

# Mild Regiospecific Synthesis of 1-Alkoxy-isochromenes Catalyzed by Well-Defined [Silver(I)(Pyridine-Containing Ligand)] Complexes

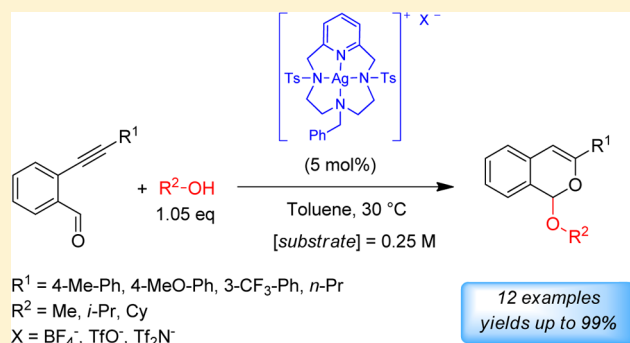
Monica Dell'Acqua,<sup>†</sup> Brunilde Castano,<sup>‡</sup> Clara Cecchini,<sup>†</sup> Tommaso Pedrazzini,<sup>‡</sup> Valentina Pirovano,<sup>†</sup> Elisabetta Rossi,<sup>†</sup> Alessandro Caselli,<sup>\*,‡</sup> and Giorgio Abbiati<sup>\*,†</sup>

<sup>†</sup>Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, Via Venezian, 21, 20133 Milano, Italy

<sup>‡</sup>Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi, 19, 20133 Milano, Italy

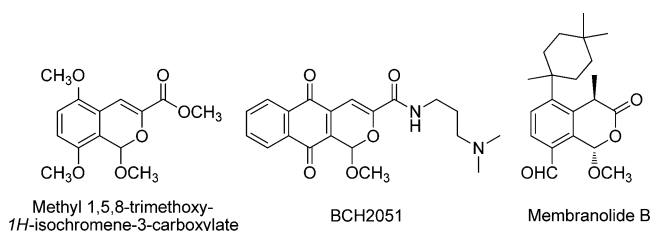
## S Supporting Information

**ABSTRACT:** The synthesis of 3-substituted-1-alkoxyisochromenes starting from 2-alkynylbenzaldehydes and different alcohols is reported. The reaction is catalyzed by a silver(I) complex with an original macrocyclic pyridine-containing ligand. The approach is characterized by absolute regioselectivity, mild reaction conditions, good to excellent reaction yields, cleanness of the reaction, and reduced purification steps. The reaction mechanism was investigated by in-depth <sup>1</sup>H NMR experiments and an aimed "trapping" experiment.



## INTRODUCTION

Isochromene and isochromane nuclei are the core of some interesting bioactive molecules and natural products. For example, the methyl 1,5,8-trimethoxy-1*H*-isochromene-3-carboxylate was patented as a potential antitumor agent against breast cancer,<sup>1</sup> and the related carboxamide derivative BCH2051 displayed an interesting activity against the human ovarian cancer cell line SKOV3 and the human colon carcinoma cell line HT-29.<sup>2</sup> Moreover, the structure of isochromane is the skeleton of a diterpene from the Antarctic sponge *Dendrilla Membranosa* called membranolid B<sup>3</sup> (Figure 1). All of these compounds are characterized by a cyclic-acetal framework due to the presence of a methoxy group on C1.



**Figure 1.** Examples of 1-alkoxy-isochromene/ane-containing bioactive molecules.

An efficient method to build up 4-unsubstituted-1-alkoxyisochromenes and related heteroaryl compounds (e.g., dihydropyranoquinolines) is the regioselective domino addition/cycloisomerization reaction of a properly substituted 2-alkynyl-(hetero)arylaldehyde with an alcohol.<sup>4</sup> These reactions are

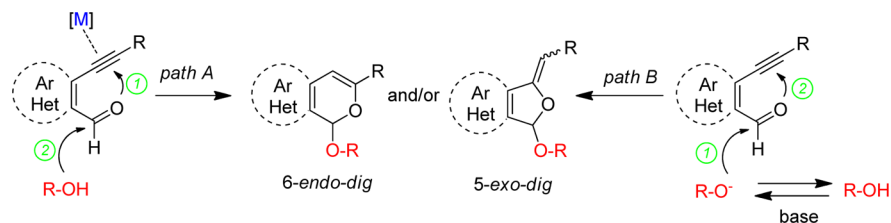
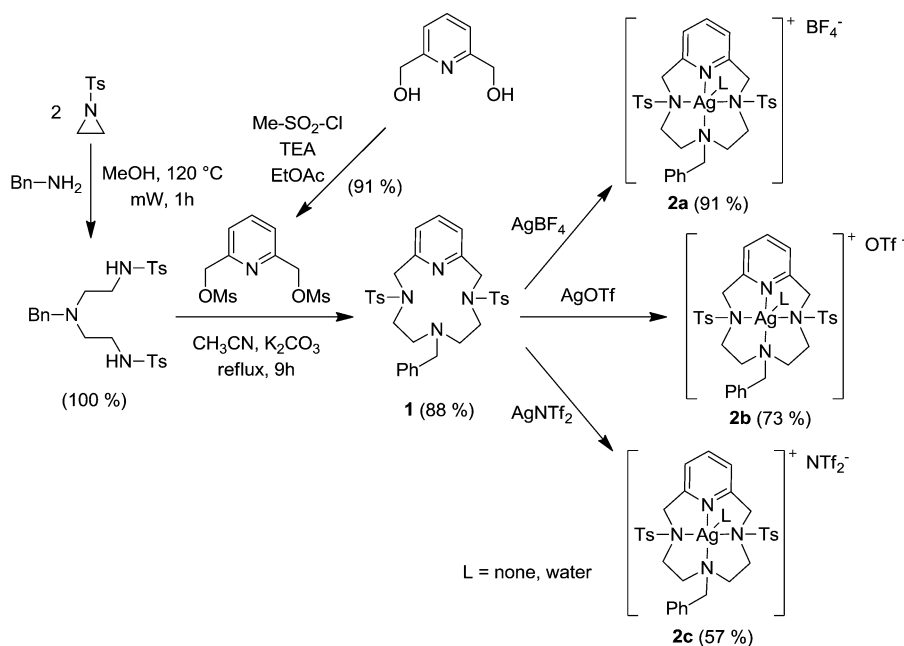
usually catalyzed by a metal salt or promoted by a base, but the regioselectivity of the cycloisomerization step (i.e., 5-*exo-dig* vs 6-*endo-dig* cyclization) is not always easy to rationalize<sup>5</sup> (Scheme 1). In general, the reactions promoted by bases lead preferentially to the 5-*exo-dig* cyclization products (i.e., dihydroisobenzofurans, dihydrofuroquinolines, or dihydrofuro-pyrimidines) via an addition/annulation sequence that probably involves the formation of a hemiacetal anion (Scheme 1, path B).<sup>6</sup> Conversely, the metal-catalyzed approaches can lead to both products depending on several factors, including the nature of the aromatic aldehyde (i.e., the presence of one or more nitrogens in the aromatic ring) and the substitution on the triple bond. Usually 6-*endo-dig* cyclization products predominate (i.e., isochromenes or dihydropyranoquinoline), whose formation is believed to occur through a highly reactive benzopyrylium intermediate (metal ate complex) followed by the nucleophilic attack from the alcohol as a mild nucleophile (Scheme 1, path A).

Several metal ions, such as Pd(II),<sup>7</sup> Cu(I),<sup>8</sup> Ag(I),<sup>9</sup> Au(I),<sup>10</sup> and In(III)<sup>11</sup> salts, have been used as catalysts for the synthesis of isochromenes and analogues following this approach. An enantioselective version of this reaction, catalyzed by chiral gold acyclic diaminocarbene (ADC) complexes has also been reported.<sup>12</sup> Aside from the above-mentioned metal-catalyzed approaches, the research groups of Barluenga<sup>13</sup> and Larock<sup>14</sup> developed two outstanding synthetic strategies for the synthesis of 4-functionalized-isochromenes by using different

Received: February 2, 2014

Published: March 18, 2014

Scheme 1. 5-Exo-dig vs 6-Endo-dig Cyclization Mode of 2-Alkynyl(hetero)arylaldehydes and Alcohols

Scheme 2. Synthesis of *Pc-L* 1 and Its Silver Complexes 2a–c

electrophiles, i.e.,  $\text{IPy}_2\text{BF}_4$  or else  $\text{X}_2$ ,  $\text{ICl}$ ,  $\text{NXS}$ ,  $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$ , and  $\text{PhSeBr}$ , respectively.

For many years, we have been interested in the development of domino synthetic strategies<sup>15</sup> for the construction of nitrogen and/or oxygen containing heterocycles<sup>16</sup> starting from alkyne derivatives.<sup>17</sup> In 2010 we reported on a regioselective synthesis of substituted 1-methoxy-3-methylen-1,3-dihydroisobenzofurans by a microwave-enhanced domino addition/cycloisomerization reaction of 2-alkynylbenzaldehydes and methanol in the presence of a suitable base.<sup>5b</sup> This approach was successfully transformed in an advantageous multicomponent process.<sup>18</sup> As a followup to these studies, in this work we focused our attention to the selective synthesis of regioisomeric 1-alkoxyisochromenes starting from the same substrates (i.e., 2-alkynylbenzaldehydes). To do this, we used an original, stable, and versatile silver(I) complex as a catalyst that was characterized by the presence of a macrocyclic pyridine-containing ligand (*Pc-L*). This approach is characterized by absolute regioselectivity, mild reaction conditions, good to excellent reaction yields, cleanness of the reaction, and reduced purification steps.

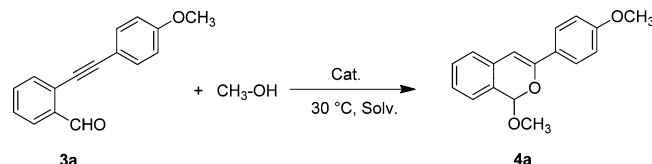
The synthesis of pyridine-containing macrocycles was first reported by Stetter and co-workers.<sup>19</sup> These macrocycles were originally engaged as ligands for the coordination of lanthanide ions in MRI contrasting agents.<sup>20</sup> Their transition metal complexes have also been successfully used in catalysis. For example,  $[\text{Cu}(\text{I})(\text{Pc-L})]$  complexes have been demonstrated to be efficient catalysts in the cyclopropanation reaction of alkenes<sup>21</sup> and in the Henry reaction.<sup>22</sup> In this work, some

unknown  $[\text{Ag}(\text{I})(\text{Pc-L})]$  complexes are presented. To the best of our knowledge, this work represents the first example of application of  $[\text{Ag}(\text{I})(\text{Pc-L})]$  complexes in catalysis.

## RESULTS AND DISCUSSION

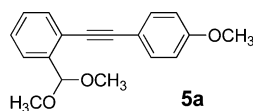
**Preparation of the Catalysts.** The selected pyridine-based 12-membered tetraaza macrocyclic *Pc-L* 1 was obtained in good overall yield from commercially available starting materials according to Scheme 2.<sup>22</sup> The synthesis involved the nucleophilic ring-opening of 1-tosylaziridine by benzylamine to give the 1,7-ditosyl-4-benzyl-1,4,7-triazaheptane in quantitative yield. Thus, by reacting the *bis*-protected triamine with 2,6-pyridinedimethanol 2,6-dimesylate in refluxing anhydrous acetonitrile in the presence of anhydrous  $\text{K}_2\text{CO}_3$ , the macrocycle 1 was obtained in 88% yield. 2,6-Pyridinedimethanol 2,6-dimesylate was obtained in 91% yield by the reaction of 2,6-pyridinedimethanol and an excess of methanesulfonylchloride in ethyl acetate in the presence of triethylamine. With respect to the method previously reported,<sup>22</sup> we improved the approach by using dielectric heating, which allowed for an overall increase in yield and a reduction of the time necessary to obtain the 1,7-Ditosyl-4-benzyl-1,4,7-triazaheptane. Moreover, the product obtained by this method was sufficiently pure and could be used for the macrocyclization step without the need for further purification. Macrocyclic ligand 1 was converted in three different “well-defined”  $\text{Ag}(\text{I})$  complexes 2a–c by reacting with three different silver salts, silver

Table 1. Optimization of the Reaction Conditions



entry	solvent	equiv MeOH	[3a] M	t (h)	catalyst	catalyst loading (mol %)	4a (yield %)
1	MeOH		0.25	5	2a	5	83 <sup>a</sup>
2	dioxane	3	0.25	5	2a	5	88
3	DCE	3	0.25	1	2a	5	94 <sup>b</sup>
4	toluene	3	0.25	2.5	2a	5	99
5	toluene	3	0.125	4	2a	5	98
6	toluene	3	0.50	2.5	2a	5	98
7	toluene	3	0.25	22	2b	5	92
8	toluene	3	0.25	24	2c	5	93
9	toluene	1.5	0.25	2.5	2a	5	99
10	toluene	1.05	0.25	2	2a	5	99
11	toluene	1.05	0.25	8	2a	2.5	82
12	toluene	1.05	0.25	36	2a	1	70
13	toluene	3	0.25	4	AgOTf	5	64 <sup>c</sup>
14	toluene	1.05	0.25	3	AgBF <sub>4</sub>	5	60 <sup>c</sup>

<sup>a</sup>Beside dimethyl acetal 5a in 15% yield. <sup>b</sup>Beside traces of acetal 5a. <sup>c</sup>Yields calculated via <sup>1</sup>H NMR using dimethyl terephthalate (DMT) as internal standard.



tetrafluoroborate, silver triflate, and silver *bis*-triflimidate, respectively.

