Homogeneous Catalysis

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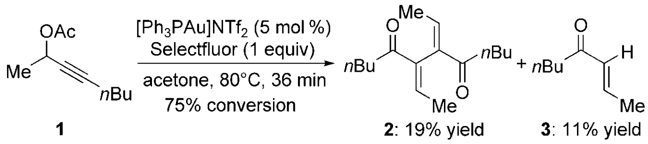
Gold-Catalyzed Homogeneous Oxidative Cross-Coupling Reactions**

Guozhu Zhang, Yu Peng, Li Cui, and Liming Zhang*

Homogeneous gold catalysis has attracted much attention lately owing to the exceptional capacity of gold complexes/salts in activating alkynes and allenes toward nucleophilic attack.[1] A variety of practically useful synthetic methods using alkyne or allene substrates have been developed. However, most of these reactions do not involve changes in the oxidation state of the metal, which is commonly observed in catalysis by late transition metals such as palladium, nickel, and rhodium. The combination of a Au(I)/Au(III) catalytic cycle with contemporary homogeneous gold chemistry based on alkyne/allene activation would substantially broaden the field of gold catalysis and offer more functionalized products.

The reduction and oxidation processes catalyzed by gold nanoparticles or supported gold have been well studied;[2–4] because of their heterogeneous nature, the reaction mechanisms in many cases are not clear, however, in some studies a Au(I)/Au(III) catalytic cycle was either proposed or highly likely to be involved.[5] This catalytic cycle has also been invoked in gold-catalyzed Suzuki and Sonogashira reactions using soluble gold catalysts at rather high reaction temperatures (130 °C), wherein the reaction homogeneity is likely but not vigorously established.[6] These encouraging results point to the feasibility of a homogeneous system involving Au(I)/Au(III) catalytic cycles. Such homogeneous Au(I)/Au(III) catalysis not only facilitates reaction mechanism studies but also permits systematic modification of gold catalysts to improve the reaction scope, selectivity, reactivity, and efficiency.



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Indeed, gold catalysis involving Au(I)/Au(III) catalytic cycles have been realized lately in the oxidative dimerization of non-activated arenes[7a] and aryl propiolates.[7b] These reactions are most likely to be homogeneous but proof of this is lacking. In the latter study by Wegner et al., the reaction also incorporated a Au(III)-catalyzed cyclization of aryl propiolates, thus combining a Au(I)/Au(III) catalytic cycle with contemporary gold chemistry using alkyne substrates. An earlier study by Hashmi et al. proceeded similarly with Au(III)-catalyzed cyclization of allenyl carbinols and subsequent dimerization albeit in a substoichiometric fashion.[8a] Although elegant proofs of concepts, these reactions often resulted in low yields and the dimerization reaction seriously limited their synthetic potential. To date, no cross-coupling reactions involving a combination of Au(I)/Au(III) catalytic cycles and contemporary gold chemistry using alkyne/allene substrates has been reported. Herein, we disclose the first example of this type of gold-catalyzed oxidative cross-coupling reaction, and synthetically useful α-arylenones are formed in one step; moreover, the homogeneity of this chemistry is supported by dynamic light scattering experiments.

In our attempts to develop a gold-catalyzed synthesis of α-fluoroenones from propargylic acetates,[9] Selectfluor was chosen as an electrophilic fluorinating reagent. To our surprise, when propargylic acetate **1** was treated with [$Ph_3PAu]NTf_2$ (5 mol %) and Selectfluor (1 equiv) in acetone in a sealed vial at 80 °C, enone dimer **2** was formed in 19 % yield along with 11 % of enone **3**[10] and some unreacted starting material [Eq. (1)]. Although the initial yield was low, we were intrigued by the reaction and proposed a working mechanism. As shown in Scheme 1, gold-catalyzed tandem reactions of propargylic acetate **1**, as established by previous studies by us and others,[10,11] should lead to the formation of intermediate **A** upon hydrolysis, which is then oxidized by Selectfluor to a give a Au(III) species (i.e., **B**). The transmetalation from **A** to **B** could lead to the diorganogold(III) intermediate **C**, which could then undergo reductive elimination to give dimer **2** and regenerate the gold(I) catalyst. The essential oxidation of **A** to **B** by Selectfluor is most likely facilitated by the 1-acylalkenyl ligand, which makes the gold center relatively electron-rich. The alternative oxidation of [$Ph_3PAu]NTf_2$ to Au(III) is less likely because of its cationic nature. Notably, other electrophilic fluorine reagents such as 1-fluoropyridinium tetrafluoroborate and *N*-fluorobenzenesulfonimide did not promote this dimerization.

