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Synthesis of Difurylmethane Derivatives *via* the Gold-Catalyzed Tandem Cycloisomerization/Dimerization of Epoxide Alkynes

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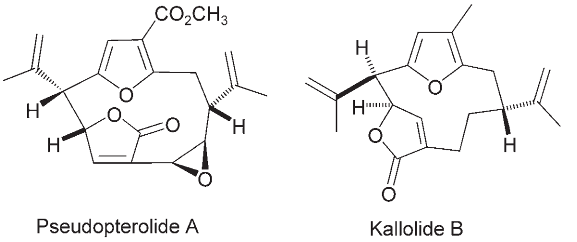
Abstract: A simple and convenient synthetic approach to difurylmethane derivatives has been developed *via* gold-catalyzed cycloisomerization of 1-oxiranyl-2-alkynyl esters and dimerization of the 2-(α-hydroxyalkyl)furans. The reaction takes place in the presence of 2 mol% of tetrachloroauric acid tetrahydrate ($HAuCl_4\cdot 4H_2O$) under very mild conditions.

Keywords: cycloisomerization; dimerization; epoxyalkynes; furans; gold

Furan rings occur widely as key structural subunits in numerous natural products, such as pseudopterolide A[1] and pseudopteranolide kallolide B,[2] while difurylmethanes look quite attractive. Difurylmethanes are of interest to the food industry as they are present as natural compounds in foods and beverages, such as licorice.[3] Furthermore, they are important intermediates in the synthesis of various heterocyclic macromolecules.[4] Consequently, the construction of this type of furan ring enjoys the continued development of new methods. However, most attention has been paid to the classical route to the difurylmethanes, which must contain the structure of the 2-substituted furan itself.[5] Only few publications have reported the employment of transition metals-catalyzed cycloisomerization reactions,[6] which have been proved as an efficient way to construct the furan ring systems.[7] For instance, Marson has reported that mercury(II)-catalyzed isomerization of alkynyl epoxides to afford difurylmethanes.[6a] Consequently, the transition metal-catalyzed cycloisomerization route to difurylmethanes remains largely unexplored.



Recently, it was reported that carbon-carbon and carbon-heteroatom bonds can be formed under mild conditions using gold catalysts.[8] Their ability to activate alkynes and promote the addition of nucleophiles has spurred growing investigations for the discovery of selective reactions.[9] Several gold-catalyzed cycloisomerizations for the preparation of furans have been developed, among which we have described the gold-catalyzed tandem cycloisomerization of 1-oxiranyl-2-alkynyl esters **1** with nucleophiles to give 2,5-disubstituted furans **4** (Scheme 1).[10] Without the addition of nucleophiles, water may play an important role in the cycloisomerization to give the 2-(α-hydroxyalkyl)furans. Then, under the gold catalysts, the latter may afford difurylmethanes through the dimerization process, which is an efficient approach to the formation of a C–C bond.

Herein, we report the gold-catalyzed tandem cycloisomerization/dimerization of epoxyalkynes, in the presence of trace amounts of water to give difurylmethanes under very mild conditions. The starting materials could be easily obtained by epoxidizing the corresponding 1-en-4-yn-3-ols following an acylation process.

Initially, we started out our investigation by using 0.5 mmol of 1-oxiranyl-2-alkynyl ester **1a** and 2 mol% of $HAuCl_4\cdot 4H_2O$ in 1,4-dioxane/H_2O systems at room temperature. Gratifyingly, the desired difurylmethane **2a** was formed, along with undimerized 2-(α-hydroxy-

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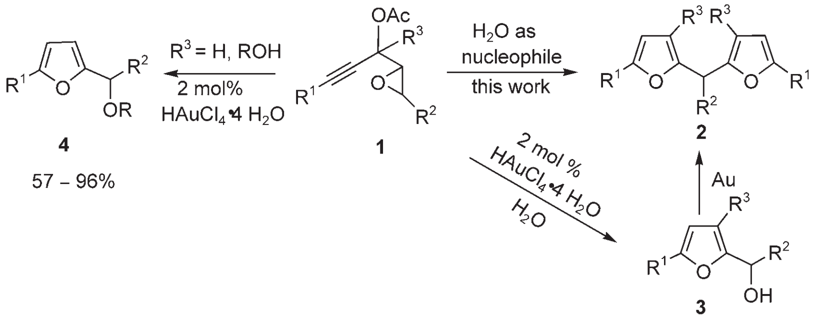
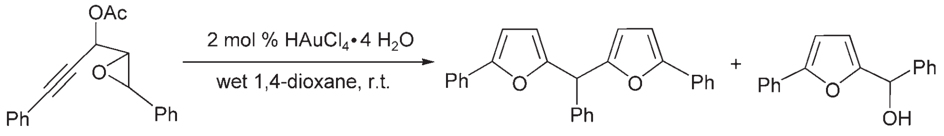