We kept the silver salts and all silver containing solutions in the dark until we isolated the final products. The three complexes 2a–c were readily formed by adding the silver salt to a 1,2-dichloroethane solution of ligand 1 under a nitrogen protecting atmosphere, yielding a yellowish solution that was stirred at room temperature (rt) for 1 h. If traces of unreacted solid were present, the solution was filtered. The reaction mixture was concentrated to half volume, and the addition of toluene or *n*-hexane to these solutions caused the precipitation of complexes 2a–c as a white powder in yields ranging from 57 to 91% (Scheme 2). All silver complexes were fully characterized by NMR, electrospray ionization mass spectrometry (ESI-MS), IR, and UV–vis spectroscopy. The metal atom was placed in the large macrocyclic cavity of the ligand, which has four potential coordination sites that, upon addition of a fifth external ligand, provide a strongly distorted trigonal bipyramidal coordination geometry. In sharp contrast to the analogous complexes of copper(I), these silver complexes do not suffer from oxidation when in contact with air. On the other hand, they have a tendency to absorb atmospheric moisture to form monoquo species (Scheme 2).

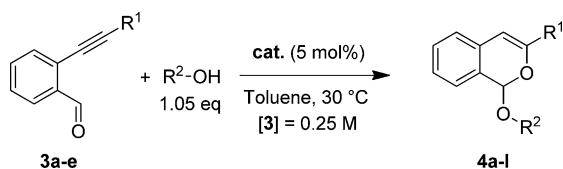
We also tried to prepare complexes with a coordinating anion such as a chloride ion. Neither the direct reaction of the ligand 1 with silver chloride, nor the anion-exchange reaction of complex 2a with tetrabutylammonium chloride led to the desired product. In the first case, no reaction occurred, whereas in the second, immediate expulsion of the metal from the ligand as silver chloride precipitate was observed. These reactions demonstrated that silver complexes 2a–c are sensitive to any chloride anion that may be present in solution.

In the absence of coordinating ligands, the silver complexes 2a–c have a tendency to cocrystallize with a molecule of

1,2-dichloroethane, as revealed by the accurate analysis of <sup>1</sup>H NMR spectra. The same pattern of signals are present in the <sup>1</sup>H NMR spectra of all complexes 2a–c, independently from the type of counterion: an apparent C<sub>s</sub> symmetry of the structure is observed in solution, with two signals for each couple of equivalent methylene groups. A <sup>1</sup>H–<sup>19</sup>F heteronuclear Overhauser effect spectroscopy (HOESY) spectrum shows that the tetrafluoroborate anion in complex 2a has weak proximity interactions with only the pyridine ring of the ligand. The UV–vis spectra of complexes 2a and 2b show the absence of absorption bands at wavelengths higher than 290 nm, which is consistent with the observed absence of color and the d<sup>10</sup> electronic configuration of the metal (no d–d transitions allowed). The shape of the UV–vis spectrum of the ligand 1 does not vary owing to complexation, while the intensities of the absorptions are quite different; therefore, the bands recorded in the near UV region can be related to ligand-centered transitions.

**Addition/Cycloisomerization Reactions.** The first experiment was performed on a model reaction with 2-[(4-methoxyphenyl)ethynyl]benzaldehyde 3a and methanol as the reagent/solvent under unoptimized conditions (Table 1, entry 1). This preliminary test revealed that the silver complex 2a (5 mol %) was able to promote the addition/cycloisomerization of 3a with methanol regioselectively yielding the corresponding isochromene 4a in very good yield (83%) after 5 h. The thin layer chromatography (TLC) analysis of the reaction crude was particularly clean and showed only two spots. Thus, the small amount of dimethyl acetal 5a was the sole byproduct detected by <sup>1</sup>H NMR of the reaction crude and accounted for the mass balance of the reaction (Table 1, entry 1).<sup>23</sup> To optimize the reaction conditions, we performed a series of new experiments. Aiming to find a proper medium to be used with different alcohols and to suppress the formation of the acetal

Table 2. Scope and Limitations of the Approach



entry	substrate	catalyst	R <sup>1</sup>	R <sup>2</sup>	t (h)	4 (yield <sup>d</sup> %)
1	3a	2a	<i>p</i> -MeO-Ph-	Me	2	4a 99
2	3b	2a	<i>p</i> -Me-Ph-	Me	22	4b 97
3	3b	2c	<i>p</i> -Me-Ph-	Me	24	4b 94
4	3c	2a	<i>m</i> -F-Ph-	Me	24	4c 98
5	3d	2a	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	Me	2	4d 96 (76) <sup>b</sup>
6	3d	2b	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	Me	2	4d 95
7	3e	2a	(CH <sub>3</sub> ) <sub>3</sub> Si-	Me	24	- (96% 3e rec.)
8	3e	2a	(CH <sub>3</sub> ) <sub>3</sub> Si-	Me	4 <sup>d</sup>	- (95% 3e rec.)
9	3e	2a	(CH <sub>3</sub> ) <sub>3</sub> Si-	Me	18 <sup>c</sup>	- (95% 3e rec.)
10	3a	2a	<i>p</i> -MeO-Ph-	<i>i</i> -Pr	6	4e 99
11	3b	2a	<i>p</i> -Me-Ph-	<i>i</i> -Pr	26	4f 97
12	3b	2c	<i>p</i> -Me-Ph-	<i>i</i> -Pr	22	4f 93
13	3c	2a	<i>m</i> -F-Ph-	<i>i</i> -Pr	24	4g 97
14	3d	2a	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	<i>i</i> -Pr	2	4h 89 (62) <sup>b</sup>
15	3d	2c	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	<i>i</i> -Pr	4	4h 88
16	3a	2a	<i>p</i> -MeO-Ph-	Cy	24	4i 92 (67) <sup>b</sup>
17	3b	2a	<i>p</i> -Me-Ph-	Cy	24	4j 94
18	3c	2a	<i>m</i> -F-Ph-	Cy	48	4k 96
19	3d	2a	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	Cy	2	4l 94
20	3d	2b	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -	Cy	2	4l 86
21	3a	2a	<i>p</i> -MeO-Ph-	<i>t</i> -Bu	27	
22	3a	2a	<i>p</i> -MeO-Ph-	<i>t</i> -Bu	72 <sup>d</sup>	

<sup>a</sup>After simple workup. <sup>b</sup>After column chromatography. <sup>c</sup>Reaction was performed at 110 °C. <sup>d</sup>Reaction was performed at 80 °C.

5a, we tried some different solvents with decreasing relative polarity<sup>24</sup> (Table 1, entries 2–4) in the presence of 3 equiv of methanol. All of the solvent tested gave excellent results, and the formation of dimethyl acetal 5a was strongly reduced (Table 1, entry 3) or completely avoided (Table 1, entries 2, 4). Even though the reaction in 1,2-dichloroethane (DCE) appeared to be slightly faster (Table 1, entry 3), the best yield and cleanness of the reaction were obtained in toluene (Table 1, entry 4). The concentration of the substrate seemed to have little effect on the course of the reaction (Table 1, entries 5 and 6), whereas the reaction with Ag(I) complexes 2b and 2c, characterized by the presence of a slightly more coordinating counterion such as triflate<sup>25</sup> or a more bulky and charge delocalized anion as triflimidate,<sup>26</sup> respectively, gave lower yields in prolonged reaction times (Table 1, entries 7, 8). We were pleased to find that the amount of the alcohol could be reduced without a loss of yield or an increase in reaction times (Table 1, entries 9, 10). Conversely, the catalyst loading seemed to be a critical factor and amounts of catalysts less than 5 mol % resulted in extended reaction times and lower reaction yields (Table 1, entries 11, 12). Finally, two control experiments in the presence of simple silver salts such as AgOTf (5 mol %) and AgBF<sub>4</sub> (5 mol %) as catalysts demonstrated the superiority of our Ag complexes (Table 1, entries 13 and 14), because in both cases the reactions appeared to have lower yield and in particular, were less clean.

It is important to emphasize that one of the additional features of our method is the neatness of the reactions, which allows, in most cases, the isolation of the pure product through a simple workup, *i.e.*, washing the crude with NaHCO<sub>3</sub>

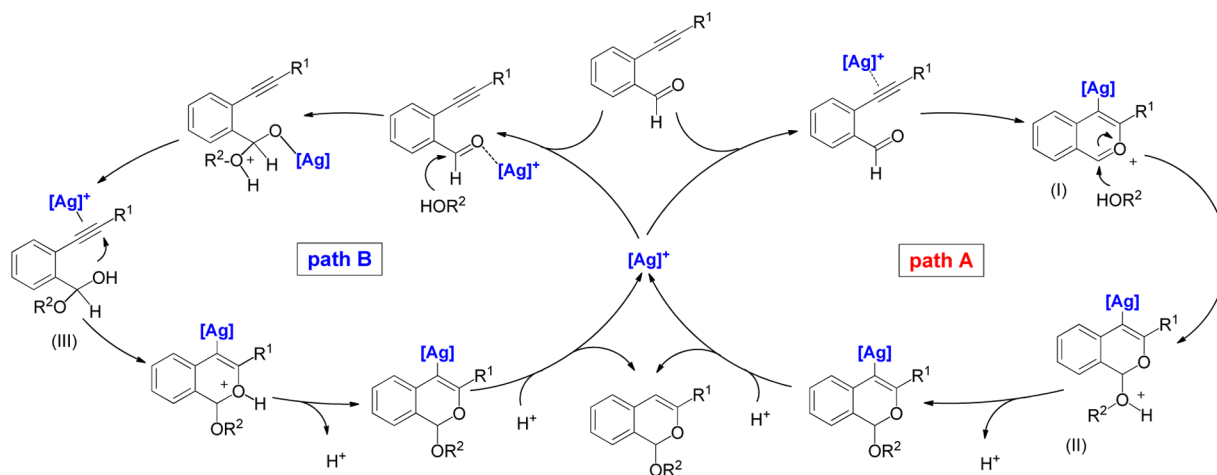
saturated solution (sat. sol.) and extraction with dichloromethane. The simplicity of the purification step represents an outstanding peculiarity of our approach, because it is well-known that the purification of 1-alkoxyisochromenes and related compounds can be quite troublesome.<sup>6,12</sup>

With the best reaction conditions in hand, we tested the scope and limitations of the approach. We selected some alkyne-substituted benzaldehydes substituted on alkyne moiety with an alkyl- or an aryl-group and characterized by the presence on the aryl moiety of electron-donating or electron-withdrawing groups. The 2-alkynylbenzaldehydes 3a–d were synthesized as previously reported<sup>15,17d</sup> starting from commercially available 2-bromobenzaldehyde and a selection of terminal acetylenes by means of a typical Sonogashira coupling,<sup>27</sup> offering good to excellent yields. Their reactivity was tested with four alcohols with increasing steric hindrance. The results are reported in Table 2.

All alkyne-substituted benzaldehydes bearing aryl or alkyl substitution on alkyne moiety 3a–d reacted with methanol to give the corresponding isochromenes 4a–d in excellent yields, and the presence of an electron withdrawing group (EWG) or an electron donating group (EDG) on the phenyl substituent was well tolerated (Table 2, entries 1–6). Surprisingly, in the presence of the trimethylsilyl group on alkyne moiety the reaction completely failed: the starting material 3e was recovered unreacted after a prolonged reaction time (Table 2, entry 7) and under higher reaction temperatures (Table 2, entries 8, 9).

More hindered secondary alcohols, such as isopropyl alcohol and cyclohexanol reacted smoothly with alkyne-substituted benzaldehydes 3a–d to give the desired isochromenes 4e–l in very

Scheme 3. Plausible Reaction Mechanisms



high yields (Table 2, entries 8–20). Unfortunately, all attempts to react **3a** with highly sterically demanding tertiary alcohols such as *tert*-butanol failed, giving rise to unidentified breakdown products (Table 2, entries 21, 22).

Catalysts **2b** and **2c** gave only slightly poorer results than **2a** (Table 2, compare entries 2/3, 5/6, 11/12, 14/15, and 19/20). Aldehyde **3d** substituted on alkynyl moiety with a *n*-propyl group reacted faster than other aldehydes with all alcohols and catalysts tested.

