SHORT COMMUNICATION

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201400066

Gold(I)-Catalyzed Hydration of Alkynylphosphonates: Efficient Access to β-Ketophosphonates

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Keywords: Synthetic methods / Gold / Hydration / Phosphonates / Alkynes / Ketophosphonates

A general, efficient, and highly regioselective protocol with the use of a gold(I) complex catalytic system for the transformation of alkynylphosphonates into the corresponding β-ketophosphonates has been successfully developed. This method produces a variety of β-ketophosphonates with the advantages of mild reaction conditions, high functional-group tolerance, and excellent yields.

Introduction

Over the past several decades, gold catalysis has emerged to become a powerful tool enabling the creation of numerous novel organic transformations.[1] Among these gold-facilitated transformations, those concerning the catalytic hydration of unactivated alkynes have received much attention, as they can yield the corresponding Markovnikov products with complete atom economy under mild reaction conditions and with the use of water as a cheap and safe oxygen resource. The first example of the gold-catalyzed hydration of alkynes was reported in 1991 by Fukuda and Utimoto.[2] Twenty years later, there was a breakthrough in this field with the independent discovery of efficient gold-catalyzed hydration reactions by the groups of Hayashi,[3] Laguna,[4] Schmidbaur,[5] Nolan,[6] Hammond,[7] Corma,[8] and others.[9] Various types of alkyne substrates have been used with gold catalysts[10] in hydration reactions, and the corresponding dialkyl or alkylaryl ketones were obtained.[11] It is surprising, however, that examples of the gold-catalyzed hydration of α-heteroatom-substituted alkynes are still limited. Very recently, we first reported the gold-catalyzed hydration of haloalkynes to synthesize α-halomethyl ketones.[12] To further explore and expand the utility of gold catalysis in hydration reactions and to provide potential access to important α-functionalized carbonyl compounds, it is necessary to broaden the scope of α-substituted alkynes.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201400066.

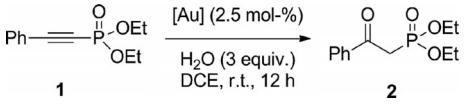
β-Ketophosphonate derivatives are extremely valuable carbonyl compounds that exhibit a variety of biological activities[13] and outstanding metal-complexing abilities.[14] They also serve as useful building blocks in organic synthesis,[15] especially as intermediates for the formation of α,β-unsaturated carbonyl compounds[16] and chiral β-hydroxy[17] and β-amino[18] phosphonic acids. To date, there have been numerous reported methods for the synthesis of β-ketophosphonate derivatives,[19] but there are still calls for novel methods, especially those that are performed under mild conditions with high functional-group tolerance. On the basis of our continuing interest in the construction of various α-functionalized carbonyl compounds through gold-catalyzed reactions,[12,20] herein we present a mild and highly efficient method for the synthesis of β-ketophosphonates.

Results and Discussion

Our initial work focused on diethyl (phenylethynyl)phosphonate (**1a**), which was subjected to a solution of $Ph_3PAuNTf_2$[21] (2.5 mol-%, Tf = trifluoromethylsulfonyl) and H_2O (1–5 equiv.) in 1,2-dichloroethane (DCE), and the reaction was then run for 12 h at room temperature. Diethyl (2-oxo-2-phenylethyl)phosphonate (**2a**) was obtained in 73% yield according to NMR spectroscopy (Table 1, entry 1). Then, we tuned the steric and electronic properties of the gold catalyst (Table 1, entries 2–9). Gratifyingly, the use of $XPhosAuNTf_2$ (2.5 mol-%, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) bearing a bulky ligand in DCE resulted in a sharp increase in the yield (Table 1, entry 8). Other gold catalysts worked equally well (Table 1, entries 6, 7, and 9). In the presence of 1.75 and 1 mol-% $XPhosAuNTf_2$, the catalytic hydration of **1a** gave **2a** in 76 and 51% yield, respectively, as determined by

NMR spectroscopy (Table 1, entries 10 and 11). In addition to DCE, methanol and THF afforded the products as well, albeit in lower yields (Table 1, entries 12–16). To confirm that gold was the true catalyst of the reaction, a series of control experiments were performed. No hydration product was detected if the reaction was performed under similar conditions without a gold catalyst (Table 1, entries 17–19). Therefore, the optimized reaction conditions are the following: alkynylphosphonate (1 equiv.), H_2O (3 equiv.), XPhosAuNTf$_2$ (2.5 mol-%) in DCE at room temperature for 12 h (Table 1, entry 8).

