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Gold-Catalyzed Electrophilic Addition to Arylalkynes. A Facile Method for the Regioselective Synthesis of Substituted Naphthalenes

Rengarajan Balamurugan* and Vanajakshi Gudla

School of Chemistry, University of Hyderabad, GachiBowli, Hyderabad, India 500046

rbsc@uohyd.ernet.in

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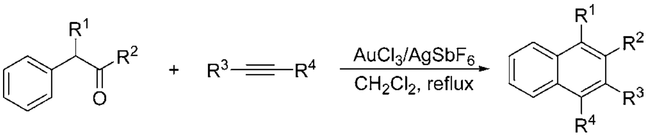
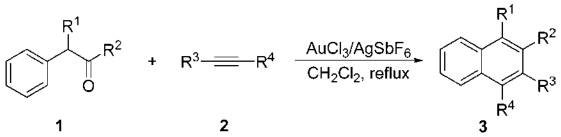
ABSTRACT



An interesting gold-catalyzed electrophilic addition to arylalkyne to synthesize substituted naphthalenes has been presented. Different metal hexafluoroantimonates have also been found to effect the transformation. Counter anion and oxo- and alkynophilicities of catalytic gold species might play an important role in this annulation reaction.

Use of homogeneous gold catalysts for organic transformations has shown tremendous potential in this decade.[1] Several reactions are now viable under mild conditions with great efficiencies using gold catalysts. In most of the reported gold-catalyzed reactions gold acts as a soft carbophilic Lewis acid to activate carbon−carbon multiple bonds. The activated species is then employed in the nucleophilic attack with carbon or heteroatom nucleophiles. In this paper, we report an electrophilic addition to arylalkynes catalyzed by gold. Electrophilic addition to an alkyne catalyzed by gold is rather an interesting case considering the Lewis acidity of gold toward an alkynic bond. Catalytic amounts of $AuCl_3/AgSbF_6$ were sufficient for the annulation of arylacetaldehydes with arylalkynes to generate substituted naphthalenes in a regioselective manner (Scheme 1).

Scheme 1. Gold-Catalyzed Annulation of Arylacetaldehydes with Arylalkynes



Substituted naphthalenes are part of many biologically important compounds.[2] Eventually, different strategies were developed to generate substituted naphthalene derivatives in a regioselective manner.[3] Recently, Gevorgyan et al.[4] and Yamamoto et al.[5] have reported the synthesis of naphthalene derivatives involving gold-catalyzed nucleophilic attack on the triple bond. However, the present reaction involving

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(1) For selected reviews, see: (a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (b) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (d) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (e) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (g) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (h) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (i) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (j) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (k) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (l) Widenhoefer, R. A. *Chem.−Eur. J.* **2008**, *14*, 5382.

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$AuCl_3$/$AgSbF_6$ is believed to involve an electrophilic attack on the triple bond.

We carried out several experiments to ascertain the nature of gold species responsible for the transformation and to find out the optimum reaction conditions (Table 1). For this purpose, simple substrates, phenylacetaldehyde and phenylacetylene, were used. Our first attempt using 2 mol % of $AuCl_3$ in anhydrous CH_2Cl_2 was not encouraging as only less than 3% yield of 1-phenylnaphthalene was obtained. The yield did not improve even in the presence of 4 Å molecular sieves, which improved the yields in other attempts (vide supra) after 12 h of reflux (entry 1). To our delight, reaction using a mixture of $AuCl_3$ (2 mol %) and $AgSbF_6$ (6 mol %) in CH_2Cl_2 gave 41% of 1-phenylnaphthalene in 4 h at room temperature (entry 2). The yield improved considerably when the reaction was refluxed in the presence of 4 Å molecular sieves (entries 4 and 5). Notably, only 5% of the product was obtained when $AgSbF_6$ (6 mol %) alone was used as the catalyst (entry 3). It indicates that the cationic character of gold which is achieved by the addition of $AgSbF_6$ to $AuCl_3$ might helped the annulation to occur.[6] However, the $AuCl_3$/AgOTf combination was not as effective as $AuCl_3$/$AgSbF_6$ (entry 10). While there was no product formation with $(Ph_3P)AuCl$, cationic $(Ph_3P)AuCl$/$AgSbF_6$-catalyzed reaction yielded only 3% of the product (entries 11 and 12).

