Tetrahedron Letters 49 (2008) 7046–7049

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Gold-catalyzed transesterification of *ortho*-alkynylbenzoic acid esters: a novel protecting group for alcohols and phenols

Kazuteru Umetsu [a], Naoki Asao [a,b,*]

[a] Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan
[b] Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

ARTICLE INFO

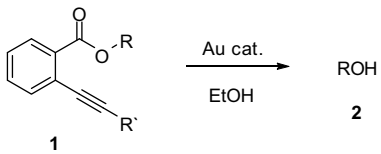
Article history:
Received 28 July 2008
Revised 21 September 2008
Accepted 25 September 2008
Available online 30 September 2008

ABSTRACT

Treatment of *ortho*-alkynylbenzoic acid esters with excess amounts of EtOH in the presence of a gold catalyst results in the liberation of alcohols or phenols in high yields under mild conditions. The protection of alcohols and phenols proceeds smoothly by use of *ortho*-alkynylbenzoic acid or *ortho*-iodobenzoyl chloride. Highly chemoselective deprotections are described.

Transesterification under acidic conditions is one of the most fundamental transformations in organic synthesis not only for preparation of new ester compounds but also for release of alcohols and phenols as a deprotection method.[1,2] A number of catalysts have been developed for promoting the deprotection so far. However, such conditions sometimes have encountered limitations on its applications for multifunctional substrates having acid-labile groups. While some catalysts have been developed for promoting the transesterification under neutral conditions, high temperatures were generally needed.[3] In this Letter, we describe a gold-catalyzed transesterification of *ortho*-alkynylbenzoic acid esters with EtOH under mild conditions, which can be used as a novel deprotection process of ester-protected alcohols and phenols (Scheme 1). Moreover, it provides an effective discriminative deprotection approach over other protected alcohols.[4]

Recently, we have reported that *ortho*-alkynylbenzoic acid alkyl ester **1** is a masked electrophile, and it behaves as an effective alkylating agent for etherification and Friedel–Crafts alkylation in combination with a gold catalyst.[5] The process would proceed through the indirect activation of the ester moiety of **1** through the formation of zwitterionic intermediate **5** (vide infra) by the alkynophilic gold catalyst.[6] To expand the synthetic utility of this activation method of ester functionalities, we examined the transesterification of **1** as a new deprotection method of ester-protected alcohols, and the results are shown in Table 1. When the ester **1a** (R = $PhCH_2CH_2$, R′ = Bu) was treated with a mixture of Ph_3PAuCl (1 mol %) and AgOTf (1 mol %) at rt in a 1:1 mixture of benzene and EtOH as solvent, the desired phenethylalcohol **2a** was obtained in 91% yield in 20 min (entry 1). On the other hand, the reaction of phenethyl benzoate, having no alkynyl group, did not take place at all under the same reaction conditions, and the starting material was recovered nearly quantitatively even after 1 d. These results clearly indicated that the alkynyl group of the ester **1** plays a crucial role in this reaction. Other silver additives, such as $AgBF_4$ and $AgSbF_6$, were less effective. Without silver catalysts, no reaction took place. The chemical yield of **2a** was increased up to 100% by using **1c**, having *ortho*-methoxyphenyl (*o*-anisyl) group at the terminus of the alkynyl moiety (entry 3). Besides benzene, other solvents such as toluene, hexane, CH_2Cl_2, and THF are suitable although longer reaction times were needed for completion (entries 4–7). The reaction also proceeded smoothly, in ethanol without any co-solvents (entry 8). To know the generality of the current protocol, we conducted the reaction with other substrates. Deprotection of dodecanol from **1d** proceeded quantitatively (entry 9). Benzyl alcohol was obtained from **1e** in 83% yield together with benzyl ethyl ether in 13% yield (entry 10). The reactions with *cis*- and *trans*-4-phenyl-cyclohexyl esters **1f–g** proceeded smoothly and the corresponding cyclohexanol derivatives were obtained nearly quantitatively in both cases (entries 11–12). Deprotections are conducted not only with alkyl esters but also with aryl esters **1h–j**, and the corresponding phenol analogs **2f–h** were obtained in high yields (entries 13–15). On the other hand, the present protocol is not suitable for deprotection of esters derived from cinnamyl alcohol and 1-phenylcyclohexanol due to the formation of the corresponding ethyl ethers in high yields.[5] In the current catalyst system, TfOH might be produced during the reaction. However, deprotection of **1c** did not proceed at all with 10 mol % of

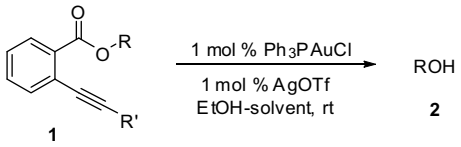


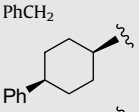
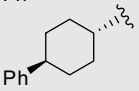
Scheme 1.