In some cases, the products obtained after the standard workup were not sufficiently pure and needed to be purified by flash column chromatography (Table 2, entries 5, 14, and 16). In these cases, the resulting yields were lower than usual because 1-alkoxyisochromenes are not very stable and during the chromatographic purification partial decomposition of the product was observed. In particular, we think that the acidic character of silica is mainly responsible for the degradation of 1-alkoxyisochromenes due to their acetal nature. To confirm this hypothesis we made two experiments to test the stability of 1-alkoxyisochromenes. A 0.25 M solution of **4a** in ethyl acetate was treated under alkaline or acidic conditions. We observed that in the presence of a base, such as triethylamine (TEA, 0.2 equiv), the product remained unmodified even after stirring for 3.5 days, whereas in the presence of an acid, such as *p*-toluenesulfonic acid (*p*-TSA, 0.2 equiv), the isochromene rapidly decomposed to give a complex mixture of unidentified byproducts. The  $^1\text{H}$  NMR spectrum of the reaction crude roughly filtered on a silica gel-plug displayed the preponderance of 2-[2-(4-methoxyphenyl)-2-oxoethyl] benzaldehyde<sup>28</sup> (maybe in equilibrium with its *cis/trans* enol forms) resulting from the hydrolysis of **4a**.<sup>29</sup>

We also performed the chromatographic purification of the new synthesized isochromenes **4** with a basified eluent mixture, but all the same, a slight reduction of yields was observed due to partial decomposition of the product.

**Mechanistic Studies.** As mentioned above, the most accepted mechanism to explain the silver catalyzed synthesis of isochromenes invokes the formation of an isochromenilium intermediate (I) (metal ate complex) stabilized by resonance, resulting from the direct nucleophilic attack of the aldehyde oxygen to the metal activated triple bond (Scheme 3, path A).<sup>30</sup> Then, the alcohol can attack the activated isochromenilium intermediate (I) to give the intermediate (II). A fast proto-demetalation leads to the isochromene and restores the

catalyst. Nevertheless, the ambivalence of silver salts and complexes, (*i.e.*,  $\sigma$ -philic vs  $\pi$ -philic character<sup>31</sup>), has been repeatedly established,<sup>5a,17b</sup> so a plausible alternative path could involve the direct nucleophilic attack of the alcohol to the metal activated aldehyde to give a hemiacetal intermediate (III), which itself is able to react with the metal activated triple bond (Scheme 3, path B). Also in this case, the following proto-demetalation is the last step that leads to the formation of the isochromene and restores the catalyst.

To gain insight into the mechanism, kinetic  $^1\text{H}$  NMR experiments were performed. In the first experiment, the preliminary reaction conditions were repurposed (see Table 1, entry 1) by reacting **3a** at 30 °C in deuterated methanol in a NMR test tube (Figure 2).

In the absence of the catalyst (Figure 2, “no cat” spectrum), we observed the formation of only a small amount ( $\approx 18\%$ ) of the deuteromethyl-hemiacetal **6a-d<sub>4</sub>** (signal at 5.99 ppm). The amount of **6a-d<sub>4</sub>** was roughly calculated based on relative integration of the hemiacetal proton signal at 5.99 ppm and the aldehydic signal at 10.59 ppm. The spectrum shape and the ratio between aldehyde **3a** and hemiacetal **6a-d<sub>4</sub>** do not change in time (20 h), thus indicating an equilibrium between the two compounds. Then, **2a** (5 mol %) was added (Figure 2,  $t^0$  spectrum). After 20 min (Figure 2,  $t^1$  spectrum), two new signals at 5.75 ppm and 6.16 ppm were detected relative to the deuterodimethyl-acetal **5a-d<sub>6</sub>** and the isochromene **4a-d<sub>4</sub>**, respectively. The spectra appeared very clean, and the reaction proceeded with complete disappearance of the signals relative to aldehyde **3a** (10.59 ppm) and methyl-hemiacetal **6a-d<sub>4</sub>** (5.99 ppm). The reaction was complete in 20 h (Figure 2,  $t^9$  spectrum) when only the signals relative to isochromene **4a-d<sub>4</sub>** and the acetal **5a-d<sub>6</sub>** were detectable. It should be noted that, although the reagent concentration in this case was slightly different, and despite the use of deuterated methanol instead of methanol, the relative ratio of the integrals of these signals at the end of the reaction was consistent with the yields of **4a** and **5a** obtained in the catalytic run (see Table 1, entry 1). The signal relative to acetal **5a-d<sub>6</sub>** at 5.75 ppm was attributed by the comparison with those observed in the spectrum of a pure sample of the dimethyl-acetal **5a**. It is interesting to note that in all spectra no signal around 10.1 ppm, attributable to a possible isochromenilium intermediate,<sup>32</sup> was ever detected (Figure 2). Moreover, the analysis of the integrals at different times of the signals relative to deuterodimethyl-acetal **5a-d<sub>6</sub>** (5.75 ppm) with respect to those relative to  $\text{CH}_3$  of 4-methoxyphenyl moieties

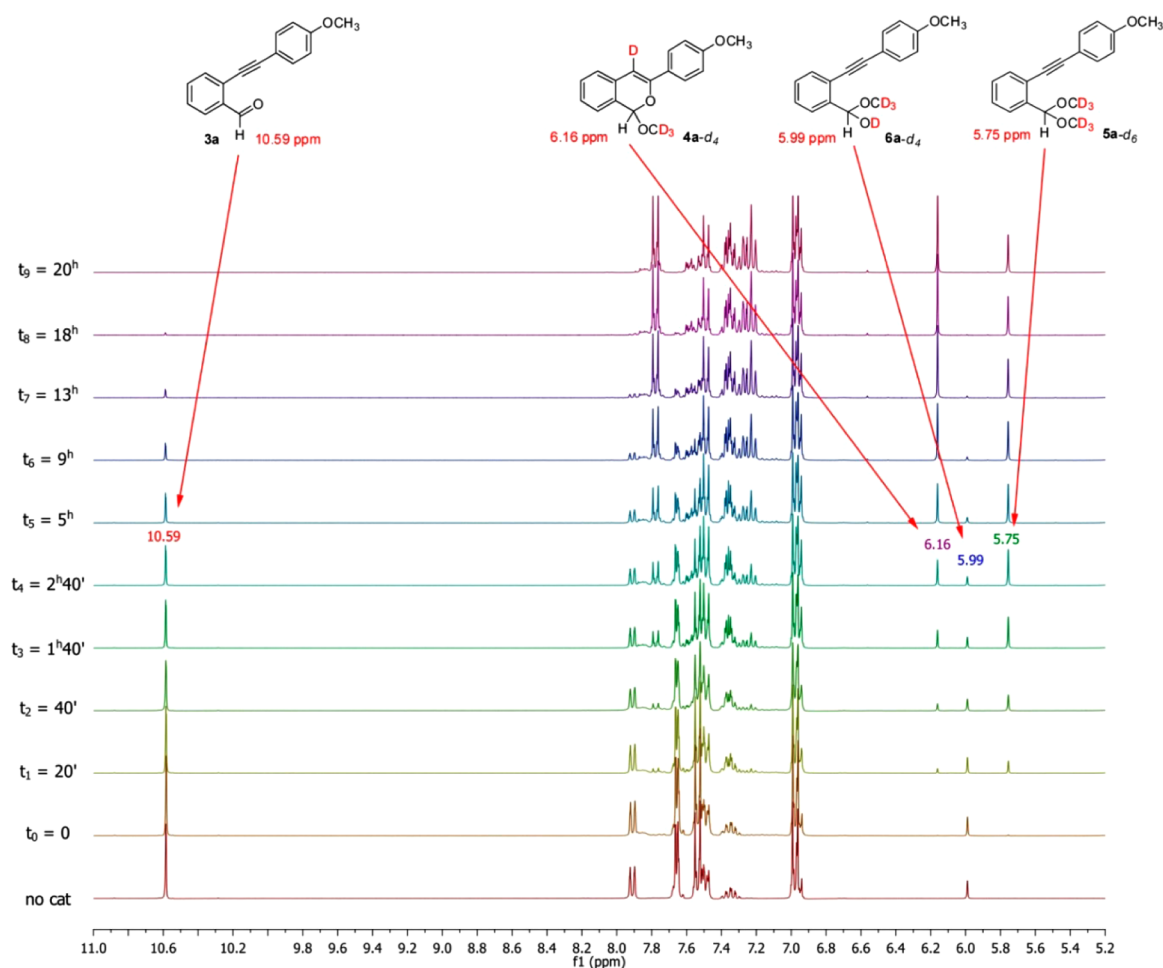


Figure 2. Kinetic  $^1\text{H}$  NMR experiment of **3a** in  $\text{CD}_3\text{OD}$  in the presence of **2a** (5 mol %),  $T = 30^\circ\text{C}$ .

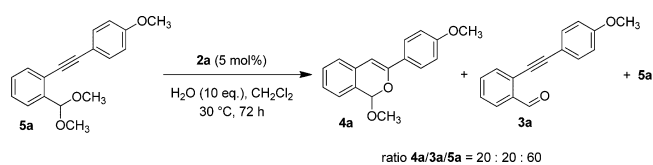
Table 3. Integrals of Selected Signals of Kinetic  $^1\text{H}$  NMR Experiment

time	ref.( <b>3a</b> + <b>4a</b> + <b>5a</b> + <b>6a</b> ) (3.84–3.85 ppm) $\text{CH}_3\text{O-Ph-}$	aldehyde <b>3a</b> (10.59 ppm) $-\text{CHO}$	hemiacetal <b>6a</b> (5.99 ppm) $-\text{CH}(\text{OD})\text{OCH}_3$	acetal <b>5a</b> (5.75 ppm) $-\text{CH}(\text{OCH}_3)_2$	isochromene <b>4a</b> (6.16 ppm) $-\text{CH}(\text{OCH}_3)\text{O-}$
0	3	0.57	0.12	0	0
20 min	3	0.48	0.10	0.08	0.03
40 min	3	0.43	0.09	0.12	0.05
1 h 40 min	3	0.33	0.07	0.19	0.11
2 h 40 min	3	0.27	0.06	0.22	0.15
5 h	3	0.20	0.04	0.23	0.23
9 h	3	0.12	0.03	0.24	0.34
13 h	3	0.06	0.01	0.23	0.42
18 h	3	0.02	0	0.23	0.48
20 h	3	0	0	0.23	0.50

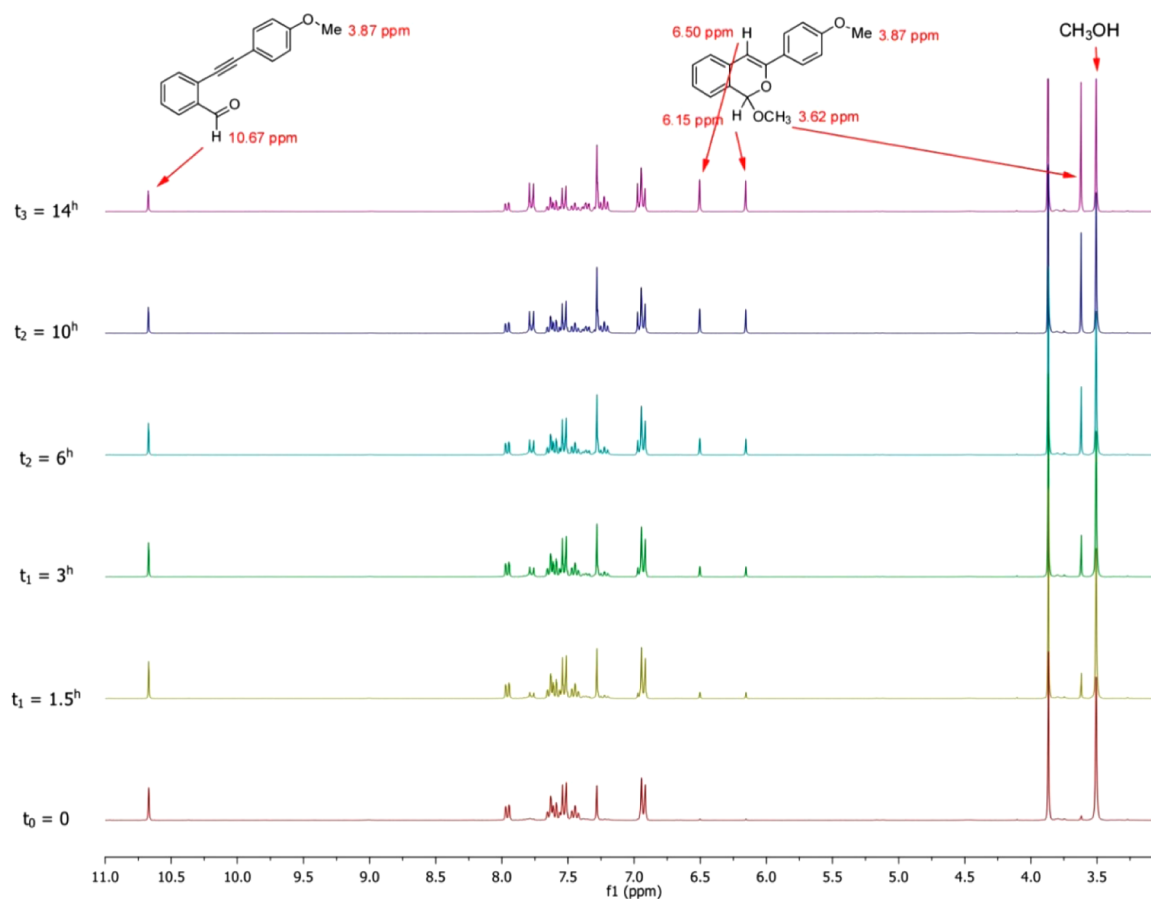
chosen as reference (all these signals fall around 3.84–3.85 ppm and their overall integral is invariable), revealed that under these reaction conditions, the hydrolysis of deuterodimethyl-acetal **5a-d<sub>6</sub>** to give the methyl-hemiacetal **6a-d<sub>4</sub>** is a very slow process (Table 3).

