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Synthesis of Bicyclic Ethers by a Gold/Palladium/Gold-Catalyzed Cyclization/Cross Coupling Sequence

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The stereoselective gold-catalyzed 6-*endo* cyclization of various β-hydroxyallenes in the presence of *N*-iodosuccinimide affords iodinated dihydropyrans in good yield. Subsequent functionalization by palladium-catalyzed cross coupling opens an access to α-hydroxyallenes that are converted in a second gold-catalyzed cyclization into furopyrans which occur in various natural products.

Introduction

The synthesis of annulated cyclic ethers is of high interest in organic chemistry due to the occurrence of this heterocyclic structure unit in a variety of natural products and biologically active compounds (Figure 1).

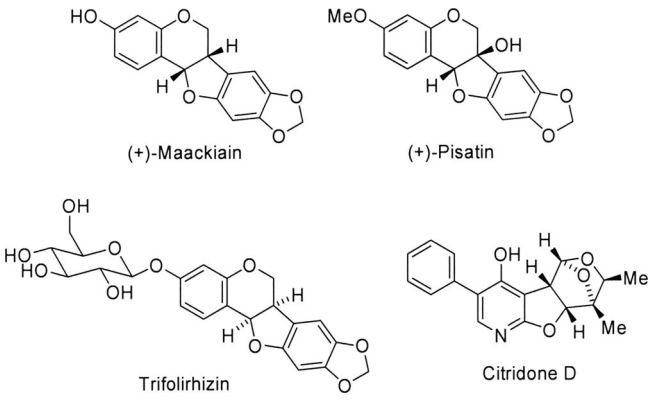
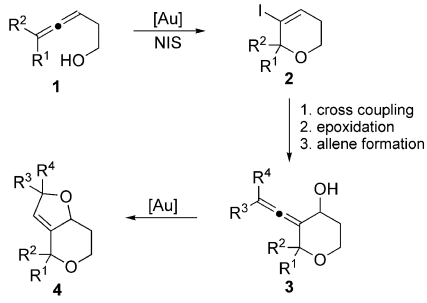


Figure 1. Natural products containing annulated cyclic ethers.

The phytoalexins (+)-Maackiain and (+)-Pisatin are produced by garden pea and chickpea and have antifungal activity.[1] Furthermore, (+)-Maackiain shows antimalarial activity against *P. falciparum*[2] and antitumor activity in mice.[3] Trifolirhizin also exhibits antitumor activity, has tyrosinase inhibitory effects and suppresses the melanin synthesis in B16 melanoma cells,[3,4] whereas Citridone D displays miconazole activity against *Candida albicans*.[5]

A common structural feature of these target molecules is the furopyran core. Previously, these bicyclic ethers have been prepared by radical cyclization or alkyne trimerization.[6] Based on our experience in the stereoselective synthesis of chiral five- and six-membered heterocycles by gold-catalyzed[7] cycloisomerization of functionalized allenes,[8,9] we envisaged an alternative route to these heterocycles (Scheme 1). Thus, gold-catalyzed cyclization of β-hydroxyallenes **1**[8c] in the presence of *N*-iodosuccinimide (NIS) should afford iodinated dihydropyrans **2** which are converted into exocyclic α-hydroxyallenes **3** by Sonogashira coupling, epoxidation, and copper-mediated S_N2'-substitution. Finally, a second gold-catalyzed cyclization of **3**[8] should give the desired furopyrans **4**.



Scheme 1. Proposed route to furopyrans **4**.

Herein we report the synthesis of bicyclic ethers **4** by the gold/palladium/gold-catalyzed cyclization/cross coupling sequence shown in Scheme 1. Besides affording an efficient and stereoselective access to furopyrans, the use of NIS induces a tremendous acceleration of the gold-catalyzed cyclization of functionalized allenes, a behavior that is both very useful in synthesis and highly interesting from the mechanistic point of view.

