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Synthesis of 4-Furan- and 4-Pyrrol-3-yl-2*H*-chromenes from Naturally-occurring Compounds by Gold(I)-Catalyed Domino Reactions

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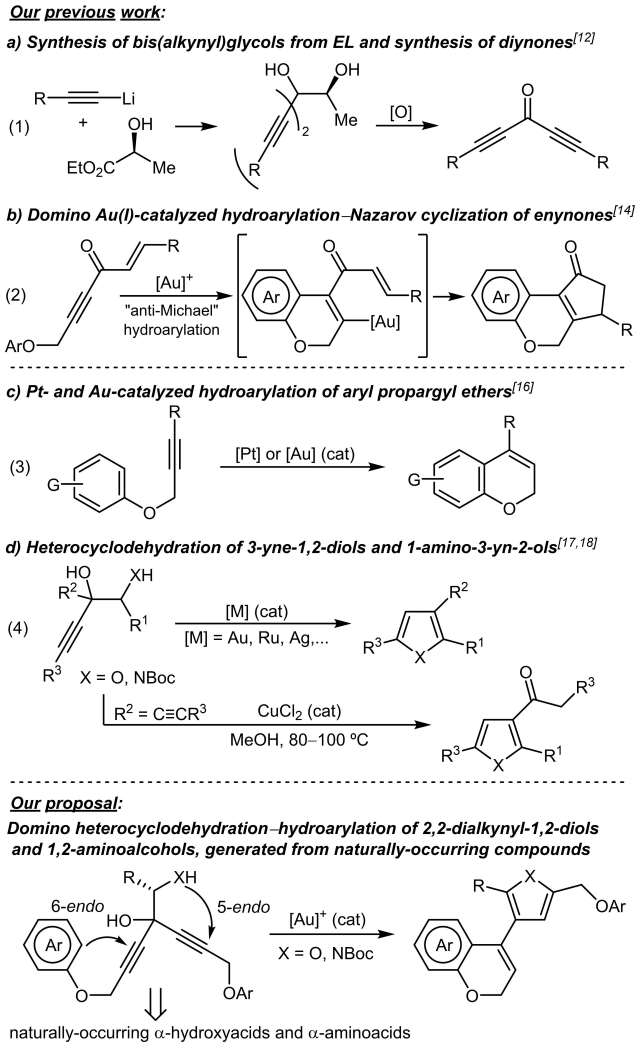
Abstract: A gold-catalyzed cascade double cyclization reaction has been designed to synthesize heterobiaryl compounds such as furanyl and pyrrolyl 2*H*-chromenes from bis(alkynyl)-1,2-diols and 1,2-amino alcohols. The starting materials are readily available from biomass platform molecules such as α-hydroxy acids and α-amino acids. The process involves an initial heterocyclodehydration step enabling the formation of the furan or pyrrole ring, followed by an alkyne hydroarylation to form the chromene core.

Keywords: annulation; chromenes; furans; gold; hydroarylation; pyrroles

Heterobiaryls are versatile scaffolds frequently found in biologically active compounds as well as in organic materials or ligands for organometallic complexes.[1] One of the main approaches for their preparation is based on the transition metal-catalyzed formation of the biaryl C–C bond via cross-couplings or cross-dehydrogenative couplings.[2] Less developed is the approach in which the two heterocyclic fragments are formed in a domino reaction from a properly functionalized acyclic substrate. In this field, the use of gold-catalysis has allowed significant advances toward the synthesis of heterocyclic compounds mainly by electrophilic functionalization reactions of π-systems under mild conditions.[3]

Pyrrole and furan are five-membered electron-rich heterocyclic motifs,[4] widely found in products with a plethora of properties and applications,[5] and also used as intermediates for the synthesis of high-valued chemicals and several natural products.[6] Therefore, a wide number of strategies for their synthesis have been reported during the last decades, including classical methods (Paal-Knorr, Hantzsch, Feist-Bénary, …),[7] as well as transition metal-catalyzed reactions involving cycloisomerization processes of acyclic oxo-alkynyl/allenyl precursors to furnish furans,[8] and alkynyl-functionalized imines or related compounds to provide pyrroles.[9] However, some of the starting materials require several steps for their preparation, and there is still room for improving the scope and reaction conditions of these methods. In addition, 2*H*-chromenes are among the most important oxygenated heterocycles, being prevalent moieties in many natural products, biologically active compounds, and materials.[10] Their relevance has led to the development of several methods to access these scaffolds.[11]