We reason that the organogold(I) **A** could be supplanted with external organometallic reagents for transmetalation. Consequently, cross-coupling product **4**, instead of dimer **2**, would be formed by the reductive elimination of intermediate **D**. This oxidative cross-coupling reaction would open up a novel area for gold catalysis and bridge contemporary gold catalysis, using alkyne/allene substrates, and the well-established late transition metal catalyzed cross-coupling reactions.

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[*] G. Zhang, Dr. Y. Peng, Dr. L. Cui, Prof. Dr. L. Zhang
Department of Chemistry, University of Nevada, Reno
1664 North Virginia Street, Reno, NV 89557 (USA)
Fax: (+1) 775-784-6804
E-mail: lzhang@chem.unr.edu
Homepage: http://wolfweb.unr.edu/homepage/lzhang/

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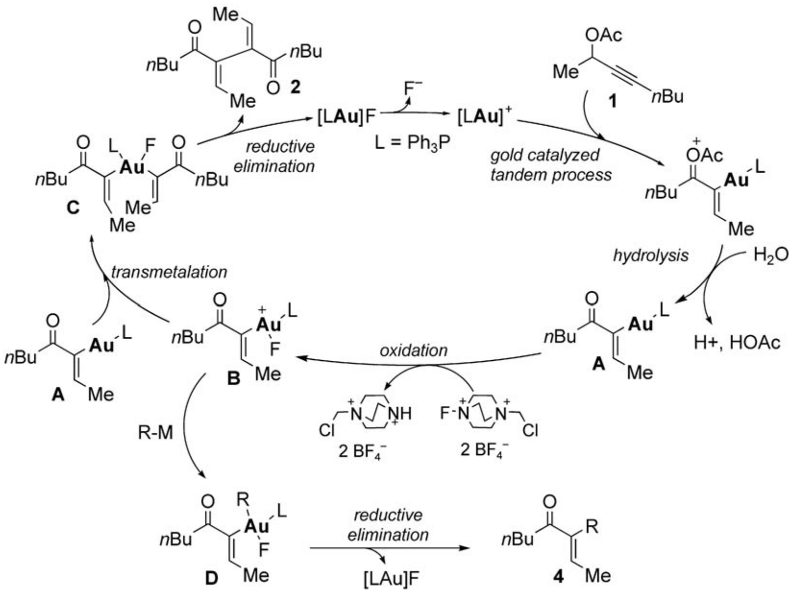
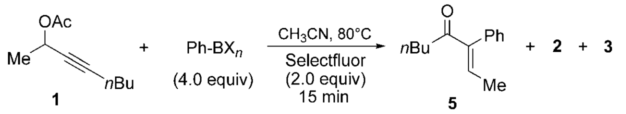


Scheme 1. Proposed reaction mechanism and design.