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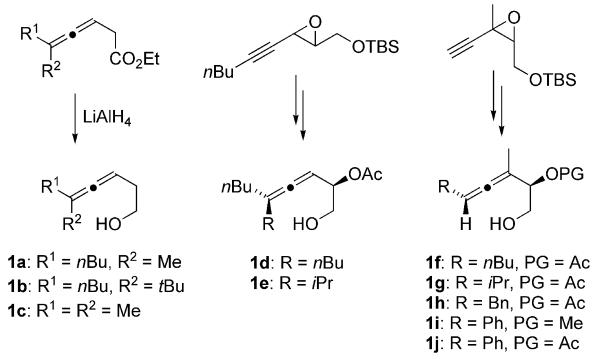
Results and Discussion

The starting materials of our study, the β-hydroxyallenes **1a**–**j**, were prepared in two different ways (Scheme 2). The terminally disubstituted allenes **1a**–**c** were obtained by reduction of the corresponding β-allenic esters[10] which were synthesized by either 1,6-cuprate addition to 2-en-4-ynoates[11] or by orthoester Claisen rearrangement of propargylic alcohols.[12] In contrast, the β-hydroxyallenes **1d**–**j** were formed by copper-mediated S_N2'-substitution of propargylic oxiranes,[8] followed by a protection-deprotection sequence.[13,14] The allenes **1e**–**i** were obtained in diastereomerically pure form, whereas compound **1j** had a diastereomeric ratio of 92:8.



1a: R^1 = *n*Bu, R^2 = Me
1b: R^1 = *n*Bu, R^2 = *t*Bu
1c: R^1 = R^2 = Me

1d: R = *n*Bu
1e: R = *i*Pr

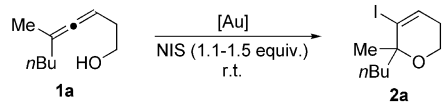
1f: R = *n*Bu, PG = Ac
1g: R = *i*Pr, PG = Ac
1h: R = Bn, PG = Ac
1i: R = Ph, PG = Me
1j: R = Ph, PG = Ac

Scheme 2. Synthesis of β-hydroxyallenes **1**.

Previously, it has been shown that *N*-iodosuccinimide (NIS) can be used successfully as electrophile in gold-catalyzed transformations of acetylenic substrates.[15] Moreover, a tremendous accelerating effect of NIS in the gold-catalyzed cyclization of bis(α-hydroxyallenes) was discovered recently.[8j] β-Hydroxyallenes (e.g., **1a**) are also quite unreactive substrates and require several days at room temperature for a complete cyclization with gold(I) or gold(III) chloride alone.[8c] In contrast, it takes *just one minute* for the full conversion of **1a** to iodinated dihydropyran **2a**[16] in the presence of 5 mol-% of $AuCl_3$, AuCl, or $Ph_3PAuCl/AgBF_4$[17] and 1.1–1.5 equiv. of NIS[18] (Table 1, entries 1, 4, 6)! Very fast reactions were also observed with decreased catalysts loadings of 0.5 mol-% (Table 1, entries 2, 5, 7) and even 0.05 mol-% (Table 1, entry 3). The cyclization product **2a** was obtained with 42–67% yield under these conditions. Attempts to improve the yield by decreasing the reaction temperature to –20 °C (Table 1, entry 8) or by using pyridine as additive[8c,8d] (Table 1, entry 9) were not successful. *N*-bromo- and *N*-iodosuccinimide (as well as iodine) are known to induce cyclization reactions of functionalized allenes in the absence of a transition metal.[19,20] In the case of β-hydroxyallene **1a**, it takes two days at room temperature to complete the conversion to dihydropyran **2a** with NIS alone (Table 1, entry 10), proving a cooperative effect of the gold catalyst and NIS.

We next extended the scope of the reaction to the β-allenols **1b**–**d** (Table 2). Expectedly, the sterically less hindered substrate **1c** gave a good yield of 61% in a very fast reaction

Table 1. Gold-catalyzed cyclization of β-hydroxyallene **1a** to dihydropyran **2a** in the presence of NIS.