Table 1. Screening of Different Catalysts and Conditions in the Annulation of Phenylacetaldehyde and Phenylacetylene

entry	catalyst	solvent and condition	time (h)	yield^g (%)
1	$AuCl_3{}^a$	CH_2Cl_2/4 Å MS, reflux	12	3
2	$AuCl_3{}^a/AgSbF_6{}^b$	CH_2Cl_2, rt	4	41
3	$AgSbF_6{}^b$	CH_2Cl_2/4 Å MS, reflux	12	5
4	$AuCl_3{}^a/AgSbF_6{}^b$	CH_2Cl_2/4 Å MS, rt	4	51
5	$AuCl_3{}^a/AgSbF_6{}^b$	CH_2Cl_2/4 Å MS, reflux	5	69
6	$AuCl_3{}^a/AgSbF_6{}^b$	CH_2Cl_2/4 Å MS, reflux	5	51^h
7	$AuCl_3{}^a/AgSbF_6{}^b$	DCE, rt	24	40
8	$AuCl_3{}^a/AgSbF_6{}^b$	DCE, reflux	4	59
9	$AuCl_3{}^a/AgSbF_6{}^b$	DCE/4 Å MS, reflux	5	64
10	$AuCl_3{}^a/AgOTf^b$	CH_2Cl_2/4 Å MS, rt	20	16
11	$(Ph_3P)AuCl^a$	CH_2Cl_2/4 Å MS, reflux	14	0
12	$(Ph_3P)AuCl^a/AgSbF_6{}^a$	CH_2Cl_2/4 Å MS, reflux	12	3
13	$AuCl_3{}^a/AgSbF_6{}^c$	CH_2Cl_2/4 Å MS, reflux	5	25
14	$AuCl_3{}^a/AgSbF_6{}^a$	CH_2Cl_2/4 Å MS, reflux	5	7
15	$NaAuCl_4.2H_2O^a$	CH_2Cl_2/4 Å MS, reflux	12	14
16	$CuCl_2{}^a/AgSbF_6{}^c$	CH_2Cl_2/4 Å MS, reflux	22	67
17	$CuCl^a/AgSbF_6{}^a$	CH_2Cl_2/4 Å MS, reflux	14	21
18	$Cu(OTf)_2{}^a$	CH_2Cl_2/4 Å MS, reflux	16	7
19	$FeCl_3{}^a/AgSbF_6{}^b$	CH_2Cl_2/4 Å MS, reflux	20	32
20	$TiCl_4{}^a/AgSbF_6{}^d$	CH_2Cl_2/4 Å MS, reflux	16	62
21	$HCl/AgSbF_6{}^b$	CH_2Cl_2/4 Å MS, reflux	5	24
22	$Sn(OTf)_2{}^e$	CH_2Cl_2/4 Å MS, rt	20	trace
23	$Sn(OTf)_2{}^f$	CH_2Cl_2/4 Å MS, rt	20	61

[a] 2 mol %. [b] 6 mol %. [c] 4 mol %. [d] 8 mol %. [e] 5 mol %. [f] 100 mol %. [g] Isolated yield. [h] Reaction carried with premixed catalysts.

The [Au^+] species in $(Ph_3P)AuCl$ and $(Ph_3P)AuCl$/$AgSbF_6$ is considered to be π-philic, whereas the [Au^{3+}] in $AuCl_3$ is oxophilic.[7] In a similar reported $TiCl_4$-assisted annulation,[3c] $TiCl_4$ was needed in stoichimetric amounts, and moreover, no reaction was observed when 2 equiv of aldehyde with respect to $TiCl_4$ were used. The authors claimed that the $TiCl_4$−bis(carbonyl) complex formed with 2 equiv of the aldehyde did not give room for the coordination of Ti to alkyne. Hence, with the catalytic amounts of gold in the present reaction, it gives the impression that the alkynophilicity of gold might play a role for the reaction to take place by bringing the alkyne close to the carbonyl function. The above observations reveal that a gold species which is both oxo- and alkynophilic is essential. This postulation was supported by carrying out two distinct experiments with lesser amounts of $AgSbF_6$ added to $AuCl_3$, which is expected to proportionately lower the cationic character of [Au^{3+}] compared to that when 3 equiv of $AgSbF_6$ with respect to the amount of $AuCl_3$ was used. Keeping the catalyst loading of $AuCl_3$ at 2 mol %, when the amount of $AgSbF_6$ was varied to 4 mol % and 2 mol % the reactions resulted in lower yields in proportion to the amount of $AgSbF_6$ used (entries 13 and 14). In order to draw more support, we carried out the reaction with $CuCl_2$/$AgSbF_6$ as copper also has the ability to complex with alkynes. Fascinatingly, it gave the naphthalene derivative with a yield comparable to that of the $AuCl_3$/$AgSbF_6$-catalyzed reaction (entry 16). However, the reaction required more time. The reactions employing CuCl/$AgSbF_6$ and $Cu(OTf)_2$ were not that effective (entries 17 and 18).