The above statement was confirmed by an additional experiment: the reaction of a pure sample of the dimethyl-acetal **5a** in  $\text{CH}_2\text{Cl}_2$  in the presence of **2a** (5 mol %) and 10 equiv of water gave a mixture of isochromene **4a**, aldehyde **3a**, and unreacted starting material **5a** in a 20:20:60 ratio (roughly calculated on the  $^1\text{H}$  NMR of the reaction crude), after a prolonged reaction time (72 h at  $30^\circ\text{C}$ ) (Scheme 4).

Scheme 4. Reactivity of Acetal **5a**



On the basis of these results, we could make some preliminary considerations: (1) the formation of dimethyl-acetal **5a-d<sub>6</sub>** in the reaction performed in deuterio-methanol in the presence of complex **2a** confirmed its oxo-philic character (as yet previously observed for  $\text{Ag}(\text{I})$  salts),<sup>5a,17b</sup> and its ability to promote



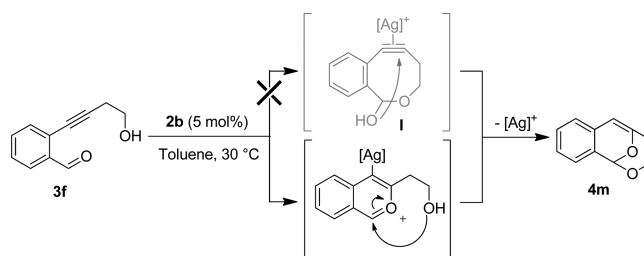
**Figure 3.** Kinetic  $^1\text{H}$  NMR experiment of **3a** in  $\text{CDCl}_3$  in the presence of 2 equiv of methanol and **2a** (5 mol %),  $T = 30^\circ\text{C}$ .

the acetalization of methyl-hemiacetal **6a-d**<sub>4</sub>; (2) such acetalization was probably a competitive side reaction; (3) when the reaction was performed in deuterio-methanol, the methyl-hemiacetal **6a-d**<sub>4</sub> was surely an intermediate in the acetalization, but it could also have been an intermediate in the formation of isochromene **4a** (Scheme 3, path B). Conversely, the absence of any signal in  $^1\text{H}$  NMR spectra referable to an isochromenilium intermediate (Scheme 3, I) does not seem to be sufficient evidence to rule out its involvement in the process, probably with very fast kinetics.

The latter concept seemed to be confirmed by a new kinetic  $^1\text{H}$  NMR experiment. When the reaction was performed in a NMR tube at  $30^\circ\text{C}$ , using  $\text{CDCl}_3$  as a solvent and in the presence of complex **2a** (5 mol %), and only 2 equiv of methanol, no traces of hemiacetal **6a**, acetal **5a**, or isochromenilium intermediates were observed. Only a slow direct conversion of aldehyde **3a** into the desired product **4a** was detected (Figure 3).

Thus, to point out the possible involvement of an isochromenilium intermediate in the reaction mechanism, a conclusive intramolecular trapping experiment was performed by reacting the new synthesized alkyne **3f**, characterized by the presence of a hydroxyethyl pendant at alkyne terminus, under standard conditions in the absence of any other alcohol (Scheme 5). Because of geometric requirements, the hypothetical formation of the corresponding tricyclic isochromene derivative **4m** can only occur by formation of an isochromenilium intermediate, because an alternative oxa-benzocyclooctyne hemiacetal (I) is a strongly improbable intermediate and such oxa-benzocyclooctyne bicyclic structures were never observed in the

### Scheme 5. Intramolecular Addition/Cycloisomerization of Alkyne **3f**



literature.<sup>33</sup> Moreover, the feasibility of the synthesis of **4m** was verified independently by the group of Wu and Hammond by  $\text{AgOTf}$ <sup>34</sup> and triazole-Au<sup>35</sup> catalyzed processes, respectively.

We were pleased to find that the reaction in the presence of  $\text{Ag(I)}$  complex **2b** yielded the attained product **4m** in 5 h (50% yield), thus confirming that an isochromenilium ion is presumably the main intermediate involved in the reaction mechanism.

### CONCLUSION

The  $[\text{Ag(I)}(\text{Pc-L})]$  complexes **2a-c** demonstrated to be suitable catalysts for the synthesis of 1-alkoxyisochromenes starting from various 2-alkynylbenzaldehydes and different primary and secondary alcohols. The best results were obtained with  $\text{BF}_4^-$  complex **2a**. The approach is characterized by absolute regioselectivity, mild reaction conditions, good to excellent reaction yields, cleanness of the reaction, and reduced

purification steps. The  $[\text{Ag}(\text{I})(\text{Pc-L})]$  complexes **2a–c** are quite stable, versatile, and can be used under open-air atmosphere. The reaction mechanism was investigated by in depth NMR studies and an aimed intramolecular trapping experiment. Our efforts are now devoted to the development of an enantioselective version of this transformation. Some preliminary results with Ag(I) complexes of previously synthesized chiral pyridine-containing ligands<sup>21b</sup> are encouraging. We are working on a synthesis of some new chiral  $[\text{Pc-L}]^*$  ligands characterized by a well-planned chiral profile.

## EXPERIMENTAL SECTION

**General Experimental Details.** All of the reactions that involved the use of reagents sensitive to oxygen or hydrolysis were carried out under an inert atmosphere. The glassware was previously dried in an oven at 110 °C and was set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set under a nitrogen atmosphere. All chemicals and solvents were commercially available and were used after distillation or treatment with drying agents. The chromatographic column separations were conducted by a flash technique, using silica gel (pore size 60 Å, particle size 230–400 mesh, Merck grade 9385) or neutral aluminum oxide (Brockman grade I, 0.05–0.15 mm, pH 7 ± 0.5). For TLC, silica was used on TLC Alu foils with fluorescent indicator (254 nm) and the detection was performed by irradiation with UV light ( $\lambda = 254$  nm or 366 nm). <sup>1</sup>H NMR analyses were performed with 200, 300, or 400 MHz spectrometers at room temperature. The coupling constants (*J*) are expressed in hertz (Hz), and the chemical shifts ( $\delta$ ) in ppm. The multiplicity of the proton spectra were described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), hex (sextet), hept (septet), dt (double triplet), dd (double doublet), td (triple doublet), m (multiplet), and br (broad). <sup>13</sup>C NMR analyses were performed with the same instruments at 50.3, 75.5, and 100 MHz, and attached proton test (APT) sequence was used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. All <sup>13</sup>C NMR spectra were recorded with complete proton decoupling. The <sup>1</sup>H NMR signals of the ligand described in the following have been attributed by correlation spectroscopy (COSY) and nuclear Overhauser effect spectroscopy (NOESY) techniques. Assignments of the resonance in <sup>13</sup>C NMR were made using the APT pulse sequence and heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC) techniques. The <sup>15</sup>N NMR signals of the compound described have been attributed by HMBC technique. Low resolution MS spectra were recorded with instruments equipped with electron ionization (EI), ESI/ion trap (using a syringe pump device to directly inject sample solutions), or fast atom bombardment (FAB) (for Pc-L and metal complexes) sources. The values are expressed as mass–charge ratio and the relative intensities of the most significant peaks are shown in brackets. High resolution MS spectra were recorded with an instrument equipped with an electrospray source and a ion cyclotron resonance-Fourier transform mass spectroscopy (ICR-FTMS) analyzer. UV–vis spectra of the ligand and its silver complexes were recorded in CHCl<sub>3</sub>. The melting points of the solid products are uncorrected. The syntheses of the silver complexes were carried out in a nitrogen atmosphere by employing standard Schlenk techniques. 1,2-Dichloroethane and *n*-hexane were distilled prior to use by standard procedures and stored under nitrogen. Microwave promoted reactions were performed with a single-mode Personal Chemistry microwave synthesizer “Emrys Creator,” using sealed glass vessels. The temperature was detected with an infrared sensor.

**Synthesis of 2-(Tosylamino)ethyl Tosylate.**<sup>20b</sup> Tosyl chloride (41.88 g, 220 mmol) was suspended in pyridine (25 mL) and the mixture was cooled to –40 °C. A solution of 2-aminoethanol (6.22 g, 102 mmol) in pyridine (10 mL) was added dropwise over 15 min under vigorous stirring, resulting in a dark orange mixture. The reaction temperature was adjusted to –10 °C for 2 h and then to rt.

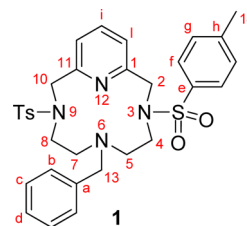
The yellow crude was filtered, washed with ethanol, and recrystallized three times from ethanol, until pyridine was completely removed. The product was obtained as a white powder (18.05 g, 49% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>,  $\delta$ ): 7.76 (d, *J* = 8.2 Hz, 2H, H<sub>ar</sub>), 7.72 (d, *J* = 8.2 Hz, 2H, H<sub>ar</sub>), 7.37 (d, *J* = 8.0 Hz, 2H, H<sub>ar</sub>), 7.32 (d, *J* = 8.0 Hz, 2H, H<sub>ar</sub>), 4.83 (t, *J* = 6.1 Hz, 1H, NH), 4.07 (t, *J* = 5.1 Hz, 2H, CH<sub>2</sub>O), 3.25 (pq, *J* = 5.5 Hz, 2H, CH<sub>2</sub>NH), 2.48 (s, 3H, CH<sub>3</sub>), 2.45 (s, 3H, CH<sub>3</sub>).

**Synthesis of 1-Tosylaziridine.**<sup>20b</sup> A solution KOH (3.86 g, 68.8 mmol) in water (20 mL) was added dropwise to a suspension of 2-(tosylamino)ethyl tosylate (7.48 g, 20.2 mmol) in toluene (80 mL). After being stirred for 2 h, water (80 mL) and toluene (20 mL) were added, the organic layer separated, washed with water, and dried over Mg<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The product was obtained as a white powder (3.69 g, 93% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>,  $\delta$ ): 7.85 (d, *J* = 8.2 Hz, 2H, H<sub>ar</sub>), 7.37 (d, *J* = 8.2 Hz, 2H, H<sub>ar</sub>), 2.47 (s, 4H, CH<sub>2</sub>), 2.39 (s, 3H, CH<sub>3</sub>).

**Synthesis of 1,7-Ditosyl-4-benzyl-1,4,7-triazaheptane.**<sup>22</sup> A solution of tosyl aziridine (1.60 g, 8.13 mmol) and benzylamine (0.396 g, 0.40 mL, 3.69 mmol) in toluene (15 mL) was stirred and heated by microwave irradiation for 1 h at 120 °C. The mixture was dried and used without any further purification. Yield quantitative (1.85 g, 3.69 mmol). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>,  $\delta$ ): 7.73 (d, *J* = 8.0 Hz, 4H, H<sub>ar</sub>), 7.29 (d, *J* = 8.0 Hz, 4H, H<sub>ar</sub>), 7.27–7.25 (m, 3H, H<sub>ar</sub>), 7.13 (m, 2H, H<sub>ar</sub>), 5.17 (br, 2H, NH), 3.44 (s, 2H, CH<sub>2</sub>), 2.93 (m, 4H, CH<sub>2</sub>), 2.52 (m, 4H, CH<sub>2</sub>), 2.43 (m, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>,  $\delta$ ): 143.5 (C<sub>q</sub>), 137.9 (C<sub>q</sub>), 136.8 (C<sub>q</sub>), 129.9 (CH<sub>Ar</sub>), 129.0 (CH<sub>Ar</sub>), 128.7 (CH<sub>Ar</sub>), 127.6 (CH<sub>Ar</sub>), 127.3 (CH<sub>Ar</sub>), 58.6 (CH<sub>2</sub>), 53.3 (CH<sub>2</sub>), 40.8 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>). MS (EI): *m/z* (%) = 501 (100) [M]<sup>+</sup>.

