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**GOLD-CATALYZED FORMAL [3+2] CYCLOADDITION OF *p*-QUINONES AND 1-PHENYLPROPENES IN IONIC LIQUID: ENVIRONMENTALLY FRIENDLY AND STEREOSELECTIVE SYNTHESIS OF 2,3-DIHYDROBENZOFURAN NEOLIGNANS**

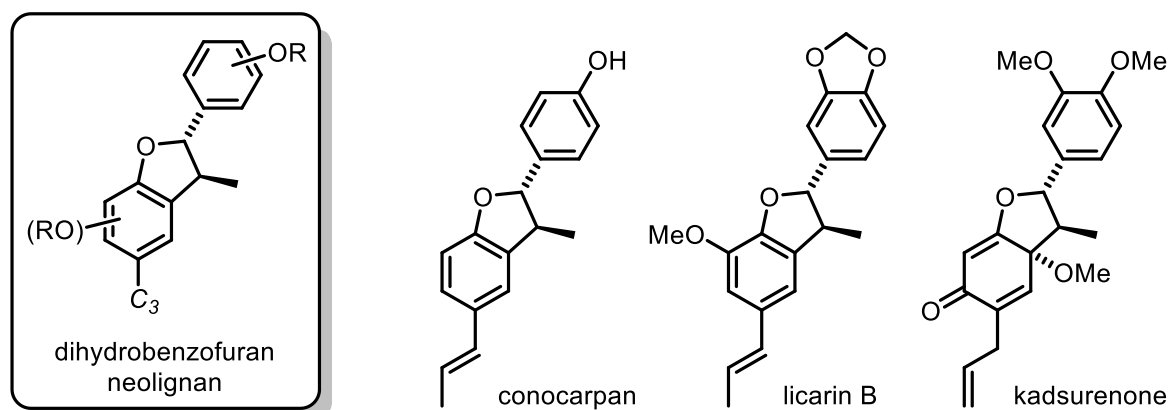
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This paper is dedicated to Prof. Dr. Yasuyuki Kita, on the occasion of his 77th birthday.

**Abstract** – Gold(III)-catalyzed formal [3+2] cycloaddition of *p*-quinones with 1-phenylpropenes in ionic liquid, [EMIM][NTf<sub>2</sub>], enabled environmentally friendly, stereoselective synthesis of 2,3-dihydrobenzofuran neolignans in good yields. The gold catalyst/ionic liquid could be recycled at least five times.

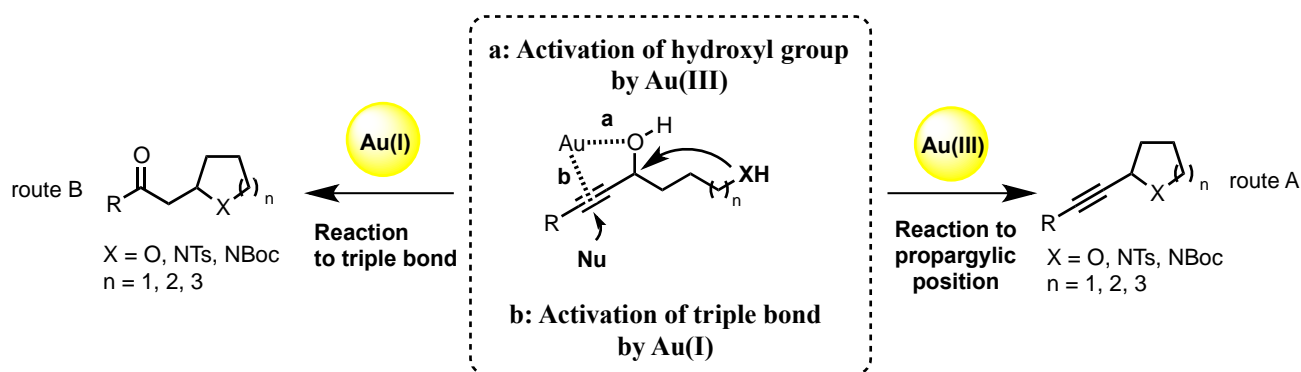
Naturally occurring 2,3-dihydrobenzofuran neolignans, such as conocarpan, licarin B and kadsurenone, are secondary metabolites with important biological activities, including cytotoxicity, anti-inflammatory activity and inhibition of platelet-activating factor (PAF)-induced effects (Figure 1).<sup>1</sup>



