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Silver-Catalyzed Domino Hydroarylation/Cycloisomerization Reactions of *ortho*-Alkynylbenzaldehydes: An Entry to Functionalized Isochromene Derivatives

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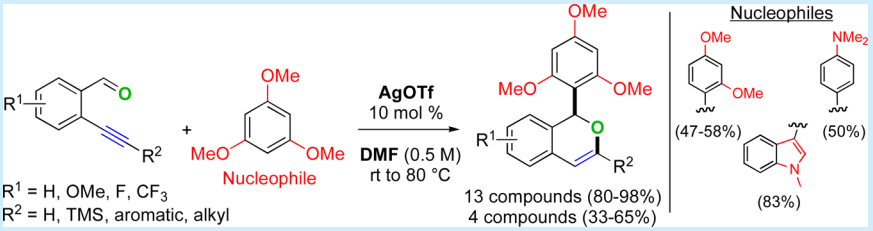
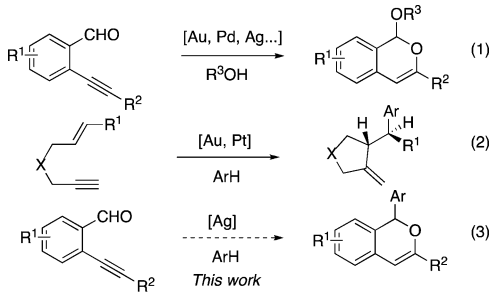
Supporting Information



ABSTRACT: A Ag-catalyzed versatile and efficient access to 1*H*,1-arylisochromenes is reported. Starting from *ortho*-alkynylbenzaldehydes bearing various substitution patterns on the benzaldehyde and alkynyl units, the use of silver triflate (10 mol %) allowed a domino hydroarylation/cycloisomerization reaction process, leading to aryl-functionalized 1*H*-isochromene (>10 compounds, 80−98% yields). Notably, the reaction conditions were also compatible with benzaldehydes bearing an aliphatic-substituted alkynyl moiety with modest to good yields (34−88%, 10 compounds).

Metal-catalyzed cycloisomerization reactions have become in recent years an efficient and useful tool for access to highly functionalized carbo- and heterocycles.[1] Among them, the cyclization processes implying an alkynyl partner and thus π-metal-complexes as intermediates have been thoroughly studied and have allowed the discovery of novel skeleton rearrangements and new reactions. The privileged reactivity of various polyunsaturated partners such as 1,*n*-enyne,[2] allenyne[3] or carbonyl-yne[4] derivatives has opened the way to original scaffolds under racemic or enantioselective conditions. The complexity of the resulting polycyclic structures has been heightened by the intervention of other nucleophiles (oxygen, carbon, nitrogen nucleophiles), favoring domino processes. As part of our ongoing programs toward cycloisomerization processes implying carbophilic π-activation in the presence of gold,[5,6] platinum,[7] or silver[8] catalysts, we became interested in the carbonyl-yne cycloisomerization reactions in the presence of an external nucleophile, which is of particular interest since it allows the direct access to oxygen-containing heterocycles of high biological value.[9] We[8] and others contributed in some key developments for the domino cyclofunctionalization in the presence of terminal alkynes,[10] phosphites,[11] nitrogen,[12] activated methylenes,[13] allyl trialkylsilanes,[4a,g] and hydride[14] as nucleophiles, or oxygen-containing[15] nucleophiles, the latter being the most successful ones (Scheme 1, eq 1).[16] The implication of aromatics and heteroaromatics as external nucleophiles has been scarcely studied and to the best of our knowledge limited to indole as a nucleophile in the presence of silver and palladium complexes.[17] Considering our previous report on domino hydroarylation/cycloisomerization reactions of enynes[18] (Scheme 1, eq 2), we anticipated that carbonyl-yne derivatives may be suitable substrates for such processes. We wish therefore to report our preliminary results on the domino functionalization of *ortho*-alkynylbenzaldehydes in the presence of electron-rich aromatic rings, leading to original 1*H*-isochromenes (Scheme 1, eq 3).[19]

