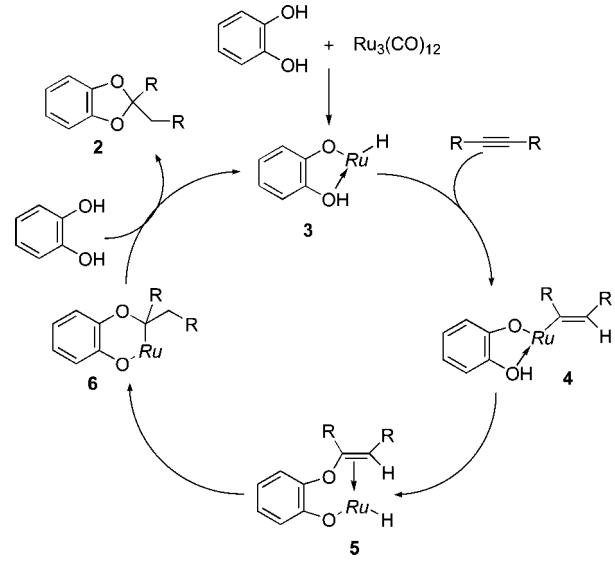
[a] Reactions were carried out with 1.1 mmol of **1**, 1.0 mmol of **2a**,and 2 mol % of $Ru_3(CO)_{12}$ in 1.0 mL of toluene in a sealed tube for 12 h. [b] Isolated yields.

benzodioxole (**3a**) in 20% GC yield (entry 2). The structure of **3a** was characterized by its spectroscopic data, and it is apparent that **3a** results from the selective double Markovnikov addition of **2a** with **1a** via activation of O−H bonds.

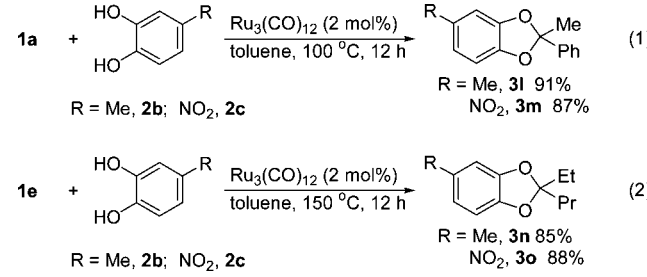
It is well-known that $Ru_3(CO)_{12}$ could efficiently catalyze the addition reaction of carboxylic acids[8] and diphenylphosphinic acid[6a] to terminal alkynes via cleavage of the O−H bond. Therefore, the reaction of **1a** with **2a** was also examined in the presence of $Ru_3(CO)_{12}$, and found that $Ru_3(CO)_{12}$ showed high catalytic activity and selectivity for the cyclic addition reaction of **1a** with **2a** to afford **3a** in high yields (entries 3−6). The analyses of the reaction mixtures disclosed that neither 1,4-benzodioxan nor *anti*-Markovnikov adduct(s) were formed under the reaction conditions.

To evaluate the generality of the present addition reaction, the reactions of catechol (**2a**) with terminal and internal alkynes were examined. As shown in Table 2, a number of 2,2-disubstituted 1,3-benzodioxoles could be obtained by the addition reactions of **2a** with a variety of alkynes in the presence of $Ru_3(CO)_{12}$. Terminal alkynes such as 4-(methylphenyl)acetylene (**1b**) and 1-heptyne (**1c**) reacted with **2a** at 100 °C to selectively afford 2-methyl-2-*p*-tolyl-1,3-benzodioxole (**3b**) and 2-methyl-2-*n*-pentyl-1,3-benzodioxole (**3c**) in 89% and 82% isolated yields, respectively (Table 2, entries 1 and 2). Symmetrical internal alkynes reacted with **2a** to give the