We have previously reported the synthesis of diynones by the oxidative cleavage of 2,2-dialkynyl-1,2-diols, which were efficiently prepared by alkynylation of biomass-derived ethyl lactate (Scheme 1, eq 1).[12] The symmetrical skipped diynones undergo a regiodivergent hydration-cyclization under gold(I)-catalysis leading to 4-pyranones or 3-(2*H*)-furanones, depending on the catalytic system employed.[13] Very recently, we have also described a domino hydroarylation-Nazarov Au(I)-catalyzed double cyclization of related skipped alkenynones that leads to cyclopenta[*c*]chromenones, even in an enatioselective

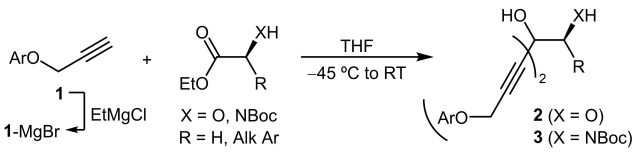


Scheme 1. Previous work and our proposal.

way when chiral bisphosphine-gold complexes were employed (Scheme 1, eq 2).[14] Platinum and gold complexes are valuable catalysts for intramolecular hydroarylation reactions that produced a wide range of fused heterocyclic compounds.[15] With aryl propargyl ethers this type of process has been employed for producing chromene derivatives (Scheme 1, eq 3).[16] In addition, 3-yne-1,2-diols and 1-amino-3-yn-2-ols have been described to undergo heterocyclodehydration reactions under the catalysis of different transition metals,[17] whereas with 2,2-dialkynyl-1,2-diols, or aminoalcohols, 3-acylfurans or pyrroles were obtained, respectively, under Cu(II)-catalysis (Scheme 1, eq 4).[18] In this context, we envisaged that readily available 2,2-dialkynyl-1,2-diols and related 1,2-aminoalcohols, appropriately functionalized with a propargyl ether moiety, could evolve under gold-catalysis through a domino heterocyclodehydration-hydroarylation reaction to produce highly functionalized heterobiaryl derivatives (Scheme 1, eq 5). We herein report a new Au-catalyzed double cyclization sequence of readily available acyclic starting materials, arising from naturally occurring α-hydroxy acid and α-amino acid derivatives to the preparation of a wide variety of furanyl- and pyrrolyl-chromenes.

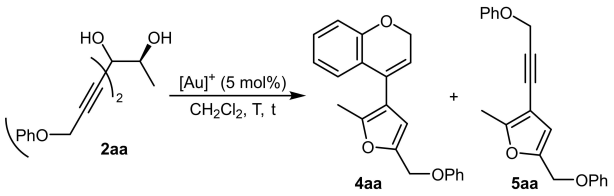
The preparation of proposed bis(alkynyl)-1,2-diols **2** and bis(alkynyl)-1,2-aminoalcohols **3** is outlined in Scheme 2. As mentioned above, we have previously described an efficient protocol for the synthesis of 1,1-dialkynyl-1,2-diols by addition of acetylides, prepared from the treatment of propargyl ethers **1** with EtMgCl, to ethyl lactate, which is a readily available biomass-derived feedstock that can be produced from renewable carbohydrates.[12] Considering that the transformation of renewable and abundant natural sources to high value-added chemicals is a relevant goal in modern synthetic chemistry, we have extended this methodology to other naturally occurring compounds, such as α-hydroxy acids and α-amino acids derivatives, to synthesize alkynyl-functionalized glycols **2** and 1,2-aminoalcohols **3**.[19]

