Au(I)/Au(III)-catalyzed Sonogashira-type reactions of functionalized terminal alkynes with arylboronic acids under mild conditions

Deyun Qian[1] and Junliang Zhang[*1,2]

Full Research Paper

Open Access

Address:
[1]Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, 3663 N, Zhongshan Road, Shanghai 200062 (P. R. China) and [2]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Ling Ling Road 345 Shanghai 200032 (P. R. China)

Email:
Deyun Qian - 51100606057@ecnu.cn; Junliang Zhang[*] - jlzhang@chem.ecnu.edu.cn

* Corresponding author

Abstract

A straightforward, efficient, and reliable redox catalyst system for the Au(I)/Au(III)-catalyzed Sonogashira cross-coupling reaction of functionalized terminal alkynes with arylboronic acids under mild conditions has been developed.

Introduction

The Sonogashira reaction has become the most important and widely used method for the synthesis of arylalkynes and conjugated enynes, which are precursors for natural products, pharmaceuticals and other materials [1-3]. In the past decade, considerable efforts have been made to enhance the efficiency and generality of this reaction. All kinds of palladium catalyst systems [4-10] and other metal catalyst systems [3] have been developed for facilitating the Sonogashira cross-coupling, as well as expanding the substrate scope [11-14]. Various exam-

ples have recently been reported for the palladium-catalyzed Sonagashira-type cross-coupling of terminal alkynes with arylboronic acids [13], and the Pd(0)/Pd(II) catalytic cycles have been well studied. Nevertheless, this transformation catalyzed by gold, involving Au(I)/Au(III) catalytic cycles has, as yet, been less explored [15-22]. In the few examples already documented some conditions, such as rather high reaction temperatures (130 °C), high catalysis loading or special reagents were required [23]. Herein, we report a straightforward, efficient and

robust catalyst system for the Sonogashira-type cross-coupling, in which Au(I)/Au(III) catalyzed C_{sp}^2–C_{sp} bond formation of terminal alkynes from arylboronic acids under mild conditions.

By analogy with other d^{10} species, Au(I) has the same electronic structure as Pd(0) and can easily interact with the acetylenic group, and has the ability to undergo the Au(I)/Au(III) redox cycles [24,25]. In addition, with an increasing interest in the chemistry of gold(I) and gold(III) compounds, more and more studies have provided strong evidence for the existence of Au(I)/Au(III) catalytic cycles [26-32]. For instance, Zhang and co-workers have developed a gold-catalyzed oxidative cross-coupling reaction of arylboronic acids with propargyl esters [27], and Selectfluor® – a source of electrophilic fluorine – was used to oxidize the resulting Au(I) intermediate to Au(III) species. Recently, Toste reported the first experimental evidence for alkylgold(III) fluorides undergoing C–C bond forming reactions with arylboronic acids [32]. Inspired by these results, we envisioned that terminal alkynes would react with arylboronic acids in the presence of oxidant (Selectfluor®) and base, and undergo a Au(I)/Au(III)-catalyzed Sonogashira-type cross-coupling reaction (Scheme 1).

Scheme 1: Previous work and our projected gold-catalyzed Sonogashira-type cross-coupling.
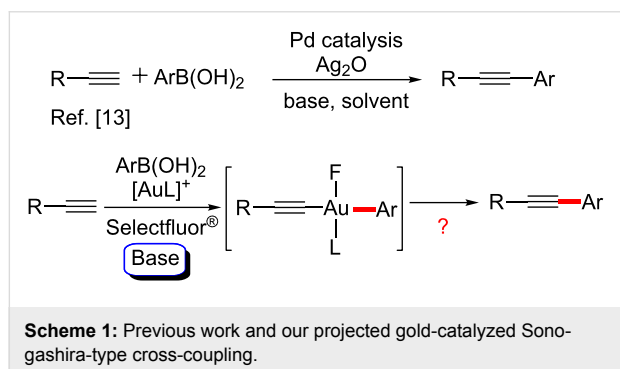
Results and Discussion

