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Au-Catalyzed Formation of Functionalized Quinolines from 2-Alkynyl Arylazide Derivatives

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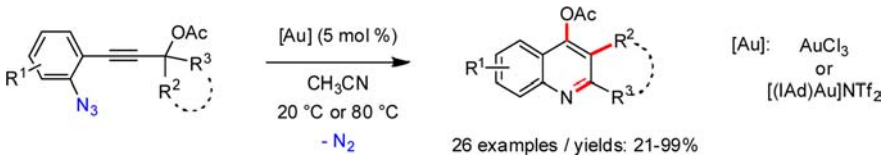
ABSTRACT



A new method for converting 2-alkynyl arylazide derivatives into functionalized polysubstituted quinolines following a gold-catalyzed 1,3-acetoxy shift/cyclization/1,2-group shift sequence has been developed. This transformation proceeds under mild reaction conditions, is efficient, and tolerates a large variety of functional groups.

The quinoline motif is of major importance in medicinal chemistry given its appearance in the structure of numerous natural or synthetic products possessing biological activities.[1] While consequent efforts have been made over the years to develop a synthetic access to quinolines,[2] the number of methods allowing the efficient and selective synthesis of polysubstituted quinolines with a good functional group tolerance remains limited.

As part of our work on gold catalysis,[3] we recently reported that 2-alkynyl arylazides **1** could be converted into indoles **3** via the trapping of an intermediate gold carbenoid **2** by a nucleophile (Scheme 1).[4] On the basis of these studies, we reasoned that a divergence in reactivity might potentially operate if an acyloxy group is introduced at the propargylic position of the substrate (Scheme 1). Indeed, upon treatment with a gold catalyst, substrate **4** should undergo an alternative and more favorable 1,3-acetoxy shift[5] that would furnish allene **5**. A nucleophilic addition of the azide[6] onto this gold-activated species would then lead to the cyclized intermediate **6** which could subsequently evolve into quinoline **9** after a 1,2-shift of the R^2 group and regeneration of the catalyst. Cationic intermediate **7** could be formed directly from **6** (path A) or alternatively via a gold carbenoid of type **8** (path B). We report herein our investigations in this field which have led to the development of a new synthetic route to polyfunctionalized quinolines.[7]

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(2) For a recent review, see: Kouznetsov, V. V.; Vargas Méndez, L. Y.; Meléndez Gómez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141.

(3) For selected recent contributions, see: (a) Henrion, G.; Chavas, T. E. J.; Le Goff, X.; Gagosz, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 6277. (b) Cao, Z.; Gagosz, F. *Angew. Chem., Int. Ed.* **2013**10.1002/anie.201304497. (c) Bolte, B.; Gagosz, F. *J. Am. Chem. Soc.* **2011**, *133*, 7696.

(4) (a) Wetzel, A.; Gagosz, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7354. (b) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8358.

(5) The 1,3-acyloxy shift is an easy process and should therefore be more favorable than the 5-*endo* cyclization leading to the gold carbenoid **2**. For reviews on Au-catalyzed acyloxy shifts, see: (a) Shiroodi, R. K.; Gevorgyan, V. *Chem. Soc. Rev.* **2013**, *42*, 4991. (b) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, 692.

(6) For the use of azides in Au catalysis, see: (a) Yan, Z.-Y.; Xiao, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8624. (b) Huo, Z.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2010**, *75*, 1266. (c) Huo, Z.; Yamamoto, Y. *Tetrahedron Lett.* **2009**, *50*, 3651. (d) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (e) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349.

(7) For selected Au-catalyzed synthesis of quinolines and their derivatives, see: (a) Tu, X.-F.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 11346. (b) Gronnier, C.; Odabachian, Y.; Gagosz, F. *Chem. Commun.* **2011**, *47*, 218. (c) Praveen, C.; Jegatheesan, S.; Perumal, P. T. *Synlett* **2009**, 2795. (d) Hashmi, A. S. K.; Ata, F.; Haufe, P.; Rominger, F. *Tetrahedron* **2009**, *65*, 1919. (e) Liu, X. Y.; Che, C. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3805. (f) Yadav, J. S.; Reddy, B. V. S.; Yadav, N. N.; Gupta, M. K.; Sridhar, B. *J. Org. Chem.* **2008**, *73*, 6857. (g) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645.