We started our investigation by using glycol **2aa** as the model substrate and evaluated its reactivity under the catalysis of different gold(I) complexes (Table 1). When using $XPhosAuNTf_2$ as catalyst 4-furan-3-yl-2*H*-chromene derivative **4aa** was obtained in 35% yield after only 10 min at room temperature, with no more than trace amounts of the corresponding furan derivative **5aa** (entry 1). Although in moderate yield, this result showed that our proposal for the tandem heterocyclodehydration-hydroarylation reaction was feasible. Then, other cationic gold(I) complexes were tested to improve the efficiency of the process. A complex bearing a phosphite ligand led to decomposition (entry 2), whereas with Gagosz's catalyst[20] no better results were achieved (entry 3). The use of $IPrAuNTf_2$ as catalyst led to **4aa** in 53% yield (entry 4). Moreover, the yield of the desired product improved, carrying out the reaction at 0 °C (entry 5). Looking for more effective conditions, we screened various gold catalysts with different silver salts as halide scavengers (entries 6–12). IPrAuCl and JohnPhosAuCl, in combination with $AgNTf_2$, gave comparable results leading to the formation of the furanyl-2*H*-chromene **4aa** in moderate yield (entries 6 and 9). Gratifyingly, the benefit of SbF_6^- counteranion was demonstrated (entries 8 and 12). Notably, the silver salt



Scheme 2. Preparation of starting bis(alkynyl)-1,2-diols **2** and bis(alkynyl)-1,2-aminoalcohols **3**.

Table 1. Optimization of the reaction conditions for the obtention of **4 aa**.

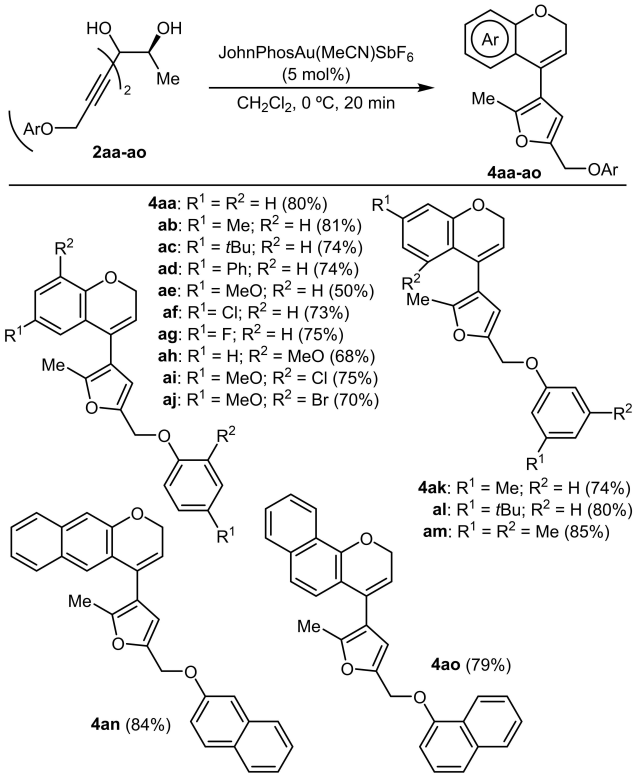


Ent	$[Au]^+$	T [°C]	t [min]	Ratio **4 aa**/**5 aa**[a]	Yield [%][b]
1	$XPhosAuNTf_2$	RT	10	>20/1	35
2	$(ArO)_3PAuCl/AgSbF_6$	RT	10	–	–[c]
3	$Ph_3PAuNTf_2$	RT	10	>20/1	16
4	$IPrAuNTf_2$	RT	10	>20/1	53
5	$IPrAuNTf_2$	0	20	>20/1	68
6	$IPrAuCl/AgNTf_2$	RT	10	–	<5
7	$IPrAuCl/AgNTf_2$	0	20	>20/1	40
8	$IPrAuCl/AgSbF_6$	0	20	>20/1	69
9	$JohnPhosAuCl/AgNTf_2$	RT	10	>20/1	41
10	$JohnPhosAuCl/AgBF_4$	RT	10	>20/1	56
11	JohnPhosAuCl/AgOTf	RT	10	–	–[c]
12	$JohnPhosAuCl/AgSbF_6$	RT	10	>20/1	71
13	$JohnPhosAu(MeCN)SbF_6$	RT	10	>20/1	70
14	$JohnPhosAu(MeCN)SbF_6$	0	20	>20/1	86
15	$AgSbF_6$	RT	60	0/1	81

