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Synthesis of Functionalized 1*H*-Isochromene Derivatives via a Au-Catalyzed Domino Cycloisomerization/Reduction Approach

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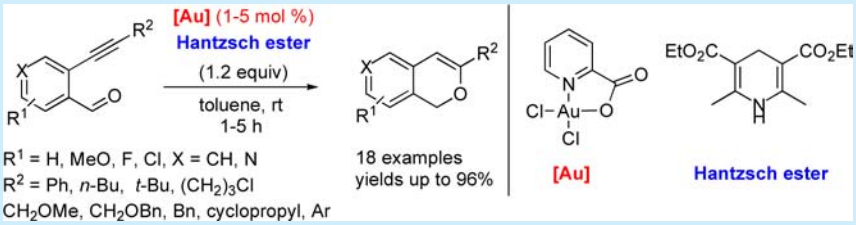
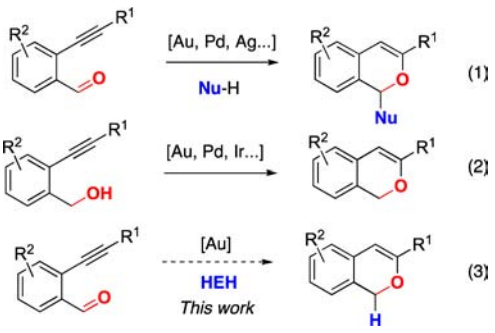
Supporting Information



ABSTRACT: A Au-catalyzed versatile and efficient access to 1*H*-isochromenes is reported. The efficiency of the [$AuCl_2$(Pic)] complex (1−5 mol %) was demonstrated and allowed a domino cycloisomerization/reduction reaction process starting from a wide range of functionalized *ortho*-alkynylbenzaldehydes and one example of *ortho*-alkynylpyridinylaldehyde. The smooth reaction conditions were amenable to aryl- and alkyl-substituted alkynyl derivatives, as well as functionalized halogen and ether moieties, leading to a chemo- and regioselective 6-*endo*-cyclization with good to excellent yields.

Functionalized 1*H*-isochromene frameworks are found in a variety of natural products, bioactive molecules, and pharmaceuticals.[1] They have important biological effects including antitumor properties,[2] and their efficient and versatile synthesis has been a great source of inspiration to chemists.[3] Among various methods to prepare the isochromene skeleton, one particularly straightforward and atom economical process has been the use of transition-metal-catalyzed cyclization of *ortho*-alkynylarylaldehydes or *ortho*-alkynylbenzylalcohols.[4−7] Inspired by the seminal work of Asao, Yamamoto and co-workers on gold-catalyzed formal [4 + 2] benzannulation of *ortho*-alkynylbenzaldehydes,[5] further contributions implied domino processes in the presence of C, O, or N nucleophiles.[6,7] (Scheme 1, eq 1). The implication of hydride as an external nucleophile has been only studied very recently and, to the best of our knowledge, has been limited to ketones as a carbonyl moiety and mostly aryl-substituted alkynes (2 examples with *n*-Bu group) in the presence of copper and silver complexes.[8] An alternative strategy for the synthesis of isochromene involves the use of functionalized benzylic alcohols, but it suffers from regiocontrol as well as a longer synthetic pathway for the preparation of starting alcohols (Scheme 1, eq 2).[3] Considering our previous reports on gold-catalyzed cyclization of alcohols and carboxylic acids[9] and our interest in diversity-oriented synthesis (DOS),[10] we anticipated that readily available *ortho*-alkynylaryl aldehyde derivatives may be suitable substrates for such a domino cycloisomerization/reduction reaction process. We wish, therefore, to report therein our preliminary results on the general, efficient, and unprecedented synthesis of original and functionalized 1*H*-isochromenes starting from *ortho*-alkynylaryl-aldehydes (Scheme 1, eq 3).