Scheme 1.

alkyl)furan **3a** in 28–30% after 12 h (Table 1, entries 1 and 2). To our delight, when the reaction was carried out in wet 1,4-dioxane, the desired product **2a** was obtained in 68% yield after 10 min (Table 1, entry 3). With other gold catalysts, such as $NaAuCl_4 \cdot 2H_2O$, $AuCl_3$, AuCl and $Au(PPh_3)Cl/AgBF_4$, no superior results were obtained (Table 1, entries 4–7). Other transition metal catalysts such as $AgBF_4$, $PtCl_2$ and $PdCl_2$ were ineffective (entries 6–10). Protic acids such as TFA and TsOH have also been applied to the reaction under identical conditions, but no reaction occurred (entries 11 and 12). Other solvents such as THF, ether and 1,2-dimethoxyethane produced lower yields of the desired products (entries 13–15). Thus, the use of $HAuCl_4 \cdot 4H_2O$ (2 mol%) in wet 1,4-dioxane at room temperature was found to be the most efficient and was utilized as the standard conditions.

With the optimized conditions in hand, the scope of this reaction was then examined, as depicted in Table 2. We first investigated a range of esters of 1-oxiranyl-2-alkyn-1-ols.[11] The reaction works well with aromatic R^2 groups (entries 1–3). Electron-rich aryl groups showed equal results to those with an electron-withdrawing group in this cycloisomerization and dimerization process (entries 2 *vs.* 3). While substrates like **1d** and **1e** gave the corresponding products in lower yields (entries 4 and 5), compounds having an aliphatic or H R^2 group would be less stabilized for forming the intermediates **C** and the process of dimerization (*vide infra*). Various aryl substituents on the

Table 1. Efficiency of transition-metal catalysts for the transformation of **1a** to **2a**.[a]

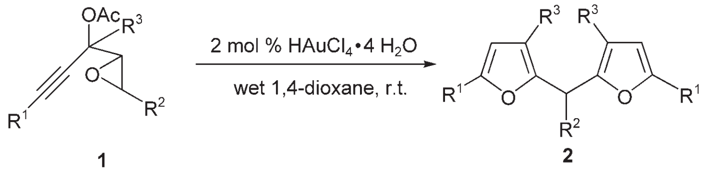


1a **2a** **3a**

Solvent	Catalyst	Solvent	Time	Yield [%][b]	
				2a	**3a**
1	$HAuCl_4 \cdot 4H_2O$	1,4-dioxane/H_2O = 1:1	12 h	20	30
2	$HAuCl_4 \cdot 4H_2O$	1,4-dioxane/H_2O = 10:1	12 h	25	28
3	$HAuCl_4 \cdot 4H_2O$	1,4-dioxane	10 min	68	0
4	$NaAuCl_4 \cdot 2H_2O$	1,4-dioxane	30 min	64	0
5	$AuCl_3$	1,4-dioxane	25 min	38	0
6	AuCl	1,4-dioxane	30 min	61	0
7	$Au(PPh_3)Cl/AgBF_4$	1,4-dioxane	30 min	60	0
8	$AgBF_4$	1,4-dioxane	2 h	0	0
9	$PtCl_2$	1,4-dioxane	2 h	0	0
10	$PdCl_2$	1,4-dioxane	2 h	0	0
11	10 mol% TFA	1,4-dioxane	2 h	0	0
12	10 mol% TsOH	1,4-dioxane	2 h	0	0
13	$HAuCl_4 \cdot 4H_2O$	THF	10 min	50	0
14	$HAuCl_4 \cdot 4H_2O$	ether	20 min	60	0
15	$HAuCl_4 \cdot 4H_2O$	1,2-dimethoxyethane	30 min	29	0

[a] *Conditions:* 0.5 mmol of **1a** with 2 mol% of catalyst in wet 1,4-dioxane (2.0 mL) at room temperature (23–25 °C).
[b] Isolated yield.