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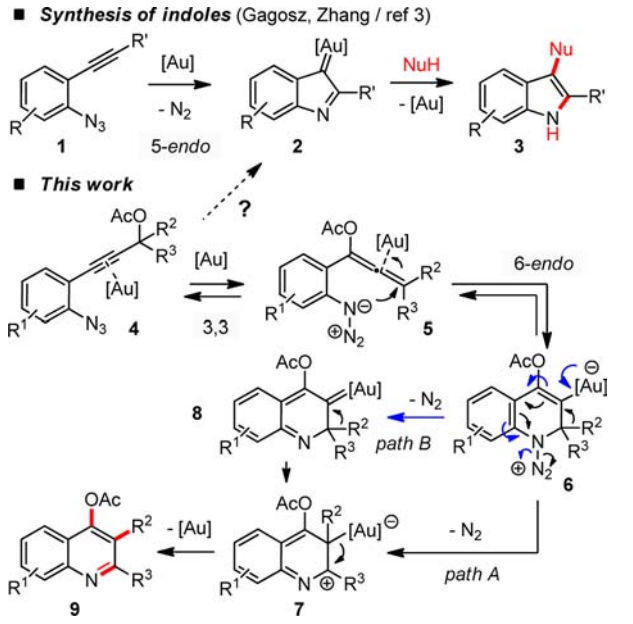
Scheme 1. Synthetic Approach to Functionalized Quinolines from 2-Alkynyl Arylazide Derivatives: Divergence in Reactivity

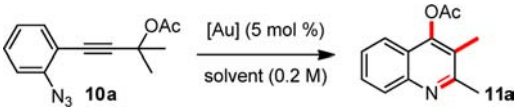


The easily accessible arylazide derivative **10a** was first chosen as a model substrate and a series of experiments were performed in order to validate our approach and determine optimal conditions for the formation of the desired quinoline **11a** (Table 1). The catalytic potential of the $[(IAd)Au]NTf_2$ gold complex **12** was first evaluated given its previously reported high activity for the conversion of 2-alkynyl arylazides into indoles (Scheme 1).[4] Gratifyingly, upon exposure of **12** to 5 mol % of $[(IAd)Au]NTf_2$ in refluxing $CDCl_3$, a clean reaction took place and the desired quinoline **11a** was formed in 87% NMR yield after 2 h (entry 1). The reaction time was significantly reduced when the transformation was run in refluxing CD_3CN. Under these conditions, **11a** was formed in an improved 93% NMR yield (90% isolated) after only 0.5 h of reaction (entry 2). While several other gold(I) complexes proved to be suitable catalysts, their use did not allow an improvement in the yield or time of the reaction (entries 3 and 4). Contrastingly, $AuCl_3$ was shown to be a very active catalyst since **11a** was formed in 79% isolated yield after only 10 min of reaction in refluxing CD_3CN (entry 4). With this catalyst, the reaction could be even run at 20 °C to produce **11a** in a extended reaction time (4.5 h) but with the same efficiency (79%) (entry 5).[8]

Having in hand two sets of viable catalytic conditions (5 mol % of $[(IAd)Au]NTf_2$ or $AuCl_3$ in acetonitrile at 80 °C) for the efficient formation of **11a** from **10a**, we next examined their applicability to other substrates. We first focused our attention on 2-alkynyl arylazide **10b**–**h** possessing a substitution on the aromatic nucleus (Table 2). Whatever the catalyst, the reactions were generally rapid

(8) No quinoline was formed when $AgNTf_2$ or $HNTf_2$ was used as the catalyst (5 mol %).

Table 1. Optimization of the Catalytic System[a]

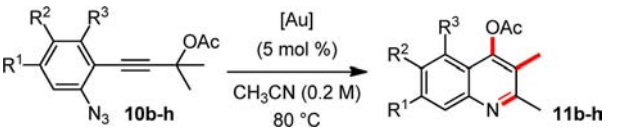


entry	catalyst	solvent	temp (°C)	conversion of **10a** (%) 0.5 h	1 h	2 h	yield of **11a**[a] (%)
1	$[(IAd)Au]NTf_2$ **12**	$CDCl_3$	60	55	77	95	87
2	$[(IAd)Au]NTf_2$ **12**	CD_3CN	80	100			93 (90)
3	$[(Ph_3P)Au]NTf_2$	CD_3CN	80	79	80	80	78
4	$[(XPhos)Au]NTf_2$	CD_3CN	80	69	82	95	92
5	$AuCl_3$	CD_3CN	80	100[b]			82 (79)
6	AuCl	CD_3CN	20	60	73	86	82[c]

[a] NMR yields. Isolated yields in parentheses. [b] 100% conversion after 10 min. [c] NMR and isolated yields after 4.5 h, 100% conversion.