**Synthesis of 2,6-bis(Methanesulfonyloxymethyl)pyridine.**<sup>36</sup> 2,6-Pyridinedimethanol (0.50 g, 3.57 mmol) was suspended in ethyl acetate (10 mL). Triethylamine (1.82 g, 2.50 mL, 17.90 mmol) was added and the mixture was cooled to 0 °C. Methanesulfonylchloride (1.27 g, 0.86 mL, 11.10 mmol) was slowly added and the mixture was stirred for 15 min, after which the reaction was quenched by the addition of sat. aq NaHCO<sub>3</sub> (10 mL). The mixture was extracted with ethyl acetate (3 × 15 mL), and the organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. A white solid was obtained (0.96 g, 91% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>,  $\delta$ ): 7.88 (t, *J* = 7.8 Hz, 1H, H<sub>ar</sub>), 7.52 (d, *J* = 7.8 Hz, 2H, H<sub>ar</sub>), 5.36 (s, 4H, CH<sub>2</sub>), 3.13 (s, 6H, CH<sub>3</sub>).

**Synthesis of 6-Benzyl-3,9-ditosyl-3,6,9,15-tetraazabicyclo[9,3,1]-pentadeca-1(15),11,13-triene 1.**<sup>22</sup>



A solution of 1,7-ditosyl-4-benzyl-1,4,7-triazaheptane (1.85 g, 3.69 mmol), 2,6-bis(methanesulfonyloxymethyl)pyridine (1.09 g, 3.70 mmol), and micronized anhydrous potassium carbonate (1.53 g, 11.08 mmol) in freshly distilled acetonitrile (85 mL) was stirred and heated under reflux for 9 h. The mixture was washed with water (150 mL) and extracted with ethyl acetate (3 × 100 mL). The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure. The crude product was then crystallized in ethyl acetate, yielding a white solid. Yield = 1.97 g, 88%. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>,  $\delta$ ): 7.73 (t, *J* = 7.7 Hz, 1H, H<sup>i</sup>), 7.59 (d, *J* = 8.0 Hz, 4H, H<sup>i</sup>), 7.33 (d, *J* = 7.7 Hz, 2H, H<sup>i</sup>), 7.32–7.30 (m, 3H, H<sub>ar</sub>), 7.24 (d, *J* = 8.0 Hz, 4H, H<sup>g</sup>), 7.18 (m, 2H, H<sub>ar</sub>), 4.34 (m, 4H, CH<sub>2</sub><sup>10</sup>, CH<sub>2</sub><sup>2</sup>), 3.48 (s, 2H, H<sup>13</sup>), 3.10 (m, 4H, CH<sub>2</sub><sup>4</sup>, CH<sub>2</sub><sup>8</sup>), 2.40 (s, 6H, CH<sub>3</sub><sup>14</sup>), 2.31 (m, 4H, CH<sub>2</sub><sup>5</sup>, CH<sub>2</sub><sup>7</sup>). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>,  $\delta$ ): 155.0 (C<sup>1</sup>), 143.3 (C<sup>b</sup>), 139.2 (C<sup>c</sup>), 138.8 (C<sup>h</sup>), 136.0 (C<sup>a</sup>), 129.8 (C<sup>6</sup>H), 128.6 (C<sup>ph</sup>H), 128.3 (C<sup>ph</sup>H), 128.2 (C<sup>ph</sup>H), 127.1 (C<sup>f</sup>H), 124.0 (C<sup>h</sup>), 59.4 (C<sup>13</sup>H<sub>2</sub>), 54.3 (C<sup>5</sup>H<sub>2</sub>), 50.0 (C<sup>2</sup>H<sub>2</sub>), 44.2 (C<sup>4</sup>H<sub>2</sub>), 21.5 (C<sup>14</sup>H<sub>3</sub>).



$^{15}\text{N}$  NMR (40 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 312 ( $\text{N}^{12}$ ), 94 ( $\text{N-Ts}$ ), 32 ( $\text{N}^6$ ). MS (FAB):  $m/z$  (%) = 605 (80)  $[\text{MH}]^+$ , 449 (100)  $[\text{M} - \text{Ts}]^+$ . UV ( $5.2 \times 10^{-5}$  mol  $\text{L}^{-1}$ ,  $\text{CHCl}_3$  in 1-cm cuvettes)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 241 (4.19), 263 nm (3.93).

**General Procedure for the Synthesis of Silver Complexes 2a–c.** The silver salt and all silver-containing solutions were kept in the dark until the final isolation of the product. The ligand **1** was dissolved in 1,2-dichloroethane, the silver salt (weighed under a nitrogen atmosphere) was added, and the mixture was stirred for 1 h. The mixture was then filtered to remove any unreacted solid. The solvent was evaporated to dryness, *n*-hexane was added, and the product was recovered by filtration.

**2a: 1** (MW = 604.78; 0.5135 g; 0.849 mmol),  $\text{AgBF}_4$  (MW = 194.67; 0.1653 g; 0.849 mmol),  $\text{C}_2\text{H}_4\text{Cl}_2$  (42 mL), *n*-hexane (40 mL). Yield 0.66 g (MW = 799.46) 91%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.77 (t,  $J = 7.7$  Hz, 1H) overlapping with 7.74 (d,  $J = 8.0$  Hz, 4H), 7.60 (d,  $J = 6.9$  Hz, 2H), 7.45 (d,  $J = 8.0$  Hz, 4H) overlapping with 7.42 (m, 3H), 7.28 (d,  $J = 7.7$  Hz, 2H), 5.04 (d,  $J = 15.2$  Hz, 2H), 3.97 (s, 2H), 3.70 (d,  $J = 15.2$  Hz, 2H), 3.51 (m, 2H), 2.94 (m, 2H), 2.65 (m, 2H), 2.49 (s, 6H), 2.06 (m, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 153.4, 145.9, 140.5, 135.6, 130.9, 130.7, 130.6, 128.8, 128.6, 128.4, 125.0, 58.4, 56.3, 52.9, 47.5, 21.9.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): -152.8. MS (FAB):  $m/z$  (%) = 711  $m/z$  (100)  $[\text{M}^+ - \text{BF}_4]^-$ , 605 (94)  $[\text{MH} - \text{AgBF}_4]^+$ . UV ( $5.2 \times 10^{-5}$  mol  $\text{L}^{-1}$ ,  $\text{CHCl}_3$  in 1-cm cuvettes)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 243 (4.26), 263 nm (3.89).

**2b: 1** (MW = 604.78; 0.2088 g; 0.345 mmol),  $\text{AgOTf}$  (MW = 256.94; 0.0887 g; 0.345 mmol),  $\text{C}_2\text{H}_4\text{Cl}_2$  (17 mL), *n*-hexane (15 mL), Yield 0.22 g (MW = 861.72) 73%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.83 (t,  $J = 7.7$  Hz, 1H), 7.72 (d,  $J = 8.0$  Hz, 4H), 7.65 (d,  $J = 7.1$  Hz, 2H), 7.50 (m, 3H) overlapping with 7.45 (d,  $J = 8.0$  Hz, 4H), 7.33 (d,  $J = 7.7$  Hz, 2H), 5.01 (d,  $J = 14.9$  Hz, 2H), 3.89 (s, 2H) overlapping with 3.85 (m, 2H), 3.53 (m, 2H), 3.04 (m, 2H), 2.87 (m, 2H), 2.51 (s, 6H), 2.22 (m, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 153.7, 145.9, 140.5, 136.0, 130.9, 130.7, 130.6, 129.1, 128.7, 128.2, 125.0, 120.7 (q,  $\text{CF}_3$ ,  $J = 320.4$  Hz), 58.9, 56.4, 53.5, 47.7, 21.8.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): -78.7. MS (FAB):  $m/z$  (%) = 711  $m/z$  (100)  $[\text{M}^+ - \text{CF}_3\text{SO}_3]^-$ , 605 (90)  $[\text{MH} - \text{AgCF}_3\text{SO}_3]^+$ . UV ( $5.1 \times 10^{-5}$  mol  $\text{L}^{-1}$ ,  $\text{CHCl}_3$  in 1-cm cuvettes)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 242 (4.32), 263 nm (3.94).

**2c: 1** (MW = 604.78; 0.1812 g; 0.300 mmol),  $\text{AgNTf}_2$  (MW = 388.09; 0.1163 g; 0.300 mmol),  $\text{C}_2\text{H}_4\text{Cl}_2$  (13 mL), *n*-hexane (15 mL), Yield 0.17 g (MW = 992.80) 57%.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.84 (t,  $J = 7.7$  Hz, 1H), 7.73 (d,  $J = 8.0$  Hz, 4H), 7.65 (d,  $J = 7.1$  Hz, 2H), 7.48 (m, 3H) overlapping with 7.47 (d,  $J = 8.0$  Hz, 4H), 7.29 (d,  $J = 7.7$  Hz, 2H), 5.07 (d,  $J = 14.9$  Hz, 2H), 3.93 (s, 2H), 3.70 (m, 2H), 3.54 (m, 2H), 3.02 (m, 2H), 2.70 (m, 2H), 2.52 (s, 6H), 2.17 (m, 2H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 153.7, 146.3, 140.9, 136.2, 131.04, 130.97, 130.85, 129.4, 129.0, 128.5, 125.2, 120.1 (q,  $\text{CF}_3$ ,  $J = 321.9$  Hz), 58.9, 56.6, 53.4, 47.8, 22.1.  $^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): -78.9.

**General Procedure for the Synthesis of 2-Alkynylbenzaldehydes 3a–e.** The appropriate alkyne (3.89 mmol) and *trans*-dichlorobis-(triphenylphosphine)palladium(II) (2 mol %) were added to a solution of *o*-bromobenzaldehyde (600 mg, 3.24 mmol) in dry TEA (30 equiv), under a nitrogen atmosphere. The reaction was stirred at rt for 10 min, and then  $\text{CuI}$  (1 mol %) was added. The reaction mixture was stirred at 50 °C until no more starting product was detectable by TLC analysis (eluent: hexane/ethyl acetate). The solvent was then evaporated under reduced pressure and the crude material was purified by flash chromatography over a silica gel column. Alkynylbenzaldehydes **3a**,<sup>37</sup> **3b**,<sup>17d</sup> **3c**,<sup>17d</sup> **3d**,<sup>38</sup> and **3e**<sup>17d</sup> are known compounds. They were characterized by  $^1\text{H}$  NMR and spectral data were in agreement with literature values.

**Synthesis of 2-(4-Hydroxybut-1-ynyl)benzaldehyde 3f.**<sup>39</sup> But-3-yn-1-ol (0.5 g, 0.539 mL, 7.13 mmol) and *trans*-dichlorobis-(triphenylphosphine)palladium(II) (90.9 mg, 0.13 mmol) were added to a solution of *o*-bromobenzaldehyde (1.20 g, 6.48 mmol) and TEA (1.18 g, 1.62 mL, 11.67 mmol) in dry DMF (10 mL) under a nitrogen atmosphere. The reaction was stirred at rt for 10 min, and then  $\text{CuI}$  (24.7 mg, 0.13 mmol) was added. The reaction mixture was stirred at rt overnight, until no more starting product was detectable

by TLC analysis (eluent: hexane/ethyl acetate = 6:4). The reaction mixture was poured into water (200 mL) and was extracted with ethyl acetate (3  $\times$  50 mL). The organic layer was dried with  $\text{Na}_2\text{SO}_4$  and then evaporated to dryness under reduced pressure. The crude was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 8:2) yielding corresponding 2-(4-hydroxybut-1-ynyl)benzaldehyde (1.12 g, 99%) as a viscous yellow oil.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 10.44 (s, 1H, CHO), 7.86 (d,  $J = 7.7$  Hz, 1H,  $\text{H}_{\text{ar}}$ ), 7.54–7.39 (m, 3H,  $\text{H}_{\text{ar}}$ ), 3.87 (t,  $J = 6.2$  Hz, 2H,  $\text{CH}_2\text{-O}$ ), 2.76 (t,  $J = 6.2$  Hz, 2H,  $\text{C}_{\text{sp}}\text{-CH}_2$ ). Spectral data are in good agreement with literature values.

**General Procedure for the Synthesis of 1-Alkoxyisochromenes 4 a–l.** The catalyst **2a** (5 mol %) and the alcohol (1.05 equiv) were added to a stirred solution of the appropriate *o*-alkynylbenzaldehyde **3a–e** (60 mg) in dry toluene ( $[\text{3}] = 0.25$  M). The reaction mixture was stirred at 30 °C until no more starting product was detectable by TLC analysis (eluent: toluene/ethyl acetate = 100:1). The reaction mixture was diluted with sat. aq  $\text{NaHCO}_3$  (20 mL) and extracted with ethyl acetate (3  $\times$  10 mL). The organic layer was dried with  $\text{Na}_2\text{SO}_4$  and then evaporated to dryness under reduced pressure. Unless otherwise stated, after this workup the products **4** were sufficiently pure and did not require further purification.

