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A New Gold-Catalyzed Domino Cyclization and Oxidative Coupling Reaction

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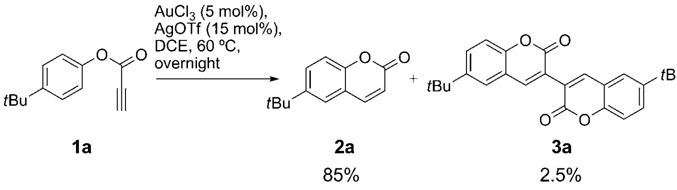
Although gold was long thought to be an unreactive metal, the first gold-catalyzed reactions were reported over 30 years ago.[1] Since then, especially in recent years, this area of investigation has been growing rapidly.[2–4] The unique properties of Au as a π Lewis acid enable the development of novel routes to complex molecular structures.[5] Herein, we report a new gold-catalyzed domino cyclization and oxidative coupling reaction for the synthesis of dicoumarins.

Metal-catalyzed cyclization of arylpropionic esters has been used to form coumarins for a number of years.[6–10] During our investigations into coumarin precursors, we discovered a second product formed in the reaction, which originated from a cyclization followed by an oxidative coupling of two coumarin subunits (Scheme 1). Such homo-couplings of vinyl-Au species have been reported for reactions employing stoichiometric amounts of Au.[11]



Scheme 1. Formation of dicoumarins in the Au-catalyzed cyclization of aryl propargylesters (DCE = 1,2-dichloroethane).

This dicoumarin framework is present in a variety of natural products.[12] Some of them show moderate inhibitory activity on cell growth of various leukemia and carcinoma cell lines.[12b] Current syntheses of dicoumarins rely on oxidative coupling,[13] Ullmann coupling[14a] or the Perkin reaction.[14b] However, all of them suffer from low yields or low substrate scope.

Different oxidants and Au-sources were screened with compound **1** (Scheme 1) as test substrates to regenerate Au^{III}, to allow for use of catalytic amounts of the gold species. Anhydrous *tert*-butylhydroperoxide in combination with $HAuCl_4$ gave the best catalytic performance and afforded the desired dimer in good yields. The process was highly solvent-dependent, and the best results were obtained in 1,2-dichloroethane (DCE), whereas protic solvents, such as ethanol, gave only the monomer (determined by ^{1}H NMR spectroscopy).

The catalyst loading was lowered to 1 mol %, without loss of yield or selectivity. However, reaction times for complete conversion were considerably longer (1 h with 5 mol % catalyst, compared to 24 h with 1 mol %). Variations in concentration also altered results. The ratio of monomer to dimer changed from 2:3 for a substrate concentration of 50 $mmol\,L^{-1}$in DCE, to 4:3 for a concentration of 12 $mmol\,L^{-1}$. If the reaction was performed at a higher concentration of 460 $mmol\,L^{-1}$, the conversion (4 %) and the monomer/dimer ratio (9:10) both dropped dramatically. Addition of bases, such as Cs_2CO_3 or NaOMe, or water absorbing materials, such as molecular sieves or $MgSO_4$, did not improve the results. Conversely, in most cases the reaction failed completely. Not even a dimerization of the alkyne by Glaser-type coupling was observed under basic conditions, rendering a gold–acetylene species an unlikely intermediate.[15]

The reaction generally proceeded in moderate-to-good yields, tolerating a variety of substituents on the aromatic moiety. Even substitution in the *ortho*-position was tolerated (Table 1, entries 3–5). Interestingly, in contrast to the simple cyclization, high regioselectivity was detected in cases where two possible regioisomers could be formed (Table 1, entries 6 and 7).[16] The depicted isomers were the only ones isolated. Substrates with an electron-rich aromatic group gave the highest dimerization yields. Furthermore, the ester

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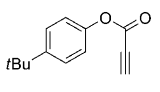
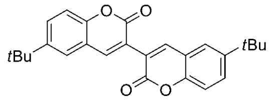
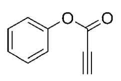
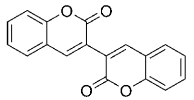
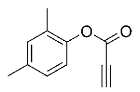
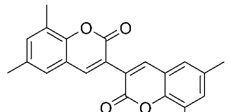
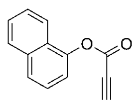
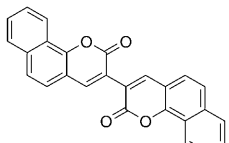
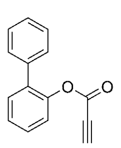
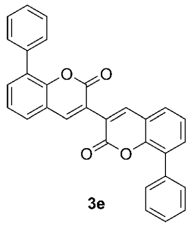
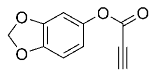
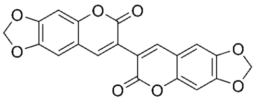
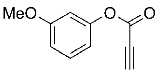
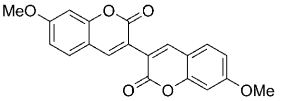
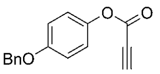
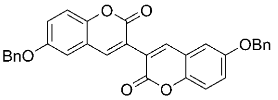
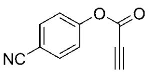
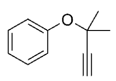
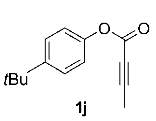
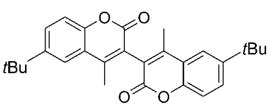
Table 1. Substrate scope of the domino cyclization/oxidative coupling reaction.[a]