(5–30 min) producing the corresponding quinolines **11b**–**h** in excellent yields (72–99%). The reaction proved to be compatible with the presence of several functional groups (alkyl, ether, halogen, ester, CF_3) located at various positions of the aryl group. A methyl group at the *ortho* position to the alkynyl functionality led, however, to a slower reaction (entry 7). In this case, the reaction could only be performed with catalyst **12**.

Table 2. Substrate Scope: Aryl Substitution



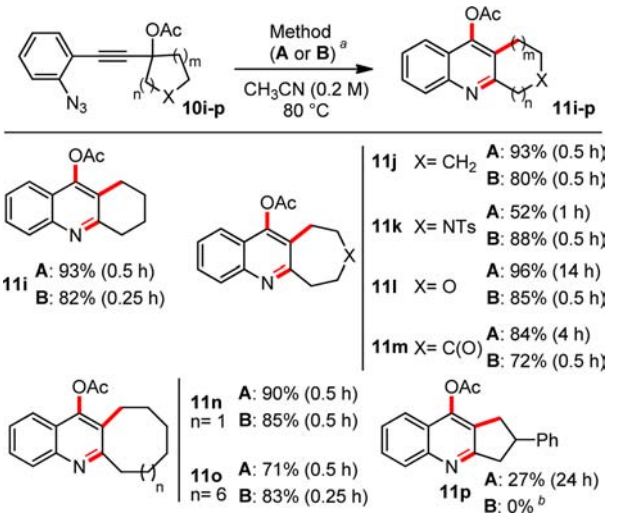
	substrate				[Au]: $[(IAd)Au]NTf_2$ **12**			$AuCl_3$	
entry	**10**	R^1	R^2	R^3	product	time	yield[a] (%)	time (min)	yield[a] (%)
1	**10b**	OMe	H	H	**11b**	20 min	81	10	87
2	**10c**	Me	H	H	**11c**	15 min	99	10	88
3	**10d**	Cl	H	H	**11d**	15 min	88	10	85
4	**10e**	CO_2Me	H	H	**11e**	30 min	87	10	83
5	**10f**	H	CO_2Me	H	**11f**	10 min	83	10	76
6	**10g**	H	CF_3	H	**11g**	15 min	88	10	91
7	**10h**	H	H	Me	**11h**	8 h	72[b]		[c]

[a] Yield of isolated products. [b] 80% conversion. [c] Degradation of **11h**.

We next examined the possibility of modifying the substitution pattern at the propargylic position of the substrate. A disubstitution with a cyclic motif was first considered as the reaction would lead in this case to the formation of a fused polycylic quinoline derivative after a ring expansion step. As seen from the results compiled in Scheme 2, the reaction was also efficient. Various 2-alkynyl arylazide **10i**–**p** could be converted into compounds **11i**–**p**

in yields ranging from 83 to 96%.[9] The functional group tolerance was further examplified with the formation of **11k**−**m** possessing respectively a tosylamide, an ether, and a ketone.

Scheme 2. Substrate Scope: Formation of Quinolines Involving a Ring Expansion



[a] Methods: (A) [(IAd)Au]NTf_2 (5 mol %); (B) $AuCl_3$ (5 mol %). Yields of isolated products. Reaction time in parentheses. [b] Degradation of **10p**.

We then explored briefly the behavior of substrates possessing migrating groups of different nature at the propargylic position (Table 3). For these 1,2-group shift selectivity studies, one of the substituents was fixed as a methyl, while the second one was varied. As seen from Table 3, various substrates **10q**−**t** could be cyclized with moderate to good efficiency (59−79% yields) and selectivity (2:1 to 1:0). Unsurprisingly, experiments showed that the methyl group had a poor migratory aptitude compared to functionalized alkyl moieties (entries 1, 2 and 4) or a vinyl residue (entry 3). It is noteworthy that more selective transformations were obtained when $AuCl_3$ was used as the catalyst.[10] For substrate **10q**, the reaction could only be perfomed with the [(IAd)Au]NTf_2 gold(I) complex due to the instability of the dimethyl ketal group in the presence of the highly Lewis acidic $AuCl_3$ catalyst.

