[Ag(PcL)]-Catalyzed Domino Reactions of 2-Alkynylbenzaldehydes with Electron-poor Anilines: Synthesis of 1-Aminoisochromenes

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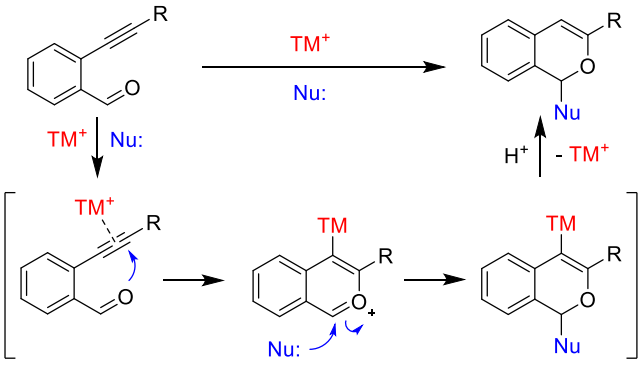
Abstract

In this paper, we describe the synthesis of neglected 1-aminoisochromene derivatives starting from 2-alkynylbenzaldehydes and electron-poor anilines. The domino reaction is catalyzed by original [Ag(I)PcL] complexes and occurs with complete regioselectivity under mild conditions. The approach well-tolerates different aryl, heteroaryl, alkyl and cycloalkyl substituents on alkyne terminus to give the desired products in modest to very good yields.

Introduction

Isochromene[1] is a bicyclic oxygen-containing heterocyclic motif that characterizes some interesting synthetic bioactive molecule[2] and natural products.[3] Isochromene ring can be synthesized by a regioselective 6-*endo-dig* domino addition/cycloisomerization reaction of 2-alkynylbenzaldehyde derivatives in the presence of a nucleophilic partner. These regioselective reactions can be sometimes promoted by the presence of an electrophilic partner[4] or, in most cases, catalyzed by a transition metal,[5] mainly palladium,[6] copper,[7] gold,[8] and silver,[9] able to activate the triple bond to nucleophilic

attack. To justify the high degree of regioselectivity (*6-endo*-dig vs *5-exo*-dig), a mechanism that involves the preliminary metal promoted formation of an isochromenylium ion[10] stabilized by resonance that undergoes the subsequent addition from a suitable nucleophile, has been frequently proposed[11] (Scheme 1).

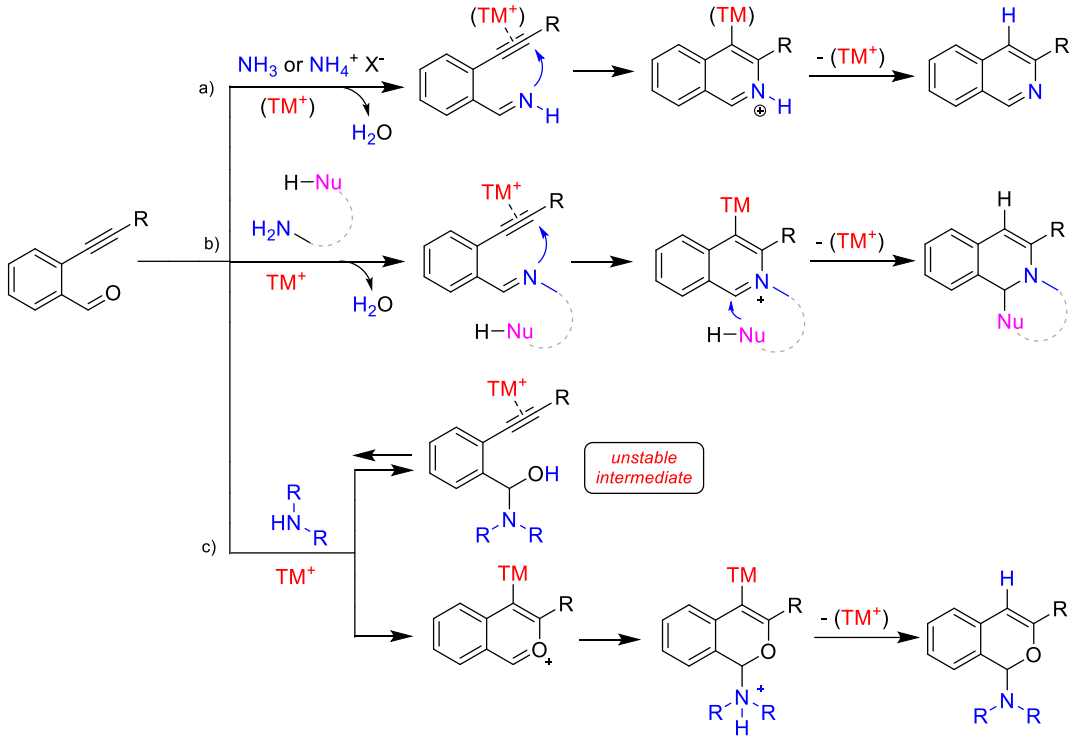


Scheme 1: Most acknowledged mechanism for cycloisomerization/addition reaction of 2-alkynylbenzaldehydes under TM catalysis in the presence of nucleophiles.