We then went to the extent of attempting the reaction with catalytic amounts (2 mol %) of $FeCl_3$ and $TiCl_4$ in combination with $AgSbF_6$. To our delight, the reaction worked well with catalytic TiCl4/AgSbF6 as well. This finding hints that the counteranion $SbF_6{}^-$ could also play a certain role in the

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(3) For a review, see: (a) de Koning, C. B.; Rousseau, A. L.; van Otterlo, W. A. L. *Tetrahedron* **2003**, *59*, 7. For the latest syntheses, see: (b) Viswanathan, G. S.; Wang, M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2138. (c) Kabalka, G. W.; Ju, Y.; Wu, Z. *J. Org. Chem.* **2003**, *68*, 7915. (d) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2003**, *5*, 4121. (e) Zhang, X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 236. (f) Wang, Y.; Xu, J.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 7780. (g) Duan, S.; Sinha-Mahapatra, D. K.; Herndon, J. W. *Org. Lett.* **2008**, *10*, 1541.

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(6) One of the reviewers of this manuscript evoked the possibility that Bronsted acid $HSbF_6$, which could form under the reaction conditions, could have catalyzed the reaction. We examined the reaction using $HSbF_6$ (formed by passing HCl gas through a solution of $AgSbF_6$ in CH_2Cl_2, see the Supporting Information for complete details). However, the yield of the product was roughly 1/3 of that of obtained employing $AuCl_3$/$AgSbF_6$. Further, he had revealed that their attempts to generate cationic [Au^{3+}] were unsuccessful as gold precipitated quickly. In our attempts we did not see any precipitation of gold. We believe that, in the presence of excess aldehyde, the [Au^{3+}] species is stabilized by the coordination to aldehyde molecules. This draws support from one of our observations that when phenylacetylene and phenylacetaldehyde were added after 15 min to premixed $AuCl_3$ and $AgSbF_6$, the yield of the naphthalene derivative dropped to 51%.

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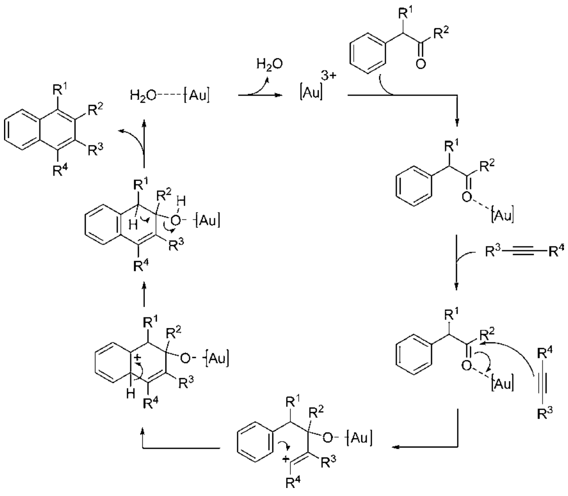
reaction. The counteranions such as Cl^- and TfO^- can quench the intermediate vinyl cation shown in the mechanism of the reaction (Scheme 2), thereby hindering the progress of the reaction. There have been reports of Cl^- quenching the vinyl carbocation generated in the reaction of alkyne involving $TiCl_4$,[8] whereas counteranion SbF_6^- will not quench such vinyl cation. It has to be mentioned that pentavalent antimony catalyzes aromatic electrophilic substitution.[9] Hence, the possibility of SbF_6^- promoting aromatic electrophilic substitution of the vinyl carbocation on the phenyl ring could not be excluded. Further, in the presence of oxophilic Lewis acid $Sn(OTf)_2$, the reaction proceeded only when it was used in stoichiometric amounts and not when 5 mol % was used (entries 22 and 23).

Scheme 2. Tentative Mechanism for the Catalytic Cycle



We then examined different reaction conditions to explore the optimum conditions for the formation of substituted naphthalenes. Similar trends were observed when dry dichloroethane was used as solvent, however, with slightly lesser efficiencies (entries 7−9).