Table 2. Au(III)-catalyzed synthesis of difurylmethanes **2** by cyclization of esters of 1-oxiranyl-2-alkyn-1-ols **1**.[a]



Entry	**1**[b]	R^1	R^2	R^3	Time [min]	**2**	Yield [%][c]
1	**1a** (7:5)	Ph	Ph	H	10	**2a**	68
2	**1b** (10:7)	Ph	p-CH_3-C_6H_4	H	10	**2b**	72
3	**1c** (2:1)	Ph	p-Cl-C_6H_4	H	10	**2c**	70
4	**1d** (2:1)	Ph	CH_3	H	20	**2d**	55[d]
5	**1e** (9:7)	Ph	H	H	20	**2e**	49[d]
6	**1f** (16:7)	p-CH_3-C_6H_4	Ph	H	10	**2f**	61
7	**1g** (7:5)	m-CH_3-C_6H_4	Ph	H	10	**2g**	62
8	**1h** (2:1)	m-Cl-C_6H_4	Ph	H	20	**2h**	64
9	**1i** (2:1)	p-Cl-C_6H_4	Ph	H	25	**2i**	61
10	**1j** (2:1)	2-thienyl	Ph	H	10	**2j**	60
11	**1k** (1:0)	Ph	Ph	CH_3	10	**2k**	70
12	**1l** (1:0)	Ph	p-Cl-C_6H_4	CH_3	10	**2l**	72
13	**1m** (1:0)	Ph	Ph	Et	20	**2m**	55

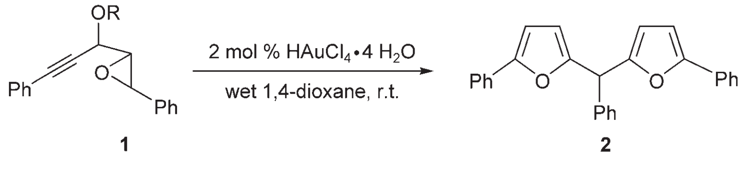
[a] *Conditions:* 0.5 mmol of **1** with 2 mol% of catalysts in wet 1,4-dioxane (2.0 mL) at room temperature (23–25 °C).
[b] *syn/anti* mixtures of the substrate were used; *syn:anti* ratio determined by ^1H NMR.
[c] Isolated yield.
[d] Reaction run with 10 mol% catalyst loading.

alkyne moiety, including electron-rich, electron-poor and heteroaromatic ones such as the 2-thienyl group, were compatible with this reaction and generally good yields of the corresponding difurylmethanes were obtained (entries 6–10). We have also investigated the reactions of alkynyloxiranes containing different R^3 which afforded the desired products in good yields (entries 11–13).

Furthermore, considering the impact of the leaving groups on the reaction, we examined 1-oxiranyl-2-alkyn-1-ols with different protective groups, as shown in Table 3. The reaction works well with carbonate protective groups (entries 1–3), while it affords the desired product in lower yields when using 1-oxiranyl-2-alkyn-1-ols that bear an aliphatic protective group (entries 4 and5). Substrates such as **1p** bearing a methyl as protective group, only afford the desired product in 35% yield.

In order to uncover the mechanism for the reaction, we started out our investigation by using esters of 1-

Table 3. Synthesis of difurylmethanes **2** by cyclization of 3-phenyl-1-(3-phenyloxiran-2-yl)prop-2-yl-1-ol (**1**) bearing different protective groups.[a]



Entry	**1**[b]	R	Time [min]	Yield [%][c]
1	**1a** (7:5)	$COCH_3$	10	68
2	**1n** (2:1)	$COOCH_3$	20	66
3	**1o** (1:1)	$COOC(CH_3)_3$	10	65
4	**1p** (1:1)	Me	60	35
5	**1q** (1:1)	$CH_2CH{=}CH_2$	25	40

[a] *Conditions:* 0.5 mmol of **1** with 2 mol% of catalysts in wet 1,4-dioxane (2.0 mL) at room temperature (23–25 °C).
[b] *syn/anti* mixtures of the substrate were used; *syn:anti* ratio determined by ^1H NMR.
[c] Isolated yield.