Among the nucleophiles suitable for these approaches to 1-substituted-isochromenes, oxygen,[12] and carbon[13] nucleophiles are the most studied. Conversely, the reaction in the presence of nitrogen nucleophiles gives generally different cyclization products.[14] Ammonia (as free base[15] or generated in situ starting from suitable reagents[16]) reacts very quickly with the aldehyde group to give the corresponding imine intermediate; the subsequent cyclization gives an isoquinoline. The reactions with ammonia are usually performed without the presence of a transition metal catalyst,[15] whereas when ammonia is generated in situ a silver catalyst can be necessary[16] (Scheme 2, a). When primary amines are used, an additional (pro)nucleophile[17] (also tethered to amino group[18]) is necessary to obtain dihydroisoquinoline as neutral final product (Scheme 2, b). In these cases, the formation of (dihydro)isoquinoline derivatives is related to the strong nucleophilicity of primary amine nitrogen and its tendency to quickly give an addition/elimination reaction to yield an imine intermediate able to undergo nucleophilic addition to the – eventually activated - triple bond. Therefore, under these conditions, the imination reaction is usually faster than the formation of the isochromenylium ion.

On the other hand, the reaction with secondary amines as nucleophiles is very scarcely explored. That is most probably related to the fast reaction of secondary amines with the aldehyde group, which is unable to eliminate so yielding highly unstable hemiaminal intermediates (Scheme 2, c). The only examples of this kind of reaction have been recently reported by Slaughter and co-workers within a study on gold-catalyzed aminative homodimerization of 2-alkynylbenzaldehydes.[19] The authors were able to isolate for the very first time a couple of 2-aminoisochromene derivatives in moderate yields,

but only when the reactions were performed in poorly polar THF as the solvent and by using hindered secondary amines.[19]



Scheme 2: Possible paths with different amine nucleophiles.

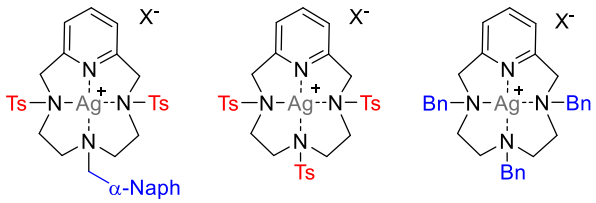
Based on these premises and in connection with our ongoing interest in the cascade synthesis of new isochromene derivatives through silver catalysis,[20] we are pleased to report here the first example of effective [Ag(I)(PcL)][21] catalyzed domino approach to 1-aminoisochromenes starting from 2-alkynylbenzaldehydes and electron-poor anilines.

Results and discussion

The reaction between 2-(*p*-tolylethynyl)benzaldehyde **1a** and 2-aminoacetophenone **2a** was selected as a model reaction to explore the possibility to obtain the desired 1-aminoisochromene derivative and find the best reaction conditions. 2-Aminoacetophenone **2a** was chosen as model aniline compound because we argued that the presence of the electron-withdrawing acetyl group in the *ortho* position to the amino group would reduce the nucleophilicity of the nitrogen atom from both electronic and steric standpoints. This would slow down the possible formation an imine intermediate and favor the formation of the reactive isochromenylium, key intermediate for the formation of the desired product. Homogeneous silver-catalyzed organic transformations highlight the unique properties of silver, capable of catalyzing reactions with high stereo- and/or regioselectivities. We

recently discovered that the synthesis of 1-alkoxyisochromenes starting from 2-alkynylbenzaldehydes and alcohol was efficiently catalyzed by new silver complexes characterized by the presence of a macrocyclic pyridine-containing ligand.[20a] Compared with simple silver salts, the advantage of [Ag(PcL)] complexes rely on the increased solubility, the enhanced stability and the easiness of handling. Thus, besides the activity of simple silver salts we evaluate the activity of some [Ag(PcL)] complexes characterized by different electronic and steric properties (Figure 1).

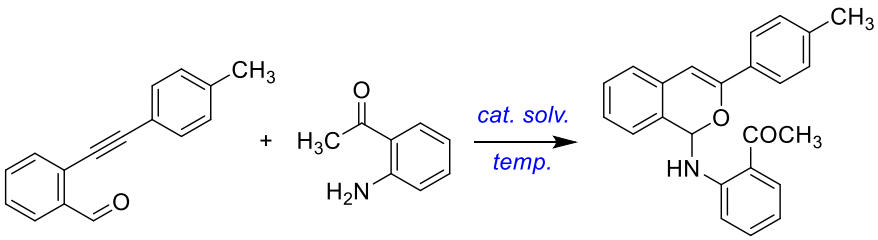
Figure 1: [Ag(PcL)] complexes involved in the preliminary study.



[Ag(PcL$_1$)] **[Ag(PcL$_2$)]** **[Ag(PcL$_3$)]**

The results of this preliminary screening are reported in the following table 1.