**1-Methoxy-3-(4-methoxyphenyl)-1H-isochromene 4a.** Reaction time: 2 h. White solid. Yield: 99% (67 mg); mp 124–126 °C.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.76 (d,  $J = 8.8$  Hz, 2H,  $\text{H}_{\text{ar}}$ ), 7.40–7.16 (m, 4H,  $\text{H}_{\text{ar}}$ ), 6.94 (d,  $J = 8.8$  Hz, 2H,  $\text{H}_{\text{ar}}$ ), 6.49 (s, 1H,  $\text{C}_{\text{sp}^2}\text{-H}$ ), 6.13 (s, 1H,  $\text{C}_{\text{sp}^3}\text{-H}$ ), 3.85 (s, 3H,  $\text{OCH}_3$ ), 3.60 (s, 3H,  $\text{OCH}_3$ ).  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 160.4 ( $\text{C}_q$ ), 149.7 ( $\text{C}_q$ ), 130.8 ( $\text{C}_q$ ), 129.6 ( $\text{CH}_{\text{ar}}$ ), 127.4 ( $\text{C}_q$ ), 127.0 ( $\text{C}_q$ ), 126.6 ( $\text{CH}_{\text{ar}}$ ), 126.5 ( $\text{CH}_{\text{ar}}$ ), 126.0 ( $\text{CH}_{\text{ar}}$ ), 124.5 ( $\text{CH}_{\text{ar}}$ ), 114.1 ( $\text{CH}_{\text{ar}}$ ), 100.0 (C–H), 99.0 (C–H), 55.6 ( $\text{CH}_3$ ), 55.3 ( $\text{CH}_3$ ). MS ESI(+):  $m/z$  (%) = 291.0 (45)  $[\text{M} + \text{Na}]^+$ , 269.3 (4)  $[\text{M} + \text{H}]^+$ , 237.2 (100)  $[\text{M} - \text{OCH}_3]^+$ . HRMS ESI ( $\text{M} + \text{H}$ )<sup>+</sup> calcd for  $\text{C}_{17}\text{H}_{17}\text{O}_3$ , 269.1172; found, 269.1170.

**1-Methoxy-3-(*p*-tolyl)-1H-isochromene 4b.**<sup>12</sup> Reaction time: 24 h. White solid. Yield: 97% (67 mg); mp 100–102 °C.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.74 (d,  $J = 8.3$  Hz, 2H,  $\text{H}_{\text{ar}}$ ), 7.29–7.22 (m, 6H,  $\text{H}_{\text{ar}}$ ), 6.59 (s, 1H,  $\text{C}_{\text{sp}^2}\text{-H}$ ), 6.16 (s, 1H,  $\text{C}_{\text{sp}^3}\text{-H}$ ), 3.62 (s, 3H,  $\text{OCH}_3$ ), 2.41 (s, 1H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 149.9 ( $\text{C}_q$ ), 139.0 ( $\text{C}_q$ ), 132.0 ( $\text{C}_q$ ), 130.7 ( $\text{C}_q$ ), 129.7 ( $\text{CH}_{\text{ar}}$ ), 129.4 ( $\text{CH}_{\text{ar}}$ ), 127.2 ( $\text{C}_q$ ), 126.7 ( $\text{CH}_{\text{ar}}$ ), 126.0 ( $\text{CH}_{\text{ar}}$ ), 125.1 ( $\text{CH}_{\text{ar}}$ ), 124.6 ( $\text{CH}_{\text{ar}}$ ), 100.0 (C–H), 99.9 (C–H), 55.3 ( $\text{CH}_3$ ), 21.5 ( $\text{CH}_3$ ). MS ESI(+):  $m/z$  (%) = 253.1 (20)  $[\text{M} + \text{H}]^+$ , 221.2 (100)  $[\text{M}^+ - \text{OCH}_3]^+$ . Spectral data are in good agreement with literature values.

**3-(3-Fluorophenyl)-1-methoxy-1H-isochromene 4c.** Reaction time: 24 h. White solid. Yield: 98% (68 mg); mp 93–95 °C.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.59 (m, 1H,  $\text{H}_{\text{ar}}$ ), 7.51 (m, 1H,  $\text{H}_{\text{ar}}$ ), 7.42–7.15 (m, 5H,  $\text{H}_{\text{ar}}$ ), 7.04 (ddt,  $J = 8.3, 2.6, 0.9$  Hz, 1H,  $\text{H}_{\text{ar}}$ ), 6.62 (s, 1H,  $\text{C}_{\text{sp}^2}\text{-H}$ ), 6.15 (s, 1H,  $\text{C}_{\text{sp}^3}\text{-H}$ ), 3.61 (s, 3H,  $\text{OCH}_3$ ).  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 163.3 (d,  $^1J_{\text{C-F}} = 245$  Hz,  $\text{C}_q\text{-F}$ ), 148.4 (d,  $^4J_{\text{C-F}} = 3.0$  Hz,  $\text{C}_q$ ), 137.1 (d,  $^3J_{\text{C-F}} = 8.0$  Hz,  $\text{C}_q$ ), 130.2 (d,  $^3J_{\text{C-F}} = 8.4$  Hz,  $\text{CH}_{\text{ar}}$ ), 130.1 ( $\text{C}_q$ ), 129.8 ( $\text{CH}_{\text{ar}}$ ), 127.4 ( $\text{C}_q$ ), 127.3 ( $\text{CH}_{\text{ar}}$ ), 126.1 ( $\text{CH}_{\text{ar}}$ ), 125.0 ( $\text{CH}_{\text{ar}}$ ), 120.6 (d,  $^4J_{\text{C-F}} = 2.7$  Hz,  $\text{CH}_{\text{ar}}$ ), 115.7 (d,  $^2J_{\text{C-F}} = 21.4$  Hz), 112.0 (d,  $^2J_{\text{C-F}} = 23.4$  Hz), 101.6 (CH), 100.1 (CH), 55.5 ( $\text{CH}_3$ ). MS ESI(+):  $m/z$  (%) = 225.3 (30)  $[\text{M}^+ - \text{OCH}_3]^+$ . HRMS ESI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{14}\text{FO}_2$ , 257.0972; found, 257.0967.

**1-Methoxy-3-propyl-1H-isochromene 4d.**<sup>8</sup> Reaction time: 2 h. Yellow oil. Yield (simple workup): 98% (69 mg). Flash column chromatography: Celite plug/neutral alumina 50%/silica 50%. eluent: hexane/ $\text{CH}_2\text{Cl}_2$  = 8:2 + 5% TEA. Yield (after column): 76% (53 mg).  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 7.32–7.18 (m, 4H,  $\text{H}_{\text{ar}}$ ), 7.05 (d,  $J = 7.4$  Hz, 2H,  $\text{H}_{\text{ar}}$ ), 5.95 (s, 1H, C–H), 5.79 (s, 1H, C–H), 3.53 (s, 3H,  $\text{OCH}_3$ ), 2.29 (dt,  $J = 7.2, 4.4$  Hz, 2H,  $\text{CH}_2$ ), 1.67 (hex,  $J = 7.3$  Hz, 2H,  $\text{CH}_2$ ), 0.98 (t,  $J = 7.3$  Hz, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (50.3 MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 154.3 ( $\text{C}_q$ ), 130.6 ( $\text{C}_q$ ), 129.5 ( $\text{CH}_{\text{ar}}$ ), 126.5 ( $\text{C}_q$ ), 126.1 ( $\text{CH}_{\text{ar}}$ ), 126.0 ( $\text{CH}_{\text{ar}}$ ), 123.6 ( $\text{CH}_{\text{ar}}$ ), 100.5 (C–H), 99.9 (C–H), 55.2 ( $\text{CH}_3$ ), 36.2 ( $\text{CH}_2$ ), 20.6 ( $\text{CH}_2$ ), 13.8 ( $\text{CH}_3$ ). MS ESI(+):  $m/z$  (%) = 205.1 (32)  $[\text{M} + \text{H}]^+$ , 173.2 (78)  $[\text{M}^+ - \text{OCH}_3]^+$ . Spectral data are in good agreement with literature values.

**1-Isopropoxy-3-(4-methoxyphenyl)-1H-isochromene 4e.** Reaction time: 6 h. Yellow solid. Yield (simple workup): 99% (74 mg); mp 120–122 °C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.75 (d, *J* = 9.0 Hz, 2H, H<sub>ar</sub>), 7.38–7.17 (m, 4H, H<sub>ar</sub>), 6.94 (d, *J* = 9.0 Hz, 2H, H<sub>ar</sub>), 6.50 (s, 1H, C<sub>sp2</sub>-H), 6.30 (s, 1H, C<sub>sp3</sub>-H), 4.38 (hept, *J* = 6.2 Hz, 1H, CH *i*-Pr), 3.85 (s, 3H, OCH<sub>3</sub>), 1.32 (d, *J* = 6.2 Hz, 3H, CH<sub>3</sub> *i*-Pr), 1.19 (d, *J* = 6.2 Hz, 3H, CH<sub>3</sub> *i*-Pr). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>, δ): 160.3 (C<sub>q</sub>), 149.7 (C<sub>q</sub>), 130.9 (C<sub>q</sub>), 129.3 (CH<sub>ar</sub>), 127.7 (C<sub>q</sub>), 127.6 (C<sub>q</sub>), 126.5 (CH<sub>ar</sub>), 126.4 (CH<sub>ar</sub>), 125.7 (CH<sub>ar</sub>), 124.5 (CH<sub>ar</sub>), 114.1 (CH<sub>ar</sub>), 99.0 (C<sub>sp2</sub>-H), 97.2 (C<sub>sp3</sub>-H), 70.0 (CH *i*-Pr), 55.5 (CH<sub>3</sub>), 23.8 (CH<sub>3</sub>), 22.2 (CH<sub>3</sub>). MS ESI(+): *m/z* (%) = 319.1 (10) [M + Na]<sup>+</sup>, 297.2 (5) [M + H]<sup>+</sup>, 237.3 (100) [M - OCH(CH<sub>3</sub>)<sub>2</sub>]<sup>+</sup>. HRMS ESI (M + H)<sup>+</sup> calcd for C<sub>19</sub>H<sub>21</sub>O<sub>3</sub>, 297.1485; found, 297.1479.

**1-Isopropoxy-3-(*p*-tolyl)-1H-isochromene 4f.** Reaction time: 24 h. Yellow solid. Yield: 97% (77 mg); mp 76–78 °C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.69 (d, *J* = 8.3 Hz, 2H, H<sub>ar</sub>), 7.42–7.14 (m, 6H, H<sub>ar</sub>), 6.55 (s, 1H, C<sub>sp2</sub>-H), 6.29 (s, 1H, C<sub>sp3</sub>-H), 4.37 (hept, *J* = 6.1 Hz, 1H, CH *i*-Pr), 2.38 (s, 3H, CH<sub>3</sub>), 1.31 (d, *J* = 6.1, 3H, CH<sub>3</sub> *i*-Pr), 1.17 (d, *J* = 6.1 Hz, 3H, CH<sub>3</sub> *i*-Pr). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>, δ): 149.9 (C<sub>q</sub>), 138.8 (C<sub>q</sub>), 132.3 (C<sub>q</sub>), 130.8 (C<sub>q</sub>), 129.3 (CH<sub>ar</sub>), 127.8 (C<sub>q</sub>), 126.6 (CH<sub>ar</sub>), 125.7 (CH<sub>ar</sub>), 125.0 (CH<sub>ar</sub>), 124.6 (CH<sub>ar</sub>), 99.8 (C<sub>sp2</sub>-H), 97.2 (C<sub>sp3</sub>-H), 70.0 (CH *i*-Pr), 23.8 (CH<sub>3</sub>), 22.2 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), (one CH<sub>ar</sub> signal is obscured). MS ESI(+): *m/z* (%) = 303.1 (100) [M + Na]<sup>+</sup>, 221.2 (10) [M - OCH(CH<sub>3</sub>)<sub>2</sub>]<sup>+</sup>. HRMS ESI (M + H)<sup>+</sup> calcd for C<sub>19</sub>H<sub>21</sub>O<sub>2</sub>, 281.1536; found, 281.1531.