Scheme 1. [M]-Catalyzed Domino Processes



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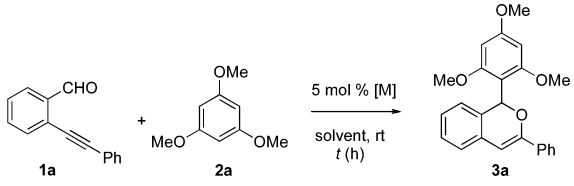
First, the readily available *ortho*-phenylacetylenyl benzaldehyde **1a** was chosen as a model substrate, trimethoxybenzene **2a** was the external nucleophile, and silver salts were the catalytic source of electrophilic activation. Various silver salts had already given rise selectively to 5-*exo*-dig or 6-*endo*-dig cyclization modes in the presence of alcohols.[8] It is noteworthy that Beeler, Porco and co-workers had tested the reactivity of trimethoxybenzene in the presence of various transition metal complexes including a silver catalyst without success.[13] The use of 5 mol % AgOTf in dichloromethane at rt led to 100% conversion but a 16% isolated yield of the adduct **3a** resulting from a hydroarylation/6-*endo*-dig cyclization process (entry 1, Table 1). The use of other silver salts ($AgSbF_6$, $AgPF_6$, Table 1, entries 2, 3), did not bring any improvement, and solvent switching to DCE allowed isolating **3a** in 32% yield along with undesired compounds (Table 1, entry 4). Increasing the amount of **2a** (6 equiv) was detrimental (14% yield, Table 1, entry 5). A significant improvement was observed when DMF was used as the reaction solvent (32%, Table 1, entry 6), and the yield increased up to 52% when the amount of **2a** was doubled (6 equiv, entry 7).

Table 1. Optimization of Reaction Conditions[a]



entry	[M]	solvent	time (h)	yield[b] (conv) %
1	AgOTf	DCM	8	16
2	$AgPF_6$	DCM	8	14
3	$AgSbF_6$	DCM	8	14
4	AgOTf	DCE	6.5	32
5[c]	AgOTf	DCE	6.5	14
6	AgOTf	DMF	21	32
7[c]	AgOTf	DMF	40	52
8[d]	AgOTf	DMF	28	71
9[d,e]	AgOTf	DMF	19	81
10[d,e,f]	**AgOTf**	**DMF**	**3**	**91**
11[e,f]	/	DMF	3–24	0
12[e,f,g]	/	DMF	3–8	0[h]

[a]For all entries, unless noted differently, 5 mol % [AgOTf], **2a** (3 equiv), room temperature, solvent (0.25 M). [b]Isolated yields or conversion by ^{1}H NMR are indicated. [c]6 equiv of **2a**. [d][M] (10 mol %). [e]DMF (0.5 M). [f]Reaction performed at 80 °C. [g]Reaction performed with HOTf (10 mol %). [h]Along with unidentified products.

The main drawback was the reaction time (40 h); therefore, we successively increased the AgOTf amount (Table 1, entry 8), concentrated the reaction medium (Table 1, entry 9), and performed the reaction at 80 °C (Table 1, entry 10), and this resulted in access to arylisochromenes **3a** in an excellent 91% yield in only 3 h. Control experiments achieved in the absence of catalysts (entry 11) or in the presence of HOTf (entry 12) showed clearly the crucial role of silver in the catalysis, putting aside the impact of Brønsted acid traces. The reactivity of diverse metallic salts such as Cu-, Au-, Pd-, or Pt-based catalysts was studied showing either no conversion or lower isolated yields.

The use of silver salts led selectively to the heterocycle resulting from a 6-*endo*-dig cyclization. This was unambiguously confirmed by X-ray spectroscopy analysis of a bromo analogue (Figure 1 and Supporting Information).

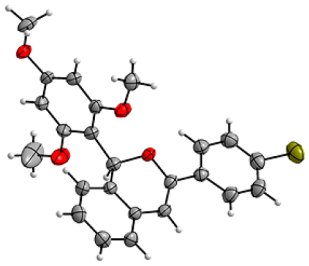
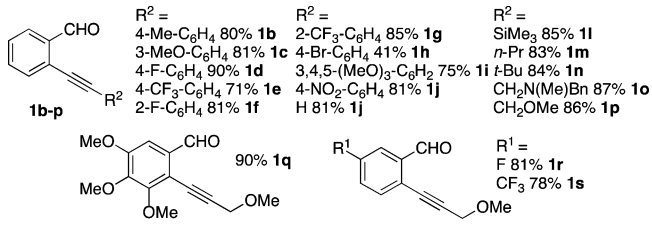


Figure 1. X-ray structure of 3-(4-bromophenyl)-1-(2,4,6-trimethoxyphenyl)-1*H*-isochromene **3h**.