[a] Determined by ^1H NMR analysis of the crude reaction mixture.
[b] Yield by NMR using 1,3,5-trimethoxybenzene as internal standard.
[c] Full conversion, but decomposition with unidentified compounds, was observed.

was not required as the use of Echavarren's catalyst,[21] $JohnPhosAu(MeCN)SbF_6$, provided similar results (entry 13). Finally, when performing the reaction at 0 °C for 20 min the heterobiaryl **4 aa** was obtained selectively in 86% yield (entry 14). By contrast, the use of $AgSbF_6$ catalyst gave rise selectively to the alkynylfuran derivative **5 aa** (entry 15). Other metal or Brønsted acid catalysts were also tested, although any transformation took place.[19]

Once we have established the optimal reaction conditions (Table 1, entry 14), the substrate scope with respect to the aryl moiety involved in the hydroarylation process was investigated. The optimized conditions were applied to a wide variety of bis(alkynyl)-1,2-diols **2 aa-ao**, easily obtained by alkynylation of ethyl lactate, providing a family of furanyl-2*H*-chromenes **4 aa-ao** in high yields (Scheme 3). This gold-catalyzed domino reaction proceeds efficiently, with good to high yields, for starting diols bearing aryloxy rings functionalized with alkyl or aryl groups at *para*- and/or *meta*-positions, (**4 ab**–**ad**, **ak**–**am**). Glycols bearing aryloxy substituents with either electron-donating groups or electron-withdrawing groups were also well tolerated providing access to furanyl-chromenes **4 ae-aj** in good yields. Moreover, bis(alkynyl)-1,2-diols possessing naphthyl groups as substituents of the propargyl ether moiety, were also



Scheme 3. Synthesis of furanyl-2*H*-chromenes **4 aa–ao**.

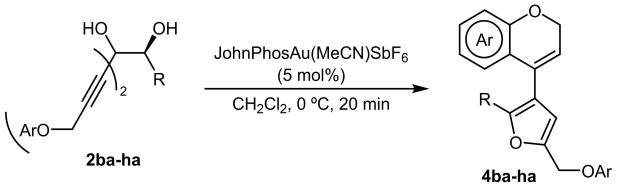
suitable substrates leading selectively to functionalized heterobiaryls **4 an** and **4 ao**.

The effect of the substituent at the homopropargylic position on 1,1-bis(alkynyl)-1,2-diols **2** was then studied, as summarized in Table 2. The formation of the corresponding heterobiaryls took place smoothly in excellent yields when employing glycols **2 ba–bg** bearing a primary alcohol group (R=H), including those bearing halide-substituted aryl groups (entries 1–7). Similarly, starting diols **2** with other alkyl groups, apart from methyl, as R substituents were tested, leading to the expected furanylchromenes **4 ca–ea** in good yields (entries 8–11). In addition, by using the catalytic conditions established in the optimization study, a variety of 4-furanyl-2*H*-chromenes possessing different aryl frameworks at the C-4 position of the furan ring, including the simplest phenyl group as well as 4-halophenyl groups, were synthesized in good yields (entries 12–19).

Having developed and evaluated the scope for the synthesis of furanyl-2*H*-chromenes **4** from glycols **2**, we decided to extend this domino sequence of heterocyclodehydration-hydroarylation to obtain related *N*-heterocycles, i.e. pyrrolylchromenes, from starting bis(alkynyl)-1,2-aminoalcohols **3**. Gratifyingly, the previously established conditions were found to be effective for the gold-catalyzed cyclization of the 1-amino-3-bis(alkynyl)-2-ols **3** that provides access to the corresponding 4-pyrrol-3-yl-2*H*-chromenes **6** (Table 3). First, when the starting aminoalcohol **3 a**, derived from *N*-Boc-glycine methyl ester, was reacted with catalytic amounts of JohnPhosAu(MeCN)SbF_6, the pyrrolylchromene derivative **6 a** was produced in high yield (entry 1). Aliphatic branched *β*-aminoalcohols evolved in the presence of the gold catalyst and gave the corresponding pyrrol-3-yl-2*H*-chromenes **6 b**,**c**,**g** in high yields (entries 2, 3, and 7). Furthermore, substrates **3 d** and **3 e**, with benzyl groups at the homopropargylic position, also led to the corresponding 2,4,5-trisubstituted pyrroles in good yields (entries 4 and 5). Finally, aminoalcohol **3 f**, easily prepared from a serine ester derivative, was tolerated in this domino reaction and transformed in the pyrrolylchromene **6 f** (entry 6).