We embarked on developing a general protocol for Sonogashira-type cross-coupling by using propargyl tosylamide (**1a**) and phenylboronic acid as the model substrates because of their stability, availability, and broad spectrum of nucleophilicity (Table 1). With commercially available Ph$_3$PAuCl as the catalyst, we treated **1a** and phenylboronic acid in CH$_3$CN at room temperature for 18 h (Table 1, entry 1). Disappointedly, only trace amounts of product was observed under the above conditions. Taking into account the counter ion effects in gold-catalyzed reactions [33-35], Ph$_3$PAuOTf, produced from a combination of Ph$_3$PAuCl and AgOTf in a 1:1 ratio, was investigated. To our delight, the expected product **2a** could be isolated in 56% yield (Table 1, entry 2). Moreover, a control experiment was carried out to determine whether AgOTf by itself could catalyze this transformation. However, no **2a** was

Table 1: Initial screenings of Au(I)/Au(III)-catalyzed Sonogashira coupling[a].

Entry	AuL (5 mol %)	AgX (mol %)	Time (h)	Yield (%)[b]
1	Ph$_3$PAuCl	—	18	trace
2	Ph$_3$PAuCl	AgOTf (5)	22	56
3	—	AgOTf (5)	24	0
4	AuCl	AgOTf (5)	24	21
5	AuCl$_3$	AgOTf (15)	24	37[c]
6[d]	Ph$_3$PAuCl	AgOTf (5)	22	0
7[e]	Ph$_3$PAuCl	AgOTf (5)	22	41
8	Ph$_3$PAuCl	AgBF$_4$ (5)	10	65
9	Ph$_3$PAuCl	AgSbF$_4$(5)	10	62
10	(XPhos)AuCl	AgOTf (5)	24	0
11[f]	dppm(AuCl)$_2$	AgOTf (5)	16	83[c]
12[f]	dppm(AuBr)$_2$	—	16	trace
13[f,g]	Ph$_3$PAuCl	AgOTf (5)	12	72 (73[c])
14[f]	Ph$_3$PAuCl	AgBF$_4$ (5)	12	75 (80[c])

[a]Reaction conditions: The reaction was carried out by using **1a** (0.4 mmol) and phenylboronic acid (0.8 mmol, 2.0 equiv), and 1.05 equiv of Et$_3$N in 2 mL of CH$_3$CN stirred at room temperature. [b]Isolated yields. [c]Yield determined by ^{1}H NMR with dibromomethane as an internal standard. [d]Selectfluor® (0 equiv). [e]PhB(OH)$_2$ (1.5 equiv). [f]Under an atmosphere of nitrogen (N$_2$). [g]The reaction temperature was 50 °C.

produced in the absence of Ph$_3$PAuCl (Table 1, entry 3). Without the phosphine ligand, both AuCl/AgOTf or AuCl$_3$/AgOTf could catalyze this reaction, but the efficiency was quite low (Table 1, entries 4, 5). Without Selectfluor® as additive, the cross-coupling reaction did not occur (Table 1, entry 6), indicating that it was crucial for this transformation via oxidation of gold(I) to the gold(III) species [26-32]. Reducing the amount of phenylboronic acid resulted in a lower yield (Table 1, entry 7). The counter ion effect was then examined on cross-coupling reaction by variation of the silver salts. Alternative catalyst systems led to better yields (Table 1, entries 8, 9 and notably 11 vs entry 2). To optimize the reaction conditions, commonly employed well recognized and commercially available phosphine ligands [17,18], such as dppm, dppe, dppp, dppf, and XPhos, were screened to test the feasibility of this gold-catalyzed cross-coupling (Table 1, entries 10–12, see also Supporting Information File 1). In addition, a series of inorganic and organic bases was also investigated: K$_2$CO$_3$, K$_3$PO$_4$, K$_3$PO$_4$·3H$_2$O, NaHCO$_3$, NaOAc were substantially less effective, whilst organic bases such as iPr$_2$NH, Et$_2$NH, TMEDA, Bu$_3$N, PhNMe$_2$ were not effective bases in this catalytic system (see Supporting Information File 1). These results indicated that Et$_3$N might also play an

important role in this process. Furthermore, it was also found that neither slow addition nor a significant excess of alkyne was required to obtain selective and almost quantitative conversion (see Supporting Information File 1). When the reaction was carried out under an atmosphere of nitrogen (N$_2$) there was a 10% increase in yield (Table 1, entry 8 vs 14). Although the conditions (Table 1, entry 11) seemed the best, this was not the general case for other substrates. Therefore, the optimum conditions were chosen as Ph$_3$PAuCl/AgBF$_4$ as the catalyst, Et$_3$N as the base and under an atmosphere of nitrogen (Table 1, entry 14) .

