Published in final edited form as:
Synlett. 2012 January ; 2012(1): 54–56. doi:10.1055/s-0031-1289567.

Gold-Catalyzed Regioselective Dimerization of Aliphatic Terminal Alkynes

Sheng Sun, **Julien Kroll**, **Yingdong Luo**, and **Liming Zhang***
Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106

Abstract

A gold-catalyzed regioselective homodimerization of aliphatic terminal alkynes is described. Bulky and less Lewis acidic tBuXPhosAuNTf$_2$ is the preferred catalyst, and the additive, anhydrous NaOAc, substantially facilitates the reaction.

Keywords

gold; dimerization; regioselectivity; terminal alkynes; enynes

Dimerization of terminal alkynes provides a rapid and atom-economic access to synthetically versatile enynes[1] and can be promoted by an amazingly broad range of metals including various transition metals such as Ni,[2] Y,[3] Ru,[4] Rh,[5] Pd,[6] Ir,[7] lanthalides,[8] and actinides[9] and main group metals.[10] Three enyne isomers, *Z*-linear, *E*-linear and branched (*gem*) can be obtained with various levels of regio- and/or stereoselectivities following either a 'head-to-head' or a 'head-to-tail' union.

Albeit recent rapid development in homogeneous gold catalysis,[11] there are still many well-established reactions, including dimerization of terminal alkynes, that have not succumbed to gold catalysis. As a part of our general interest in discovering new gold chemistry and probing potential unique reactivities of gold catalysts, we decided to study dimerization of terminal alkynes using soluble gold catalysts. Since gold complexes can readily activate alkynes toward nucleophilic attacks and alkynylgolds are known to be nucleophilic,[12] we anticipated, as shown in Scheme 1, that the alkynylgold **B**, formed from the terminal alkyne-gold complex **A**, might act as the nucleophile to attack its precursor, thereby affording enynes **1** and **2** upon subsequent protodeauration. Interestingly, two different gold complexes would be involved in the key C-C bond formation step. Good ratios of **1/2** was anticipated as a Markovnikov-type *anti* addition to the terminal C-C triple bond should be preferred. Herein, we disclose our preliminary results.

We began with screening different gold catalysts and reaction conditions for the dimerization of ethereal alkyne **3a**. After some preliminary studies with different solvents at various reaction temperatures, it was found that the reaction was best conducted in refluxing toluene. Gold complexes that are prone to thermal decomposition such as Ph$_3$PAuNTf$_2$ (Table 1, entry 1) was totally ineffective due to gold precipitation. Bulky and less Lewis

Fax: (805)893-4120, zhang@chem.ucsb.edu.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synlett and can be cited using the following DOI: (number will be inserted prior to online publication).

acidic gold catalysts are more stable upon heating and therefore capable of promoting the dimerization. These catalysts included $IPrAuNTf_2$[13] (Table 1, entry 2), $BrettPhosAuNTf_2$[14] (Table 1, entry 3) and $tBuXPhosAuNTf_2$ (Table 1, entry 4). Among them, $tBuXPhosAuNTf_2$ was the most effective. However, catalyst decomposition still occurred, and the overall yields were low. We reasoned that the addition of a base might make the gold catalyst more stable and moreover facilitate the formation of alkynylgold intermediates of type **B**. Consequently, various bases (2 equivalents) were tested. While stronger bases such as Na_2CO_3 (Table 1, entry 5) and Cs_2CO_3 (Table 1, entry 6) were proven deleterious, $NaHCO_3$ (Table 1, entry 7) was surprisingly effectively in facilitating the reaction. Anhydrous NaOAc proved to be even better, and the isolated yield was 83% (Table 1, entry 8). Importantly, the branched 'head-to-tail' dimer **4a** was formed with high selectivity over the linear *Z*-enyne **5a**, formed via a 'head-to-head' dimerization. We were curious whether soluble acetate would perform the same feat. To our surprise, no reaction was observed with either 2 equivalents or 6 mol % of $Me_4N^+OAc^-$. It is most likely that soluble OAc^- reacted with the gold catalyst to form tBuXPhosAuOAc, which is not catalytically active. 2-bromopyridine (pK_a of its conjugated acid: 0.71[15]), a soluble base but less basic than AcO^- (pK_a of HOAc: 4.76), could promote the reaction but to a less extent (Table 1, entry 11). 1,2-Dichloroethane was an inferior solvent for this reaction (Table 1, entry 12). Control experiments (Table 1, entries 13 and 14) established the indispensable role of the gold catalyst in this reaction as neither its absence nor substituting it with $AgNTf_2$ led to any observable reaction.