The scope of the reaction was then studied, and for this purpose, various *ortho*-alkynyl benzaldehydes (Scheme 2) were synthesized according to a classical Sonogashira cross-coupling starting from the corresponding *ortho*-bromo benzaldehydes **4**–**7**.[20] We selected not only known derivatives such as **1a**–**1c**, **1e**, **1h**–**1n**, and **1p** but also novel fluoro-functionalized compounds (**1d**, **1f**, **1g**, **1r**, **1s**), amino- **1o**, or trimethoxy substituted **1q**, their preparations being performed overall in excellent yields.[20]

Scheme 2. Structures of Substrates 1b–s



The optimized hydroarylation/cyclization conditions (Table 1, entry 10) were screened for a large array of *ortho*-alkynyl benzaldehydes, with trimethoxybenzene (**2a**) as the nucleophile (Scheme 3). The influence of the substitution on the aromatic ring of the alkynyl moieties was first investigated (**3b**–**i**). The yields were all excellent (80–98%), regardless of the substitution pattern on the phenyl ring. Indeed, all the *para*-substituted derivatives (methyl **3b** 83%, fluoro **3d** 85%, trifluoromethyl **3e** 98%, bromo **3h** 81%, trimethoxy **3i** 80%, nitro **3j** 93%) were obtained efficiently without influencing the nature of the substitutive electron-withdrawing or -donating groups. Comparison of *ortho*-substituted derivatives (fluoro **3f** 88%, trifluoromethyl **3g** 81%) with the *para*-substituted derivatives (fluoro **3d** 85%, trifluoromethyl **3e** 98%) showed that there was no influence by the fluoro group, a slight decrease of the yield being observed in the case of the more hindered trifluoromethyl group (98% to 81%). The main difference was in the reaction time being much longer for the *ortho* derivatives (7.5 h for **3f** and 30 h for **3g**) compared to the *para* ones (2 h). *Meta*-substituted derivatives (methoxy **3c**, 86%; trimethoxy **3i**, 80%) were also easily obtained. Following these excellent results, we decided to investigate the challenging hydroarylation/cyclization process on nude (R^2 = H), TMS-substituted and alkyl-substituted *ortho*-alkynyl benzaldehydes. It is noteworthy that alkyl-substituted-alkynyl substrates have been much less studied than their aromatic counterparts mostly due to sluggish reactions. Interestingly, starting either from

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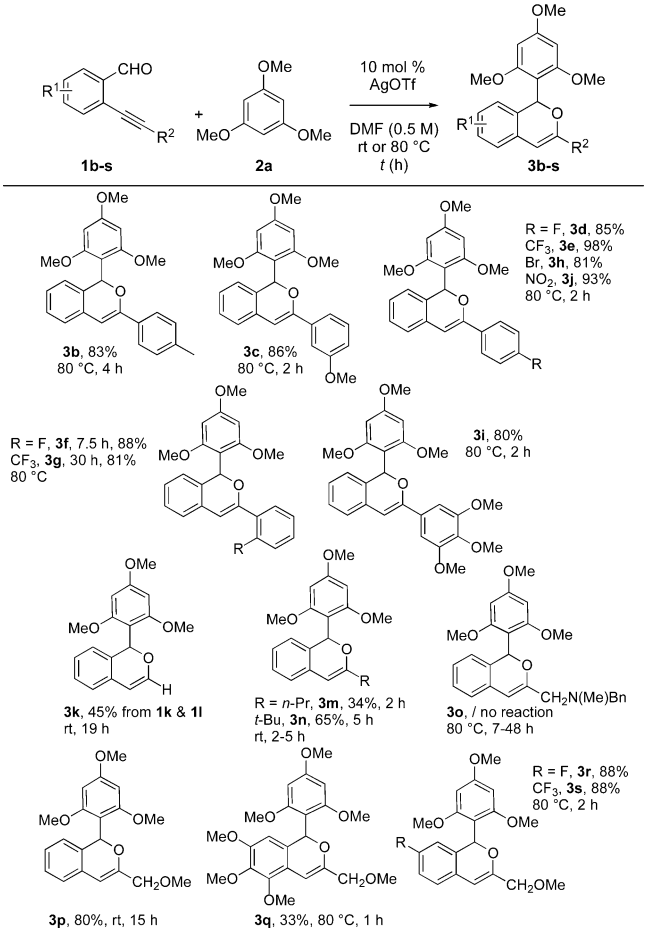
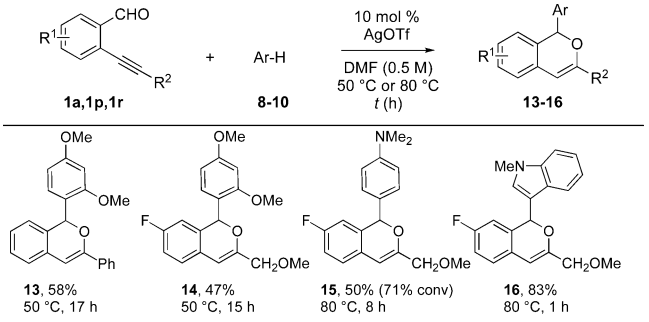
Scheme 3. Hydroarylation/Cyclization of Alkynylaldehydes with Trimethoxybenzene