Next, several control experiments were performed to gain further insights into the reaction mechanism (Scheme 4). First, when the reaction of model **2 aa** was carried out at 0 °C for 5 min the alkynylfuran **5 aa** was selectively obtained instead of 4-furan-3-yl-2*H*-chromene **4 aa**. This result supports that the heterocyclodehydration step occurs prior to the subsequent hydroarylation. Moreover, the intermediacy of **5 aa** was

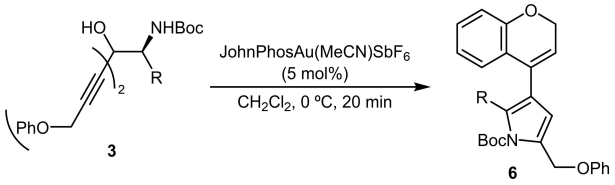
Table 2. Synthesis of furanyl-2*H*-chromenes **4 ba–ha**.



Entry	Diol	R	Ar	Product	Yield [%][a]
1	**2 ba**	H	Ph	**4 ba**	84
2	**2 bb**	H	4-MeC_6H_4	**4 bb**	95
3	**2 bc**	H	3,5-$Me_2C_6H_3$	**4 bc**	81
4	**2 bd**	H	4-MeOC_6H_4	**4 bd**	86
5	**2 be**	H	2-MeOC_6H_4	**4 be**	87
6	**2 bf**	H	4-ClC_6H_4	**4 bf**	83
7	**2 bg**	H	4-FC_6H_4	**4 bg**	84
8	**2 ca**	Et	Ph	**4 ca**	86
9	**2 cf**	Et	4-ClC_6H_4	**4 cf**	85
10	**2 da**	CH_2*i*Pr	Ph	**4 da**	83
11	**2 ea**	CH_2Ph	Ph	**4 ea**	88
12	**2 fa**	Ph	Ph	**4 fa**	62
13	**2 fb**	Ph	4-MeC_6H_4	**4 fb**	79
14	**2 fc**	Ph	3,5-$Me_2C_6H_3$	**4 fc**	62
15	**2 fd**	Ph	4-MeOC_6H_4	**4 fd**	72
16	**2 ff**	Ph	4-ClC_6H_4	**4 ff**	66
17	**2 fh**	Ph	4-PhC_6H_4	**4 fh**	63
18	**2 ga**	4-BrC_6H_4	Ph	**4 ga**	74
19	**2 ha**	4-ClC_6H_4	Ph	**4 ha**	78

[a] Isolated yield referred to the corresponding starting diol **2**.

Table 3. Synthesis of pyrrolyl-2*H*-chromenes **6**.