* Corresponding author. Tel.: +81 22 795 3898; fax: +81 22 795 3899.
E-mail address: asao@m.tains.tohoku.ac.jp (N. Asao).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.146

Table 1
Gold-catalyzed deprotection of alcohols and phenols[a]



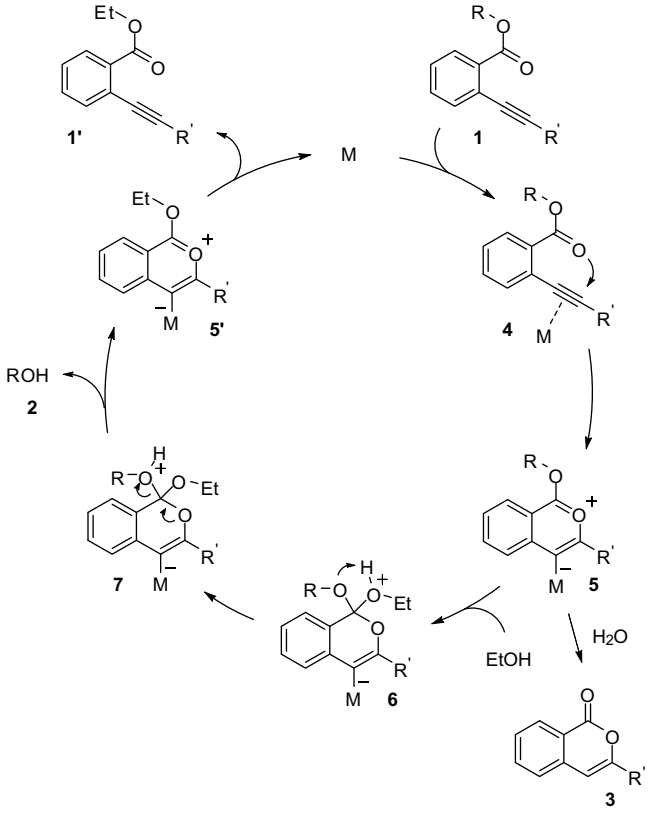
Entry	1	R	R′	Solvent	Time (h)	2	Yield[b] (%)
1	**1a**	$PhCH_2CH_2$	Bu	C_6H_6–EtOH	0.3	**2a**	91
2	**1b**	$PhCH_2CH_2$	Ph	C_6H_6–EtOH	0.3	**2a**	92
3	**1c**	$PhCH_2CH_2$	*o*-Anisyl[c]	C_6H_6–EtOH	0.3	**2a**	100
4	**1c**	$PhCH_2CH_2$	*o*-Anisyl	Toluene–EtOH	0.8	**2a**	96
5	**1c**	$PhCH_2CH_2$	*o*-Anisyl	Hexane–EtOH	0.8	**2a**	100
6	**1c**	$PhCH_2CH_2$	*o*-Anisyl	CH_2Cl_2–EtOH	1.2	**2a**	100
7	**1c**	$PhCH_2CH_2$	*o*-Anisyl	THF–EtOH	1.5	**2a**	100
8[d]	**1c**	$PhCH_2CH_2$	*o*-Anisyl	EtOH	0.5	**2a**	100
9	**1d**	$CH_3(CH_2)_{11}$	*o*-Anisyl	C_6H_6–EtOH	1.0	**2b**	100
10	**1e**	$PhCH_2$	*o*-Anisyl	C_6H_6–EtOH	1.0	**2c**	83[e]
11	**1f**		*o*-Anisyl	C_6H_6–EtOH	1.0	**2d**	99
12	**1g**		*o*-Anisyl	C_6H_6–EtOH	0.5	**2e**	99
13	**1h**	2-Naphthyl	*o*-Anisyl	C_6H_6–EtOH	0.5	**2f**	99
14	**1i**	*p*-$NO_2C_6H_4$	*o*-Anisyl	C_6H_6–EtOH	0.5	**2g**	98
15	**1j**	*p*-$MeOC_6H_4$	*o*-Anisyl	C_6H_6–EtOH	0.5	**2h**	99

[a] The reaction was carried out in the presence of 1 mol % of catalyst at rt in a 1:1 mixture of the indicated solvent and EtOH unless otherwise noted.
[b] Isolated yield.
[c] *o*-Anisyl = *ortho*-methoxyphenyl.
[d] The reaction was conducted in EtOH only.
[e] Benzyl ethyl ether was obtained in 13% yield.