Scheme 1. [M]-Catalyzed Access to 1*H*-Isochromenes



At the outset of our studies, the readily prepared *ortho*-*n*-butylacetylenyl benzaldehyde **1a** was selected as a model substrate in order to optimize the catalytic system and a Hantzsch ester[11] (HEH) was chosen as the hydride source (Table 1). Considering the supremacy of π-gold complexes as intermediates,[12] we first tested the cationic commercially available [$Au(NTf_2)(PPh_3)$] complex as the catalytic source of electrophilic activation. Pleasingly, the 6-*endo* cyclization mode smoothly operated as well as the *in situ* reduction in the presence of 5 mol % of gold and 1.2 equiv of HEH at rt, leading to the desired 1*H*-isochromene **2a** in 86% isolated yield (Table 1, entry 1).[13] Further optimization showed that the catalyst loading could be diminished for such a domino process (Table 1, entries 2−3). Interestingly, the use of the less expensive dichloro(2-pyridine-

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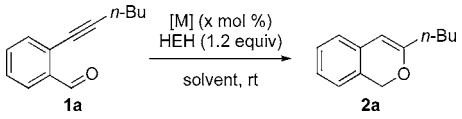
Table 1. Optimization of Reaction Conditions[a]



entry	cat. [M] (mol %)	solvent	time (h)	conv[b] (yield %)[c]
1	$[Au(NTf_2)(PPh_3)]$ (5)	toluene	16	>99 (86)
2	$[Au(NTf_2)(PPh_3)]$ (5)	CH_3CN	16	90
3	$[Au(NTf_2)(PPh_3)]$ (1)	toluene	3	>99
4	$[AuCl_2(Pic)]$ (5)	toluene	1	>99
5	$[AuCl_2(Pic)]$ (1)	toluene	1	>99 (86)
6	$AuCl_3$ (1)	toluene	1	93
7	Au_2O_3 (0.5)	toluene	1	0
8	$AgSbF_6$ (1)	toluene	24	33
9	Ag_2O (0.5)	toluene	8	0
10	Ag_2CO_3 (0.5)	toluene	8	0
11	$PdCl_2$ (1)	toluene	1	0
12	$PtCl_2$ (1)	toluene	1	41
13	$Cu(OAc)_2 \cdot H_2O$ (1)	toluene	1	0
14	–	toluene	24	0
15[d]	$[AuCl_2(Pic)]$ (1)	toluene	24	>99[e]
16	$[AuCl_2(Pic)]$ (1)	CH_2Cl_2	2	>99
17	$[AuCl_2(Pic)]$ (1)	THF	1	>99
18	$[AuCl_2(Pic)]$ (1)	CH_3CN	1	>99
19	($[AuCl_2(Pic)]$ (1)	MeOH	24	>99

[a]Conditions: aldehyde **1a** and 1.2 equiv of HEH. [b]Determined by ^1H NMR. [c]Isolated yields. [d]Reaction without HEH. [e]Decomposition of **1a**.

carboxylato)gold $[AuCl_2(Pic)]$[14] complex led to excellent results (Table 1, entries 4–5) in 1 h of reaction time. Other sources of gold(III) catalyst such as $AuCl_3$ or Au_2O_3[8] gave a lower or no conversion (Table 1, entries 6–7). Notably, no 5-*exo*-*dig* cyclization was observed whereas this mode of cyclization was found to be highly competitive in the presence of gold trichloride in the case of *ortho*-alkynylarylketones.[8a] The observed total regioselectivity in favor of the 6-*endo* adduct was in full agreement with recent findings on an α-substituent effect for gold-catalyzed cycloisomerization reactions of *ortho*-alkynyl-benzylcarbamates.[15]

Various other salts, such as silver salts, known to be efficient for domino acetalization/cycloisomerization reactions of aldehydes in either a 5-*exo* or 6-*endo* process,[7a,h,i] were tested without success (Table 1, entries 8–10). The use of Pd, Pt, or Cu electrophilic catalysts were engaged in the same domino process (Table 1, entries 11–13) and led to low or no conversion. Control experiments in the absence of catalyst or HEH (Table 1, entries 14–15) gave no conversion and decomposition of the starting material (conversion >99%) respectively, showing clearly the crucial role of gold and a hydride source.[16] Other solvents such as CH_2Cl_2, THF, CH_3CN, and MeOH were compatible with the reaction conditions despite a slower kinetic in the case of methanol (entries 16–19). Using the optimized system consisting of 1 mol % of $[AuCl_2(Pic)]$ and 1.2 equiv of HEH at rt in toluene, the aldehyde scope of the reaction was explored.