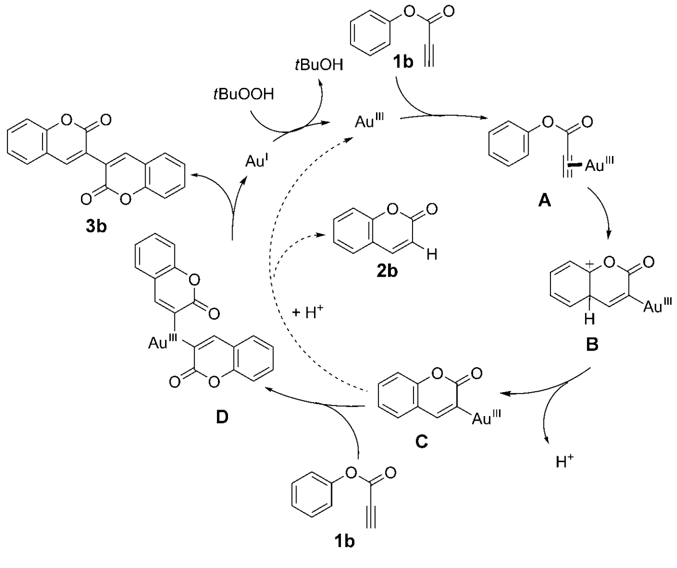
Entry	Starting material	Product	Yields [%][b] D	 M	 SM
1	 **1a**	 **3a**	55	32	–
2	 **1b**	 **3b**	27	40	–
3	 **1c**	 **3c**	28	19	–
4	 **1d**	 **3d**	67	13	–
5	 **1e**	 **3e**	37	18	12
6	 **1f**	 **3f**	50[c]	30	–
7	 **1g**	 **3g**	40	23	–
8	 **1h**	 **3h**	34[c]	8	–
9	 **1i**	No reaction	–	–	85
10	 **4**	No reaction	–	–	81
11	 **1j**	 **3j**	13	21	31

[a] Reaction conditions: $HAuCl_4$ (5 mol %), *t*BuOOH (5 equiv), DCE, 60 °C, 24 h. [b] Yields of isolated product. D = dimer **3**, M = monomer **2**, SM = starting material **1**. [c] Inseparable mixture with oxidized products.

group also seems to be essential for cyclization to occur; a precursor with an ether bridge gave no reaction (Table 1, entry 10). Although the reaction conditions are mild, in some cases, the presence of a strong oxidant, *t*BuOOH, led to partial cleavage of the ester as well as oxidation, probably to the quinone (Table 1, entries 6 and 8) .[17] Electron-withdrawing groups on the aromatic moiety, such as CN, Cl, and CO_2Et, prohibit the reaction. In these cases, only starting material was isolated, together with small amounts of the corresponding phenol, resulting from ester cleavage. Interestingly, it was even possible to isolate the dimer with a substituent on the alkyne (Table 1, entry 11). However, steric hindrance appeared to hamper the dimerization process.

The first step of the domino cyclization/oxidative coupling reaction has been studied by other groups[8,9,18] and has also been investigated in our own laboratory, by using deuteration experiments, which showed that the reaction proceeds by an electrophilic Friedel–Crafts-type mechanism. This finding explains why electron-rich aromatic rings are the best substrates for such reactions.

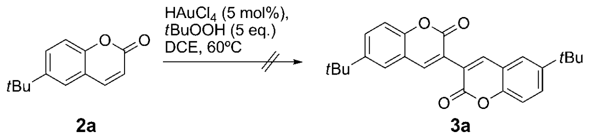
Based on these results, we propose the following mechanism for the domino cyclization/oxidative coupling reaction (Scheme 2): The Au catalyst coordinates to the alkyne **1** to activate it for electrophilic substitution. Rearomatization furnishes the σ complex **C**, which in turn catalyzes a second cyclization to form complex **D**. Protonation of complex **C** terminates the cycle and results in the formation of the monomeric coumarin **2**. However, complex **D** undergoes an oxidative coupling to the dimeric dicoumarin **3** and an Au^I species, which is subsequently reoxidized to Au^{III}, completing the catalytic cycle. An alternative rationale would be a ligand exchange of two complexes **C**. A crossover experiment, using a 1:1 mixture of naphthalen-1-yl propiolate **1d** (Table 1, entry 4) and 3-methoxyphenyl propiolate **1g** (Table 1, entry 7), was undertaken to test if the comparative



Scheme 2. Proposed mechanism for the Au-catalyzed domino cyclization/oxidative coupling reaction.

reactivities of complex **C** influenced the outcome of the reaction. However, only a mixture of the monomers, both homodimers, and the heterodimer, in approximately stochastic ratio, were obtained.