ortho-alkynyl benzaldehydes bearing a terminal alkyne (**1k**) or from a TMS-protected one (**1l**), formation of the unsubstituted isochromene **3k** in a moderate 45% yield resulted. It is noteworthy that the reaction required smoother conditions than in the case of aryl-substituted substrates and was performed at rt to diminish the formation of byproducts. Pleasingly, we could also isolate isochromenes substituted by a *n*-propyl (**3m**, 34%) or a *tert*-butyl group (**3n,** 65%). The *N*-methylbenzyl group (**1o**) was unreactive, even upon extended heating (up to 48 h), most probably due to a silver complexation by the aliphatic nitrogen.[8c] Remarkly, the reaction of *ortho*-alkynyl benzaldehyde **1p** bearing methoxymethyl (MOM) groups on the alkynyl moiety led to isochromene **3p** in high yield. Finally, the influence of the substitution of the benzaldehyde ring was investigated. The presence of electron-donating groups (such as in **1q**) had a detrimental effect, as the desired adduct was isolated in 33% yield. Remarkably, the reaction conditions were compatible with fluoro- and trifluoro-substituted benzaldehydes, as functionalized isochromenes **3r**−**3s** were obtained in 88% yield.

The scope of the Ag-catalyzed hydroarylation/cycloisomerization domino reaction was also studied in the presence of other carbon nucleophiles (Scheme 4). The use of dimethoxybenzene **8** as a nucleophile yielded isochromenes **13** and **14** in acceptable yields (58% and 47% respectively). The reactions were performed at lower temperature to avoid the formation of byproducts (50 °C, 15−17 h), and we were able to apply our

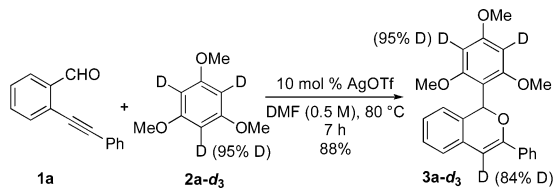
Scheme 4. Hydroarylation/Cyclization of Alkynylaldehydes with Aryl Nucleophiles



method to substrate **1r** having an alkyl substitution on the alkynyl moiety (Scheme 4). Moreover, the introduction of dimethylaniline **9** was also possible, whereas a different reactivity had been observed by Beeler and Porco's group under stoichiometric silver conditions.[13] The corresponding functionalized aniline **15** was isolated in a nonoptimized 50% yield, the conversion being 71%.[19,4h,i] Gratifyingly, the reaction conditions were compatible with *N*-Me indole **10**, as a nucleophile, yielding isochromene **16** in 83% yield, providing the fact that only 1 equiv of the nucleophile was used to avoid side-product formation. The reactions of 3-methylbenzofuran and 3-methylbenzo[*b*]thiophene with **1a** afforded only traces of the corresponding arylated derivatives.

Mechanistically, we anticipated that, after π-activation of the alkyne and domino hydroarylation/cyclization step, the source of proton involved in the protodemetalation step would come from the acidic C−H bond of the nucleophile. Thus, we performed the reaction using deuterated compound **2a-d_3**[18b] and obtained derivative **3a-d_3** with 84% deuteration at the vinyl position (Scheme 5), the slight erosion originating from traces of water in the reaction mixture.

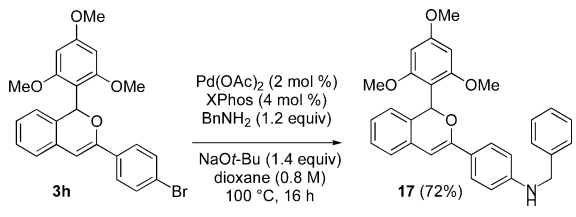
Scheme 5. Labeling Study - Protodemetallation Step



Of note is the compatibility of the reaction conditions with a bromide group (**3h**). Moreover, we were able to perform a Pd-catalyzed Hartwig−Buchwald reaction[21] on **3h** (Scheme 6) attesting to the robustness of the isochromenes (100 °C, 16 h).

In conclusion, we have developed an unprecedented silver-catalyzed hydroarylation/cycloisomerization domino reaction on *ortho*-alkynyl benzaldehydes, leading to functionalized

Scheme 6. Hartwig−Buchwald Reaction



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isochromene derivatives. The overall yields are moderate to high, the method being thoroughly investigated with a broad range of aldehydes and various carbon nucleophiles. The robustness of 1*H*-isochromenes under metal-catalyzed cross-coupling conditions was also clearly demonstrated, which opens new opportunities for the synthesis of biologically active targets. An enantioselective version is under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) These products have been postulated as intermediates upon reaction with dimethylaniline or dimethoxyphenol (ArH), but have never been isolated: see Beeler et al. ref 13. The reaction of phenol on **1a** was also tested and led to the O-arylation process in low yield.

(20) See Supporting Information for details.

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