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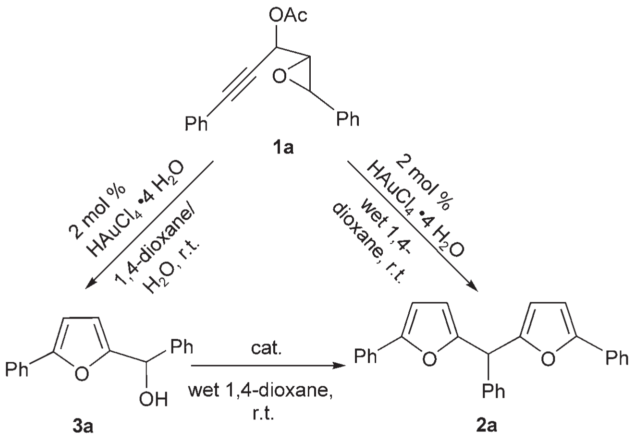


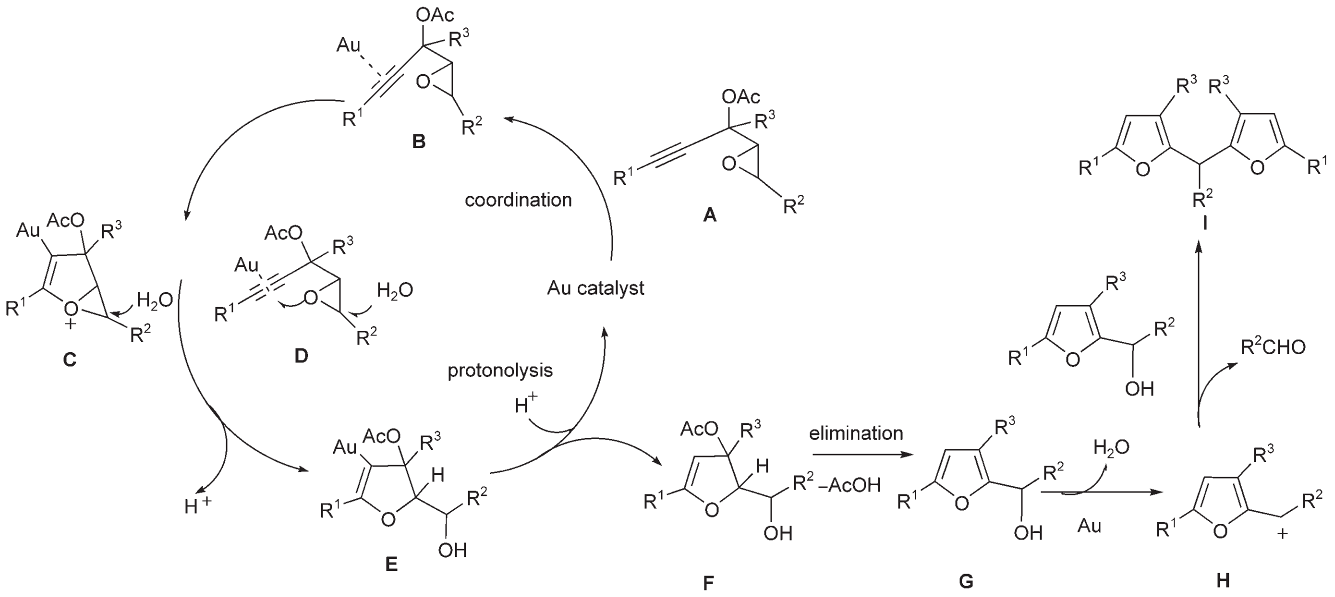
catalyst	yield [%]
$HAuCl_4 \cdot 4H_2O$	93
$NaAuCl_4 \cdot 2H_2O$	90
$AuCl_3$	85
AuCl	87
TFA	80
AcOH or $ClCH_2COOH$	0

Scheme 2.

oxiranyl-2-alkyn-1-ols **1a** in 1,4-dioxane/H_2O systems under 2 mol% of $HAuCl_4 \cdot 4H_2O$; the 2-(α-hydroxyalkyl)furan **3a** was formed along with difurylmethane **2a.** Next we investigated **3a** under the standard conditions and the desired product **2a** was formed in 93% yield after 1 min. In the presence of 2 mol% of $NaAuCl_4 \cdot 2H_2O$, $AuCl_3$ or AuCl, the reaction also gave desired product **2a** smoothly in high yields. TFA, chloroacetic acid and acetic acid have also been tested, among which only TFA was effective (Scheme 2).

