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Gold-Catalyzed Etherification and Friedel–Crafts Alkylation Using *ortho*-Alkynylbenzoic Acid Alkyl Ester as an Efficient Alkylating Agent

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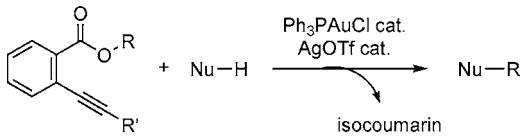
ABSTRACT



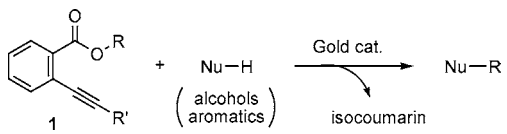
NuH: alcohols, aromatics

A gold-catalyzed alkylation of alcohols and aromatic compounds is described. The reaction of *ortho*-alkynylbenzoic acid alkyl esters with alcohols or aromatic compounds occurs in the presence of catalytic amounts of Ph_3PAuCl and AgOTf under mild conditions to produce corresponding ethers or Friedel–Crafts alkylation products in good to high yields. The reaction likely proceeds through the gold-induced in situ construction of leaving groups and subsequent nucleophilic attack of alcohols or aromatic compounds.

Lewis acid-catalyzed substitution reaction is one of the most fundamental and useful bond-forming methods in organic synthesis.[1] Generally, Lewis acids activate electrophiles by their strong affinities toward heteroatoms of the leaving groups, such as acetal and epoxide. We are interested in the possibility of applying the alkynophilicity of a gold catalyst to a substitution reaction.[2,3] In this paper, we report a gold-catalyzed alkylation of alcohols and aromatic compounds by using *ortho*-alkynylbenzoic acid alkyl ester **1**, leading to ether and Friedel−Crafts alkylation products in good to high yields under very mild reaction conditions (Scheme 1).

We have previously reported a gold-catalyzed benzannulation between *ortho*-alkynylbenzaldehydes and alkynes, which produced naphthyl ketones in good to high yields.[4] On the basis of these results, we envisaged that *ortho*-alkynylbenzoic acid alkyl ester might behave as an effective

Scheme 1



electrophile when it is treated with proper nucleophiles in the presence of the gold catalyst. Then, we examined the

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(1) For reviews, see: *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vols. 1−2.

(2) For recent reviews on the Au-catalyzed reactions, see: (a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (e) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.

(3) (a) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180. (b) Hotha, S.; Kashyap, S. *J. Am. Chem. Soc.* **2006**, *128*, 9620.

(4) (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (c) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (d) Asao, N. *Synlett* **2006**, 1645.

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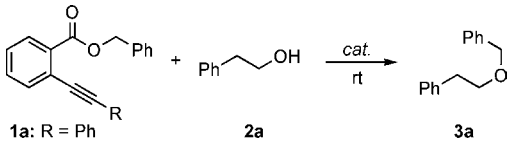
reaction of *ortho*-alkynylbenzoic acid benzyl esters **1a,b** with phenethyl alcohol **2a** under several conditions, and the results are summarized in Table 1. To our delight, treatment of **1a**

Table 1. Gold-Catalyzed Synthesis of Ethers[a]



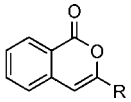
1a: R = Ph
1b: R = Bu

2a **3a**

entry	1	cat.	solvent	time	yield (%)[b] 3a	4
1[c]	**1a**	$AuBr_3$	$(ClCH_2)_2$	3 h	21	0[d]
2[c]	**1a**	$Ph_3PAuCl-AgOTf$	$(ClCH_2)_2$	3 h	64	7
3[c]	**1a**	Ph_3PAuCl	$(ClCH_2)_2$	3 h	0	0
4	**1a**	$Ph_3PAuCl-AgOTf$	$(ClCH_2)_2$	12 h	86	7
5	**1a**	$Ph_3PAuCl-AgOTf$	C_6H_6	1 h	84	8
6	**1a**	$Ph_3PAuCl-AgOTf$	C_6H_5Cl	1 h	81	9
7	**1b**	$Ph_3PAuCl-AgOTf$	C_6H_5Cl	1 h	87	6
8[e]	**1b**	$Ph_3PAuCl-AgOTf$	C_6H_5Cl	1 h	80	12
9	**1b**	TfOH	C_6H_5Cl	1 h	0	0[f]