Table 1. Optimization of the reaction conditions.



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

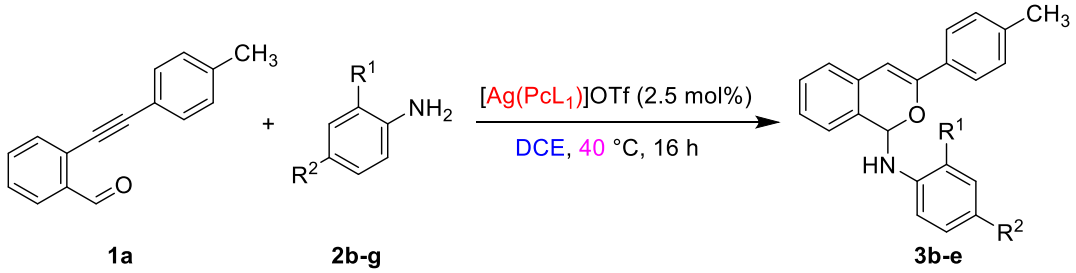
Entry	Eq. of 2a	Catalyst (mol%)	Solvent	T (°C)	t (h)	3a (yield%)[a]
1	3	AgOTf (10)	DCE	80	1	53[b]
2	1.5	AgOTf (10)	DCE	80	16	dec.
3	1.05	$AgBF_4$ (10)	DCE	40	6	55[c]
4	1.05	$AgNTf_2$ (10)	DCE	40	2	52[c]
5	1.05	[Ag(PcL$_1$)]BF_4 (5)	DCE	40	16	75[c]
6	1.05	[Ag(PcL$_1$)]NTf_2 (5)	DCE	40	16	65
7	1.05	[Ag(PcL$_1$)]OTf (5)	DCE	40	16	87 [c]
8	1.05	[Ag(PcL$_1$)]OTf (5)	Toluene	40	16	80[c]
9	1.05	[Ag(PcL$_1$)]OTf (5)	THF	40	16	82[c]
10	1.05	[Ag(PcL$_1$)]OTf (5)	DMF	40	16	7[c]
11	1.05	[Ag(PcL$_2$)]BF_4 (5)	DCE	40	16	50[c]
12	1.05	[Ag(PcL$_3$)]BF_4 (5)	DCE	40	16	n.r.
13	1.05	[Ag(PcL$_1$)]OTf (2.5)	DCE	40	16	90[d]

[a] Yields of pure isolated product. [b] Purified by flash-column chromatography on silica gel. [c] Purified by column chromatography on neutral alumina. [d] Purified by trituration/sonication with isopropyl ether.

The first attempt with an excess of **2a** in DCE in the presence of 10 mol% of silver triflate at 80 °C gave a promising result, and the desired 1-aminoisochromene **3a** was obtained in 53% yield in one hour (Table 1, entry 1). A reduction of ratio **2a**:**1a** together with an increase of reaction time untill complete consumption of the starting material resulted in the decomposition of the final product (Table 1, entry 2). We reduced the amount of **2a** and the reaction temperature and tested some other silver based catalysts with different counterions and/or ligands (Table 1, entries 3-7). We obtained the best result by using [Ag(PcL$_1$)]OTf as the catalyst at 40 °C in DCE (Table 1, entry 7). Toluene and THF as reaction solvents gave similar results (Table 1, entries 8 and 9), whereas in DMF the reaction failed (Table 1, entry 10). Finally we tried the electron-poor [Ag(PcL$_2$)]$^+$ complex obtaining moderate yields of the desired product **3a** (Table 1, entry 11), while in the presence of electron-rich complex [Ag(PcL$_3$)] the reaction failed (Table 1, entry 12). Finally, we observed that the amount of catalyst could be further reduced to 2.5 mol% with a little improvement in yields (Table1, entry 13), thus, scope and limitation of the approach has been explored with this catalyst loading. During this screening, we experienced the poor stability of **3a**, in particular under acidic conditions, and the difficulty to isolate the product by standard flash column chromatography over silica gel.

With the optimized reaction conditions in hand, we evaluated the importance of electronic *versus* steric effects in the modulation of the nucleophilic power of the aniline partner. Thus, we made the following experiments with differently substituted anilines (Table 2).

Table 2. Evaluation of electronic *versus* steric effects on aniline partner.



