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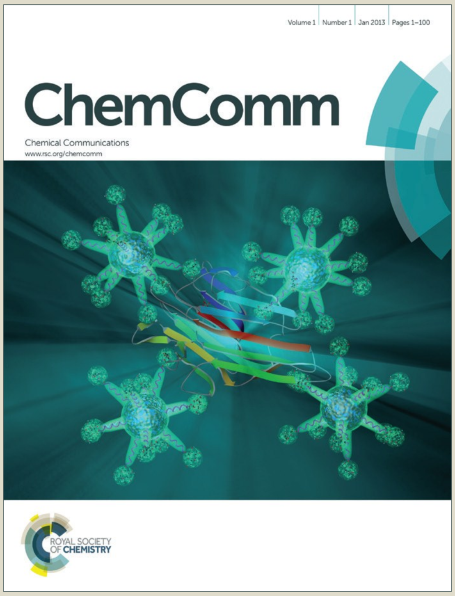

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Silver- versus gold-catalyzed sequential oxidative cyclizations of unprotected 2-alkynylanilines with oxone

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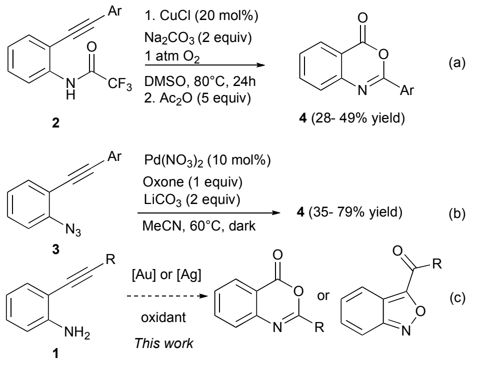
Unprecedented domino oxidative cyclization reactions of unprotected 2-alkynylanilines to give functionalized 4*H*-benzo[*d*][1,3]oxazin-4-one or benzisoxazole derivatives in moderate to good yields are achieved by silver *vs* gold selective catalysis. The search for the optimal reaction conditions revealed the divergent catalytic activity of $NaAuCl_4.H_2O$ and $AgNO_3$.

The product selectivity control by modification of the reaction conditions represents a significant challenge in organic synthesis.[1] In particular, selective catalysis that leads to different products from the same starting materials is a powerful tool for divergent synthesis.[2] 2-Alkynylaniline derivatives are usually employed as versatile building blocks to assemble indole scaffolds by means of transition metals catalysis.[3] Recently, copper mediated cyclization/oxidative reactions of 2-alkynyltrifluoroacetanilides **2** with molecular oxygen achieved a one pot/2-step synthesis of 2-arylbenzoxazinones **4** in low to moderate yield (Scheme 1a).[4] The presence of *N*-TFA-protecting group was crucial to promote the cyclization process as no reactivity was observed in the case of the free aniline. The palladium-catalyzed reaction of 2-azidoalkynylbenzenes **3**, which are prepared from alkynylanilines **1**, was disclosed to afford a variety of the 2-arylbenzoxazinones **4** in better yields by means of a domino aminopalladation/oxidative rearrangement under the presence of oxone as the oxidant (Scheme 1b).[5] We investigated the sequential gold-catalyzed cycloisomerization / fluorination reactions of unprotected 2-alkynylanilines to access to 3,3-difluoro-2-aryl-3*H*-indoles, 3-fluoro-2-aryl-indoles and indolin-3-ones in the presence of selectfluor.[6,7] As part of our continued interest in the synthesis of heterocycles based on atom-economical methodologies and easily accessible starting materials,[6,8] we wondered if unprotected 2-alkynylaniline derivatives would be suitable for oxidative cyclization rearrangements to build-up valuable nitrogen-containing heterocycle systems (Scheme 1c) and wish therefore to report therein our preliminary results.