The optimized reaction conditions were then applied to the reaction scope study. As shown in Table 2, aliphatic terminal alkynes such as 1-dodecyne (entry 1), cyclohexylacetylene (entry 2) and cyclopentylacetylene (entry 3) were all amenable to the dimerization, yielding the branched isomer (i.e., **4**) in mostly good yields. Several functional groups such as sulfide (entry 4), phenyl (entry 5), imide (entry 6) and ester (entry 7) could be readily incorporated into aliphatic terminal alkynes without compromising much of the reaction efficiency. To our surprise, phenylacetylene was a poor substrate, and only 8% of the dimer product was formed after 24 h; moreover, 2-methylbut-3-yn-1-ene was not a suitable substrate (entry 9). Extension of this chemistry to heterodimerization led to mixtures of four branched enyne products with low overall yields.

The reaction mechanism is likely following what we originally conceived in Scheme 1. The role of NaOAc is worth further commenting. It should facilitate the formation of **B** by deprotonation of complex **A** or trapping the released proton; HOAc thus formed should be capable of protodeauration under the elevated temperature in the final step. The gold complex thus generated is tBuXPhosAuOAc instead of $tBuXPhosAuNTf_2$. However, it is likely that this inactive complex can be returned to its active form by switching counter anion with the in-situ generated $NaNTf_2$, driven by the formation of crystalline and barely soluble NaOAc. On the contrary, when $Me_4N^+OAc^-$ was used, such a driving force was missing, and all the gold catalyst was in its inactive tBuXPhosAuOAc form.

In conclusion, a gold-catalyzed homodimerization of aliphatic terminal alkynes has been developed. The branched 'head-to-tail' enyne isomers are formed in mostly good yields and with excellent selectivities over the linear isomers. NaOAc was found to be effective as an additive in facilitating the reaction. The likely reaction mechanism entails a key C-C bond formation step involving two different gold species.

Supplementary Material

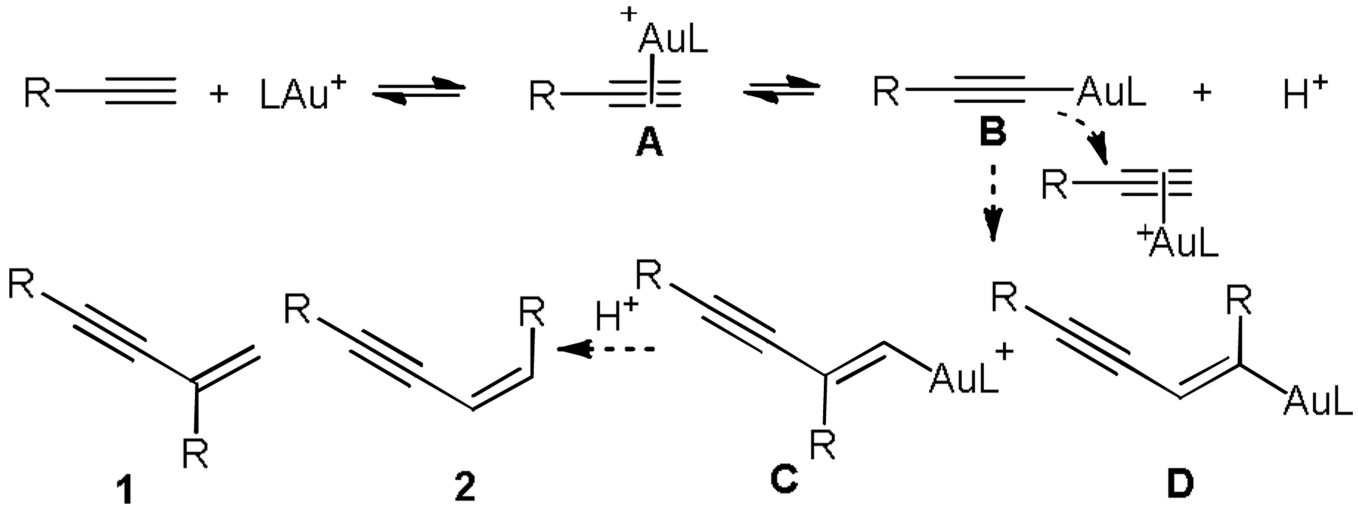
Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are grateful for the generous financial support by NIH (R01 GM084254) and UCSB. LZ is a Sloan Fellow.