Entry	[Au]	mol-%	Solvent	Time	Yield [%]
1	$AuCl_3$[a]	5	CH_2Cl_2	1 min	67
2	$AuCl_3$[a]	0.5	CH_2Cl_2	1 min	50
3	$AuCl_3$[a]	0.05	CH_2Cl_2	15 min	42
4	$Ph_3PAuCl/AgBF_4$	5	toluene	1 min	52
5	$Ph_3PAuCl/AgBF_4$	0.5	toluene	15 min	42
6	AuCl	5	CH_2Cl_2	1 min	56
7	AuCl	0.5	CH_2Cl_2	20 min	49
8[b]	AuCl	5	CH_2Cl_2	1 h	47
9	AuCl/Pyridine	5	CH_2Cl_2	1 min	50
10	–	–	toluene	2 d	45

[a] 0.166 M solution in MeCN. [b] At –20 °C.

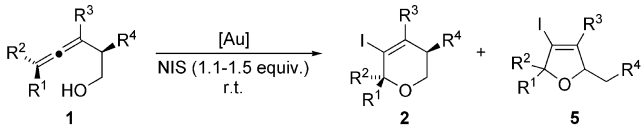
(Table 2, entry 2) whereas slower cyclizations and decreased chemical yields were observed for the substrates **1b** and **1d** bearing more bulky groups at the allene moiety (Table 2, entries 1 and 3). The presence of an acetate group in the substrate is tolerated (Table 2, entry 3).

Gold-catalyzed cycloisomerizations of α- or β-functionalized allenes to five- or six-membered heterocycles usually take place with axis-to-center chirality transfer.[8,9] In the case of the gold-catalyzed/NIS-mediated cyclization of β-hydroxyallenes **1e**–**j** to the corresponding iodinated dihydropyrans **2**, the chirality transfer was found to depend on the reaction conditions, in particular the gold precatalyst (Table 2). Whereas dihydropyrans **2e** and **2i** were obtained with good yield (69:68%) and diastereoselectivity (*dr* = 88:12:93:7) with 5 mol-% of AuCl in CH_2Cl_2 (Table 2, entries 4 and 11), diminished yield and selectivity was observed with allene **1f** under identical conditions (Table 2, entry 5). Thus, extensive epimerization of the allenic chirality axis is taking place.[8d,9a] The stereoselectivity was improved slightly by performing the reaction at –20 °C (Table 2, entry 6) or without the gold catalyst (Table 2, entry 7). In contrast to this, use of the cationic gold catalyst Ph_3PAuBF_4 instead of AuCl afforded dihydropyran **2f** with an improved yield of 73% and a high level of chirality transfer (*dr* = 89:11; Table 2, entry 8). These conditions proved to be efficient for allenes **1g** and **1h** as well which gave the diastereomerically pure cyclization products **2g/h**[21] with good yield (Table 2, entries 9 and 10). Dihydropyran **2j** was also obtained with good yield of 69%, but an acceptable diastereoselectivity could only be achieved in the absence of a gold catalyst (Table 2, entry 12 vs. 13).

Another interesting observation is the formation of the iodinated 2,5-dihydrofurans **5** as side product (up to 14% yield; Table 2, entries 4–10, 12, 13). These may be formed by (gold-catalyzed?) acetate migration from the secondary to the primary hydroxy group,[8c] followed by gold-catalyzed cyclization of the α-hydroxyallene formed.

At this point, there appear to be two possible explanations for the strong acceleration of the gold-catalyzed cycli-

Table 2. Gold-catalyzed cyclization of β-hydroxyallenes **1b–j** in the presence of NIS.