Table 1. Screening of the optimized reaction conditions.[a]



1 2

Entry	Catalyst	Solvent	Yield [%][b]
1	$Ph_3PAuNTf_2$	DCE	73
2	$(RO)_3PAuNTf_2$[c]	DCE	82
3	$Cy_3PAuNTf_2$	DCE	65
4	$Et_3PAuNTf_2$	DCE	61
5	IPrAuNTf$_2$	DCE	85
6	MePhosAuNTf$_2$	DCE	90
7	SPhosAuNTf$_2$	DCE	92
8	XPhosAuNTf$_2$	DCE	98[d]
9	BrettphosAuNTf$_2$	DCE	98
10	XPhosAuNTf$_2$	DCE	76[e]
11	XPhosAuNTf$_2$	DCE	51[f]
12	XPhosAuNTf$_2$	DCM	86
13	XPhosAuNTf$_2$	CH_3OH	85
14	XPhosAuNTf$_2$	THF	72
15	XPhosAuNTf$_2$	CH_3CN	–
16	XPhosAuNTf$_2$	DMF	–
17	$AgSbF_6$ (r.t. to 85 °C)[g]	DCE	–
18	$AgNTf_2$ (r.t. to 85 °C)[g]	DCE	–
19	$HNTf_2$[g]	DCE	–

[a] In a vial; [**1a**] = 0.1 M. Cy = cyclohexyl, IPr = 1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1*H*-imidazole, MePhos = 2-(dicyclohexylphosphino)-2′-methylbiphenyl, SPhos = 2-(dicyclohexylphosphino)-2′,6′-dimethoxybiphenyl, BrettPhos = dicyclohexyl[3,6-dimethoxy-2′,4′,6′-tris(1-methylethyl)-1,1′-biphenyl-2-yl]phosphine. [b] Estimated by ^{1}H NMR spectroscopy by using diethyl phthalate as an internal reference. [c] R = 2,4-(tBu)$_2$Ph. [d] Yield of isolated product was 96%. [e] 1.75 mol-% XphosAuNTf$_2$ was used; 19% of **1a** remained unreacted. [f] 1 mol-% XPhosAuNTf$_2$ was used; 45% of **1a** remained unreacted. [g] 10 mol-% catalyst was used.

After optimizing the reaction conditions, we explored the substrate scope, and the results are illustrated in Table 2. The outcome of this hydration reaction was found to be only slightly influenced by the electronic properties of the diethyl (phenylethynyl)phosphonates, and a variety of β-ketophosphonates substituted with electron-donating or electron-withdrawing groups were readily synthesized in excellent yields (see **2b**–**h**). The bromine atom was compatible with this reaction sequence by providing a handle for further functionalization (see **2f** and **2h**). The conversion rate of **1c** and **1d** were slow under the optimized conditions, and 10% of the substrates was recovered after the reaction was allowed to run overnight. It is remarkable that reactions with substrates bearing bioactive groups such as piperonyl and thienyl also proceeded smoothly (see **2i** and **2j**). If *ortho*-substituted (phenylethynyl)phosphonates such as diethyl [2-oxo-2-(*o*-tolyl)ethyl]phosphonate and diethyl [2-(2-bromophenyl)-2-oxoethyl]phosphonate were used, only trace amounts of the desired products were observed, likely due to steric hindrance. Many synthetically important substituent groups including alkyl (see **2k**), chloro (see **2l**), ester (see **2m**), sulfonoxyl (see **2n**), silyl ether (see **2o**), and phthalimide groups (see **2p**) were well tolerated with excellent yields of the desired isolated products. Interestingly, the presence of bulky groups (cyclopropyl, cyclohexenyl, and cyclohexyl groups) in the 3-position of the alkylalkyne had no negative effect on the efficiency of the transformation (see **2q**–**s**). By using other phosphonates as substrates, this alkyne hydration strategy was extended to access the corresponding β-ketophosphonates (see **2t**–**v**).

Conclusions

In summary, we developed a simple method for the gold-catalyzed regioselective hydration of alkynylphosphonates. β-Ketophosphonates were prepared in high yields under milder conditions than with other catalytic systems. Notably, functional groups such as halogen atom, ester, sulfonoxyl, silyl ether, and phthalimide groups were readily carried through the hydration reaction, which allowed subsequent elaboration of the products.