1a **2b-g** **3b-e**

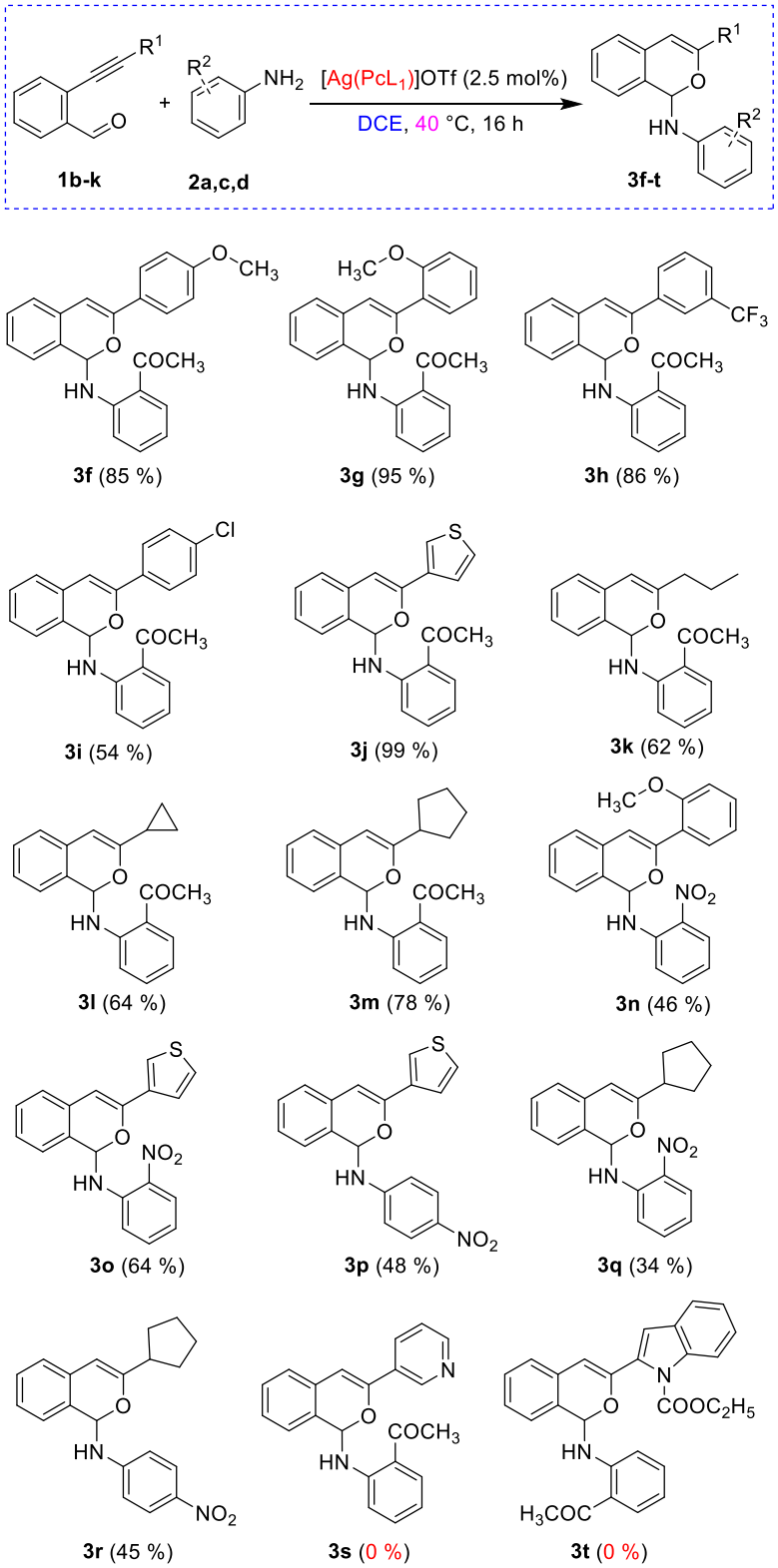
Entry	2	R^1	R^2	3	Yield (%)[a]
1	**b**	-H	-COCH$_3$	**b**	40[b]
2	**c**	-H	-NO$_2$	**c**	75[b]
3	**d**	-NO$_2$	-H	**d**	56[c]
4	**e**	-F	-H	**e**	81[c]
5	**f**	-CH$_3$	-H	-	-[d]
6	**g**	-H	-CH$_3$	-	-[d]

[a] Yields of pure isolated product. [b] Purified by trituration/sonication with isopropyl ether. [c] Purified by column chromatography on neutral alumina. [d] A mixture of unreacted starting materials with a number of by products have been obtained.

The results demonstrated that the electronic features of the aniline reaction partner are fundamental for the formation of the 1-aminoisochromene products **3**. In fact the reaction gave the 1-aminoisochromene also when electron-withdrawing groups, such as the acetyl and nitro group are in *para* position (Table 2, entries 1 and 2). Nitro and fluorine group are well tolerated also in *ortho* position, furnishing the corresponding 1-aminoisochromenes in good yields (Table 2, entries 3 and 4). The importance of electronic aspects was definitively demonstrated by the complete failure of the reactions with *ortho*- and *para*-toluidines (Table 2, entries 5 and 6). In these reactions, the tlc analysis and the ^{1}H NMR spectra of the crudes revealed only the presence of a complex mixture of the starting materials and unidentified by-products (see also Figure 2, below).