Scheme 1 [M]-catalyzed synthesis of 4*H*-benzo[*d*][1,3]oxazin-4-ones

First, the readily available 2-(phenylethynyl)aniline **1a** was chosen as a model substrate to carry out oxidative cyclization sequences with a variety of oxidants in the presence of gold or silver catalysts. The results of Table 1 show that only the cycloisomerization reaction **1a** was observed in high yield in the presence of molecular oxygen as the oxidant and $NaAuCl_4·2H_2O$ as the catalyst (entry 1). The expected gold-catalyzed intramolecular hydroamination of **1a**/gold-catalyzed oxidative hydroxylation[6a] or C-H bond[9]/Bayer-Villiger sequence failed to occur under the present reaction conditions. Noteworthy that the reported gold-catalyzed domino cycloisomerization/C-H oxidative homocoupling process of alkynylanilines **1** to give 3,3'-biindoles under heterogeneous conditions was also precluded.[10] The unique formation of 2-substituted indole **5a** with 2,6-lutidine *N*-oxide as the oxidant (entry 2) was in agreement with the recent results which highlighted that the intramolecular hydroamination was prevalent over the intermolecular gold-catalyzed oxidation with internal alkynes.[11] Sequential cycloisomerization/oxidation reactions were not observed even in the presence of *m*-CPBA and H_2O_2 (entries 3, 4), which

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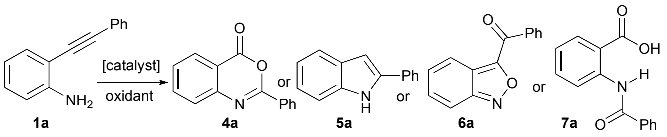
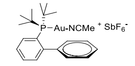
are known to promote peroxidation reaction of indoles.[12] Similarly, the use of $AgNO_3$ catalyst resulted in the same observations and the cyclization of **1a** to form **5a** was favored albeit in a lower efficiency (entries 5, 6, 7). Interestingly, the reaction of **1a** in the presence of H_2O_2 as the oxidant and $AgNO_3$ as the catalyst led to the formation of a new compound, identified as the (benzo[*c*]isoxazol-3-yl)(phenyl)methanone **6a** (entry 8). The formation of this adduct in a moderate yield could come from a divergent oxidation/annulation process. Further screening of oxidants revealed that oxone showed higher efficiency in both the gold-catalyzed cycloisomerization/oxidative hydroxylation / Bayer-Villiger sequence of **1a** and in its divergent silver-catalyzed oxidation/annulation cascade process to give **6a**. Indeed, the 2-phenylbenzoxazinone **4a** was isolated in satisfactory yield by reacting **1a** (1 equiv) with oxone as the oxidant (1 equiv) in the presence of $NaAuCl_4·2H_2O$ in dry CH_3CN at 80 °C (entry 9). The amount of water on the reaction medium played a critical role, as the 2-phenylbenzoxazinone **4a** was prone to undergo hydrolysis to give the *N*-benzoyl anthranilic acid **7a**.[4]

Table 1 Optimization of the reaction conditions[a]

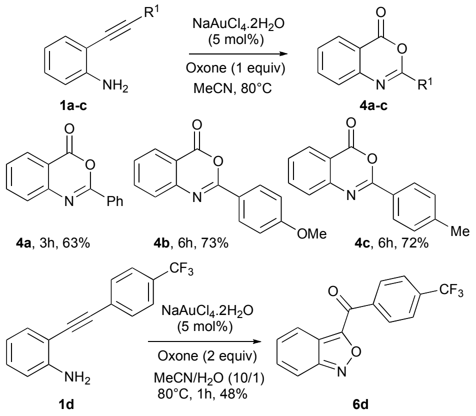


Entry	Catalyst (mol%)	Solvent	t (h)	Oxidant	Product Yield[b] (%)
1	$NaAuCl_4·2H_2O$	CH_3CN	7	O_2[c]	**5a** (95)
2	$NaAuCl_4·2H_2O$	CH_3CN	7	*N*-oxide	**5a** (94)
3	$NaAuCl_4·2H_2O$	CH_3CN	7	*m*-CPBA	**5a** (39)
4	$NaAuCl_4·2H_2O$	CH_3CN	7	H_2O_2	**5a** (63)
5	$AgNO_3$ (10)	CH_3CN	7	O_2[c]	**5a** (20)[d]
6	$AgNO_3$ (10)	CH_3CN	7	*N*-oxide	**5a** (15)[d]
7	$AgNO_3$ (10)	CH_3CN	7	*m*-CPBA	-[e]
8	$AgNO_3$ (10)	CH_3CN	7	H_2O_2	**6a** (21)
9	$NaAuCl_4.2H_2O$	CH_3CN	2	oxone	**4a** (63)
10	$NaAuCl_4·2H_2O$	CH_3CN/H_2O	2	oxone	**7a** (67)[f]
11	$[(PPh_3)Au(NTf_2)]$	CH_3CN/H_2O	8	oxone	**4a** (36)[g,h]
12		CH_3CN/H_2O	8	oxone	**7a** (44)[g,i]
13	$NaAuCl_4·2H_2O$	CH_3NO_2	4	oxone	**7a** (40)[j]
14	$AgNO_3$ (10)	CH_3CN/H_2O	0.2	oxone	**6a** (49)[f]
15	Ag_2CO_3 (10)	CH_3CN/H_2O	24	oxone	**6a** (50)[g]
16	AgOTf (10)	CH_3CN	24	oxone	**6a** (26)
17	$AgNO_3$ (10)	CH_3CN/H_2O	1.5	oxone	**6a** (72)[f,k,l]
18	/	CH_3CN/H_2O	1.5	oxone	**6a** (29)[f,l]