By using the above optimized conditions, the reaction scope was next studied by varying arylboronic acids. As shown in Scheme 2, functional groups including methyl, chloro, fluoro and ester in the para positions of the phenyl ring were tolerated. Reduced yields were observed with both electron-rich and electron-poor coupling partners (Scheme 2, **2a**–**f**). Arylboronic acids with electron-withdrawing groups afforded **2c**–**2e** in moderate to good yields. Notably, the slightly electron-deficient 4-chlorophenylboronic acid gave the best yield. On the other hand, the more electron-rich 4-methoxyphenylboronic

acid produced the lowest yield, likely due to a competing oxidation of the boronic acid by Selectfluor® [27,30]. Gratifyingly, a number of potentially reactive functionalities, such as tertiary amine, 4-methylbenzenesulfonate, 1,6-enyne and 1,6-diyne, were compatible and remained unaffected, which illustrated the robustness of the catalyst system (Scheme 2, **3**–**8**).

On the basis of these results, a plausible mechanism is outlined in Scheme 3. Initially, unlike traditional C–X oxidative addition as shown by Pd in cross-coupling reactions, the active cationic gold(I) species **A** is oxidized by Selectfluor® to give a gold(III) species **B** [26-32,36]. With the aid of base, the reaction between **B** and alkyne affords intermediate **C**. The weak Au–F bond and the strong B–F bond drive the trans-metalation to produce intermediate **D** [29,36,37]. Finally, **D** undergoes reductive elimination to give the desired product and gold(I) species **A**. In addition, **C** also could experience a five-centered transition state **D'**, which leads to the C–C bond-forming reaction through a bimolecular reductive elimination [30-32]. Notably, we believed that the key step of this mechanism is the generation of cationic gold species **B** by Selectfluor®. In the absence of Selectfluor®, no coupling is possible (Table 1, entry
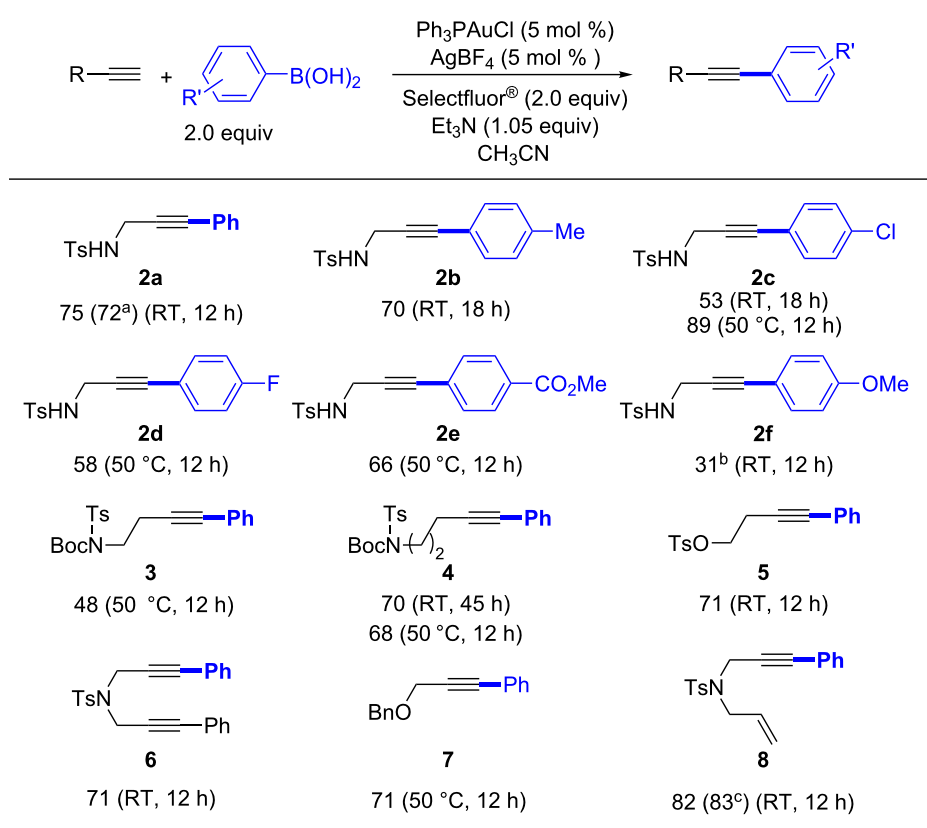
Scheme 2: Scope of the Sonogashira-type cross-coupling reaction (isolated yield). [a]AgOTf in place of AgBF$_4$. [b]Yield determined by ^{1}H NMR, the prouduct could not be separated from the unreacted starting material. [c]AgOTf in place of AgBF$_4$, RT, 36 h.