References

1. For a review, see: Bustelo E, Dixneuf PH. Dyker G. Handbook of C-H Transformations : Applications in Organic Synthesis. 2005; Vol. 1Wiley-VCH: Weinheim:62–72.
2. For an example, see: Ogoshi S, Ueta M, Oka M-a, Kurosawa H. Chem. Commun. 2004:2732–2733.
3. For an example, see: Komeyama K, Kawabata T, Takehira K, Takaki K. J. Org. Chem. 2005; 70:7260–7266. [PubMed: 16122246]
4. For an example, see: Chen X, Xue P, Sung HHY, Williams ID, Peruzzini M, Bianchini C, Jia G. Organometallics. 2005; 24:4330–4332.
5. (a) Kovalev IP, Yevdakov KV, Strelenko YA, Vinogradov MG, Nikishin GI. J. Organomet. Chem. 1990; 386:139–146.(b) Boese WT, Goldman AS. Organometallics. 1991; 10:782–786.(c) Lee C-C, Lin Y-C, Liu Y-H, Wang Y. Organometallics. 2004; 24:136–143.(d) Weng W, Guo C, Celenligil-Cetin R, Foxman BM, Ozerov OV. Chem. Commun. 2006:197–199.
6. For earlier examples, see: Trost BM, Chan C, Ruhter G. J. Am. Chem. Soc. 1987; 109:3486–3487. Luo FT, Fwu SL, Huang WS. Tetrahedron Lett. 1992; 33:6839–6840.
7. (a) Ohmura T, Yorozuya S-i, Yamamoto Y, Miyaura N. Organometallics. 2000; 19:365–367.(b) Ghosh R, Zhang X, Achord P, Emge TJ, Krogh-Jespersen K, Goldman AS. J. Am. Chem. Soc. 2007; 129:853–866. [PubMed: 17243822] (c) Ez-Zoubir M, d'Herouville FLB, Brown JA, Ratovelomanana-Vidal V, Michelet V. Chem. Commun. 2010; 46:6332–6334.
8. For examples, see: Heeres HJ, Teuben JH. Organometallics. 1991; 10:1980–1986. Yoshida M, Jordan RF. Organometallics. 1997; 16:4508–4510.
9. For examples, see: Dash AK, Wang JX, Berthet JC, Ephritikhine M, Eisen MS. J. Organomet. Chem. 2000; 604:83–98. Dash AK, Gourevich I, Wang JQ, Wang J, Kapon M, Eisen MS. Organometallics. 2001; 20:5084–5104.
10. For an example, see: Dash AK, Eisen MS. Org. Lett. 2000; 2:737–740. [PubMed: 10814423]
11. For selected reviews, see: Fürstner A, Davis PW. Angew. Chem. Int. Ed. 2007; 46:3410–3449. Hashmi ASK. Chem. Rev. 2007; 107:3180–3211. [PubMed: 17580975] Arcadi A. Chem. Rev. 2008; 108:3266–3325. [PubMed: 18651778] Corma A, Leyva-Pérez A, Sabater MJ. Chem. Rev. 2011; 111:1657–1712. [PubMed: 21391565] Abu Sohel SM, Liu R-S. Chem. Soc. Rev. 2009; 38:2269–2281. [PubMed: 19623349] Li Z, Brouwer C, He C. Chem. Rev. 2008; 108:3239–3265. [PubMed: 18613729] Wang S, Zhang G, Zhang L. Synlett. 2010:692–706.
12. (a) Li C-J. Acc. Chem. Res. 2010; 43:581–590. [PubMed: 20095650] (b) Skouta R, Li C-J. Tetrahedron. 2008; 64:4917–4938.(c) Lo VK-Y, Liu Y, Wong M-K, Che C-M. Org. Lett. 2006; 8:1529–1532. [PubMed: 16597102]
13. For earlier studies using this catalyst, see: Li G, Zhang L. Angew. Chem. Int. Ed. 2007; 46:5156–5159. Ricard L, Gagosz F. Organometallics. 2007; 26:4704–4707.
14. For the initial report on BrettPhos ligand, see: Fors BP, Watson DA, Biscoe MR, Buchwald SL. J. Am. Chem. Soc. 2008; 130:13552–13554. [PubMed: 18798626] For the first study using $BrettPhosAu^{+}$, see: Ye L, He W, Zhang L. Angew. Chem. Int. Ed. 2011; 50:3236–3239.
15. Linnell R. J. Org. Chem. 1960; 25:290–290.