We chose arylboronates/arylboronic acids as the external organometallic reagent because of their stability, availability, and broad spectra of nucleophilicity. With $[Ph_3PAu]NTf_2$ as the catalyst, $PhBF_3K$ was highly active for transmetalation, and as a result biphenyl[5a] was formed predominantly because of premature phenyl transfer from $PhBF_3K$ to $[Ph_3PAu]NTf_2$ instead of transfer to **B**; 3-phenyl-oct-2-en-4-one (**5**) was not observed (Table 1, entry 1). To our delight, 2-phenyl[1,3,2]dioxaborolane gave cross-coupling product **5** albeit in a low yield, and the major product was enone dimer **2** (Table 1, entry 2). The formation of **2** suggested that the phenyl transfer from the boronate was not facile enough. While searching for a boronate with a reactivity between that of $PhBF_3K$ and 2-phenyl[1,3,2]dioxaborolane, other boronates were used without much success (Table 1, entries 3 and 4). Since tetracoordinated, negatively charged boronates are well accepted as the species undergoing transmetalation in many transition metal catalyzed reactions,[12] including the Suzuki–Miyaura reaction, we reasoned that such species were the ones undergoing the phenyl transfer to the Au(III) complex **B**, and the low reactivity of dialkoxylphenylboronates (Table 1, entries 2–4) might be a result of low concentrations of $[PhB(OR)_2(OH)]^-$ formed by the reaction of $PhB(OR)_2$ with a small amount of H_2O in acetonitrile. Consequently, we examined the effect of H_2O using 2-phenyl-[1,3,2]dioxaborinane. Gratifyingly, a much improved yield of **5** was realized by using a $MeCN/H_2O$ (100:1) solvent mixture (Table 1, entry 5). We anticipated that commercially available phenylboronic acid should also be effective as the phenyl source as dialkoxyphenylboronates can hydrolyze to boronic acids. A quick search for the optimal water concentration using phenylboronic acid revealed that a $MeCN/H_2O$ (20:1) solvent mixture offered the best yield as determined by NMR methods (Table 1, entry 7). Other gold catalysts including **6** (Table 1, entry 9) and $[(4\text{-}CF_3C_6H_4)_3PAu]NTf_2$ (Table 1, entry 10) gave similar results. In entry 7 of Table 1, the major side product was enone **3**, likely formed by the protodeauration of **A** or **B** by in situ generated $HNTf_2$. We reasoned that a weaker in situ generated acid would minimize this side reaction. The enone formation indeed decreased by using $[(Ph_3PAu)_3O]H_2F_3$[13] (Table 1, entry 11) or $Ph_3PAuOBz$ (Table 1, entry 12). Surprisingly, Ph_3PAuCl catalyzed this cross-coupling reaction exceptionally well, and **5** was formed in 72 % yield as determined by NMR analysis (Table 1, entry 13). The reaction could not be additionally improved by using additives such as LiF or by using fewer equivalents of the reagents (Table 1, entry 14). The role of Ph_3PAuCl, which is normally catalytically inert, in this reaction was examined. The treatment of Ph_3PAuCl with Selectfluor (20 equiv) in $MeCN/H_2O$ (20:1) at 80 °C for 15 minutes gave a clear yellow solution and, moreover, $Ph_3P{=}O$[14] was detected by both ^{31}P NMR and ES^+ MS analyses. Although the nature of the gold

Table 1: Gold-catalyzed cross-coupling reactions: Reaction conditions optimization.[a]



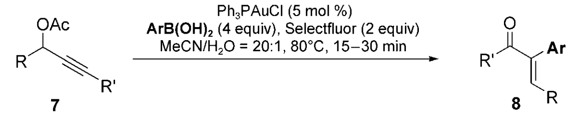
Entry	Catalyst (5 mol %)	$PhBX_n$	Reaction conditions	Yield [%][c] 5	2	3
1[b]	$[Ph_3PAu]NTf_2$	$PhBF_3K$	MeCN[d]	0	0	0
2[b]	$[Ph_3PAu]NTf_2$	$PhB(OCH_2)_2$	MeCN	30	60	0
3[b]	$[Ph_3PAu]NTf_2$	PhB(pin)	MeCN	21	66	<5
4[b]	$[Ph_3PAu]NTf_2$	$PhB[O(CH_2)_3O]$	MeCN	30	44	<5
5	$[Ph_3PAu]NTf_2$	$PhB[O(CH_2)_3O]$	$MeCN/H_2O$ 100:1	50	17	9
6	$[Ph_3PAu]NTf_2$	$PhB(OH)_2$	$MeCN/H_2O$ 100:1	25	14	13
7	$[Ph_3PAu]NTf_2$	$PhB(OH)_2$	$MeCN/H_2O$ 20:1	53	9	23
8	$[Ph_3PAu]NTf_2$	$PhB(OH)_2$	$MeCN/H_2O$ 5:1	39	10	24
9	**6**[e]	$PhB(OH)_2$	$MeCN:H_2O$ 20:1	54	10	<5
10	$[(CF_3Ph)_3PAu]NTf_2$	$PhB(OH)_2$	$MeCN/H_2O$ 20:1	50	8	21
11	$[(Ph_3PAu)_3O]H_2F_3$	$PhB(OH)_2$	$MeCN/H_2O$ 20:1	64	8	11
12	$Ph_3PAuOBz$	$PhB(OH)_2$	$MeCN/H_2O$ 20:1	59	8	5
13	Ph_3PAuCl	$PhB(OH)_2$	$MeCN/H_2O$ 20:1	72	9	6
14[f]	Ph_3PAuCl	$PhB(OH)_2$	$MeCN/H_2O$ 20:1	50	9	15
15	$AuCl_3$	$PhB(OH)_2$	$MeCN/H_2O$ 20:1	25	16	14