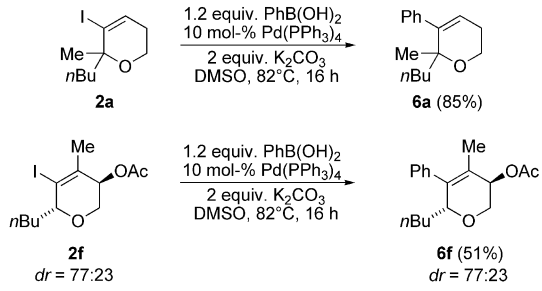
1 **2** **5**

Entry	**1**	R^1	R^2	R^3	R^4	Conditions[a]	Time	**2**	Yield [%]	*dr*	**5**	Yield [%]
1	**1b**	*n*Bu	*t*Bu	H	H	**A**	1 h	**2b**	24	–	–	–
2	**1c**	Me	Me	H	H	**B**	1 min	**2c**	61	–	–	–
3	**1d**	*n*Bu	*n*Bu	H	OAc	**B**	10 min	**2d**	52	–	–	–
4	**1e**	*i*Pr	*n*Bu	H	OAc	**C**	50 min	**2e**	69	88:12	**5e**	traces
5	**1f**	H	*n*Bu	Me	OAc	**C**	1 min	**2f**	52	61:39	**5f**	12
6	**1f**	H	*n*Bu	Me	OAc	**D**	10 h	**2f**	52	82:18	**5f**	8
7	**1f**	H	*n*Bu	Me	OAc	**E**	2 h	**2f**	22	71:29	**5f**	11
8	**1f**	H	*n*Bu	Me	OAc	**A**	1 min	**2f**	73	89:11	**5f**	10
9	**1g**	H	*i*Pr	Me	OAc	**A**	1 min	**2g**	73	>95:5	**5g**	traces
10	**1h**	H	Bn	Me	OAc	**A**	1 min	**2h**	71	>95:5	**5h**	14
11	**1i**	H	Ph	Me	OMe	**C**	1 h	**2i**	68	93:7	–	–
12	**1j**[b]	H	Ph	Me	OAc	**C**	30 min	**2j**	69	60:40	**5j**	4
13	**1j**[b]	H	Ph	Me	OAc	**E**	1 d	**2j**	69	89:11	**5j**	11

[a] Conditions: **A**: 5 mol-% $Ph_3PAuCl/AgBF_4$, toluene; **B**: 1 mol-% AuCl, CH_2Cl_2; **C**: 5 mol-% AuCl, CH_2Cl_2; **D**: 5 mol-% AuCl, CH_2Cl_2, –20 °C; **E**: without gold salt in CH_2Cl_2. [b] *dr* (**1j**) = 92:8.

zation of β-hydroxyallenes **1** in the presence of *N*-iodosuccinimide. Thus, the nature of the gold catalyst might be changed in the presence of electrophilic iodine, e.g., by formation of gold iodide species and/or oxidation of gold(I) to gold(III). Alternatively, the accepted mechanistic model (consisting of activation of the allene by the carbophilic gold catalyst, intramolecular attack, and electrophilic capture of the σ-gold species formed)[8c,9a] might not be operative in the presence of NIS. Investigations dedicated to clarify this point will be subject of subsequent publications.

With the iodinated dihydropyrans in hand, we examined their utility in palladium-catalyzed cross coupling reactions.[22] Thus, the Suzuki coupling of heterocycles **2a** and **2f** under standard conditions proceeded smoothly to afford the expected products **6a** and **6f** with 85% and 51% yield, respectively (Scheme 3). In the case of dihydropyran **2f**, the ratio of diastereomers remained unchanged.



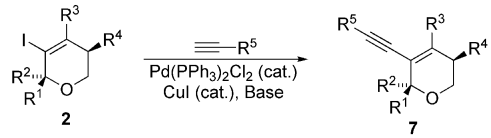
Scheme 3. Suzuki coupling of dihydropyrans **2a** and **2f**.

For the conversion into furopyrans **4**, the iododihydropyrans **2** have to undergo a Sonogashira coupling.[22,23] The reaction of heterocycles **2a**, **2c**, **2d**, **2f**, and **2g** with a variety of terminal alkynes was examined under two reaction conditions, either using the "classical" catalyst system [cat. $(Ph_3P)_2PdCl_2$/CuI, NEt_3] in THF as solvent,[24] or a palladium/copper catalyst in the presence of an *N*-heterocyclic carbene as ligand.[25] The former conditions gave acceptable to good yields (49–81%) only for substrate **2a** (Table 3, entries 1–3) whereas very slow conversion (Table 3, entries 4 and 5) or no reaction at all (Table 3, entries 10 and 12) was observed with other dihydropyrans. This issue was solved by using the more reactive combination of $(Ph_3P)_2PdCl_2$/CuI and SIMes·HCl which gave the desired coupling products **7** with excellent yield (80–95%; Table 3, entries 6–9, 11, 13), except for enyne **7gd** which was obtained with 54% yield (Table 3, entry 14). The reaction tolerates acetate groups at the dihydropyran, and alkyl, phenyl and silyl groups, as well esters and benzyl ethers at the alkyne. The diastereomeric ratio of the coupling products obtained from dihydropyrans **2f** and **2g** was identical to that of the precursor.