To complete the study, the effect of the substitution on the alkyne terminus of 2-alkynylbenzaldehydes **1** has been evaluated. The reactions were performed under the best reaction conditions. The structures of the new compounds have been determined by ^{1}H and ^{13}C NMR spectroscopies, and MS spectrometry. Yields are referred to pure isolated products, although in some cases the purification was troublesome and probably caused partial product loss due to degradation. The results, as illustrated in Scheme 3, demonstrated that the approach is quite versatile. Electron-rich (**3f,g,n**) and electron-poor (**3h,i**) aryl groups on the alkyne are both well tolerated. Also alkyl-alkynes gave the desired product in modest to excellent yields (**3k,l,m,q,r**). Heterocyclic substituents on the alkyne gave good results only when they are electron-rich (**3,j,o,p**), whereas with electron-poor heterocycles the reaction failed (**3s,t**). In general, solid products that can be purified by trituration in diisopropyl ether gave better yields than oily products that required a chromatographic purification.

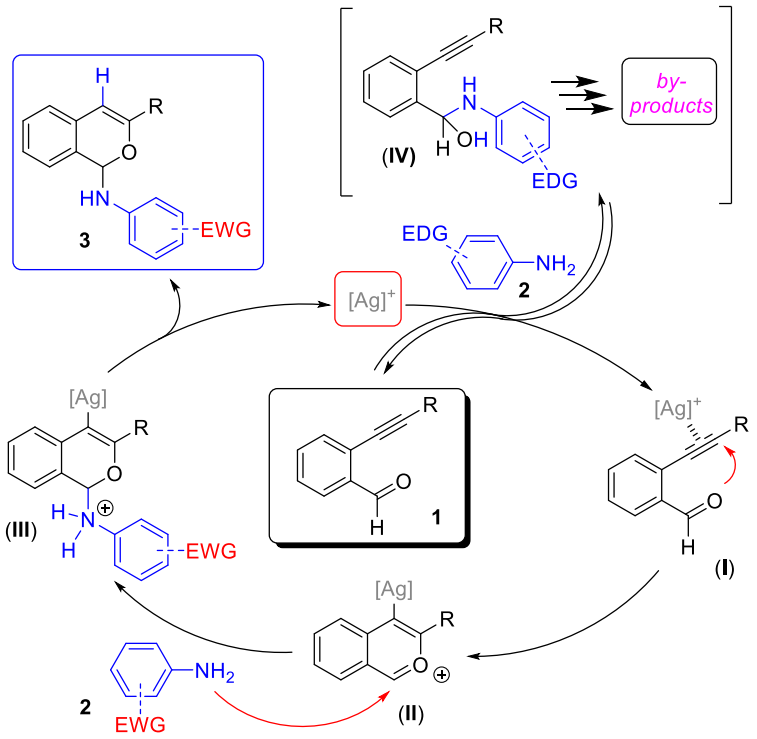
With the aim to explain the difficulties encountered in the purification of the 1-aminoisochromenes, we tested the stability of **3a**, as model compound, as follows: 10 mg of the product were dissolved in i) 0.5 mL of toluene, ii) 0.5 mL of toluene with 5 mol% of TEA, iii) 0.5 mL of toluene with 5 mol% of *p*-TSA, iv) 0.5 mL of dichloromethane, 0.5 mL of methanol. The behavior was followed by visual analysis of the solutions and time-lapse thin layer chromatography. The TLC analyses demonstrated that the product rapidly decomposes in different spots under acidic conditions, with complete disappearance of the spot due to **3a** in less than 24h. During this period, the colorless solution became first pale yellow, then dark yellow and finally brown. Conversely, the 1-aminoisochromene **3a** was stable under basic conditions and in toluene, whereas in dichloromethane a slow degradation was observed over 48 h. Finally, **3a** was almost completely insoluble in methanol.



Scheme 3. Evaluation of the scope and limitations of the approach.

As stated above, the mechanism proposed for this domino silver-catalysed synthesis of 1-substituted isochromenes **3** involves the formation of a isochromenylium intermediate (**II**) (metal ate complex) stabilized by resonance, resulting from the intramolecular nucleophilic attack of the aldehyde oxygen