6). In a current study, Xu and co-workers have provided strong evidence for the oxidation of Au(I) to Au(III) by Selectfluor® in their XPS measurements [36].
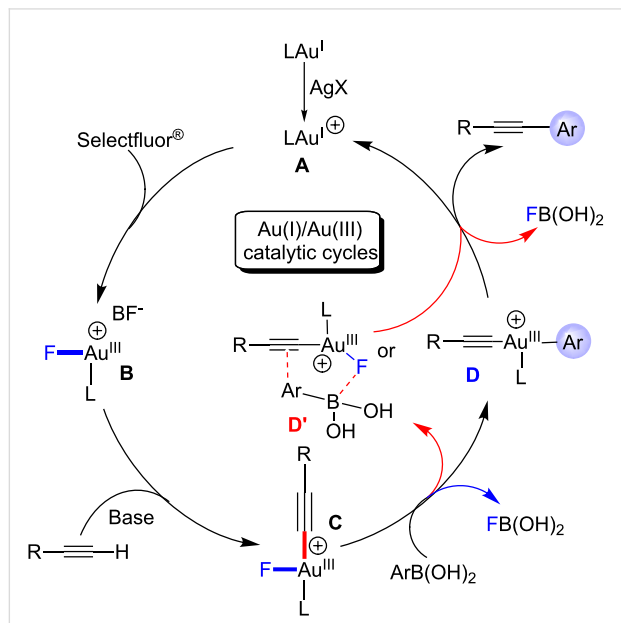
Scheme 3: Proposed mechanism for the Au(I)/Au(III)-catalyzed Sonogashira-type cross-coupling.

Conclusion

In conclusion, we have developed an unprecedented Au(I)/Au(III)-catalyzed Sonogashira-type cross-coupling reaction of terminal alkynes and arylboronic acids under mild conditions. Selectfluor® and counter ion effects play a significant role in the development of an exceptionally mild catalyst system. This chemistry strongly suggests the feasibility of Au(I) and Au(III) catalytic redox cycles, which would substantially broaden the field of gold catalysis and offer more functionalized products. Furthermore, the good tolerance toward many functional groups of substrates considerably extends the scope of a number of organic transformations and performs modular C_{sp}^2–C_{sp} bond constructions at appropriate stages in the whole synthetic sequence.

Supporting Information

Supporting information features experimental procedure and spectroscopic data.

Supporting Information File 1

Experimental details and spectra of new compounds. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-92-S1.pdf]