[a] The reaction was carried out using **1** (1 equiv) and **2a** (3 equiv) in the presence of catalyst (5 mol %) at rt unless otherwise noted. [b] Determined by ^1H NMR spectra using *p*-xylene as an internal standard. [c] The reaction was carried out using **1a** (1 equiv) and **2a** (1.5 equiv) in the presence of catalyst (10 mol %) at rt. [d] **1a** was recovered in 50% yield. [e] The reaction was conducted using **1b** (3 equiv) and **2a** (1 equiv). [f] **1b** was recovered nearly quantitatively.

$(PhCH_2)_2O$ **4**

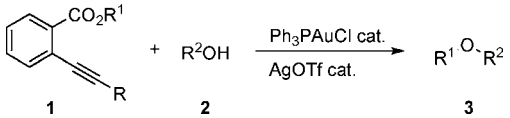


5

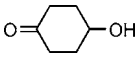
(1 equiv) with **2a** (1.5 equiv) in the presence of 10 mol % of $AuBr_3$ at rt for 3 h resulted in the formation of the desired benzyl phenethyl ether **3a** in 21% yield. Besides **3a**, isocoumarin **5a** (R = Ph) and the recovered starting material **1a** were obtained in 28 and 50% yields, respectively (entry 1). The chemical yield of **3a** was improved significantly by cationic gold catalyst, derived from Ph_3PAuCl and AgOTf, and **3a** was obtained in 64% yield along with a small amount of dibenzyl ether **4** (entry 2). To know the effect of the alkynyl group of **1a**, the reaction of benzyl benzoate, having no alkynyl group at the *ortho*-position, with **2a** was examined. As we anticipated, no reaction occurred, and the benzyl ester was recovered nearly quantitatively. These results clearly indicate that the alkynyl group of **1a** is essential for the current etherification. Other silver additives, such as $AgBF_4$ and $AgSbF_6$, were less effective. Without silver catalysts, no reaction took place (entry 3). While the use of 3 equiv of **2a** and 5 mol % of catalyst increased the chemical yield, a longer reaction time was needed for completion (entry 4). Interestingly, when the solvent was changed from $(CH_2Cl)_2$ to benzene or chlorobenzene, the reaction was dramatically accelerated and **3a** was obtained in high yields within a shortened period (1 h) (entries 5 and 6). Besides **1a**, *ortho*-hexynylbenzoic acid benzyl ester **1b** works well as an effective alkylating agent (entry 7). In entries 4−7, isocoumarins **5** were formed nearly quantitatively in each reaction, which would be generated by the gold-catalyzed electrocyclization of **1** (vide infra).[5] The reaction also proceeded smoothly when 3 equiv of **1a** was used over **2a** (entry 8). In the current catalyst system, TfOH might be produced. However, no reaction occurred with a catalytic amount of TfOH (entry 9).

To know the scope of the current etherification, we examined reactions with various combinations of esters **1** and alcohols **2**, and the results are shown in Table 2. The

Table 2. Gold-Catalyzed Synthesis of Ethers[a]