SCHEME 1. Proposed Mechanism for the Addition of Catechols to Alkynes



corresponding 1,3-benzodioxoles in good to high isolated yields at an elevated temperature (150 °C) (Table 2, entries 3−6). When unsymmetrical internal alkynes were used, two adduct isomers might form, and the ratio of isomers depends on the nature of alkynes. 2-Ethyl-2-phenyl-1,3-benzodioxole (**3h**) could be regioselectively isolated in 86% yield from the reaction of 1-phenyl-1-propyne (**1h**) with **2a**, and only a small amount of regioiosmer (2-methyl-2-benzyl-1,3-benzodioxole) was found in the reaction mixture, revealed by GC-MS analysis of the reaction mixture (Table 2, entry 7). However, in the cases of 1-phenyl-1-butyne (**1i**) and 1-phenyl-1-hexyne (**1j**) employed, the adducts 2-alkyl-2-phenyl-1,3-benzodioxoles **3i** and **3j**, which were expected to form from the same regioselective addition reaction as the reaction of **1h** with **2a** did, were formed as the minor products, and the predominant products were their regioisomers **3i′** and **3j′** (Table 2, entries 8 and 9). All the regioisomers could be isolated analytically pure by careful preparative TLC separation (silica, eluted with petroleum ether). The reaction of methyl phenylpropiolate (**1k**) with **2a** gave **3k** as the exclusive adduct, in which the addition of H took place at the carbon adjacent to the ester group (Table 2, entry 10).



In addition, catechols bearing the electron-donating group CH_3 (**2b**) and electron-withdrawing group of NO_2 (**2c**) could also react with both terminal and internal alkynes smoothly to give the corresponding adducts in high isolated yields.

The mechanism of the present addition of alkyne with catechols is considered to be similar to those of the $Ru_3(CO)_{12}$-catalyzed addition reaction of carboxylic acids and diphenylphosphinic acid with alkynes.[6a,8] Therefore, a proposed mechanism is depicted in Scheme 1. It involves the tandem activation of O−H bonds by the oxidative addition of the O−H

bond to ruthenium complexes[9] and their intermolecular addition to the C≡C bond and subsequent intramolecular addition to the C═C bond to afford 2-substituted 1,3-benzodioxoles **3**.

In conclusion, we have established an atom-economic and efficient method for the synthesis of 2,2-disubstituted 1,3-benzodioxales in good to high yields via the tandem addition of two O−H bonds of catechols to alkynes in the presence of $Ru_3(CO)_{12}$. When terminal alkynes were used, the cyclic addition reactions afforded Markovnikov adducts selectively, while the regioselectivity in the reaction of unsymmetrical internal alkynes with catechols depends on the structural nature of alkynes.

Experimental Section

Typical Experimental Procedure for Addition of Phenylacetylene (1a) with 1,2-Benzenediol (2a) To Afford 3a (Table 1, entry 6): A mixture of phenylacetylene (**1a**) (112.3 mg, 1.1 mmol), catechol (**2a**) (110.0 mg, 1mmol), $Ru_3(CO)_{12}$ (12.7 mg, 0.02 mmol), and toluene (1.0 mL) under nitrogen in a screw-capped tube was heated with stirring at 80 °C for 12 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 to 3.0 mL, and *n*-octadecane (38.1 mg, 0.15 mmol) was added as internal standard material for GC analysis. After GC and GC-MS analyses, solvents and volatiles were removed under vacuum, and the residue was then purified by column chromatography (silica gel, eluted with petroleum ether) to afford **3a** (179.0 mg, 0.84 mmol, 84.0%) as a yellow oil. GC analysis of the reaction mixture revealed that **3a** was formed in 90% yield. **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61−7.58 (m, 2H), 7.38−7.32 (m, 3H), 6.80−6.76 (m, 4H), 1.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 141.3, 129.0, 128.5, 125.1, 121.5, 116.7, 108.8, 27.2; GCMS *m*/*z* (% rel intensity) 212 (M^+, 68), 197 (100), 166 (2), 151 (3), 135 (12), 110 (67), 103 (69), 91 (4), 77 (27).

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Supporting Information Available: General experimental method, characterization data, and charts of ^{1}H, ^{13}C NMR for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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