Epoxidation of the enynes **7cc/cd** with *m*CPBA and subsequent copper-mediated S_N2'-substitution[8,26] afforded the diastereomerically pure α-hydroxyallenes **3a–c** with good yield (52–60% over 2 steps; Scheme 4). The low yield of 17% for allene **3d**, however, is due to a very sluggish S_N2'-substitution reaction of the corresponding propargyl oxirane with *n*-butylmagnesium cuprate. In all cases, the allene formation took place with complete *anti*-stereoselectivity.[8,26]

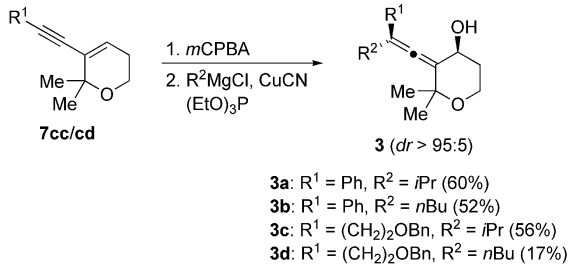
The same reaction sequence was used for the synthesis of the α-hydroxyallenes **3e–g** (Scheme 5). In the case of enynes **7aa** and **7fa**, the trimethylsilyl group was removed with nBu_4NF prior to the copper-mediated S_N2'-substitution. The chemical yields of the α-hydroxyallenes **3e–g** were comparable to those of their counterparts **3a–c**. Since the epoxidation of the chiral enynes took place with modest diastereoselectivity only, the allenes **3e–g** were obtained as mixtures of diastereomers (the diastereomeric ratio could not be determined for **3g**).

Table 3. Sonogashira coupling of iodinated dihydropyrans **2**.

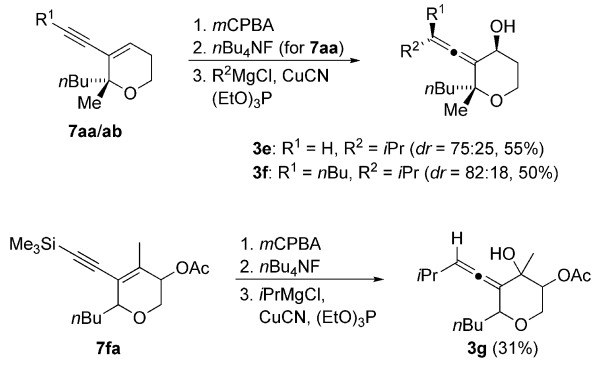


Entry	**2**	R^1	R^2	R^3	R^4	R^5	Conditions[a]	Time	**7**	Yield [%]	Yield [%] of recovered **2**
1	**2a**	Me	*n*Bu	H	H	$SiMe_3$	**A**	20 h	**7aa**	81	–
2	**2a**	Me	*n*Bu	H	H	*n*Bu	**A**	6 d	**7ab**	49[c]	43[c]
3[b]	**2a**	Me	*n*Bu	H	H	Ph	**A**	2 d	**7ac**	64[c]	12[c]
4	**2c**	Me	Me	H	H	$SiMe_3$	**A**	3 d	**7ca**	26[c]	32[c]
5	**2c**	Me	Me	H	H	*n*Bu	**A**	2 d	**7cb**	24[c]	35[c]
6	**2c**	Me	Me	H	H	Ph	**B**	14 h	**7cc**	95	–
7	**2c**	Me	Me	H	H	$(CH_2)_2OBn$	**B**	14 h	**7cd**	85	–
8	**2c**	Me	Me	H	H	$(CH_2)_8CO_2Et$	**B**	14 h	**7ce**	85	–
9	**2d**	*n*Bu	*n*Bu	H	OAc	$(CH_2)_2OBn$	**B**	17 h	**7dd**	80	–
10	**2f**	H	*n*Bu	Me	OAc	$SiMe_3$	**A**	3 d	**7fa**	–	87
11	**2f**	H	*n*Bu	Me	OAc	$SiMe_3$	**B**	18 h	**7fa**	93	–
12	**2f**	H	*n*Bu	Me	OAc	Ph	**A**	7 d	**7fc**	–	96
13	**2g**	H	*i*Pr	Me	OAc	Ph	**B**	18 h	**7gc**	86	–
14	**2g**	H	*i*Pr	Me	OAc	$(CH_2)_2OBn$	**B**	18 h	**7gd**	54	–