1 **2** **3**

entry	1	R	R^1	2	R^2OH	conditions	3	yield of 3 (%)[b]
1[c]	**1c**	Ph	$C_{12}H_{25}$	**2b**	$C_{12}H_{25}OH$	80 °C, 5 h	**3b**	50
2[c]	**1d**	*o*-anisyl	$C_{12}H_{25}$	**2b**	$C_{12}H_{25}OH$	80 °C, 12 h	**3b**	80
3[c,d]	**1d**	*o*-anisyl	$C_{12}H_{25}$	**2b**	$C_{12}H_{25}OH$	80 °C, 18 h	**3b**	86
4	**1e**	Bu	^{i}Pr	**2a**	$PhCH_2CH_2OH$	rt, 12 h	**3c**	73
5	**1f**	Bu	PMB	**2a**	$PhCH_2CH_2OH$	rt, 1 h	**3d**	92[e]
6	**1b**	Bu	$PhCH_2$	**2c**	*c*-$C_6H_{11}OH$	rt, 3 h	**3e**	70[f,g]
7	**1b**	Bu	$PhCH_2$	**2d**	*t*-BuOH	rt, 1 h	**3f**	90
8	**1f**	Bu	PMB	**2e**	$EtOCOCH_2OH$	rt, 1 h	**3g**	70[h]
9	**1b**	Bu	$PhCH_2$	**2f**	$AcO(CH_2)_2OH$	rt, 1 h	**3h**	70[i]
10	**1f**	Bu	PMB	**2g**		rt, 1 h	**3i**	69[j]
11	**1b**	Bu	$PhCH_2$	**2h**	$NC(CH_2)_2OH$	rt, 16 h	**3j**	75[i]

[a] The reaction was carried out using **1** (1 equiv) and **2** (3 equiv) in the presence of Ph_3PAuCl (5 mol %) and AgOTf (5 mol %) in C_6H_5Cl unless otherwise mentioned. [b] Isolated yields. [c] The reaction was conducted in C_6H_6. [d] The reaction was conducted using **1d** (3 equiv) and **2b** (1 equiv). [e] **6** was obtained in 8% yield. [f] **4** was obtained in 9% yield. [g] Determined by ^1H NMR spectra using *p*-xylene as an internal standard. [h] **6** was obtained in 9% yield. [i] **4** was obtained in 7% yield. [j] **6** was obtained in 12% yield.

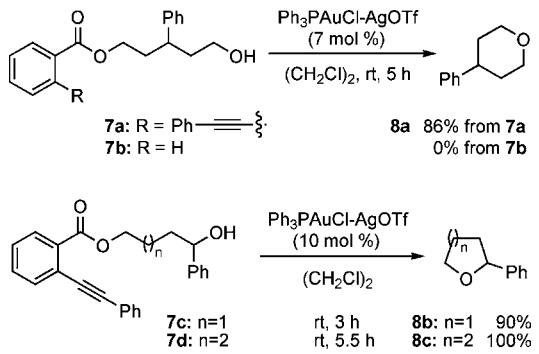
reaction of primary alkyl ester **1c** with dodecanol **2b** did not give any products in benzene at rt. However, when the reaction was conducted at 80 °C for 5 h, etherification proceeded to give didodecyl ether **3b** in 50% yield (entry 1). Interestingly, the chemical yield was increased up to 86% by changing the substituent at the terminus of the alkynyl moiety of **1** from a phenyl group to an *ortho*-anisyl group (entries 2 and 3). Other examined reactions proceeded smoothly at rt to give the corresponding ether products in good to high yields (entries 4−11). The reactions with *p*-methoxybenzyl (PMB) ester **1f** afforded the corresponding ethers in good to high yields together with a small amount of 4-(4-methoxybenzyl)-3-butyl-1*H*-isochromen-1-one **6** (entries 5, 8, and 10).[6] It is noteworthy that ester, ketone, and nitrile groups in **2e−h** were inert during the reaction and the corresponding products **3g−j** were obtained in good yields, respectively (entries 8−11). A large number of

(5) Electrocyclization of *ortho*-alkynylbenzoic acid alkyl ester has been reported for synthesis of isocoumarin. For examples, see: (a) Oliver, M. A.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 558. (b) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067. (c) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936.

catalytic etherification methods have been reported on the basis of the substitution reactions.[7] Dehydration of alcohols with metal catalysts is a direct approach for the synthesis of ethers, and such protocols have been recently studied.[8] Transition-metal-catalyzed allylic and propargylic etherification reactions are also attractive.[9] However, there are still limitations on substrates and drawbacks such as the requirement of elevated temperature and long reaction time in the known procedures. In contrast, neither severe reaction conditions nor highly reactive electrophiles are necessary in the current catalytic system.