The applicability of the $AuCl_3/AgSbF_6$ catalytic system in naphthalene synthesis was examined with different phenylacetaldehydes/phenylmethyl ketones (Table 2). Diverse alkynes including terminal, internal, aryl, and aliphatic alkynes were tested in the annulation reaction. Arylalkynes only gave the corresponding naphthalene derivatives and not the aliphatic counterparts. The regioselectivity was excellent as only the 1-arylnaphthalene derivatives were obtained. Both substituted phenlylacetaldehydes and phenylmethyl ketones could be employed. Yields were generally good except in a few cases. Importantly, tetrahydrophenanthrene derivatives could be obtained from 2-phenylcyclohexanone (entries 8−10). A similar reaction is not possible with ethyl phenylacetate (entry 6). Bromo-substituted naphthalenes could also be obtained in good yields using this methodology. However, some amounts of corresponding debrominated products were also obtained when phenylmethyl ketones were used which required longer reaction times and more catalysts.

Table 2. Scope of Gold-Catalyzed Annulation Reaction in the Synthesis of Substituted Naphthalenes

	1		2				
entry	R^1	R^2	R^3	R^4	time (h)	3	yield[a] (%)
1	H	H	H	Ph	5	**a**	69
2	H	H	Br	Ph	4	**b**	61
3	H	H	Me	Ph	10	**c**	87
4	H	H	H	CH_2OBn	4		NR
5	H	H	CH_2OBn	CH_2OBn	10		NR
6	H	OEt	H	Ph	13		NR
7	H	H	Ph	Ph	5	**d**	67
8	$-CH_2(CH_2)_2CH_2-$		H	Ph	10	**e**	60
9	$-CH_2(CH_2)_2CH_2-$		Br	Ph	24[b]	**f**	44[d,f]
10	$-CH_2(CH_2)_2CH_2-$		Me	Ph	20[b]	**g**	77
11	*n*-Bu	H	H	Ph	13	**h**	80
12	*n*-Bu	H	Ph	Ph	14	**i**	78
13	Ph	H	H	Ph	14[c]	**j**	58
14	H	Me	Br	Ph	13	**k**	40[e,f]
15	H	Me	H	Ph	12[b]	**l**	58

[a] Isolated yield. [b] $AuCl_3$ (4 mol %)/$AgSbF_6$ (12 mol %). [c] $AuCl_3$ (3 mol %)/$AgSbF_6$ (9 mol %). [d] The corresponding debrominated product was obtained in 7% yield. [e] The corresponding debrominated product was obtained in 14% yield. [f] Yields were calculated based on the integrals in the ^1H NMR spectrum of the column-purified inseparable mixture. NR: no reaction.

Based on the above observations, a catalytic cycle as indicated in Scheme 1 could be proposed to explain the mechanism of the reaction. Initially, the $[Au^{3+}]$ species coordinates with the carbonyl oxygen.[10] Electrophilic attack of the carbonyl carbon on the arylalkyne takes place to form a new C−C bond at the β carbon of the arylalkyne as the resulting vinyl carbocation is stabilized by the aryl group. SbF_6^--assisted aromatic electrophilic reaction takes place to form the bicycle, which subsequently gives up two protons in order to aromatize the rings to form the product. In this event, the hydrated gold species is expelled which later gives up a water molecule. This makes the gold species to go back to its $[Au^{3+}]$ state, which subsequently involves in the next catalytic cycle.

In conclusion, we have shown a simple protocol to synthesize substituted naphthalene derivatives involving gold-catalyzed electrophilic addition on a C−C triple bond followed by benzannulation. Other transition-metal catalysts such as $CuCl_2$ and $TiCl_4$ in combination with $AgSbF_6$ were also effective for the transformation. The oxo- and alkynophilicities of $AuCl_3/AgSbF_6$ in addition to the counteranion SbF_6^- might have made the catalyst more effective. A

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(10) We tried to follow the reaction of phenylacetaldehyde and phenylacetylene involving 2, 5, 10, and 25 mol % of the catalyst ($AuCl_3/3AgSbF_6$) by NMR spectroscopy using $CDCl_3$ as the solvent. We did not see the peaks corresponding to the alkyne coordinated species in the ^{13}C spectrum, and the product peaks started to appear. It is important to note that with 100 mol % of the catalyst the reaction was complete in less than 5 min in an NMR tube. For the same reaction using equimolar $Sn(OTf)_2$ and $TiCl_4$[3c] it has taken 20 and 3 h, respectively, to reach completion.

detailed study on the actual contribution of these effects is being carried out. Further, application of this methodology and exploration of other applications of this catalytic system are under examination. Capitalizing the advantage of counteranion SbF_6^- might facilitate the discovery of new reactions that could take place catalytically.

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Supporting Information Available: Experimental details and characterization data of the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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