[a] Conditions: **A**: 1.05 equiv. alkyne, 2 mol-% $(PhP_3)_2PdCl_2$, 4 mol-% CuI, 1.5 equiv. NEt_3, THF, room temp.; **B**: 1.3 equiv. alkyne, 2 mol-% $(Ph_3P)_2PdCl_2$, 5 mol-% SIMes·HCl, 5 mol-% CuI, iPr_2NH, 80 °C. [b] 2.1 equiv. of alkyne was used. [c] Separation of the starting material from the product by column chromatography was not possible.



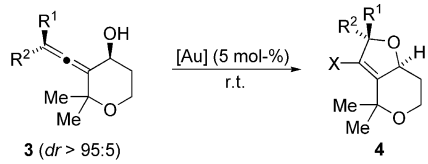
Scheme 4. Synthesis of α-hydroxyallenes **3a**–**d**.



Scheme 5. Synthesis of α-hydroxyallenes **3e**–**g**.

The final gold-catalyzed cycloisomerization of the α-hydroxyallenes **3a**–**d** to the corresponding furopyrans **4** was carried out with $Ph_3PAuCl/AgBF_4$ as precatalyst in toluene (Table 4, entries 1–4). The desired bicyclic products were obtained with good to excellent yield (76–96%). Whereas the phenyl-substituted allenes reacted rather slowly with slight epimerization of the allenic chirality axis (Table 4, entries 1 and 2),[8d] the corresponding benzyloxyethyl-substi-

Table 4. Gold-catalyzed cyclization of α-hydroxyallenes **3a**–**d** to furopyrans **4**.

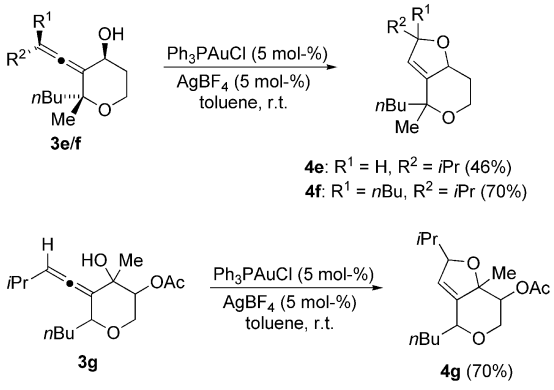


Entry	**3**	R^1	R^2	X	Cond.[a]	**4**	Yield [%]	*dr*
1	**3a**	Ph	*i*Pr	H	**A**, 2 h	**4a**	76	89:11
2	**3b**	Ph	*n*Bu	H	**A**, 1.5 h	**4b**	96	96:4
3	**3c**	$(CH_2)_2OBn$	*i*Pr	H	**A**, 1 min	**4c**	84	> 95:5
4	**3d**	$(CH_2)_2OBn$	*n*Bu	H	**A**, 1 min	**4d**	77	> 95:5
5	**3a**	Ph	*i*Pr	I	**B**, 25 min	**4a′**	84	> 95:5
6	**3a**	Ph	*i*Pr	I	**C**, 1 min	**4a′**	79	> 95:5

[a] Conditions: **A**: $Ph_3PAuCl/AgBF_4$, toluene; **B**: 1.5 equiv. NIS, $Ph_3PAuCl/AgBF_4$, toluene; **C**: 1.5 equiv. NIS, AuCl, CH_2Cl_2.

tuted allenes cyclized very quickly and with complete axis-to-center chirality transfer (Table 4, entries 3 and 4). The accelerating effect of *N*-iodosuccinimide was again observed in the cyclization of α-hydroxyallene **3a** which afforded the iodinated furopyran **4a′**[27] with $Ph_3PAuCl/AgBF_4$ or AuCl as precatalyst (Table 4, entries 5 and 6 vs. 1). This opens the possibility for attaching another dihydrofuran ring to the furopyran **4a′** which, however, was not examined further.