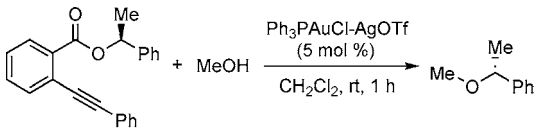
The current etherification was applied to the synthesis of cyclic ether compounds. Treatment of **7a** with the gold catalyst resulted in the formation of the corresponding six-membered cyclic ether product **8a** in 86% yield. On the other hand, no reaction occurred with **7b**, which has no alkynyl group at the *ortho*-position. The reactions of **7c** and **7d** also gave the corresponding products **8b** and **8c** in 90 and 100% yields, respectively (Scheme 2).

Scheme 2



From a mechanistic point of view, we investigated the reaction of (*S*)-**1g** (99% ee) with MeOH **2i** (Scheme 3). The reaction proceeded smoothly at rt for 1 h in CH_2Cl_2, and the corresponding ether **3k** was obtained in 78% yield. The absolute configuration of **3k** was determined to be *R* by comparison of the observed optical rotation to a literature value for (*R*)-(1-methoxyethyl)benzene.[10] The enantiomeric

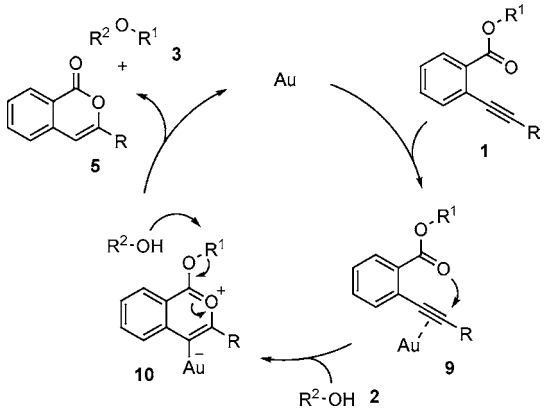
Scheme 3



excess was 37%, which suggests that the reaction between **1g** and **2i** involves S_N1 mechanism having some S_N2 character.

On the basis of these results, a plausible mechanism is illustrated in Scheme 4. The coordination of the triple bond

Scheme 4



of **1** to the gold catalyst enhances the electrophilicity of alkyne, and the subsequent nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne would form the zwitterionic intermediate **10**.[11,12] Due to the enhanced leaving ability of the isocoumarin moiety, the nucleophilic attack of alcohol **2** to **10** would occur to give ether compound **3** together with isocoumarin **5**.

We next turned our attention to the Friedel−Crafts alkylation.[13] Generally, alkylation of π-rich heteroaromatics, such as furan, is difficult under the traditional Friedel−Crafts conditions because of catalyst-promoted polymerization and polyalkylation.[14] Recently, some effective catalysts, such as lanthanide triflates[15] and transition metal catalysts,[16] have

(6) $PtCl_2$-catalyzed cyclization of benzoic acid ester through carboalkoxylation of the alkyne has been reported; see: Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. For recent other examples of metal-catalyzed intramolecular carboalkoxylation of alkynes, see: (a) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (b) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062.

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(8) For examples of metal-catalyzed dehydration of alcohols, see: (a) Nishibayashi, Y.; Wakiji, I.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 11019. (b) Sherry, B. D.; Radosevich, A. T.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 6076. (c) Miller, K. J.; Abu-Omar, M. M. *Eur. J. Org. Chem.* **2003**, 1294. (d) Shibata, T.; Fujiwara, R.; Ueno, Y. *Synlett* **2005**, 152. (e) Bustelo, E.; Dixneuf, P. H. *Adv. Synth. Catal.* **2007**, *349*, 933. (f) Corma, A.; Renz, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 298.

(9) For reviews, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (c) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641.

(10) Yoshida, M.; Weiss, R. G. *Tetrahedron* **1975**, *31*, 1801.