TfOH even after 1 d. Besides alcohols **2**, *ortho*-alkynylbenzoic acid ethyl esters **1′** were formed together with a small amount of isocoumarins **3** in each reaction in Table 1.[7]

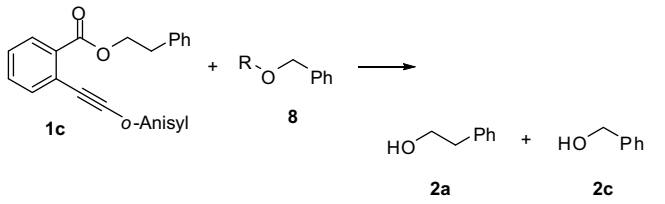
On the basis of these results, a plausible mechanism is illustrated in Scheme 2.[8] The coordination of the triple bond of **1** to the gold catalyst enhances the electrophilicity of alkyne, and the subsequent nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne forms the intermediate **5** through **4**.[9,10] Then, the nucleophilic attack of EtOH to **5** gives *ortho*-ester type intermediate **6**. Elimination of ROH **2** occurs through **7** to afford **5′**. The gold catalyst is reproduced by the formation of transesterification product **1′** via retro-cyclization of **5′**. Obviously, all processes in this scheme are reversible, but the deprotection reaction proceeds due to the existence of a large amount of EtOH. Previously, we reported the gold-catalyzed etherification with **1** as a masked electrophile.[5] In that case, even if intermediate **5′** would be formed from **5**, it would be changed back to **5** reversibly because the amount of alcohol was small and finally, etherification products would be obtained. On the other hand, even with excess amounts of EtOH, etherification products were obtained from several esters derived from benzyl, cinnamyl, and 1-phenylcyclohexyl alcohols as mentioned before. In these cases, EtOH would attack R group of **5** preferably because R–O bond would be significantly weakened due to the high stability of the resulting carbocation intermediates. The formation of **3** might be accounted for by the hydrolysis of the intermediate **5** with small amounts of water, which might exist in the reaction medium.

We next investigated the selective deprotection using **1c** and other protected alcohols **8**, and the results are summarized in Table 2. Treatment of 1:1 mixture of **1c** and benzyl acetate **8a** with the gold catalyst resulted in the chemoselective deprotection of **1c** over **8a**, and phenethyl alcohol **2a** was produced quantitatively



Scheme 2.

Table 2
Selective deprotection between **1c** and **8**[a]



Entry	8	R	Conditions	Yield[b] (%)	
				2a	2c
1	**8a**	Ac	Ph_3PAuCl–AgOTf[c]	100	0[d]
2	**8b**	Bz	Ph_3PAuCl–AgOTf[c]	100	0[d]
3	**8c**	TBS	Ph_3PAuCl–AgOTf[c]	100	0[d]
4	**8c**	TBS	TBAF[e]	0[f]	99
5	**8d**	THP	Ph_3PAuCl–AgOTf[c]	100	0[d]
6	**8d**	THP	TsOH[g]	0[f]	99

[a] The reaction was carried out with 1:1 mixture of **1c** and **8**.
[b] Isolated yield.
[c] The reaction was carried out with a mixture of Ph_3PAuCl (1 mol %) and AgOTf (1 mol %) in a 1:1 mixture of benzene and EtOH at rt within 1 h.
[d] **8** was recovered, quantitatively.
[e] The reaction was carried out with TBAF (1.1 equiv) in THF at rt for 1 h.
[f] **1c** was recovered quantitatively.
[g] The reaction was carried out with TsOH (10 mol %) in a mixture of MeOH and THF at rt for 1 h.

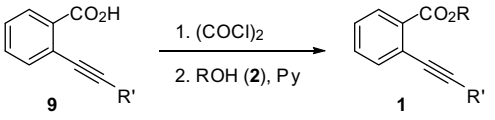
together with the recovered **8a** (entry 1). The selective deprotection of **1c** was also observed against benzyl benzoate **8b** (entry 2). In the case of a mixture of **1c** and TBDMS ether **8c**, each of them was deprotected selectively by use of the gold catalyst and 1.1 equiv of TBAF, respectively (entries 3 and 4). Analogously, selective deprotections of **1c** and THP ether **8d** were achieved with the gold catalyst and a 10 mol % of TsOH, respectively (entries 5 and 6).

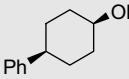
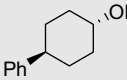
The protection of alcohols and phenols can be achieved easily by the esterification with *ortho*-alkynylbenzoic acid **9**, using oxalyl chloride under the standard conditions. Irrespective of alcohols and phenols, the protection proceeded smoothly, and the corresponding esters **1** were obtained in good to high yields (Table 3).