On the basis of the above observations, a possible reaction mechanism is proposed as shown in Scheme 3, which may involve the following steps: (i) coordination of the alkynyl moiety of **A** to the Au catalyst gives the complex **B**, (ii) attack of the trace amounts of water, *anti-endo-dig* cyclization affords the organogold intermediate **E**, (iii) protonation of **E** yields 2,3-dihydrofuran **F** and regenerates the catalyst Au, (iv) **F** undergoes direct reductive elimination of acetic acid, presumably *via* the corresponding oxonium ion, to afford the 2-(α-hydroxyalkyl)furans **G**,[12] (v) under the gold catalysis, **G** eliminates one molecule water to afford ion intermediate **H**, (vi) ion intermediate **H** attacks another molecule **G** to afford the difurylmethanes **I**[6b] with loss of one molecule of aldehyde, which is an intermolecular Friedel–Crafts-type reaction.[13] Alternatively, the reaction may involve an oxonium ion **C**,[12] which is formed by attack of trace amounts of H_2O on the epoxide oxygen to afford the gold-coordinated alkynes.[10,14] The oxonium ion **C** then undergoes subsequent reaction with traces of water followed by protonation to regenerate the Au catalyst and eliminate one molecule of acetic acid to produce 2,3-dihydrofuran **F.**

In summary, a novel and flexible method for the synthesis of difurylmethanes has been developed through the cycloisomerization/dimerization of esters of 1-oxiranyl-2-alkyn-1-ols at room temperature under gold catalysis. The starting materials are easily accessible. Further studies, including detailed investigations into the mechanism and the scope of this reaction, are in progress in our laboratory.



Scheme 3. Proposed reaction mechanism for Au-catalyzed cyclization.

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Experimental Section

General Remarks

Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$. IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm^{-1}. Melting points were determined on a microscopic apparatus and are uncorrected. All compounds were further characterized by elemental analysis; copies of their ^{1}H NMR and ^{13}C NMR spectra are provided in the Supporting Information. Room temperature is 23–25 °C. Commercially available reagents and solvents were used without further purification. THF was distilled immediately before use from Na/benzophenone.

General Procedure for Cycloisomerization/Dimerization at Room Temperature in Wet 1,4-Dioxane

To a solution of the esters of 1-oxiranyl-2-alkyn-1-ols **1** (0.50 mmol) in wet 1,4-dioxane (2.0 mL) was added 4.00 mg (0.01 mmol, 2 mol%) of $HAuCl_4 \cdot 4H_2O$ under air at room temperature. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was diluted with ethyl ether (40 mL), washed with water, saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford corresponding difurylmethanes **2**.

General Procedure for Cycloisomerization at Room Temperature in 1,4-Dioxane/H_2O (1:1)

To a solution of the acetate of 1-oxiranyl-2-alkyn-1-ol **1a** (0.50 mmol) in 1,4-dioxane/H_2O(1:1) was added 4.00 mg (0.01 mmol, 2 mol%) of $HAuCl_4 \cdot 4H_2O$ under air at room temperature. After 12 h, the reaction mixture was diluted with ethyl ether (40 mL), washed with water, saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford 2-(α-hydroxyalkyl)furan **3a** in 30% yield as a solid, along with difurylmethane **2a** in 20% yield.

Acknowledgements

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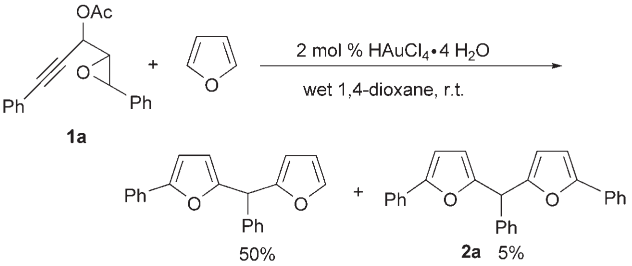
[13] According to the referee's opinion to further uncover the mechanism and enhance the synthetic utility, we investigated the reaction of epoxyalkyne **1a** with furan under the standard conditions. The desired asymmetric product 2-[furan-2-yl(phenyl)methyl]-5-phenylfuran was obtained. This is consistent with the proposed mechanism in Scheme 3. After losing one molecule of H_2O, 2-(α-hydroxyalkyl)furans **G** might lead to the formation of the cation intermediates **H**, which undergo the Friedel–Crafts-type reaction to afford the difurylmethanes **I**.



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