**Figure 1**

Therefore, extensive efforts have been made to develop synthetic methods for these compounds over several decades. Reported syntheses of 2,3-dihydrobenzofuran neolignans can be mainly divided into three categories: (A) oxidative dimerization of *p*-alkenylphenols,<sup>2</sup> (B) intramolecular reaction of phenylalkyne or alkene compounds<sup>3</sup> and (C) intermolecular reaction of *p*-quinones, *p*-quinone derivatives or *p*-quinone precursors with 1-phenylpropenes.<sup>4</sup> Although category (C) is convergent and can afford various types of 2,3-dihydrobenzofurans, it has some drawbacks from an environmental point of view, such as the need for a stoichiometric amount of reagents and the use of a toxic and volatile halogenated solvent (CHCl<sub>3</sub> or CH<sub>2</sub>Cl<sub>2</sub>). To overcome these problems, environmentally benign methods have been developed by two groups. Itoh's group reported the iron salt-catalyzed cycloaddition of *p*-quinone with 1-phenylpropenes in ionic liquid to afford 2,3-dihydrobenzofurans,<sup>5</sup> and Kouznetsov's group reported Lewis acid-promoted cycloaddition reactions of *p*-quinone with 1-phenylpropenes in PEG-400.<sup>6</sup> However, the scope of these procedures is quite limited, and an efficient, environmentally friendly method for the construction of a broad range of 2,3-dihydrobenzofurans is still required.

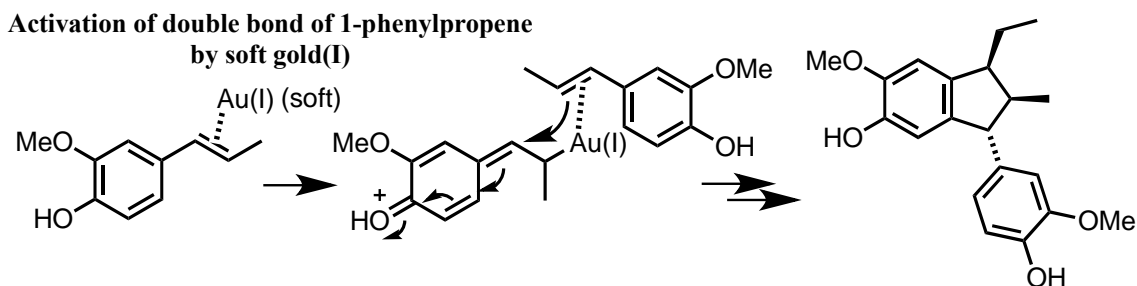
We have previously developed gold(I)/(III)-catalyzed intramolecular reactions of propargylic alcohols for the synthesis of cyclic compounds (cyclic ethers/piperidines/azepanes)<sup>7-9</sup> by utilizing the difference of valence between gold(I) and gold(III) catalysts. Thus, strategic use of oxophilic (hard) gold(III) and  $\pi$ -philic (soft) gold(I) catalysts activates different sites of the starting propargylic alcohols (**a**: activation of hydroxyl group by hard gold(III) / **b**: activation of triple bond by soft gold(I)) to control the reaction pathway (routes A and B), affording two types of products from the same starting propargylic alcohols (Scheme 1). We also extended this procedure to gold-catalyzed intermolecular reactions of propargylic alcohols with carbon nucleophiles, furnishing cyclic compounds (indenes/dihydropyrans/oxazoles).<sup>10-12</sup>



**Scheme 1**

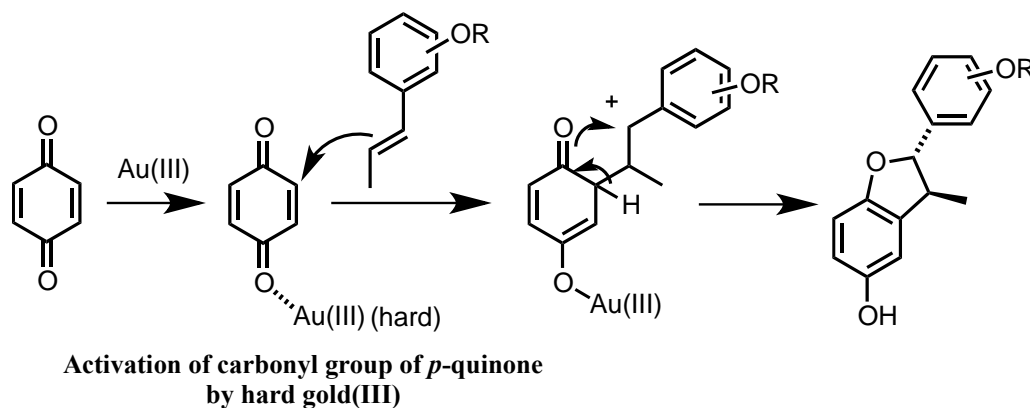
These reactions included gold(I)-catalyzed dimerization of isoeugenol and related 1-phenylpropenes in ionic liquid to afford 1,2,3-trisubstituted 2,3-dihydro-1*H*-indenes (Scheme 2).<sup>13</sup> In the first step of this