As stated before, the commercially availability and functional diversity of *ortho*-bromo-arylaldehydes is much higher than those for the corresponding benzylic alcohols. For this purpose, various *ortho*-alkynyl arylaldehydes (Figure 1) were synthesized according to a classical Sonogashira cross-coupling starting from the corresponding commercially available *ortho*-bromo

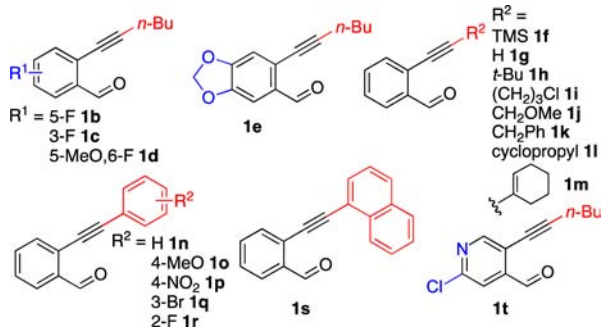
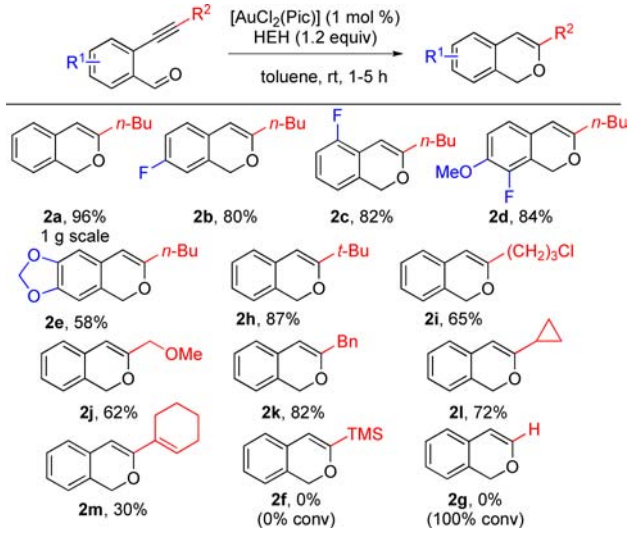


Figure 1. Structures of substrates **1b–t**.

derivatives (Supporting Information (SI)).[17] Considering the importance of organofluorine compounds in various areas including pharmaceuticals, agrochemicals, and materials,[18] we selected **1b–d** as potential key building blocks for the development of potential drug candidates. An aldehyde bearing an electron-donating group such as **1e** was also prepared. Regarding the substitution on the alkynyl moiety, several other groups other than *n*-butyl have been targeted such as silyl (**1f**), hindered alkyl and cycloalkyl (**1h**, **1l**) groups as well as functionalized alkyl (**1i–j**), benzyl (**1k**), and cycloalkenyl (**1m**) groups. Aryl-substituted alkynes bearing either electron-donating or -withdrawing groups (**1p–r**) and a naphthyl-functionalized aldehyde **1s** were also prepared from **1g**. A pyridinyl derivative **1t** was also prepared starting from 5-bromo-2-chloropyridine-4-carbaldehyde.

We first investigated the influence of the substitution on the alkyl-substituted alkynes under the optimized conditions (Scheme 2). The yields were good for fluoro-substituted

Scheme 2. Domino Cyclization/Reduction of Alkyl-Substituted Alkynes



arylaldehydes (**2b–d**) (~80%). A slight decrease of the isolated yield was observed in the case of an electron-donating substituted aldehyde such as 1,3-benzo dioxolane derivative **2e**. The mild reaction conditions were compatible with hindered *tert*-butyl, cyclopropanyl, or benzyl groups (**2h**, **2l**, and **2k**, 87%, 72%, and 82% yields respectively) and functionalized alkyl groups such as chloropropanyl and methoxymethyl moieties (**2i–j**). The presence of an alkenyl group (such as in **1m**) had a detrimental