[a] Unless otherwise noted, all reaction were performed with 0.6 mmoles of **1a**, 1 equivalents of oxidant and 5 mol% catalyst at 80 °C. [b] Isolated yield. [c] 1 atm O_2. [d] **1a** was recovered in 75% yield. [e] **1a** was recovered in 70% yield. [f] $CH_3CN:H_2O$ = 1:1. [g] $CH_3CN:H_2O$ = 10:1. [h] **7a** was isolated in 32 % yield. [i] **4a** was isolated in 33 % yield. [j] 10 °C, **4a** was isolated in 31 % yield. [k] 60 °C. [l] 2 equivalents of oxone.

Accordingly compound **7a** was isolated as the main product when CH_3CN/H_2O (1:1) was used as the reaction medium (entry 10). Mixtures of **4a** and **7a** derivatives were isolated when other gold(I) complexes were tested as the catalysts (entries 11, 12). Considering that the oxidation of 2-arylindoles to the corresponding 2-arylbenzoxazinones with oxone as the sole oxidant was carried out in CH_3NO_2,[13] we also examined our domino process in this reaction medium without any improvement (entry 13). The $AgNO_3$-catalyzed reaction of 1a (1 equiv) with oxone as the oxidant (1 equiv) in CH_3CN/H_2O (1:1) at 80°C led to the formation of the (benzo[*c*]isoxazol-3-yl)(phenyl)methanone **6a** as the sole product (entry 14). Among the different silver catalysts tested, $AgNO_3$ gave the best result (entries 15, 16). The reaction temperature was also decreased to 60°C, 40°C and room temperature, the best result being observed at 60°C (entry 17). Finally, a control experiment demonstrated that **6a** was isolated only in low yield without the silver catalyst (entry 18).

The substrate scope of the new approach to the synthesis of 4*H*-benzo[*d*][1,3]oxazin-4-ones **4** was briefly evaluated for anilines bearing electron-donating groups on the aromatic ring of the alkyne (Scheme 2). The domino gold-catalyzed hydroamination/oxidation sequence cleanly resulted in the formation of **4b** and **4c** in 73% and 72% isolated yields respectively. Very likely, the presence of the CF_3 substituent on the aryl group slowed down the intramolecular gold-catalyzed hydroamination process as a consequence of the poorer π-coordination of the gold catalyst at the alkyne and the competitive oxidation/annulation cascade could occur to some extent. The heterocycle **6d** was isolated in 48% yield. This is in full agreement with some observations in the case of electron-withdrawing-substituted alkynes.[14]



Scheme 2 [Au]-catalyzed oxidative cyclization

Mechanistically, according to previous results,[15] the Au-catalyzed process presumably occurs via the fast hydroamination reaction (Scheme 3, intermediates **A** and **B**) leading to 2-phenylindole **5a**, which then undergoes C-H bond/Bayer-Villiger oxidation[13] with a potential initiation by the gold catalyst considering the recent study in the presence of copper chloride.[16] This was confirmed, when the cyclization of 2-alkynylanilines **1a** was combined in a one-pot sequential procedure with the oxidation of the *in situ* formed 2-substituted indole **5a** by oxone, the formation of 4*H*-benzo[*d*][1,3]oxazin-4-ones **4a** was observed in similar yield (Scheme 3). The silver-catalyzed domino process is more intricate as the obtained anthranyl skeleton may come from different pathways.