References

1. Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007,** *107,* 874–922. doi:10.1021/cr050992x
2. Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007,** *46,* 834–871. doi:10.1002/anie.200602761
3. Plenio, H. *Angew. Chem., Int. Ed.* **2008,** *47,* 6954–6956. doi:10.1002/anie.200802270
4. Tougerti, A.; Negri, S.; Jutand, A. *Chem.–Eur. J.* **2007,** *13,* 666–676. doi:10.1002/chem.200600574
5. Ahlquist, M.; Norrby, P.-O. *Organometallics* **2007,** *26,* 550–553. doi:10.1021/om0604932
6. Liang, Y.; Xie, Y.; Li, J. *J. Org. Chem.* **2006,** *71,* 379–381. doi:10.1021/jo051882t
7. Yi, C.; Hua, R. *J. Org. Chem.* **2006,** *71,* 2535–2537. doi:10.1021/jo0525175
8. Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005,** *70,* 391–393. doi:10.1021/jo048599z
9. Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004,** *69,* 5752–5755. doi:10.1021/jo049325e
10. Finke, A. D.; Elleby, E. C.; Boyd, M. J.; Weissman, H.; Moore, J. S. *J. Org. Chem.* **2009,** *74,* 8897–8900. doi:10.1021/jo902015w
11. R'kyek, O.; Halland, N.; Lindenschmidt, A.; Alonso, J.; Lindemann, P.; Urmann, M.; Nazaré, M. *Chem.–Eur. J.* **2010,** *16,* 9986–9989. doi:10.1002/chem.201001524
12. Choy, P. Y.; Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. K. *Chem.–Eur. J.* **2010,** *16,* 9982–9985. doi:10.1002/chem.201001269
13. Zhou, M.-B.; Wei, W.-T.; Xie, Y.-X.; Lei, Y.; Li, J.-H. *J. Org. Chem.* **2010,** *75,* 5635–5642. doi:10.1021/jo101063p
14. Mitsudo, K.; Shiraga, T.; Mizukawa, J.; Suga, S.; Tanaka, H. *Chem. Commun.* **2010,** *46,* 9256–9258. doi:10.1039/C0CC02633F
15. Hashmi, A. S. K. *Chem. Rev.* **2007,** *107,* 3180–3211. doi:10.1021/cr000436x
16. Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008,** *108,* 3239–3265. doi:10.1021/cr068434l
17. Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008,** *108,* 3351–3378. doi:10.1021/cr068430g
18. Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008,** *108,* 3326–3350. doi:10.1021/cr0684319
19. Arcadi, A. *Chem. Rev.* **2008,** *108,* 3266–3325. doi:10.1021/cr068435d
20. Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010,** *49,* 5232–5241. doi:10.1002/anie.200907078
21. Shapiro, N. D.; Toste, F. D. *Synlett* **2010,** 675–691. doi:10.1055/s-0029-1219369
22. Garcia, P.; Malacria, M.; Aubert, C.; Gandon, V.; Fensterbank, L. *ChemCatChem* **2010,** *2,* 493–497. doi:10.1002/cctc.200900319
23. Li, P.; Wang, L.; Wang, M.; You, F. *Eur. J. Org. Chem.* **2008,** 5946–5951. doi:10.1002/ejoc.200800765
24. Carrettin, S.; Guzman, J.; Corma, A. *Angew. Chem., Int. Ed.* **2005,** *44,* 2242–2245. doi:10.1002/anie.200462560
25. González-Arellano, C.; Abad, A.; Corma, A.; García, H.; Iglesias, M.; Sánchez, F. *Angew. Chem., Int. Ed.* **2007,** *46,* 1536–1538. doi:10.1002/anie.200604746

26. Hashmi, A. S. K.; Ramamurthi, T. D.; Rominger, F.
J. Organomet. Chem. **2009,** *694,* 592–597.
doi:10.1016/j.jorganchem.2008.11.054

27. Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009,**
48, 3112–3115. doi:10.1002/anie.200900585

28. Peng, Y.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2009,** *131,*
5062–5063. doi:10.1021/ja901048w

29. Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010,** *132,*
1474–1475. doi:10.1021/ja909555d

30. Brenzovich, W. E., Jr.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.;
Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *Angew. Chem., Int. Ed.*
2010, *49,* 5519–5522. doi:10.1002/anie.201002739

31. Melhado, A. D.; Brenzovich, W. E.; Lackner, A. D.; Toste, F. D.
J. Am. Chem. Soc. **2010,** *132,* 8885–8887. doi:10.1021/ja1034123

32. Mankad, N. P.; Toste, F. D. *J. Am. Chem. Soc.* **2010,** *132,*
12859–12861. doi:10.1021/ja106257n

33. LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D.
J. Am. Chem. Soc. **2007,** *129,* 2452–2453. doi:10.1021/ja068819l

34. Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007,** *317,*
496–499. doi:10.1126/science.1145229

35. LaLonde, R. L.; Wang, Z. J.; Mba, M.; Lackner, A. D.; Toste, F. D.
Angew. Chem., Int. Ed. **2010,** *49,* 598–601.
doi:10.1002/anie.200905000

36. Wang, W.; Jasinski, J.; Hammond, G. B.; Xu, B.
Angew. Chem., Int. Ed. **2010,** *49,* 7247–7252.
doi:10.1002/anie.201003593

37. Okabayashi, T.; Nakaoka, Y.; Yamazaki, E.; Tanimoto, M.
Chem. Phys. Lett. **2002,** *366,* 406–411.
doi:10.1016/S0009-2614(02)01586-5