It is worth mentioning that *ortho*-halo-benzoyl chloride is an alternative protecting agent for the present protocol. Indeed, the protection of **2a** with commercially available *ortho*-iodobenzoyl chloride gave **10a** in 97% yield. Deprotection of **10a** can be conducted by the conversion of iodo group to the alkynyl group by the Sonogashira coupling, followed by the gold-catalyzed transesterification; **2a** is obtained in 96% overall yield from **10a** as shown in Scheme 3. We also examined the same protocol with chiral (*S*)-2-octanol **2i**. Successive protection and deprotection reaction afforded (*S*)-**2i** via the formation of **10b** without loss of enantiomeric purity, which was determined from its benzoate derivative **2j** by HPLC analysis with a Daicel Chiralpak AD-H column (Scheme 4).

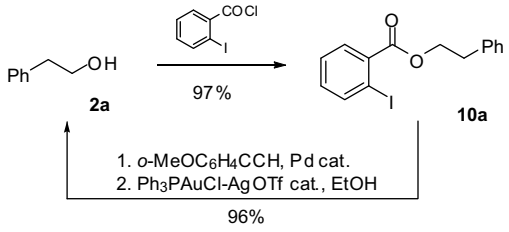
In conclusion, *ortho*-alkynyl benzoyl moiety was found to be useful protecting group for alcohols and phenols due to its easy protection and deprotection procedure. The alkynophilicity of the gold catalyst enables the chemoselective deprotections over other protected alcohols, such as acetate, benzoate, TBS ether, and THP ether. The protection can be conducted easily by esterification with *ortho*-alkynylbenzoic acid **9**. Alternatively, *ortho*-iodobenzoyl chloride can be used as a protecting agent. The resulting esters can be cleaved by successive alkynylation and gold-catalyzed transesterification. Further, studies to extend the scope of synthetic utility are in progress in our laboratory.

Table 3
Protection of alcohols and phenols with **9**

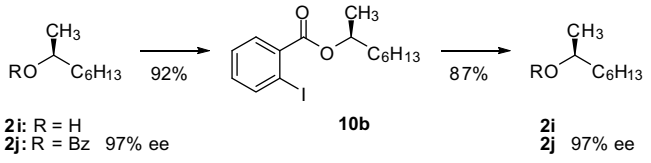


Entry	9	R′	ROH (**2**)	1	Yield[a] (%)
1	**9a**	Bu	$PhCH_2CH_2OH$ (**2a**)	**1a**	77
2	**9b**	Ph	$PhCH_2CH_2OH$ (**2a**)	**1b**	80
3	**9c**	*o*-Anisyl	$PhCH_2CH_2OH$ (**2a**)	**1c**	81
4	**9c**	*o*-Anisyl	 (**2d**)	**1f**	85
5	**9c**	*o*-Anisyl	 (**2e**)	**1g**	93
6	**9c**	*o*-Anisyl	2-Naphthol (**2f**)	**1h**	86
7	**9c**	*o*-Anisyl	*p*-$NO_2C_6H_4OH$ (**2g**)	**1i**	83
8	**9c**	*o*-Anisyl	*p*-$MeOC_6H_4OH$ (**2h**)	**1j**	85

[a] Isolated yield.



Scheme 3.



2i: R = H
2j: R = Bz 97% ee

2i
2j 97% ee

Scheme 4.

References and notes

1. For reviews, see: (a) Otera, J. *Chem. Rev.* **1993**, *93*, 1449–1470; (b) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971–985; (c) Hoydonckx, H. E.; De Vos, D. E.; Chavan, S. A.; Jacobs, P. A. *Top. Catal.* **2004**, *27*, 83–96.
2. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999; (b) Kocienski, P. J. *Protective Groups*, 3rd ed.; Thieme: Stuttgart, 2003.
3. For examples, see: (a) Xiang, J.; Toyoshima, S.; Orita, A.; Otera, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3670–3672; (b) Baumhof, P.; Mazitschek, R.; Giannis, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3672–3674; (c) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Tetrahedron Lett.* **2002**, *43*, 879–882.
4. For recent reviews on the Au-catalyzed reactions, see: (a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387–391; (b) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296; (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896–7936; (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333–346; (e) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403; (f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211; (g) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449; (h) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903; (i) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917–4938.
5. Asao, N.; Aikawa, H.; Tago, S.; Umetsu, K. *Org. Lett.* **2007**, *9*, 4299–4302.
6. 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*, 558–559; (b) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.;

Mannina, L., *Tetrahedron* **2003**, *59*, 2067–2081; (c) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936–5942; (d) Marchal, E.; Uriac, P.; Legouin, B.; Toupet, L.; Van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979–9990.
7. The deprotected alcohols **2** were easily separated from byproducts **1**′ and **3** by standard purification procedure with silica gel column chromatography.
8. (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650–12651; (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921–10925; (c) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458–7459; (d) Asao, N. *Synlett* **2006**, 1645–1656.
9. Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239–1243.
10. Kusama, H.; Iwasawa, N. *Chem. Lett.* **2006**, *35*, 1082–1087.