scheme 1.
Proposed gold-catalyzed dimerization of terminal alkynes.

Table 1

Reaction optimization[a]

entry	catalyst	additive[b]	yield[c]	4a/5a[d]
1	$Ph_3PAuNTf_2$	-	-	-
2	$IPrAuNTf_2$	-	20%	4.5/1
3	$BrettPhosAuNTf_2$	-	22%	14/1
4	$tBuXPhosAuNTf_2$	-	28%	10/1
5	$tBuXPhosAuNTf_2$	Na_2CO_3	15%	19/1
6	$tBuXPhosAuNTf_2$	Cs_2CO_3	-	-
7	$tBuXPhosAuNTf_2$	$NaHCO_3$	68%	5/1
8	$tBuXPhosAuNTf_2$	NaOAc	83%[e]	14/1
9	$tBuXPhosAuNTf_2$	$Me_4N^+OAc^-$	-	-
10	$tBuXPhosAuNTf_2$	$Me_4N^+OAc^-$[f]	-	-
11	$tBuXPhosAuNTf_2$	2-BrPy	39%	>20/1
12[g]	$tBuXPhosAuNTf_2$	NaOAc	22%	18/1
13	-	NaOAc	-	-
14	$AgNTf_2$	NaOAc	-	-

[a] Reaction run in Schlenk tubes under nitrogen; [alkyne] = 0.1 M.

[b] 2 equivalent.

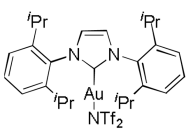
[c] NMR yield using diethyl phthalate as the internal reference.

[d] Ratio determined by crude ^1H NMR.

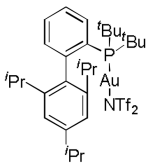
[e] Isolated yield.

[f] 6 mol % instead.

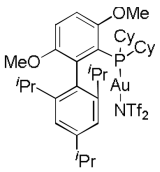
[g] DCE as the reaction solvent.



$IPrAuNTf_2$



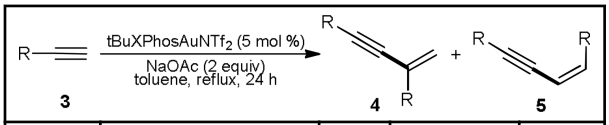
$tBuXPhosAuNTf_2$

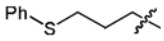
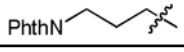
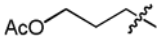


$BrettPhosAuNTf_2$

Table 2

Reaction scope of homodimerization[a]



entry	R	4	yield (4)[b]	4/5[c]
1	*n*-decyl	**4b**	72%	14/1
2	cyclohexyl	**4c**	69%	13/1
3[d]	cyclopentyl	**4d**	85%	25/1
4[d]		**4e**	61%	12/1
5	$PhCH_2CH_2$	**4f**	61%	11/1
6		**4g**	78%	10/1
7		**4h**	81%	11/1
8	Ph	**4i**	8%	12/1
9	2-propenyl	**4j**	-	-

[a] Reaction run in Schlenk tubes under nitrogen; [alkyne] = 0.1 M.

[b] Isolated yield and containing small amount of inseparable **5**.

[c] Determined by crude ^{1}H NMR.

[d] Reaction time: 48 h; catalyst loading: 10 mol %.