[a] Reaction run in a flask using MeCN distilled over CaH_2. The reaction concentration was 0.05 M. [b] Reaction run in a 7 mL vial with HPLC-grade MeCN. [c] Estimated by ^1H NMR analysis using diethyl phthalate as internal reference. [d] Reaction time: 40 min. [e] $[(2\text{-Biphenyl})Cy_2PAu]NTf_2$. [f] Used 1.5 equiva of Selectfluor and 3 equiv of $PhB(OH)_2$.

species generated needs to be studied additionally, this yellow solution was indeed catalytically active, affording **5** in 60% yield (NMR). At this stage the gold catalyst for the initial conversion of propargylic substrate **1** into intermediate **A**, whether it be Au(I) or Au(III), is not clear as our previous work[10,11] showed that both species were viable. Finally, $AuCl_3$ did catalyze this reaction albeit with low efficiency (Table 1, entry 15).

By using the optimized conditions (Table 1, entry 13) the reaction scope was first studied by varying propargylic acetates. As shown in Table 2, a range of acetates having various functionalized or nonfunctionalized alkyl groups on both ends of the propargyl moiety were tolerated, yielding 2-phenylenones **8b**, **8d–8g**, and **8i** in respectful yields. Similarly, substrates having aryl substituents such as phenyl or 4-bromophenyl groups at either end of the propargyl moiety reacted smoothly, yielding **8a**, **8c**, and **8h** in fairly good yields. In addition, β-unsubstituted-α-phenylenone **8j** was obtained in 61% yield from a substrate without substitution at the propargylic position. The scope of arylboronic acids was examined next. Electron-withdrawing groups including ester and chloro moieties were tolerated in the *meta* (Table 2, entry 14) or *para* (Table 2, entries 12 and 13) positions of the phenyl ring, affording α-arylenones **8l–8n** in mostly acceptable yields; notably, less water was used for the ester substrates so as to minimize enone formation (Table 2, entries 12 and 14). In addition, *p*-tolylboronic acid (Table 2, entry 11) reacted very well. The more electron-rich 4-methoxyphenylboronic acid did not afford any of the desired product, likely because of the incompatibility of the anisole ring with strongly oxidative Selectfluor. *Ortho*-substituents including methyl, MeO, and Cl were generally detrimental to this reaction, suggesting that this reaction is sensitive to the steric bulk on the aromatic ring.

Table 2: Gold-catalyzed oxidative cross-coupling reactions: Scope.[a]



Entry	R	R′	$ArB(OH)_2$	**8** (Yield [%])
1	Ph	*n*-butyl	$PhB(OH)_2$	**8a** (62)
2	*i*Pr	*n*-butyl	$PhB(OH)_2$	**8b** (65)
3	Me	Ph	$PhB(OH)_2$	**8c** (59)
4	Me	$MeOCH_2CH_2$	$PhB(OH)_2$	**8d** (60)
5	Me	cyclohexyl	$PhB(OH)_2$	**8e** (68)
6	cyclohexyl	cyclohexyl	$PhB(OH)_2$	**8f** (70)
7	$PhCH_2CH_2$	*n*-butyl	$PhB(OH)_2$	**8g** (70)
8	*p*-BrC_6H_4	*n*-butyl	$PhB(OH)_2$	**8h** (59)
9	$AcOCH_2CH_2$	*n*-butyl	$PhB(OH)_2$	**8i** (61)
10	H	cyclohexyl	$PhB(OH)_2$	**8j** (61)
11	cyclohexyl	*n*-butyl	*p*-$MePhB(OH)_2$	**8k** (72)
12	cyclohexyl	*n*-butyl	*p*-$MeO_2CPhB(OH)_2$	**8l** (57)[b]
13	cyclohexyl	*n*-butyl	*p*-$ClPhB(OH)_2$	**8m** (58)
14	cyclohexyl	*n*-butyl	*m*-$MeO_2CPhB(OH)_2$	**8n** (45)[c]

[a] Reactions run in flasks using MeCN distilled over CaH_2. The reaction concentration was 0.05 M. [b] $CH_3CN/H_2O = 100:1$. [c] $MeCN/H_2O = 200:1$.