The α-hydroxyallenes **3e**–**g** also underwent cycloisomerization to afford the corresponding furopyrans **4** with moderate to good yield (46–70%) in the presence of 5 mol-% of $Ph_3PAuCl/AgBF_4$ (Scheme 6). The bicyclic ethers were formed as complex mixtures of diastereomers, indicating that the gold catalyst induces epimerization of the allene and/or the heterocyclic rings (possibly by ring-opening/ring-closing).[8d,9a]



Scheme 6. Gold-catalyzed cycloisomerization of α-hydroxyallenes **3e**–**g** to furopyrans **4**.

Conclusions

We have developed an efficient and stereoselective access to furopyrans **4** from β-hydroxyallenes **1** by a gold/palladium/gold-catalyzed cyclization/cross coupling sequence. In the first of three transition metal-catalyzed steps, a tremendous accelerating effect of *N*-iodosuccinimide (NIS) on the gold-catalyzed cyclization of β-hydroxyallenes **1** was utilized for the rapid formation of iodinated dihydropyrans **2** in good yield. Reactivity problems in the subsequent Sonogashira coupling were solved by using a highly reactive catalyst prepared in situ from $(Ph_3P)_2PdCl_2/CuI$ and an *N*-heterocyclic carbene. After allene formation by epoxidation and copper-mediated S_N2'-substitution, a second gold-catalyzed cyclization afforded the desired furopyrans **4** with good to excellent yield. Whereas the bicyclic ethers **4a**–**4d** were obtained in diastereomerically enriched or pure form, epimerization was observed during the formation of products **4e**–**g**. Further investigations are devoted to elucidate a mechanistic rationale for the strong accelerating effect of NIS on gold-catalyzed transformations, as well as to the application of the Au/Pd/Au-catalyzed cyclization/cross coupling sequence in target-oriented synthesis.

Experimental Section

General Procedure for the Gold-Catalyzed Cyclization of β-Hydroxyallenes 1 in the Presence of NIS: To a solution of 1 equiv. of the allene in dry toluene (60 μL/mg **1**) was added under argon 1.1–1.5 equiv. of NIS, 5 mol-% of Ph_3PAuCl and 5 mol-% of $AgBF_4$. The reaction mixture was stirred until full conversion of the starting material was observed by TLC. The solvent was evaporated and the crude product was adsorbed on silica gel, followed by flash column chromatography on silica gel with cyclohexane/ethyl acetate (30:1 to 10:1). The product, still dissolved in the column eluent, was washed with an aqueous 0.5 M $Na_2S_2O_3$ solution to remove traces of iodine, dried with Na_2SO_4, and the solvent was evaporated to afford analytically pure dihydropyran **2**.

General Procedure for the Sonogashira Coupling of Dihydropyrans 2 in the Presence of SIMes: In a Schlenk tube, 2 mol-% of $(Ph_3P)_2PdCl_2$ and 5 mol-% of SIMes·HCl were dissolved under argon in dry iPr_2NH (0.4 mL/mmol **2**). The mixture was heated in the sealed tube at 80 °C for 1.5 h. After cooling down to room temp., 5 mol-% of CuI, 1 equiv. of **2**, and dry iPr_2NH (0.9 mL/mmol **2**) were added, followed by dropwise addition of 1.3 equiv. of the terminal alkyne. The reaction mixture was heated to 80 °C for 14–18 h. After cooling to room temp., the crude product was filtered through a pad of silica gel and celite (elution with Et_2O). The solvent was evaporated, followed by flash column chromatography of the residue on silica gel with cyclohexane/ethyl acetate (10:1) to afford analytically pure enyne **3**.

General Procedure for the Gold-Catalyzed Cycloisomerization of α-Hydroxyallenes 3: To a solution of 1 equiv. of the allene in dry toluene (60 μL/mg **3**) was added under argon 5 mol-% of Ph_3PAuCl and 5 mol-% of $AgBF_4$. The reaction mixture was stirred until full conversion of the starting material was observed by TLC. The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel with cyclohexane/ethyl acetate (30:1 to 10:1) to afford analytically pure furopyran **4**.

Supporting Information (see also the footnote on the first page of this article): Procedures, spectroscopic data, and copies of NMR spectra of reported compounds.

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