reaction,  $\pi$ -philic (soft) gold(I) catalyst coordinates to the double bond in isoeugenol, forming the gold-quinone methide complex as the active species. The gold center of the gold-quinone methide complex coordinates to the double bond of another isoeugenol molecule, and addition reaction is induced to afford the dimer of isoeugenol.



Scheme 2

In the case of using oxophilic (hard) gold(III) with *p*-quinone under similar conditions, the gold(III) catalyst should coordinate with carbonyl oxygen of the quinone even in the presence of 1-phenylpropene, followed by addition of 1-phenylpropene and cyclization, furnishing 2,3-dihydrobenzofurans (Scheme 3). Based on this idea, we herein present gold(III)-catalyzed formal [3+2] cycloaddition of *p*-quinones with 1-phenylpropenes in ionic liquid.<sup>14</sup>

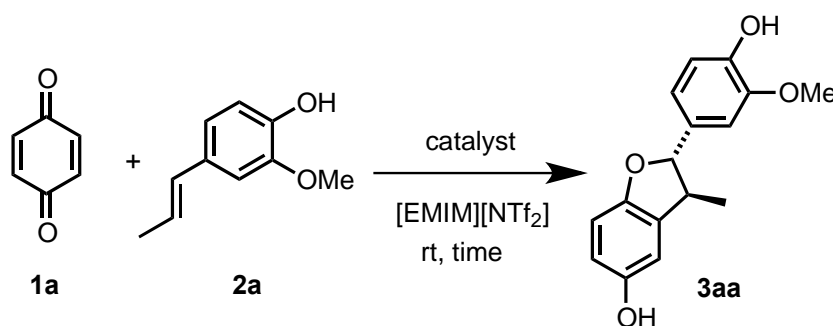


Scheme 3

We started our study by examining the reaction of *p*-quinone (**1a**) with isoeugenol (**2a**) as a nucleophile in the presence of various gold catalysts in an ionic liquid, [EMIM][NTf<sub>2</sub>] (Table 1).<sup>15</sup> Treatment of *p*-quinone (**1a**) with isoeugenol (**2a**) in the presence of gold(III) catalyst (5 mol% AuBr<sub>3</sub>) afforded the desired product **3aa** in 54% yield, with high *trans*-selectivity (entry 1). Further improvement was achieved by reducing the amount of gold(III) catalyst. Thus, the reaction of **1a** with **2a** in the presence

of AuBr<sub>3</sub> (1 mol%) in [EMIM][NTf<sub>2</sub>] gave 2,3-dihydrobenzofuran **3aa** in 70% yield with 94:6 *trans*-selectivity (entry 3).<sup>16</sup> An attempt to activate the gold catalyst by addition of silver catalyst AgOTf failed (entry 4). In contrast to the reaction of entry 3, reaction with gold(I) catalyst, AuCl (1 mol%) was less effective (entry 5). Finally, we identified 1 mol% of AuBr<sub>3</sub> in [EMIM][NTf<sub>2</sub>] at room temperature as the optimum conditions for synthesis of 2,3-dihydrobenzofuran **3aa**. The structure, including stereochemistry, of **3aa** was established by comparison of its <sup>1</sup>H-NMR spectrum with reported data.<sup>4n</sup>