The side products for this oxidative cross-coupling reaction were enones, enone dimers, and α-fluoroenones, all of which can not be completely suppressed. Importantly, all the cross-coupling reactions proceeded with excellent *E* selectivity, and the *Z* isomers were not detected.

Importantly, no precipitates were observed during these reactions, and the reaction mixtures were either colorless or slightly yellow solutions, indicating the nonexistence of gold nanoparticles, which tend to make the solution purple. To provide additional support for the homogeneous nature of the reaction, we performed dynamic light scattering experiments on the reaction mixture using **1** as the substrate.[15] Although a Microtrac Nanotrac ULTRA having a particle size detection limit of 0.8 nm was used, the filtered reaction solution[16] which was still catalytically active,[17] could not be effectively measured because of the lack of light scattering.[18] This negative result strongly supports the homogeneous nature of this oxidative cross-coupling reaction.

In summary, an unprecedented homogeneous gold-catalyzed oxidative cross-coupling of propargylic acetates and arylboronic acids has been developed, leading to a one-step synthesis of α-arylenones. Whereas the reaction mechanism deserves additional investigation, this chemistry strongly suggests the feasibility of Au(I) and Au(III) catalytic cycles, and indicates that oxidants such as Selectfluor can readily oxidize Au(I) into Au(III). Moreover, this cross-coupling reaction reveals for the first time the synthetic potential of incorporating Au(I)/Au(III) catalytic cycles into gold chemistry and promises a new area of gold research by merging powerful contemporary gold catalysis, using alkyne/allene substrates, and oxidative metal-catalyzed cross-coupling reactions.

Experimental Section

General procedure for gold-catalyzed oxidative cross-coupling reaction: Ph_3PAuCl (0.0075 mmol, 3.7 mg) was added into a solution of the propargylic acetate substrate (0.15 mmol), Selectfluor (2 equiv), and an arylboronic acid (4 equiv) in MeCN and water (anhydrous MeCN/water = 20:1 unless otherwise specified) under N_2. The reaction was heated at 80 °C for the indicated time and then cooled to room temperature. The reaction mixture was treated with aqueous $Na_2S_2O_3$ (5% w/w, 10 mL) and extracted using diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, and filtered. The filtrate was concentrated under vacuum, and the residue was purified by silica gel flash column chromatography to afford the cross-coupling product.

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[1] For selected reviews on gold catalysis, see: a) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**, *37*, 1766; b) A. Arcadi, *Chem. Rev.* **2008**, *108*, 3266; c) Z. G. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239; d) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351; e) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917; f) E. Jiménez-Núñez, A. M. Echa-

varren, *Chem. Rev.* **2008**, *108*, 3326; g) A. Fürstner, P. W. Davis, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; h) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; i) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271.

[2] For a review on Au-catalyzed oxidations and reductions including homogeneous examples, see reference [1h]; for a review on gold-catalyzed oxidation, see: D. T. Thompson, *Top. Catal.* **2006**, *38*, 231.

[3] For recent studies, see: a) A. Grirrane, A. Corma, H. Garcia, *Science* **2008**, *322*, 1661; b) B. P. Taduri, S. M. A. Sohel, H.-M. Cheng, G.-Y. Lin, R.-S. Liu, *Chem. Commun.* **2007**, 2530; c) J. Gong, C. B. Mullins, *J. Am. Chem. Soc.* **2008**, *130*, 16458.

[4] For selected gold-catalyzed oxidations, see: a) B. Guan, D. Xing, G. Cai, X. Wan, N. Yu, Z. Fang, L. Yang, Z. Shi, *J. Am. Chem. Soc.* **2005**, *127*, 18004 – 18005; b) Y. Liu, F. Song, S. Guo, *J. Am. Chem. Soc.* **2006**, *128*, 11332 – 11333; c) B. P. Taduri, S. M. A. Sohel, H.-M. Cheng, G.-Y. Lin, R.-S. Liu, *Chem. Commun.* **2007**, 2530 – 2532.