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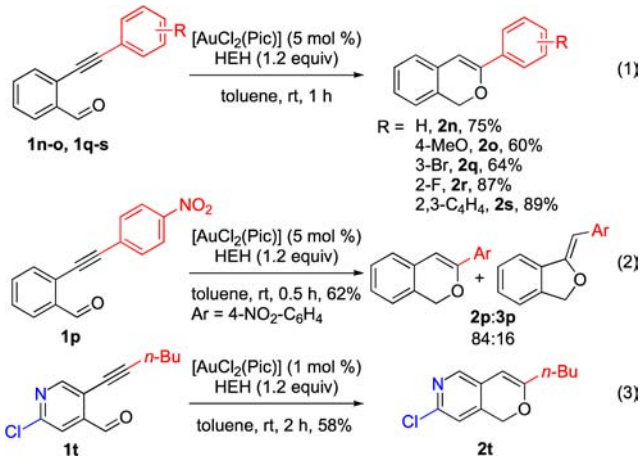
effect, presumably because of the possible reactivity of the resulting conjugated diene **2m**.[19] The only limitation was found in the reactivity of TMS-functionalized and nonsubstituted alkynyl aldehyde **1f** and **1g**: no conversion was observed for **1f**[20a] whereas full conversion was detected for **1g** with no trace of the desired adduct. The reaction led to a complex mixture of nonidentified derivatives.[20b] Finally, the domino process was successfully conducted on a gram scale in the case of aldehyde **1a**, and the resulting 1*H*-isochromene **2a** was isolated in 96% yield.

Following these valuable results, we decided to investigate the domino process on aryl-substituted alkynes, where we anticipated a trickier *endo*/*exo* process due to electronic effects (Scheme 3).[4,12] The reactivity of **1n** was studied and required 5

Scheme 3. Domino Cyclization/Reduction of Aryl-Substituted Alkynes and Heterocyclic Aldehyde



mol % catalysts for full and clean conversion of starting material. Similarly to Crabtree's report in the presence of an Ir catalyst for a benzyl alcohol analogue of **1n**, the cyclization occurred exclusively according to a 6-*endo* process.[21] Pleasingly, the cyclization/reduction reactions of other substituted patterns on the phenyl ring also allowed the exclusive formation of 6-*endo* 1*H*-isochromene derivatives (**2o**, **2q**−**s**, Scheme 3, eq 1) in good to excellent yields (60−89%).

The *para*-, *meta*- and *ortho*-substituted derivatives were obtained efficiently without significant influence from the nature of substitutive electron-withdrawing or -donating groups. It is noteworthy that the syntheses of **2n** (respectively **2o**) according to this methodology compared favorably with the literature (3 steps with 42% and 38% yields respectively starting from 1,2-bis(bromomethyl)benzene).[22] One key feature was the reactivity of the nitro adduct **1p**: as predicted,[21] the domino process led to a mixture of 6-*endo*/5-*exo* derivatives in a 84:16 ratio (Scheme 3, eq 2). Both isomers, **2p** and **3p**, were isolated and characterized by X-ray spectroscopy analysis and ^{1}H NOESY experiment respectively (see Figure 2 and SI). Rewardingly, the mild conditions were compatible with the functionalized pyridinyl aldehyde **1t**, which was smoothly and selectively transformed in the presence of 1 mol % catalyst to heterocycle **2t** in 58% yield (Scheme 3, eq 3).

In conclusion, we have demonstrated that the commercially available [$AuCl_2$(Pic)] complex associated with the Hantzsch ester allowed, under mild conditions, easy access to a large variety of 1*H*-isochromenes. This simple and efficient procedure was chemo- and stereoselective and therefore provides a powerful means for the generation of key intermediates in medicinal

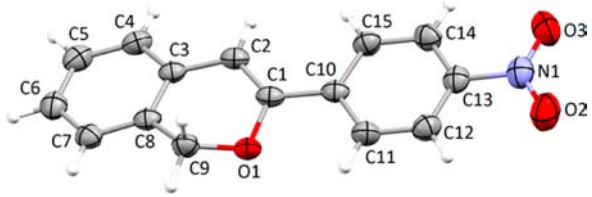


Figure 2. ORTEP-type view of the structure of **2p**.

chemistry. Further studies will focus on applications for heterocyclic carbonyl-yne derivatives[23] and postfunctionalization of the valuable functionalized 1*H*-isochromenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03146.

Experimental procedures and characterization data of new products (PDF)

X-ray diffraction data for **2p** (CIF)

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Notes

The authors declare no competing financial interest.

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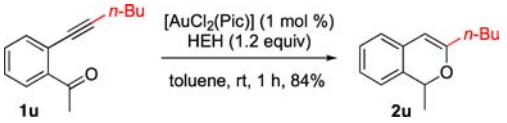

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