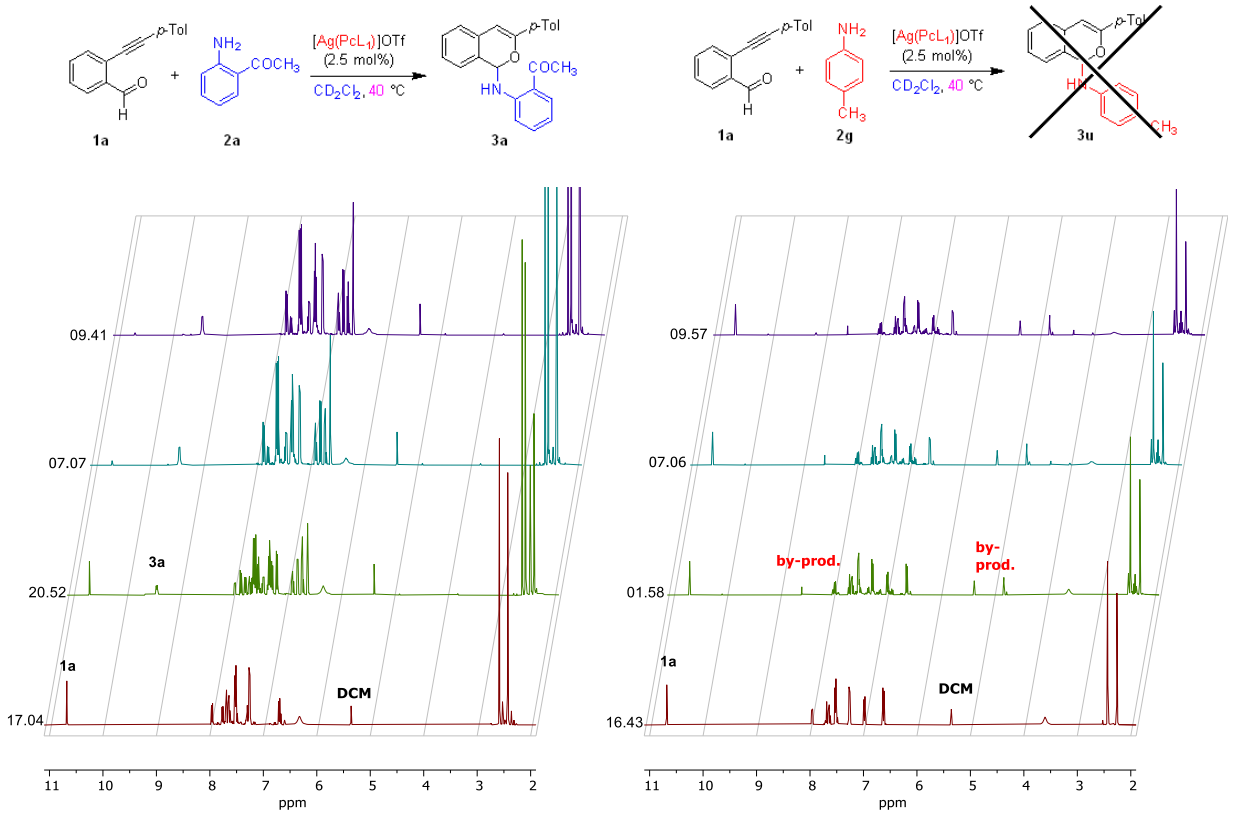
to the metal activated triple bond (**I**) (Scheme 4).[11] Then, the electron-poor aniline (**2**) attacks the activate isochromenylium intermediate to give the intermediate (**III**) and the subsequent fast protodemetallation yields the desired product **3** and renew the silver catalyst. Conversely, when a more nucleophilic electron-rich aniline is used, the direct nucleophilic addition of aniline to the carbonyl group is the quickest reaction and the formation of labile by-products hamper the process.



Scheme 4. Proposed mechanism.

This hypothesis is supported by kinetic ^{1}H NMR experiments (Figure 2). The reaction of alkynylbenzaldehyde **1a** and electron-poor aniline **2a** has been performed in a screw-capped NMR tube in CD_2Cl_2 at 40 °C in the presence of 5 mol% of [Ag(PcL1)]OTf. The reaction was followed by ^{1}H NMR for 16 hours by acquiring one spectrum each hour. The same experiment was performed with **1a** and the electron-rich aniline **2g**. Representative spectra are reported in figure 2. In the spectra of the reaction of **1a** with **2a** we can observe the regular formation of 1-aminoisochromene **3a** that is almost complete in 16 h. Conversely, in the reaction of **1a** with **2g**, the signals of the corresponding 1-aminoisochromene are not recognizable, and we can detect only some peaks ascribable to unidentified intermediates/by-products (Figure 2).

Figure 2: Kinetic ^{1}H NMR experiments.



Conclusions

In this paper, we have reported the unprecedented domino synthesis of 1-aminoisochromenes starting from 2-alkynylbenzaldehydes and electron-poor anilines. The approach well-tolerates the presence of different aryl, heteroaryl, alkyl and cycloalkyl substituents on the alkyne and always requires, as reaction partner, an electron-poor aniline, i.e. an aniline with a mild nucleophilic power. The reaction conditions are mild and the products were obtained in modest to very good yields (up to 99% of pure isolated product). We found the best catalyst for this transformation among the original series of silver pyridine-containing macrocyclic complexes (Ag[PcL]), already used in other selective synthesis of 1-substituted isochromenes studied in our research group. Despite 1-aminoisochromenes, as cyclic hemiaminals, are quite touchy compounds and their purification can be in some cases tricky, they are stable under neutral or basic condition and can be successfully isolated and characterized. A rationale for the mechanism involved has been presented and supported by ad-hoc NMR experiments.