[5] a) S. Carrettin, J. Guzman, A. Corma, *Angew. Chem.* **2005**, *117*, 2282; *Angew. Chem. Int. Ed.* **2005**, *44*, 2242; b) R. de Souza, M. S. Bittar, L. V. P. Mendes, C. M. F. da Silva, V. T. da Silva, O. A. C. Antunes, *Synlett* **2008**, 1777.

[6] For gold-catalyzed cross-coupling reactions with substrates as oxidants, see: a) C. González-Arellano, A. Corma, M. Iglesias, F. Sanchez, *J. Catal.* **2006**, *238*, 497; b) C. González-Arellano, A. Abad, A. Corma, H. Garcia, M. Iglesias, F. Sanchez, *Angew. Chem.* **2007**, *119*, 1558; *Angew. Chem. Int. Ed.* **2007**, *46*, 1536; c) J. Han, Y. Liu, R. Guo, *J. Am. Chem. Soc.* **2009**, *131*, 2060 – 2061.

[7] a) A. Kar, N. Mangu, H. M. Kaiser, M. Beller, M. K. Tse, *Chem. Commun.* **2008**, 386; b) H. A. Wegner, S. Ahles, M. Neuburger, *Chem. Eur. J.* **2008**, *14*, 11310.

[8] For dimerizations without external oxidants with substoichiometric or stoichiometric amount of Au(III), see: a) A. S. K. Hashmi, M. C. Blanco, D. Fischer, J. W. Bats, *Eur. J. Org. Chem.* **2006**, 1387; b) A. K. Sahoo, Y. Nakamura, N. Aratani, K. S. Kim, S. B. Noh, H. Shinokubo, D. Kim, A. Osuka, *Org. Lett.* **2006**, *8*, 4141.

[9] M. Yu, G. Zhang, L. Zhang, *Org. Lett.* **2007**, *9*, 2147.

[10] a) M. Yu, G. Li, S. Wang, L. Zhang, *Adv. Synth. Catal.* **2007**, *349*, 871; b) N. Marion, P. Carlqvist, R. Gealageas, P. de Fremont, F. Maseras, S. P. Nolan, *Chem. Eur. J.* **2007**, *13*, 6437.

[11] For the very first study of this tandem process, see: a) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804 – 16805; for our additional studies on this system, see: b) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442; c) S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 8414; d) S. Z. Wang, L. M. Zhang, *Org. Lett.* **2006**, *8*, 4585; for related studies by others, see: e) T. Schwier, A. W. Sromek, D. M. L. Yap, D. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2007**, *129*, 9868; f) J. Zhao, C. O. Hughes, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 7436; g) N. Marion, S. Diez-Gonzalez, P. de Fremont, A. R. Noble, S. P. Nolan, *Angew. Chem.* **2006**, *118*, 3729; *Angew. Chem. Int. Ed.* **2006**, *45*, 3647; h) A. Buzas, F. Gagosz, *J. Am. Chem. Soc.* **2006**, *128*, 12614.

[12] D. G. Hall, *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, Wiley-VCH, Weinheim, **2005**.

[13] T. Mathieson, A. Schier, H. Schmidbaur, *Z. Naturforsch. B* **2000**, *55*, 1000.

[14] Ph_3PO is likely formed by hydrolysis of the product of Ph_3P oxidation by Selectfluor.

[15] For details, see the Supporting Information.

[16] Although the reaction mixture is clear, filtration before the measurement using a Millex syringe-driven filter unit (450 nm diameter) is necessary to get rid of the contaminating dust; otherwise, the measurement gave particle sizes of approximately 700 nm, which must result from the dust particles, as gold particles of this size should be visible.

[17] Importantly, the filtrate was still catalytically active, and an additional portion of propargylic acetate **1** was converted into product **2** in the presence of additional Selectfluor and phenylboronic acid without the addition of more of the gold catalyst.

[18] Upon forcing the instrument to perform the measurement, the result was 2.50 nm. As a control experiment, we performed the same measurement of the reaction solvent (filtered), which was also used for zeroing, and an identical number (i.e., 2.50 nm) was obtained, suggesting that the instrument could not effectively give negative results.