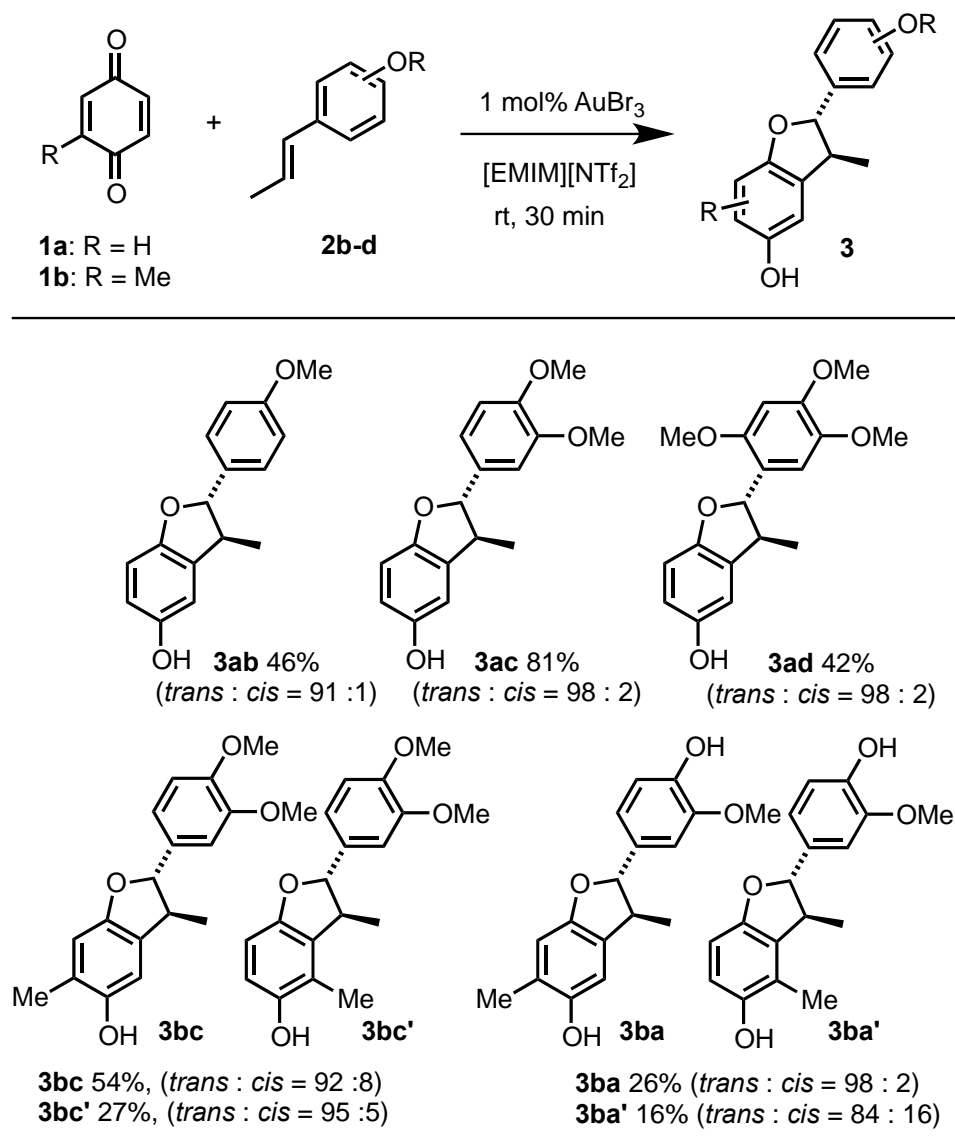
**Table 1.** Optimization of reaction conditions for gold-catalyzed formal [3+2] cycloaddition in ionic liquid



entry	catalyst (mol%)	time	yield ( <i>trans</i> : <i>cis</i> )
1	AuBr <sub>3</sub> (5 mol%)	30 min	54% (94 : 6)
2	AuBr <sub>3</sub> (2 mol%)	30 min	56% (94 : 6)
3	AuBr <sub>3</sub> (1 mol%)	30 min	70% (94 : 6)
4	AuBr <sub>3</sub> (1 mol%) AgOTf (3 mol%)	30 min	57% (93 : 7)
5	AuCl (1 mol%)	3 h	7%

Next, we examined the scope and limitations of the reaction of *p*-quinones **1a** and **1b** with various 1-phenylpropenes **2b-d** (Table 2). Treatment of *p*-quinone (**1a**) with 1-phenylpropenes **2b-d** in the presence of AuBr<sub>3</sub> (1 mol%) stereoselectively furnished the corresponding products **3ab-ad** in moderate yields. The reaction of *p*-quinone **1b** with 1-phenylpropenes **2a,c** also stereoselectively afforded the corresponding products **3bc**, **3ba** in good yields, but significant amounts of the regioisomers **3bc'**, **3ba'** were also formed.