We also considered the possibility of accomplishing the cyclization with substrates possessing an aryl group at the propargylic position (Scheme 3). With compounds **10u** and **10v**, the reaction could only be carried out in the presence of [(IAd)Au]NTf_2.[11] While quinolines **11u** and **11v**, resulting from a 1,2-hydride shift, were selectively produced,[12]

Table 3. Substrate Scope: 1,2-Group Shift Selectivity Studies

entry	substrate 10	R	product b	method	yield c	time	11:11' ratio d
1	10q	Ph	11q	A: e	60%	20 h	2:1
				B:	71%	0.25 h	5:1
2	10r		11r	A:	59%	0.25 h	2.5:1
				B:	64%	0.25 h	7.5:1
3	10s	vinyl	11s	A:	79%	0.25 h	3.2:1
				B:	74%	0.25 h	1:0
4	10t	OMe OMe	11t	A:	89%	0.25 h	1:0
				B:	0% f		

[a] Methods: (A) [(IAd)Au]NTf_2 (5 mol %); (B) $AuCl_3$ (5 mol %). [b] Major product shown. [c] Yields of isolated products (**11** + **11′**). [d] Determined by ^1H NMR spectroscopy. [e] Conversion **10q**: 66%. [f] Degradation of **10t**.

they were, however, obtained in only moderate yield along with the unexpected indolinones **13u** and **13v**. With substrates **10w**−**y**, possessing both an aryl group and a methyl at the propargylic position, the transformations could be performed either with **12** at 80 °C or with $AuCl_3$ at 20 °C.[13] With $AuCl_3$, quinolines **11w**−**y** and **11′w**−**y** were generally obtained as the sole type of products (60−80% yields). Unsurprinsingly, the **11**:**11′** ratio (5.3:1 to 1:1) was highly dependent on the migratory aptitude of the aryl group and therefore on the electronic nature of its substituents (migratory aptitude: Ph > 4-ClPh > 4-NO_2Ph). In the presence of [(IAd)Au]NTf_2, quinolines **11w**−**y** and **11′w**−**y** were produced with similar **11**:**11′** selectivities but in much more moderate yields (30−40%). Similarly to the case of substrates **10u** and **10v**, indole byproducts **14w**−**y** were also formed. It is interesting to note that their competitive production (39−60%) increased with the presence of electron-withdrawing groups on the aryl motif.

To gain further insight into the reaction mechanisms leading to the quinolines **11** and indole derivatives **13** and **14**, a series of additional experiments were performed with allene **15** (Scheme 4).[14] Quinoline **16** was obtained from **15** under gold catalysis but not under simple thermal conditions. This proves not only the intermediacy of an acetoxy allene of type **5** in the formation of quinolines **11a**−**y**, but also the involvement of gold in the whole sequence leading from **4** to **9** (see Scheme 1). The formation of a gold

(9) The low yield obtained for **11p** can be attributed to the difficulty of inducing the 1,3-acetoxy shift from the corresponding acetoxycyclobutane derivative **10p**.

(10) This difference in selectivity is difficult to rationalize at the current stage of our studies.

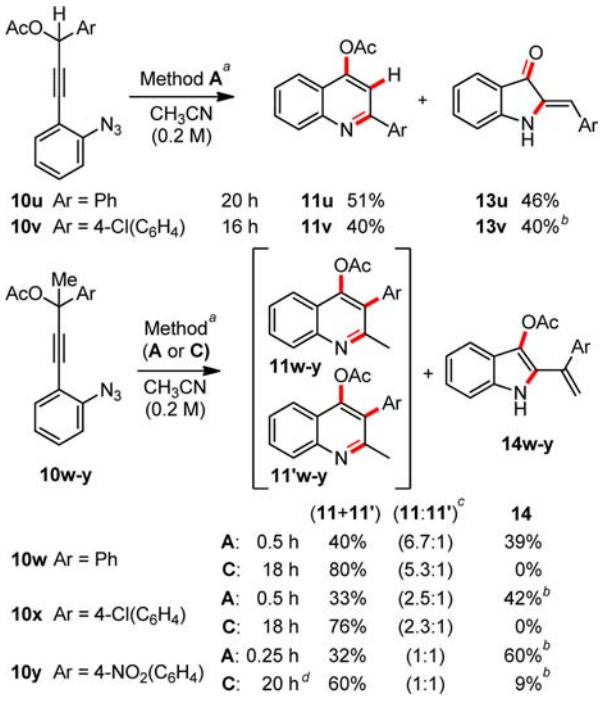
(11) Degradation (80 °C) or no reaction (20 °C) was observed with $AuCl_3$.