Experimental

General experimental details

All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under a nitrogen atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Syringes, used to transfer reagents and solvents, were previously set under nitrogen atmosphere. All chemicals and solvents are commercially available and were used without further purification. The chromatographic column separations were performed by flash technique, using silica gel (pore size 60Å, particle size 230-400 mesh, Merck Grade 9385). For thin-layer chromatography (TLC), Silica on TLC Alu foils with fluorescent indicator (254 nm) was employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 366 nm). ^{1}H NMR analyses were performed with 300 MHz or 400 MHz spectrometers at room temperature. The coupling constants (*J*) are expressed in Hertz (Hz), the chemical shifts (δ) in ppm. The multiplicity of the proton spectra were described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), dt (double triplet), dd (double doublet), m (multiplet), br (broad). ^{13}C NMR analysis were performed with the same instruments at 74.45 MHz or 100 MHz; APT sequence was used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. All ^{13}C NMR spectra were recorded with complete proton decoupling.

Low-resolution MS spectra were recorded with electron impact source and electrospray/ion trap instruments, using a syringe pump device to directly inject sample solutions. 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 ICR-FTMS electrospray equipped instrument. Melting points are uncorrected. Elemental analyses were recorded in the analytical laboratories of Università degli Studi di Milano. The alkynylbenzaldehydes **1** are known compounds and have been prepared as described in the literature.[20c] Anilines **2** are commercially available and were used as provided by chemical suppliers or, when necessary, were purified by distillation under reduced pressure (**2e**) or recrystallization (**2c**). The synthesis of ligand (PcL_1) and the corresponding silver complex [Ag(PcL_1)] have been already described.[22] The synthesis of ligands (PcL_2),[23] and (PcL_3),[23] have been already reported. Details for the preparation of [Ag(PcL_2)] and [Ag(PcL_3)] complexes are reported below.

General procedure for the synthesis of [Ag(PcL)] complexes. The silver salt and all silver-containing solutions were kept in the dark until the final isolation of the product. The ligand PcL was dissolved in DCE (~$2\cdot10^{-2}$ M), the silver salt (weighed under a nitrogen atmosphere) was added, and

the mixture stirred for 1 h, then filtered to remove any traces of eventually unreacted solid. The solvent was concentrated to half volume, then *n*-hexane was added. The mixture was evaporated to dryness and *n*-hexane was added again yielding to a well-dispersed white powder, and finally the product recovered by filtration in open air.

[Ag(PcL$_2$)]: **PcL$_2$** (MW = 668.84; 281 mg; 0.420 mmol), $AgBF_4$ (MW = 194.67; 82.0 mg; 0.420 mmol), $C_2H_4Cl_2$ (10 mL), *n*-hexane (~20 mL). Whitish solid. Yield: 79% (272 mg). ^{1}H NMR (400 MHz, $CDCl_3$, T = 330 °K): δ = 7.86-7.73 (m, 5H, Ar*H*), 7.58 (d, *J* = 8.1 Hz, 2H, Ar*H*), 7.44-7.39 (m, 6H, Ar*H*), 7.29 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.46 (br s, 4H, CH_2), 3.35 (br s, 4H, CH_2), 2.87 (br s, 4H, CH_2), 2.49 (s, 6H, CH_3), 2.41 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, T = 300 °K): δ =145.2 (C), 144.8 (C), 140.9 (CH), 130.4 (CH), 130.1 (CH), 128.2 (CH), 127.7 (CH), 125.3 (CH), 57.0 (CH_2), 51.6 (CH_2 – detected by HSQC), 49.2 (CH_2 – detected by HSQC), 21.7 (CH_3), 21.6 (CH_3), three quaternary carbons obscured. MS FAB(+): *m/z* (%) = 775.08/777.08 (100/92) $[M - BF_4]^+$. $C_{32}H_{36}AgN_4O_6S_3$ [775.08]. Anal. Calcd for $C_{32}H_{36}AgBF_4N_4O_6S_3$ (MW = 863.51): C, 44.51; H, 4.20; N, 6.49. Found: C, 44.12; H, 4.30; N, 6.78.

[Ag(PcL$_3$)]: **PcL$_3$** (MW = 476.67; 200 mg; 0.420 mmol), $AgBF_4$ (MW = 194.67; 82,0 mg; 0.420 mmol), $C_2H_4Cl_2$ (10 mL), *n*-hexane (~20 mL). White solid. Yield: 81% (228 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (t, *J* = 7.6 Hz, 2H, Ar*H*), 7.36-7.16 (m, 15H, Ar*H*) overlapping with solvent, 6.87 (d, *J* = 7.6 Hz, 2H, Ar*H*), 3.96 (s, 2H, CH_2) overlapping with 3.97-3.93 (m, 2H, CH_2), 3.80 (br s, 4H, CH_2) overlapping with 3.89-3.75 (m, 2H, CH_2), 3.33 (br s, 4H, CH_2), 3.23 (m, 2H, CH_2), 3.01 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1 (C), 137.9 (CH), 137.3 (C), 130.8 (CH), 130.0 (CH), 129.4 (CH), 129.3 (CH), 128.6 (CH), 129.1 (CH), 127.9 (CH), 120.5 (CH), 61.8 (CH_2), 58.7 (CH_2), 52.0 (CH_2), 51.4 (CH_2), 49.9 (CH_2). ^{11}B NMR (128.4 MHz, CD_2Cl_2): δ = - 0.95 (s). ^{19}F NMR (376.5 MHz, DMSO): δ = -151.45 (s, $^{10}BF_4$), -151.50 (s,$^{11}BF_4$). MS FAB(+): *m/z* (%) = 583.2/585.2 (100/92) (100/92) $[M - BF_4]^+$. $C_{32}H_{36}AgN_4$ [583.2]. Anal. Calcd for $C_{32}H_{36}AgBF_4N_4$ (MW = 671.34): C, 57.25; H, 5.41; N, 8.35. Found: C, 57.00; H, 5.05; N, 7.98.