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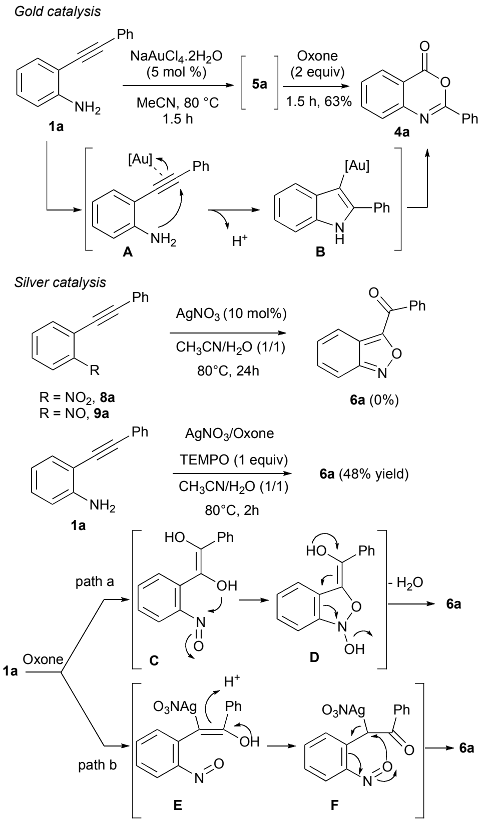
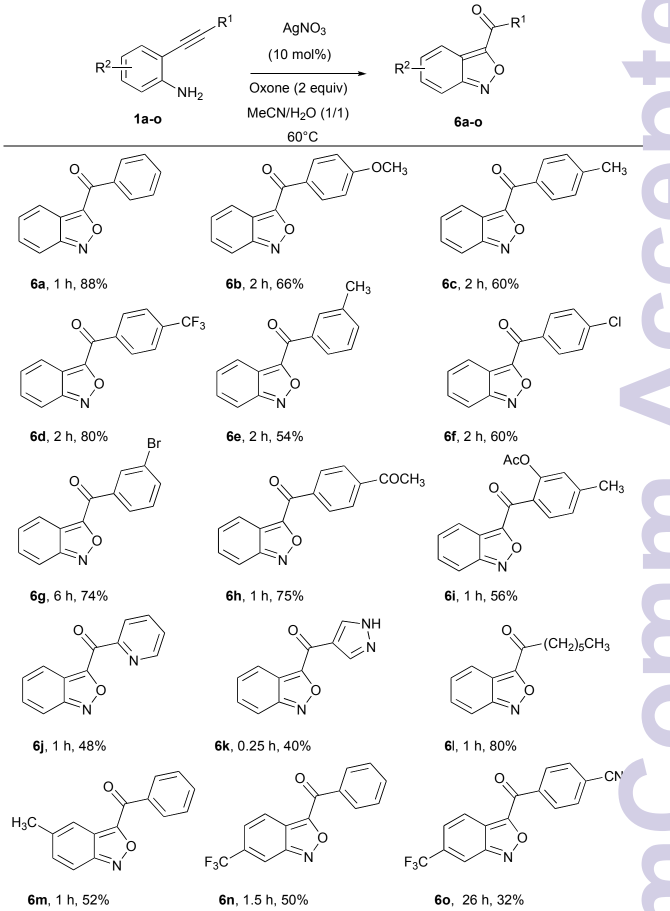