(12) These results are in agreement with the higher migrating aptitude of a hydride compared to aryl groups.

(13) A rapid degradation (5 min) was observed with $AuCl_3$ at 80 °C.

(14) Attempts to synthesize the corresponding acetoxy allene failed.

Scheme 3. Quinolines versus Indole Derivative Formation



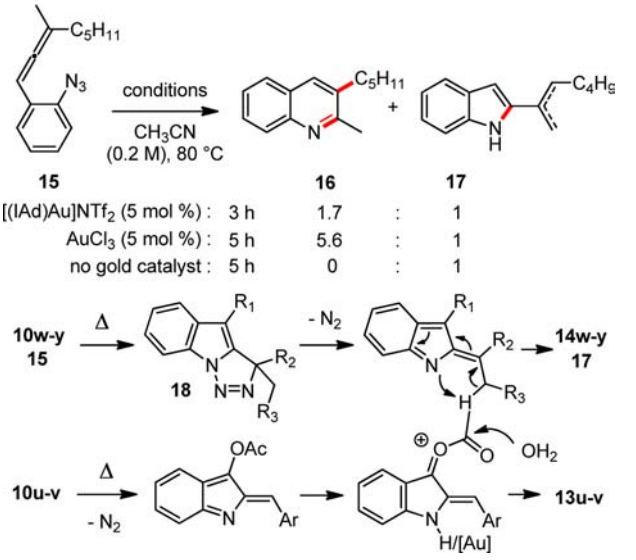
[a] Methods: (A) [(IAd)Au]NTf_2 (5 mol %), 80 °C; (C) $AuCl_3$ (5 mol %), 20 °C. [b] NMR yield, unstable compound. [c] **11**:**11′** ratio determined by ^1H NMR spectroscopy. [d] Conversion **10y**: 69%.

carbenoid of type **8** from **6** is however questionable as the formation of quinolines could be performed using catalysts possessing different electronic properties.[15] While obtained in variable amounts under gold catalysis, 2-alkenylindole **17** was the only compound produced under simple heating at 80 °C, thus showing that its formation should be thermally induced and probably not gold-catalyzed. The results obtained with allene **15** are in agreement with those obtained in the case of substrates **10u**−**y** (Scheme 3). No indole derivative was indeed produced when the reactions with substrates **10u**−**y** were performed at 20 °C using $AuCl_3$ as the catalyst. The formation of compounds of type **13** or **14** became competitive at 80 °C, as the result of a probably less favorable step in the gold-catalyzed conversion of acetoxyallene **5** into intermediate **7** (see Scheme 1).[16] A possible mechanism for the formation of compounds

(15) Contrary to gold complex **12**, $AuCl_3$ should not favor the formation of a gold carbenoid of type **8**. See: Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482.

(16) Either the cyclization (**5**→**6**), the 1,2-group shift (**6**→**7** or **8**→**7**), or the gold carbenoid formation (**6**→**8**) might be disfavored for electronic or steric reasons.

Scheme 4. Probing the Intermediacy of Allenes in the Formation of Quinolines



13u−**v** and **14w**−**y** is shown in Scheme 4. A [3 + 2] cycloaddition between the azide and the allene[17] leads to an intermediate of type **18** which could then expel a dinitrogen molecule to finally evolve into a 2-alkenylindole or an indolone derivative depending on the substitution pattern at the propargylic position of the substrate.

In conclusion, we have developed a new procedure for the synthesis of polysubstituted quinolines from 2-alkynyl arylazides. This gold-catalyzed transformation is efficient, proceeds under mild experimental conditions and tolerates a variety of commonly used functional groups. Further studies on the use of gold-catalyzed sequences for the synthesis of other heteroaromatic motifs are underway.

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Supporting Information Available. Experimental procedures and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) [3 + 2] cycloadditions between azides and allenes has already been reported; see: (a) Feldman, K. S.; Hester, D. K., II.; Iyer, M. R.; Munson, P. J.; Lòpez, C. S.; Faza, O. N. *J. Org. Chem.* **2009**, *74*, 4958. (b) Feldman, K. S.; Iyer, M. R.; Hester, D. K., II. *Org. Lett.* **2006**, *8*, 3113.

The authors declare no competing financial interest.