**3-(3-Fluorophenyl)-1-isopropoxy-1H-isochromene 4g.** Reaction time: 24 h. Yellow solid. Yield: 97% (77 mg); mp 73–75 °C. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.69–7.20 (m, 7H, H<sub>ar</sub>), 7.03 (td, *J* = 8.3, 2.3 Hz, 1H, H<sub>ar</sub>), 6.61 (s, 1H, C<sub>sp2</sub>-H), 6.30 (s, 1H, C<sub>sp3</sub>-H), 4.35 (hept, *J* = 6.1 Hz, 1H, CH *i*-Pr), 1.31 (d, *J* = 6.1 Hz, 3H, CH<sub>3</sub> *i*-Pr), 1.17 (d, *J* = 6.1 Hz, 3H, CH<sub>3</sub> *i*-Pr). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>, δ): 163.3 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245 Hz, C<sub>q</sub>), 148.5 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.9 Hz, C<sub>q</sub>), 137.4 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.9 Hz, C<sub>q</sub>), 130.2 (C<sub>q</sub>), 130.1 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.4 Hz, CH<sub>ar</sub>), 129.4 (CH<sub>ar</sub>), 128.0 (C<sub>q</sub>), 127.2 (CH<sub>ar</sub>), 125.8 (CH<sub>ar</sub>), 125.0 (CH<sub>ar</sub>), 120.6 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.9 Hz, CH<sub>ar</sub>), 115.6 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.4 Hz, CH<sub>ar</sub>), 111.9 (d, <sup>2</sup>*J*<sub>C-F</sub> = 23.4 Hz, CH<sub>ar</sub>), 101.6 (C<sub>sp2</sub>-H), 97.3 (C<sub>sp3</sub>-H), 70.3 (CH<sub>3</sub>), 23.8 (CH<sub>3</sub> *i*-Pr), 22.2 (CH<sub>3</sub> *i*-Pr). MS ESI(+): *m/z* (%) = 307.2 (65) [M + Na]<sup>+</sup>, 225.4 (42) [M - OCH(CH<sub>3</sub>)<sub>2</sub>]<sup>+</sup>. HRMS ESI (M + H)<sup>+</sup> calcd for C<sub>18</sub>H<sub>18</sub>FO<sub>2</sub>, 285.1285; found, 285.1291.

**1-Isopropoxy-3-propyl-1H-isochromene 4h.** Reaction time: 1 h. Yellow oil. Yield (simple workup): 89% (72 mg). Flash column chromatography: Celite plug/neutral alumina 50%/silica 50%. eluent: hexane/CH<sub>2</sub>Cl<sub>2</sub> = 8:2 + 5% TEA. Yield (after column): 62% (50 mg). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.30–7.14 (m, 3H, H<sub>ar</sub>), 7.03 (m, 1H, H<sub>ar</sub>), 6.11 (s, 1H, C-H), 5.77 (s, 1H, C-H), 4.24 (hept, *J* = 6.2 Hz, 1H, CH *i*-Pr), 2.25 (dt, *J* = 7.0, 3.0 Hz, 2H, CH<sub>2</sub>), 1.64 (hex, *J* = 7.4 Hz, 2H, CH<sub>2</sub>), 1.27 (d, *J* = 6.1 Hz, 3H, CH<sub>3</sub> *i*-Pr), 1.21 (d, *J* = 6.1 Hz, 3H, CH<sub>3</sub> *i*-Pr), 0.98 (t, *J* = 7.3 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>, δ): 154.2 (C<sub>q</sub>), 130.8 (C<sub>q</sub>), 129.1 (CH<sub>ar</sub>), 126.8 (C<sub>q</sub>), 126.0 (CH<sub>ar</sub>), 125.8 (CH<sub>ar</sub>), 123.7 (CH<sub>ar</sub>), 100.3 (C<sub>sp2</sub>-H), 96.9 (C<sub>sp3</sub>-H), 69.7 (CH *i*-Pr), 36.3 (CH<sub>2</sub>), 23.8 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 20.4 (CH<sub>2</sub>), 13.9 (CH<sub>3</sub>). MS ESI(+): *m/z* (%) = 255 (70) [M + Na]<sup>+</sup>, 173.3 (50) [M - OCH(CH<sub>3</sub>)<sub>2</sub>]<sup>+</sup>. Spectral data are in good agreement with literature values.

**1-(Cyclohexyloxy)-3-(4-methoxyphenyl)-1H-isochromene 4i.** Reaction time: 24 h. White solid; mp 57–59 °C. Yield (simple workup): 92% (79 mg). Flash column chromatography: Celite plug/neutral alumina 50%/silica 50%. eluent: hexane/CH<sub>2</sub>Cl<sub>2</sub> = 7:3 + 5% TEA. Yield (after column): 67% (57 mg). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.73 (d, *J* = 9.0 Hz, 1H, H<sub>ar</sub>), 7.37–7.16 (m, 4H, H<sub>ar</sub>), 6.94 (d, *J* = 9.0 Hz, 1H, H<sub>ar</sub>), 6.48 (s, 1H, C<sub>sp2</sub>-H), 6.33 (s, 1H, C<sub>sp3</sub>-H), 4.02 (m, 1H, H Cy), 3.85 (s, 3H, CH<sub>3</sub>), 2.10 (m, 1H, CH<sub>2</sub> Cy), 1.82–1.13 (m, 9H, CH<sub>2</sub>). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>, δ): 160.3 (C<sub>q</sub>), 149.8 (C<sub>q</sub>), 131.0 (C<sub>q</sub>), 129.2 (CH<sub>ar</sub>), 127.8 (C<sub>q</sub>), 127.7 (C<sub>q</sub>), 126.5 (CH<sub>ar</sub>), 126.4 (CH<sub>ar</sub>), 125.7 (CH<sub>ar</sub>), 124.4 (CH<sub>ar</sub>), 114.1 (CH<sub>ar</sub>), 99.0 (C<sub>sp2</sub>-H), 97.1 (C<sub>sp3</sub>-H), 76.0 (CH Cy), 55.5 (CH<sub>3</sub>), 33.9 (CH<sub>2</sub>), 32.3 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 24.6 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>). MS ESI(+): *m/z* (%) = 359.2 (70) [M + Na]<sup>+</sup>, 336.2 (15) [M + H]<sup>+</sup>, 237.2 (100) [M - OC<sub>6</sub>H<sub>11</sub>]<sup>+</sup>. HRMS ESI (M + H)<sup>+</sup> calcd for C<sub>22</sub>H<sub>25</sub>O<sub>3</sub>, 337.1798; found, 337.1795.

**1-(Cyclohexyloxy)-3-(*p*-tolyl)-1H-isochromene 4j.** Reaction time: 24 h. Yellow solid; mp 68–70 °C. Yield: 94% (83 mg). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.68 (d, *J* = 8.2 Hz, 2H, H<sub>ar</sub>), 7.32–7.17 (m, 6H, H<sub>ar</sub>), 6.55 (s, 1H, C<sub>sp2</sub>-H), 6.34 (s, 1H, C<sub>sp3</sub>-H), 4.02 (m, 1H, H Cy), 2.39 (m, 3H, CH<sub>3</sub>), 2.08 (m, 1H, CH<sub>2</sub> Cy), 1.81–1.13 (m, 9H, CH<sub>2</sub>). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>, δ): 150.0 (C<sub>q</sub>), 138.8 (C<sub>q</sub>), 132.4 (C<sub>q</sub>), 130.9 (C<sub>q</sub>), 129.3 (CH<sub>ar</sub>), 129.2 (CH<sub>ar</sub>), 127.9 (C<sub>q</sub>), 126.6 (CH<sub>ar</sub>), 125.8 (CH<sub>ar</sub>), 125.1 (CH<sub>ar</sub>), 124.6 (CH<sub>ar</sub>), 99.8 (C<sub>sp2</sub>-H), 97.1 (C<sub>sp3</sub>-H), 76.0 (CH Cy), 33.9 (CH<sub>2</sub>), 32.3 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 24.6 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>). MS ESI(+): *m/z* (%) = 343.5 (15) [M + Na]<sup>+</sup>, 221.4 (10) [M - OC<sub>6</sub>H<sub>11</sub>]<sup>+</sup>. Spectral data are in good agreement with literature values.

**1-(Cyclohexyloxy)-3-(3-fluorophenyl)-1H-isochromene 4k.** Reaction time: 48 h. Yellow oil. Yield: 96% (84 mg). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.65–7.20 (m, 7H, H<sub>ar</sub>), 7.05 (tdd, *J* = 8.3, 2.5, 0.9 Hz, 1H, H<sub>ar</sub>), 6.62 (s, 1H, C<sub>sp2</sub>-H), 6.36 (s, 1H, C<sub>sp3</sub>-H), 4.03 (m, 1H, H Cy), 2.11 (m, 1H, CH<sub>2</sub> Cy), 1.82–1.15 (m, 9H, CH<sub>2</sub> Cy). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>, δ): 163.3 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245 Hz, C<sub>q</sub>), 148.6 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.9 Hz, C<sub>q</sub>), 137.5 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.9 Hz, C<sub>q</sub>), 130.3 (C<sub>q</sub>), 130.1 (d, <sup>3</sup>*J*<sub>C-F</sub> = 8.3 Hz, CH<sub>ar</sub>), 129.4 (CH<sub>ar</sub>), 128.2 (C<sub>q</sub>), 127.2 (CH<sub>ar</sub>), 125.8 (CH<sub>ar</sub>), 124.9 (CH<sub>ar</sub>), 120.6 (d, <sup>4</sup>*J*<sub>C-F</sub> = 2.4 Hz, CH<sub>ar</sub>), 115.5 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.4 Hz, CH<sub>ar</sub>), 112.0 (d, <sup>2</sup>*J*<sub>C-F</sub> = 23.4 Hz, CH<sub>ar</sub>), 101.6 (C<sub>sp2</sub>-H), 97.2 (C<sub>sp3</sub>-H), 76.3 (CH Cy), 33.9 (CH<sub>2</sub>), 32.3 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 24.4 (CH<sub>2</sub>). MS ESI(+): *m/z* (%) = 347.3 (15) [M + Na]<sup>+</sup>, 363.3 (25) [M + K]<sup>+</sup>, 225.3 (85) [M - OC<sub>6</sub>H<sub>11</sub>]<sup>+</sup>. HRMS ESI (M + H)<sup>+</sup> calcd for C<sub>21</sub>H<sub>22</sub>FO<sub>2</sub>, 325.1598; found, 325.1602.

**1-(Cyclohexyloxy)-3-propyl-1H-isochromene 4l.** Reaction time: 2 h. Yellow oil. Yield: 94% (89 mg). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.30–7.13 (m, 3H, H<sub>ar</sub>), 7.02 (m, 1H, H<sub>ar</sub>), 6.16 (s, 1H, C-H), 5.76 (s, 1H, C-H), 3.89 (m, 1H, H Cy), 2.25 (dt, *J* = 7.0, 3.1 Hz, 2H), 2.07 (m, 1H, CH<sub>2</sub>), 1.95–1.48 (m, 6H, CH<sub>2</sub>), 1.40–1.15 (m, 5H, CH<sub>2</sub>), 0.98 (t, *J* = 7.3 Hz, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>, δ): 154.3 (C<sub>q</sub>), 130.8 (C<sub>q</sub>), 129.1 (CH<sub>ar</sub>), 127.2 (C<sub>q</sub>), 125.9 (CH<sub>ar</sub>), 125.9 (CH<sub>ar</sub>), 123.6 (CH<sub>ar</sub>), 100.3 (C<sub>sp2</sub>-H), 96.8 (C<sub>sp3</sub>-H), 75.8 (CH Cy), 36.4 (CH<sub>2</sub>), 34.0 (CH<sub>2</sub>), 32.2 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 24.6 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 20.4 (CH<sub>2</sub>), 13.9 (CH<sub>3</sub>). MS ESI(+): *m/z* (%) = 295.2 (100) [M + Na]<sup>+</sup>. HRMS ESI (M + H)<sup>+</sup> calcd for C<sub>18</sub>H<sub>25</sub>O<sub>2</sub>, 273.1849; found, 273.1854.

**Synthesis of 1-(Dimethoxymethyl)-2-((4-methoxyphenyl)ethynyl)-benzene 5a.** To a solution of **2a** (60 mg, 0.254 mmol) in dry MeOH (3 mL), *p*-TSA (4.4 mg, 0.026 mmol) and 60 mg of molecular sieves (3 Å) were added. The mixture was stirred at 30 °C, and the progress of the reaction was followed by TLC (eluent: toluene/ethyl acetate = 99:1). After 1.5 h, the yellow solution was poured into sat. aq NaHCO<sub>3</sub> (20 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and then evaporated to dryness under reduced pressure to give **5a** as a yellow oil (72 mg, quantitative). The crude was sufficiently pure and was used without further purification. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.65–7.60 (m, 1H, H<sub>ar</sub>), 7.56–7.48 (m, 3H, H<sub>ar</sub>), 7.40–7.26 (m, 2H, H<sub>ar</sub>), 6.89 (d, *J* = 8.9 Hz, 1H, H<sub>ar</sub>), 5.77 (s, 1H, C-H), 3.83 (s, 3H, CH<sub>3</sub>), 3.46 (s, 6H, CH<sub>3</sub>). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>, δ): 160.0 (C<sub>q</sub>), 139.7 (C<sub>q</sub>), 133.2 (CH<sub>ar</sub>), 132.4 (CH<sub>ar</sub>), 128.6 (CH<sub>ar</sub>), 128.2 (CH<sub>ar</sub>), 126.3 (CH<sub>ar</sub>), 122.8 (C<sub>q</sub>), 115.6 (C<sub>q</sub>), 114.3 (CH<sub>ar</sub>), 103.1 (C<sub>sp3</sub>-H), 94.2 (C<sub>sp</sub>), 85.9 (C<sub>sp</sub>), 55.5 (CH<sub>3</sub>), 54.6 (2 × CH<sub>3</sub>). HRMS ESI (M + H)<sup>+</sup> calcd for C<sub>18</sub>H<sub>19</sub>O<sub>3</sub>, 283.1329; found, 283.1331.