Experimental Section

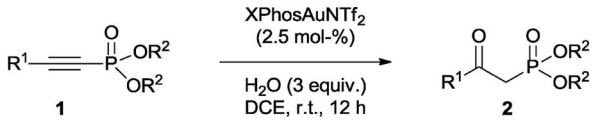
General Procedure for the Synthesis of 2a–v: To a solution of alkynylphosphonate (0.3 mmol) in DCE (3 mL) was added H_2O (0.9 mmol, 16.2 mg) and XPhosAuNTf$_2$ (0.0075 mmol, 6.7 mg). The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. The reaction typically took 12 h. Upon completion of the reaction, the mixture was concentrated, and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate) to afford **2a**–**v**.

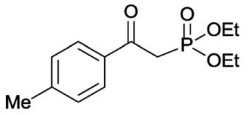
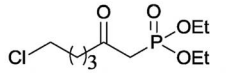
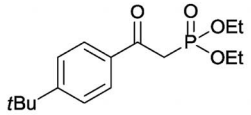
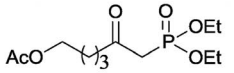
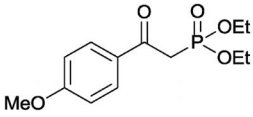
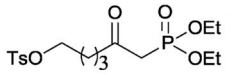
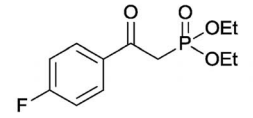
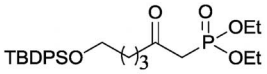
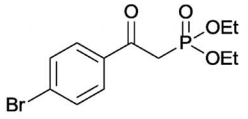
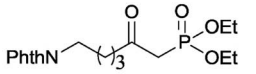
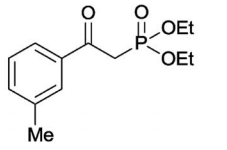
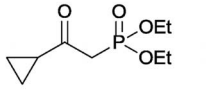
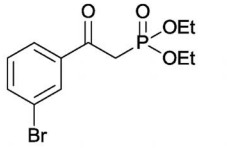
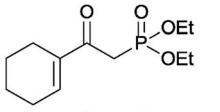
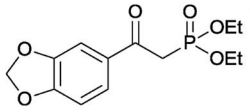
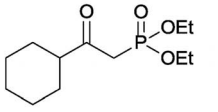
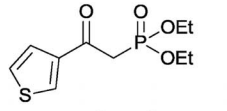
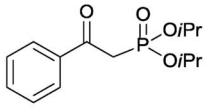
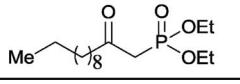
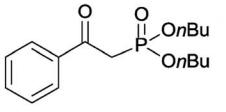
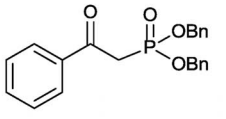
Supporting Information (see footnote on the first page of this article): General information; general procedures for the synthesis of **2a**–**v**; spectral data for **2a**–**v**; references; and ^{31}P NMR, ^{1}H NMR, and ^{13}C NMR spectra of **2a**–**v**.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (NSFC) (grant number 21302048), the Specialized Research Fund for the Doctoral Program of Higher Education (grant number 20130161120035), the China Postdoctoral Science Foundation (grant number 2013M540625), the Hunan Provincial Natural Science Foundation of China (grant number 14JJ7028), and the Department of Science and Technology Foundation of Hunan Province (grant number 2010FJ306).

Table 2. Substrate scope.[a,b]



Entry	Product		% Yield[b]	Entry	Product		% Yield[b]
1		**2b**	90	11		**2l**	96
2[c]		**2c**	86	12		**2m**	97
3[c]		**2d**	85	13[c,d]		**2n**	85
4		**2e**	95	14[d]		**2o**	95
5		**2f**	94	15[d,e]		**2p**	87
6		**2g**	93	16[c]		**2q**	85
7		**2h**	93	17[e]		**2r**	88
8		**2i**	97	18[e]		**2s**	87
9		**2j**	94	19		**2t**	94
10		**2k**	94	20		**2u**	97
				21[c]		**2v**	86

[a] [**1**] = 0.1 M. [b] Yield of isolated product. [c] 90% conversion of **1**. [d] Ts = *p*-tolylsulfonyl, TBDPS = *tert*-butyldiphenylsilyl, Phth = phthalyl. [e] 93% conversion of **1**.

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Received: January 15, 2014
Published Online: March 17, 2014