Reaction of the cyclized coumarin monomer under the usual conditions for the domino cyclization/oxidative coupling gave no dimerization product (Scheme 3), suggesting that reinsertion of Au into the α C–H of the coumarin does not occur.



Scheme 3. Submission of the monomeric coumarin to the cyclization/oxidative coupling conditions.

The UV absorption and the fluorescence properties of the dicoumarins are very similar to those for the monomers. This behavior is probably due to a twist of the two coumarin units, which limits the conjugation of the π-electron system to half of the molecule. A relative torsion angle of 38.4° can be observed in the crystal structure (Figure 1). Preliminary investigations detected an interesting photostability of these compounds, which makes them promising candidates for application as UV-absorbent materials.

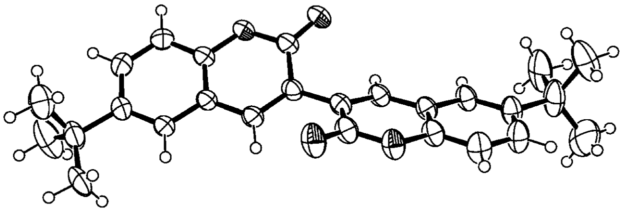


Figure 1. Solid-state molecular structure of 6,6′-di-*tert*-butyl-2*H*,2′*H*-3,3′-bichromen-2,2′-dione **3a**. Thermal ellipsoids are set at 50 % probability. For clarity, the disordered *tert*-butyl groups are shown in one conformation only.[19]

In summary, we have shown the first Au-catalyzed domino cyclization/oxidative coupling reaction. In this process the gold catalyst performed two different functions. Dicoumarins, scaffold of natural products with interesting biological properties and potential photostable UV-absorbent materials, were accessed in two steps from commercially available starting materials. In the future, this method could be applied to the synthesis of such natural products and other interesting targets.

Experimental Section

General procedure: HAuCl$_4$ (0.05 equiv) was suspended in dry 1,2-dichloroethane (10 mL per 0.5 mmol substrate). A solution of *tert*-butylhydroperoxide (5.00 equiv, 80 wt %) in cyclohexane was added and the arylpropionic ester (1.00 equiv) was dissolved in the solution. The mixture was heated to 60 °C and was stirred for 24 h. If a precipitate was formed, it was removed by filtration and recrystallized. Excess peroxide was reduced with Na$_2$S$_2$O$_3$ (10 % aq. solution). The mixture was diluted with dichloromethane (50 mL) and washed with H$_2$O. The combined organic layers were dried over Na$_2$SO$_4$, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica.

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Keywords: C–C coupling · domino reactions · gold · homogeneous catalysis

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[19] X-ray crystallographic data for 6,6′-di-*tert*-butyl-2*H*,2′*H*-3,3′-bichromen-2,2′-dione **3a**: $C_{26}H_{26}O_4$, $M_r = 402.49$, F(000) = 3852; colorless needle; crystal size 0.05 × 0.07 × 0.44 mm; trigonal; space group $R\bar{3}c$, $a = 25.3197(3)$, $b = 25.3197(3)$, $c = 18.7196(6)$ Å; $\alpha = \beta = 90°$, $\gamma = 120°$; $V = 10393.1(4)$ Å^3; $Z = 18$; $\rho_{calcd} = 1.157$ Mg m^{-3}. The crystal was measured on a Kappa APEX diffractometer at 173 K using graphite-monochromated $Mo_{K\alpha}$ radiation with $\lambda = 0.71073$ Å, $\Theta_{max} = 27.471°$. Minimal/maximal transmission 0.99/1.00, $\mu = 0.077$ mm^{-1}. The APEX suite has been used for data collection and integration. From a total of 42256 reflections, 2655 were independent (merging $r = 0.050$). From these, 1815 were considered as observed ($I > 2.0\sigma(I)$) and were used to refine 163 parameters. The structure was solved by direct methods using the program SIR92.[20] Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS[21] $R = 0.0459$ (observed data), $wR = 0.0891$ (all data), GOF = 1.2651. Minimal/maximal residual electron density = −0.30/0.31 e Å^{-3}. Chebychev polynomial weights were used to complete the refinement. Plots were produced using ORTEP3 for Windows[22] CCDC 690486 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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