Scheme 3 [Ag]- and [Au]-mechanistic investigations and proposed mechanisms

The competitive oxidation of the amino group of the 2-alkynylaniline **1a** seems to override the hydroamination step under the silver catalysis. Based on recent "green" method for the oxidation of nitrogen-rich heterocyclic amines with oxone,[17] we anticipated that either the nitro or nitroso compounds derived from **1a** could be intermediates in our domino process. Anthranyls **6** were obtained selectively through Au- or Ir-catalyzed reaction of 2-(alkylakynyl)nitrobenzenes[18] or iodine-mediated cycloisomerization of nitroheterocyclic adducts,[19] and as by-products in the specific case of Hg-catalyzed or oxone-mediated oxidation of nitrobenzenyl-substituted alkynes.[14a,b] However, our attempts to employ 1-(2-(2-nitrophenyl)ethynyl) benzene **8a** and the nitrosoadduct **9a** as the precursors of the corresponding anthranyl derivative **6a** turned out to be unfruitful in the presence of the silver catalyst (Scheme 3). The addition of TEMPO had a slight influence but did not interrupt the reaction, thus suggesting that radical intermediates were not involved in the process (Scheme 3).[20] Even though it's difficult to conclude on the mechanism implying silver complex, the sequential oxidation of **1a** would produce the nitrosobenzene intermediate **C**, which upon intramolecular nucleophilic addition of the enol oxygen (intermediate **D**) followed by dehydration reaction would give anthranil **6a**.[18a] Similarly to Jung's proposal for the oxidation of alkynes by Hg salts,[14a] an alternative mechanism involving the π-activation/hydration of the alkyne by silver salts (intermediate **E**), followed by a pericyclic cyclization of intermediate **F** cannot be ruled out.[21]

With the optimized reaction conditions established, the sequential divergent silver-catalyzed oxidative reaction of various 2-alkynylanilines **1** with oxone was investigated. Substrates bearing both electron-rich and electron-poor aromatic groups on the terminal triple bond could be efficiently converted to the corresponding benzisoxazoles **6a-o** in moderate to good yields (32-88%, Scheme 4).
Pleasingly, halo substituents, such as -Cl and –Br were well tolerated, which could provide the possibility for further functionalization. Functional groups such as acetyl and acetate moieties were also preserved during the domino process, leading to functionalized adducts **6h** and **6i** in 75% and 56% isolated yields respectively. In addition to aryl-substituted anilines, substrates bearing heteroaryl moieties as well as alkyl group (R^1 = heteroaryl, alkyl) were found to be suitable substrates for this transformation. Methyl group on the aniline moiety (R^2) was also tolerated and the corresponding product was isolated in moderate yields. It is worth noting that the previous reported $AuBr_3$-catalyzed cyclizazion of 2-(arylalkynyl)nitrobenzenes led to a mixture of isatogens (main product) and anthranils (minor product) and the selective formation of anthranils was limited only to the gold-catalyzed cyclization of 2-(alkylalkynyl)nitrobenzenes.[18]



Scheme 4 [Ag]-catalyzed oxidative cyclization – Substrate scope

The aniline moiety could also be functionalized by a CF_3 group. Interestingly, the presence of the phenylalkynyl group afforded the corresponding anthranyl derivative **6n** in a higher yield

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than in the case of a 4-cyano-substituted phenylalkynyl moiety. The presence of two electron-withdrawing groups therefore hampered the domino oxidation/cyclization process and gave rise to a mixture of the desired compound **6o** and the corresponding non-cyclized nitro derivative 4-{[2-nitro-4-(trifluoromethyl)phenyl]ethynyl}benzonitrile **8o** in 32% and 29% isolated yields respectively. The outcome of this latter reaction also supports our proposed mechanism (Scheme 4), excluding the 2-nitro-substituted derivative as a potential intermediate.

In conclusion, we have developed an unprecedented Ag-catalyzed domino oxidative cycloisomerization reaction of unprotected 2-alkynylanilines, leading to benzisoxazole derivatives in moderate to good yields. The divergent efficiency of silver and gold catalysts was demonstrated, as the gold-catalyzed process gave access to functionalized 4*H*-benzo[*d*][1,3]oxazin-4-one. The challenging and rewarding silver-catalyzed process was then further developed. The methodology implying oxone as oxidant without any acids nor bases, was compatible with several groups such as ketone and halogen groups as well as heterocycles. The alkynyl moiety could be substituted independently by aryl or alkyl groups, which opens new opportunities for the synthesis of biologically-active targets.

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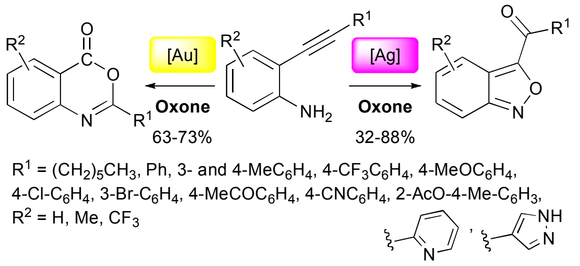

Divergent catalytic activity of gold and silver complexes towards domino oxidative cyclization reactions of unprotected 2-alkynylanilines