**Table 2.** Gold(III)-catalyzed formal [3+2] cycloaddition of various *p*-quinones **1a,b** with 1-phenylpropenes **2b-d** in ionic liquid



Reusability of the gold catalyst is critical from an environmental, as well as economic, point of view. Fortunately, the gold(III) catalyst AuBr<sub>3</sub> (1 mol%)/ionic liquid [EMIM][NTf<sub>2</sub>] could be recycled at least five times for the formal [3+2] cycloaddition of *p*-quinone (**1a**) and 1-phenylpropene **2c** with only slight loss of activity (Table 3).<sup>17,18</sup>

**Table 3.** Recycling of the gold catalyst/ionic liquid

run	time	yield
1	0.5 h	81% (98 : 2)
2	1 h	78% (98 : 2)
3	1.5 h	80% (93 : 7)
4	2 h	75% (93 : 7)
5	4.5 h	69% (98 : 2)

In summary, we present an oxophilic gold(III)-catalyzed formal [3+2] cycloaddition reaction of *p*-quinone **1** with 1-phenylpropene **2**, leading to 2,3-dihydrobenzofurans **3** in a stereoselective manner. This reaction provides an alternative, environmental friendly method for the synthesis of various 2,3-dihydrobenzofuran neolignans. We are currently applying it to synthesize biologically important 2,3-dihydrobenzofurans. Experimental and theoretical investigations on the reaction mechanism are also in progress.

## ACKNOWLEDGEMENTS

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15. The reaction in another solvent such as [EMIM][(MeO)<sub>2</sub>PO<sub>2</sub>], [EMIM][CH<sub>3</sub>CO<sub>2</sub>], or [EMIM][BF<sub>4</sub>] gave only a low yield of the product **3aa** or a complex mixture.
16. Representative procedure for the synthesis of (2*R*\*, 3*R*\*)-2-(4-hydroxy-3-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran-5-ol (**3aa**): To a solution of *p*-quinone (**1a**) (100 mg, 0.93 mmol) and isoeugenol (**2a**) (150 mg, 0.93 mmol) in [EMIM][NTf<sub>2</sub>] (1 mL) was added AuBr<sub>3</sub> (4.0 mg, 0.0093 mmol, 1 mol%). The mixture was stirred at room temperature for 30 min. After complete consumption of *p*-quinone (**1a**) (the reaction was monitored by thin layer chromatography), the product was extracted from the reaction mixture by addition of Et<sub>2</sub>O (5 mL x 10). The Et<sub>2</sub>O layer was concentrated *in vacuo* and the residue was subjected to SiO<sub>2</sub> column chromatography (hexane:AcOEt = 4:1) to give **3aa** (204 mg, 70%, *trans*:*cis* = 94:6) as a colorless oil. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ 6.96-6.80 (3H, m), 6.75-6.62 (3H, m), 5.72 (1H, s), 5.06 (1H, d, *J* = 9.6 Hz), 4.96 (1H, br s), 3.90 (3H, s), 3.39 (1H, dq, *J* = 9.6, 6.6 Hz), 1.38 (3H, d, *J* = 6.6 Hz). The <sup>1</sup>H-NMR data are identical with reported values.<sup>4n</sup>



17. Although the exact reason for elongated reaction time and decreasing yield remains unclear, one of the possibilities seems to be the leaching of gold catalyst during extraction with Et<sub>2</sub>O.<sup>14f</sup>
18. Recycling procedure: To a solution of *p*-quinone (**1a**) (100 mg, 0.93 mmol) and *O*-methylisoeugenol (**2c**) (170 mg, 0.93 mmol) in [EMIM][NTf<sub>2</sub>] (1 mL) was added AuBr<sub>3</sub> (4.0 mg, 0.0093 mmol, 1 mol%). The reaction mixture was stirred at room temperature for 30 min. After complete consumption of *p*-quinone (**1a**) (the reaction was monitored by thin layer chromatography), the product was extracted from the reaction mixture by addition of Et<sub>2</sub>O (5 mL x 10). The Et<sub>2</sub>O layer was separated for purification of the product. The ionic liquid layer containing the gold catalyst was dried under reduced pressure for 3 h and reused.