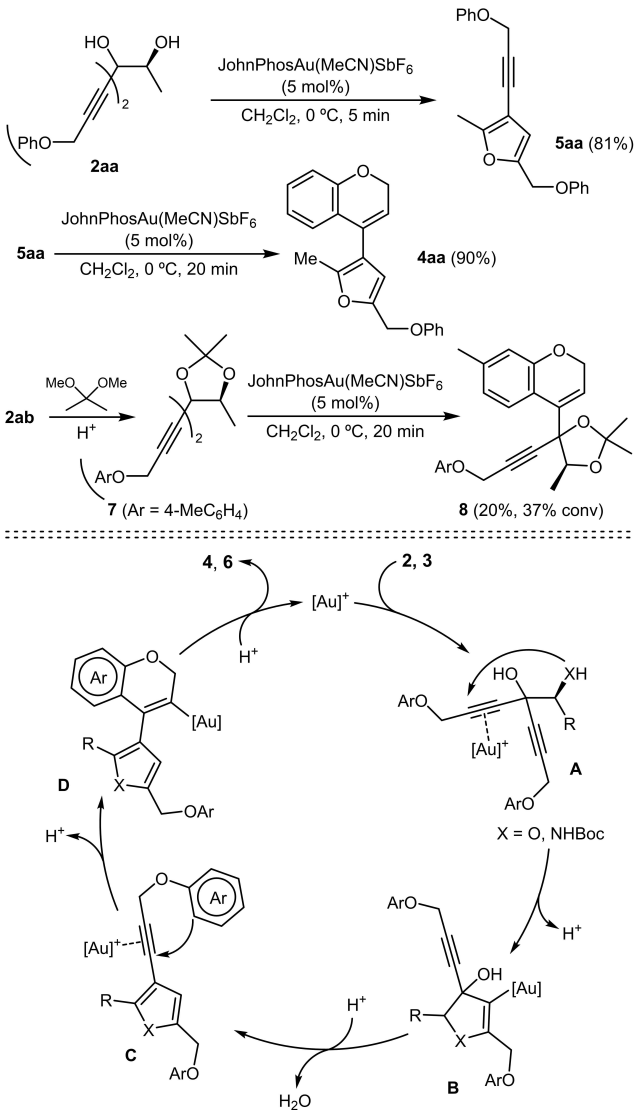
Entry	Aminoalcohol	R	Product	Yield [%][a]
1	**3a**	H	**6a**	82
2	**3b**	Me	**6b**	80
3	**3c**	*i*Pr	**6c**	77
4	**3d**	CH_2Ph	**6d**	84
5	**3e**	$CH_2(4\text{-}OHC_6H_4)$	**6e**	80
6	**3f**	CH_2OH	**6f**	69
7	**3g**	CH_2*i*Pr	**6g**	65

[a] Isolated yield referred to the corresponding starting aminoalcohol **3**.

further supported by its reaction under the same catalytic conditions that delivered **4aa** in high yield. In addition, the evolution of the reaction was also monitored by ^{1}H-NMR, observing the rapid formation of **5aa**, which was subsequently consumed, releasing **4aa**.[19] We then decided to prepare the acetal **7** from glycol **2ab** to avoid the heterocyclization event. When this acetal was submitted to the same reaction conditions, the chromene derivative **8** was isolated in low yield and conversion, which could not be significantly improved even under prolonged reaction time at RT (Scheme 4). This fact indicates that the hydroarylation step is favored once the furan or pyrrole ring has been formed. Therefore, the reaction would start with the coordination of the cationic gold complex to the triple bond of the starting glycol **2** or aminoalcohol **3** to give intermediate **A**, which would facilitate the nucleophilic attack of the homopropargylic alcohol or NHBoc group and subsequent 5-*endo-dig* cyclization, affording vinyl-gold intermediate **B**. Then, this compound evolves via protodeauration and dehydration into an alkynylfuran or pyrrole to which the gold catalyst could coordinate activating the alkyne and delivering intermediate **C**. Then, a 6-*endo* hydroarylation would take place, giving rise to heterobiaryl intermediate **D**, which after protodeauration led to the final compounds **4** and **6**, regenerating the catalytic species. Remarkably, the formation of the chromene ring via hydroarylation is favored by the previous generation of the corresponding furan or pyrrole unit.

Interestingly, chromene derivatives **4** and **6** can be readily prepared on gram-scale, enabling further transformations as shown in Scheme 5. In fact, **4aa** (757 mg, 80%) was synthesized from **2aa** (1 g, 2.97 mmol), whereas **6d** (798 mg, 83%) was obtained from **3d** (1 g, 2.16 mmol). It is worthy to note that in these cases the catalyst loading could be decreased to 2.5 mol%. First, treatment of furanylchromene **4aa** and pyrrolylchromene **6d** with MnO_2 led to the corresponding functionalized coumarins **9** and **12**. It is important to note that coumarin scaffolds are found in many biologically active compounds and are important motifs for developing new drugs.[22] Furthermore, heterobiaryl **4aa** underwent [4+2] cycloaddition with *in situ* generated benzyne to provide polycyclic scaffold **10** in good yield. On the other hand, it is well-known that the C–H bond at 2*H*-chromene C-2 position could be functionalized by reaction with different nucleophiles in the presence of DDQ, through oxonium intermediates.[23] To enrich the molecular diversity and, following this strategy, various highly substituted furanylchromene derivatives **11** were obtained in high yields using nucleophilic reagents such as *p*-toluenesulfonamide (**11a**), ethanol (**11b**), allyltrimethyl silane (**11c**) and ((1-methoxy-2-methylprop-1-en-1-yl)oxy)trimethylsilane (**11d**). Finally, the base-promoted deprotection of pyrrolyl-2*H*-chromene **6d** with NaOEt led to heterobiaryl **13** in good yield, in which, besides the expected Boc removal, a substitution of the phenoxy group by ethoxy also took place (Scheme 5).