**Reaction of Acetal 5a with the Catalyst 2a.** Catalyst **2a** (4 mg, 0.0048 mmol) and distilled water (17 mg, 17 μL, 0.95 mmol) were added to a solution of dimethyl-acetal **5a** (27 mg, 0.095 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL). The pale yellow mixture was vigorously stirred at 30 °C for 72 h. The organic phase was separated by the water drop, dried with Na<sub>2</sub>SO<sub>4</sub>, and then evaporated to dryness under reduced pressure. The <sup>1</sup>H NMR analysis of the reaction crude displayed the presence of a mixture of isochromene **4a**, aldehyde **3a**, and unreacted starting material **5a** in a 20:20:60 ratio.

**Stability Experiments of Isochromene 4a. Under Acidic Conditions.** Isochromene **4a** (80 mg, 0.298 mmol) was dissolved in ethyl acetate (1.20 mL) and *p*-toluenesulfonic acid (11.3 mg, 0.06 mmol) was added. The yellow solution was stirred at rt and the

progress of the reaction was followed by TLC (eluent: toluene/ethyl acetate = 99:1). After 2 h, the starting material had almost completely disappeared on TLC (one main new spot with lower retention factor (rf) became visible) and the solution turned orange. After 24 h, the mixture was poured into water (30 mL) and was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and then evaporated to dryness under reduced pressure to give an orange oil. The crude was roughly purified by filtration on a silica gel-plug (eluent: hexane/ethyl acetate = 1:1) to give a yellow oil (60 mg) which was analyzed by <sup>1</sup>H NMR spectroscopy.

**Under Alkaline Conditions.** Isochromene **4a** (80 mg, 0.298 mmol) was dissolved in ethyl acetate (1.20 mL) and triethylamine (6.03 mg, 8.3 μL, 0.06 mmol) was added. The pale yellow cloudy solution was stirred at rt and the progress of the reaction was followed by TLC (eluent: toluene/ethyl acetate = 99:1). After 84 h, the TLC analysis showed the starting material practically unmodified. The mixture was poured into water (30 mL) and was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and then evaporated to dryness under reduced pressure to give a white solid (77 mg). The <sup>1</sup>H NMR analysis confirmed that the product was **4a**, unmodified.

**Trapping Experiment: Synthesis of Isochromene **4m**.**<sup>35</sup> The catalyst **2b** (16.6 mg, 0.172 mmol) was added to a stirred solution of 2-(4-hydroxybut-1-ynyl)benzaldehyde **3f** (60 mg, 0.344 mmol) in dry toluene (1.4 mL). The reaction mixture was stirred at 30 °C for 4.5 h, until no more starting product was detectable by TLC analysis (eluent: hexane/ethyl acetate = 7:3). The reaction mixture was diluted with sat. aq NaHCO<sub>3</sub> (20 mL) and was extracted with ethyl acetate (3 × 10 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and then evaporated to dryness under reduced pressure. The crude was purified by flash column chromatography on a short silica gel column (eluent: hexane/ethyl acetate = 100:1, + 3% triethylamine) to give corresponding isochromene **4m** (30 mg, 50% yield) as a white solid. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>, δ): 7.31–7.17 (m, 3H, H<sub>ar</sub>), 6.97 (d, J = 7.2 Hz, 1H, H<sub>ar</sub>), 6.00 (s, 1H, C–H), 5.77 (s, 1H, C–H), 4.62 (ddd, J = 10.4, 8.7, 4.3 Hz, 1H, CH<sub>2</sub>), 3.75 (dt, J = 8.7, 3.3 Hz, 1H, CH<sub>2</sub>), 2.53 (m, 2H, CH<sub>2</sub>). Spectral data are in good agreement with literature values.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Copies of <sup>1</sup>H and <sup>13</sup>C NMR, spectra of 1,7-ditosyl-4-benzyl-1,4,7-triazahexane, ligand **1**, Ag complexes **2a–c**, isochromenes **4a–l**, and acetal **5a**. <sup>1</sup>H NMR spectra of aldehydes **3a–f** and isochromene **4m**. HOESY spectrum for complex **2a**. Superimposed UV spectra of ligand **1** and Ag complexes **2a** and **2b**. <sup>1</sup>H NMR spectrum of reaction crude of **3a** in methanol. <sup>1</sup>H NMR spectra of stability experiments on **4a** and reactivity of **5a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Authors

\*E-mail: [giorgio.abbiati@unimi.it](mailto:giorgio.abbiati@unimi.it).

\*E-mail: [alessandro.caselli@unimi.it](mailto:alessandro.caselli@unimi.it).

### Notes

The authors declare no competing financial interest.

## ■ REFERENCES

- (1) Attardo, G.; Wang, W.; Breining, T.; Li, T.; St-Denis, Y.; Kraus, J.-L. *Int. Patent* WO 9 512 588, 1995.
- (2) Wang, W.; Li, T.; Milburn, R.; Yates, J.; Hinnant, E.; Luzzio, M. J.; Noble, S. A.; Attardo, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1579–1584.
- (3) Ankisetty, S.; Amsler, C. D.; Clintock, J. B.; Baker, B. J. *J. Nat. Prod.* **2004**, *67*, 1172–1174.
- (4) General reviews: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**,

*104*, 2285–2310. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3160.

(5) Much work in this field has been done by the group of research of Belmont. For a discussion on regioselectivity issues see: (a) Godet, T.; Vaxelaire, C.; Michel, C.; Milet, A.; Belmont, P. *Chem.—Eur. J.* **2007**, *13*, 5632–5641. (b) Dell'Acqua, M.; Facoetti, D.; Abbiati, G.; Rossi, E. *Synthesis* **2010**, 2367–2378 and references cited therein.

(6) (a) Godet, T.; Bosson, J.; Belmont, P. *Synlett* **2005**, 2786–2790. (b) Cikotiene, I.; Morkunas, M.; Motiejaitis, D.; Brukstus, A. *Synlett* **2008**, 1693–1967. (c) Kanazawa, C.; Ito, A.; Terada, M. *Synlett* **2009**, 638–642.

(7) (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765. (b) Mondal, S.; Nogami, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 9496–9498.

(8) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139–5142.

(9) (a) Rudys, S.; Cikotiene, I.; Rios-Luci, C.; Perez-Roth, E.; Padron, J. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1504–1506. (b) Cikotiene, I.; Buksnaitiene, R.; Rudys, S.; Morkunas, M.; Motiejaitis, D. *Tetrahedron* **2010**, *66*, 251–258.

(10) Enomoto, T.; Girard, A.-L.; Takemoto, Y.; Yasui, Y. *J. Org. Chem.* **2009**, *74*, 9158–9164.

(11) Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462–4468.

(12) Handa, S.; Slaughter, L. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 2912–2915.

(13) (a) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028–9029. (b) Barluenga, J.; Vázquez-Villa, H.; Merino, I.; Ballesteros, A.; González, J. M. *Chem.—Eur. J.* **2006**, *12*, 5790–5805.

(14) (a) Yue, D.; Cà, N. D.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3381–3388. (b) Yue, D.; Cà, N. D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581–1584.

(15) For reviews on domino reactions, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (b) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (c) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354–366. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (e) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131–163.

(16) For reviews on domino approaches to heterocycles, see: (a) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341–5378. (b) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967–1983. (c) Padwa, A. *Pure Appl. Chem.* **2003**, *75*, 47–62.

(17) For some recent examples see: (a) Abbiati, G.; Arcadi, A.; Chiarini, M.; Marinelli, F.; Pietropaolo, E.; Rossi, E. *Org. Biomol. Chem.* **2012**, 7801–7808. (b) Dell'Acqua, M.; Abbiati, G.; Arcadi, A.; Rossi, E. *Org. Biomol. Chem.* **2011**, 7836–7848. (c) Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. *Synlett* **2010**, 2672–2676. (d) Alfonsi, M.; Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2009**, 2852–2862. (e) Facoetti, D.; Abbiati, G.; d'Avolio, L.; Ackermann, L.; Rossi, E. *Synlett* **2009**, 2273–2276. (f) Facoetti, D.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2009**, 2872–2882.

(18) Dell'Acqua, M.; Facoetti, D.; Abbiati, G.; Rossi, E. *Tetrahedron* **2011**, *67*, 1552–1556.

(19) Stetter, H.; Frank, W.; Mertens, R. *Tetrahedron* **1981**, *37*, 767–772.

(20) (a) Aime, S.; Botta, M.; Crich, S. G.; Giovenzana, G. B.; Jommi, G.; Pagliarin, R.; Sisti, M. *Inorg. Chem.* **1997**, *36*, 2992–3000. (b) Aime, S.; Gianolio, E.; Corpillo, D.; Cavallotti, C.; Palmisano, G.; Sisti, M.; Giovenzana, G. B.; Pagliarin, R. *Helv. Chim. Acta* **2003**, *86*, 615–632.

(21) (a) Caselli, A.; Cesana, F.; Gallo, E.; Casati, N.; Macchi, P.; Sisti, M.; Celentano, G.; Cenini, S. *Dalton Trans.* **2008**, 4202–4205. (b) Castano, B.; Guidone, S.; Gallo, E.; Ragaini, F.; Casati, N.; Macchi, P.; Sisti, M.; Caselli, A. *Dalton Trans.* **2013**, *42*, 2451–2562. (c) Castano, B.; Zardi, P.; Honemann, Y. C.; Galarneau, A.; Gallo, E.; Psaro, R.; Caselli, A.; Dal Santo, V. *RSC Adv.* **2013**, *3*, 22199–22205.

(22) Castano, B.; Pedrazzini, T.; Sisti, M.; Gallo, E.; Ragaini, F.; Casati, N.; Caselli, A. *Appl. Organomet. Chem.* **2011**, *25*, 824–829.

(23) The identities of isochromene **4a** and dimethyl acetal **5a** were confirmed by comparison with isolated products, see the text.

(24) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2003.

(25) Díaz-Torres, R.; Alvarez, S. *Dalton Trans.* **2011**, *40*, 10742–10750.

(26) Antoniotti, S.; Dalla, V.; Duñach, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7860–7888.

(27) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467–4469. For a recent review see: (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.

(28) The spectrum was compared with the spectrum of pure 2-(2-(4-methoxyphenyl)-2-oxoethyl) benzaldehyde reported in the literature: Zhu, S.; Liang, R.; Jiang, H.; Wu, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10861–10865.

(29) A similar behaviour was observed by Belmont and co-workers on related substrates, see ref 6a.

(30) Belmont, P. In *Silver in Organic Chemistry*; Harmata, M., Ed.; John Wiley and Sons, Inc.: Hoboken, NJ, 2010; pp 143–165.

(31) For a recent review on  $\sigma$ - and  $\pi$ -electrophilic Lewis acids see: Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817–7831.

(32) Related isochromenilium TfO<sup>-</sup> salts have been isolated and characterized, see: Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, *64*, 6499–6504.

(33) To the best of our knowledge, the most similar oxa-cycloalkyne reported in the literature is the oxa-dibenzocyclooctyne prepared by photochemical decarbonylation of corresponding cyclopropenones: McNitt, C. D.; Popik, V. V. *Org. Biomol. Chem.* **2012**, *10*, 8200–8202.

(34) Yu, X.; Ding, Q.; Wang, W.; Wu, J. *Tetrahedron Lett.* **2008**, *49*, 4390–4393.

(35) Liu, L.-P.; Hammond, G. B. *Org. Lett.* **2010**, *12*, 4640–4643.

(36) Meth-Cohn, O.; Jiang, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3737–3742.

(37) (a) Zhu, S.; Zhang, Z.; Huang, X.; Jiang, H.; Guo, Z. *Chem.—Eur. J.* **2013**, *19*, 4695–4700. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437–3444.

(38) Castedo, L.; Guitian, E.; Pena, D.; Perez, D. *Eur. J. Org. Chem.* **2003**, 1238–1243.

(39) Reddy, B. V. S.; Jalal, S.; Borkar, P.; Yadav, J. S.; Reddy, P. G.; Sarma, A. V. S. *Tetrahedron Lett.* **2013**, *54*, 1519–1523.

#### NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on March 31, 2014. The paper was corrected for chemical abbreviations in Scheme 2 and a nomenclature error in the text. The corrected version was reposted on April 3, 2014.