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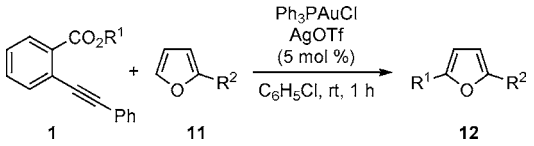
been reported for functionalization of aromatic compounds based on the substitution reactions. However, they still have drawbacks such as the necessity of high temperature and long reaction time. In this context, we examined the gold-catalyzed alkylation of furan, and the results are summarized in Table 3.[17] When esters **1a,h** were treated with furans **11a,b** in the

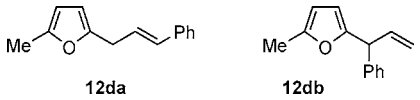
Table 3. Gold-Catalyzed Friedel−Crafts Alkylation of Furan[a]



1 11 12

entry	1	R^1	11	R^2	12	yield of 12 (%)[b]
1[c]	**1a**	$PhCH_2$	**11a**	H	**12a**	70
2	**1a**	$PhCH_2$	**11b**	Me	**12b**	80
3	**1h**	PMB	**11b**	Me	**12c**	72
4	**1i**	$PhCH{=}CHCH_2$	**11b**	Me	**12d**	61 (7:3)[d]

[a] The reaction was carried out using **1** (1 equiv) and **11** (5 equiv) in the presence of Ph_3PAuCl (5 mol %) and AgOTf (5 mol %) in C_6H_5Cl at rt within 1 h unless otherwise noted. [b] Isolated yields. [c] The reaction was conducted with 10 equiv of **11a**. [d] The ratio of **12da** and **12db**.

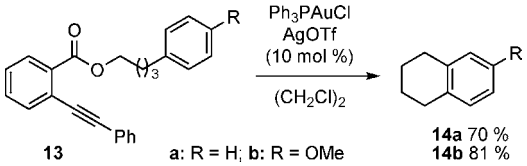


12da 12db

presence of the gold catalyst at rt for 1 h, the alkylations occurred smoothly at C2-position of the furan rings and the corresponding products **12a−c** were obtained in good yields, respectively (entries 1−3). The reaction of cinnamyl ester **1i** with **11b** gave a mixture of **12da** and **12db** in 61% yield with a 7:3 ratio (entry 4).

Intramolecular Friedel−Crafts alkylation reaction is well-known as a useful synthetic method of cyclic compounds.[18] However, only a few examples have been known for the synthesis of tetralines from primary alkyl halides, alcohols, and their derivatives.[19] It is worth mentioning that the gold-catalyzed reaction of **13a** proceeded at 100 °C for 7 h and **14a** was obtained in 70% yield. The introduction of a methoxy group on the phenyl group accelerated the reaction, and the corresponding product **14b** was obtained in 81% yield under 100 °C for 2 h (Scheme 5).

Scheme 5



13 a: R = H; b: R = OMe **14a** 70 % **14b** 81 %

In summary, we have developed a new catalytic, practical etherification method of alcohols with a designed *ortho*-alkynylbenzoic acid alkyl ester **1** as an effective alkylating agent. The reaction likely proceeds through the gold-induced in situ construction of leaving groups and subsequent nucleophilic attack of alcohols. The synthetic utility of the current protocol is further enhanced by its ability to promote the Friedel−Crafts alkylation under mild conditions. Further studies to extend the scope of synthetic utility are in progress in our laboratory.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Exploratory Research (No. 18655009) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For selected examples of transition-metal-catalyzed Friedel−Crafts alkylations, see: (a) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kočovský, P. *J. Org. Chem.* **1999**, *64*, 2751. (b) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846. (c) Kennedy-Smith, J. J.; Young, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325. (d) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964. (e) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596. (f) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913. (g) Choudhury, J.; Podder, S.; Roy, S. *J. Am. Chem. Soc.* **2005**, *127*, 6162. (h) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2006**, *348*, 691.

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