In summary, we have developed a convenient methodology to synthesize new heterobiaryls that contain two relevant substructures the chromene unit and the pyrrole or furan unit, from readily available alkynyl-functionalized glycols or 1,2-amino alcohols derived from naturally occurring compounds such as α-hydroxy acids and α-amino acids. This strategy is based on a domino gold-catalyzed reaction involving an initial heterocyclodehydration, to produce the corresponding 5-membered heterocyclic ring, furan or pyrrole, followed by an intramolecular 6-*endo* alkyne hydroarylation to generate the 2*H*-chromene moiety. The starting glycols and 1,2-amino alcohols react smoothly in short reaction times and under mild conditions, affording furanyl- and pyrrolyl-chromenes



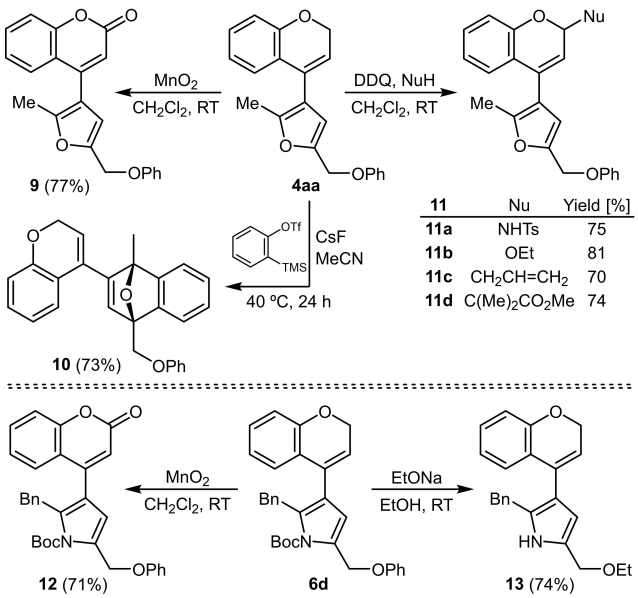
Scheme 4. Proposed mechanism for the formation of **4** and **6** from **2** and **3**, respectively.

in good to high yields. Moreover, the transformation was amenable to scale up to gram amounts, which facilitates further functionalization to access highly substituted chromene derivatives.

Experimental Section

General Procedure for the Synthesis of 4-Furan-3-yl-2H-chromenes 4 and 4-Pyrrol-3-yl-2H-chromenes 6 (Scheme 3 and Tables 2 and 3)

JohnPhosAu(MeCN)SbF_6 (5 mol%, 19 mg) was dissolved in CH_2Cl_2 (1 mL) and it was stirred for 5 min at RT. A solution of the corresponding bis(alkynyl)glycol **2** or bis(alkynyl)-1,2-aminoalcohol **3** (0.5 mmol) in CH_2Cl_2 (2 mL) was subsequently added at 0 °C. The reaction mixture was stirred at 0 °C for 20 min (until complete disappearance of the starting material as



11	Nu	Yield [%]
11a	NHTs	75
11b	OEt	81
11c	$CH_2CH{=}CH_2$	70
11d	$C(Me)_2CO_2Me$	74

Scheme 5. Further transformations of selected furanyl-2*H*-chromenes **4** and pyrrolyl-2*H*-chromenes **6**.

determined by TLC). The mixture was filtered through a short pad of silica gel and celite using a mixture of hexane/EtOAc (5/1), and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography using mixtures of hexane/EtOAc as eluents to afford the corresponding furanyl-2*H*-chromenes **4** and pyrrolyl-2*H*-chromenes **6**. Synthetic details, characterization data and NMR spectra are presented in the Supporting Information.

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