General procedure for the synthesis of 1-amonoisochromenes 3. The catalyst [Ag(PcL$_1$)]OTf (2.5 mol%) was added to a well stirred solution of the proper 2-alkynylbenzaldehyde **1a-k** (0.2 mmol) in DCE (1mL, [**1**] = 0.20 M), under a nitrogen atmosphere at 40 °C for 10 mins than the proper aniline **2a-g** (0.21 mmol, 1.05 equiv.) was added. The stirred mixture was reacted for 16 h at 40 °C, until no more starting product was detectable by TLC analysis. The reaction mixture was then diluted with CH_2Cl_2 (20 mL) and washed with $NaHCO_3$ sat. sol. (20 mL). The organic layer was dried with Na_2SO_4, and evaporated to dryness under reduced pressure. The crude was purified as described below for each product to give the desired 1-aminoisochromene **3a-r**.

1-(2-((3-(p-tolyl)-1H-isochromen-1-yl)amino)phenyl)ethanone **(3a)**: Purified by column chromatography on neutral alumina. Eluent for chromatography: hexane/EtOAc (98 : 2). White solid. Yield: 90% (64 mg); mp 145-146 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 10.07 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 6.4 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.28 (m, 2H), 7.14 (m, 2H, overlapped with C_6D_6), 7.00 (m, 2H), 6.91 (d, *J* = 8.06 Hz, 2H), 6.68 (d, *J* = 7.9 Hz, 1H), 6.55 (pt, *J* = 7.6 Hz, 1H), 6.44 (s, 1H), 2.02 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 200.4 (C), 151.2 (C), 148.4 (C), 138.4 (C), 134.5 (CH) 132.64 (C), 132.55 (CH), 131.7 (C), 129.13 (CH), 129.1 (CH), 128.1 (C), 126.6 (CH), 125.6 (CH), 124.9 (CH), 124.5 (CH), 119.5 (C), 116.6 (CH), 113.8 (CH), 100.4 (CH), 81.2 (CH), 27.3 (CH_3), 20.9 (CH_3). MS ESI(-): *m/z* (%) = 354.06 (100) $[MH]^+$. Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 80.96; H, 5.92; N, 3.97.

1-(4-((3-(p-tolyl)-1H-isochromen-1-yl)amino)phenyl)ethanone **(3b)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. White solid. Yield: 40% (29 mg); mp 143-145 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.84 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.18 (m, 1H, overlapped with C_6D_6), 7.02 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.52 (d, *J* = 8.8 Hz, 2H), 6.47 (d, *J* = 8.8 Hz, 1H), 6.41 (s, 1H), 4.51 (d, *J* = 8.8 Hz, 1H), 2.16 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 194.6 (C), 151.6 (C), 148.6 (C), 138.9 (C), 132.4 (C), 131.5 (C), 130.5 (CH), 129.5 (C), 129.4 (CH), 129.2 (CH), 126.4 (CH), 125.7 (CH), 125.6 (CH), 124.3 (CH), 113.3 (CH), 99.4 (CH), 81.0 (CH), 25.6 (CH_3), 20.9 (CH_3) one quaternary C overlapped with C_6D_6. MS ESI(-): *m/z* (%) = 354.55 (100) $[MH]^+$. Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 80.92; H, 5.90; N, 4.00.

N-(4-nitrophenyl)-3-(p-tolyl)-1H-isochromen-1-amine **(3c)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. Yellow solid. Yield: 75% (54 mg); mp 141-142 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.95 (d, *J* = 9.1 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.14 (m, 1H, overlapped with C_6D_6), 7.00 (m, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.39 (s, 1H), 6.24 (d, *J* = 8.3 Hz, 1H), 6.14 (d, *J* = 9.2 Hz, 2H), 4.45 (d, *J* = 8.3 Hz, 1H), 2.01 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 151.2 (C), 149.5 (C), 140.3 (C), 139.1 (C), 131.9 (C), 131.2 (C), 129.5 (CH), 129.1 (CH), 126.7 (C), 126.4 (CH), 125.6 (CH), 125.4 (CH), 124.2 (CH), 112.8 (CH), 99.2 (CH), 80.4 (CH), 20.8 (CH_3), two CH arom. overlapped. MS ESI(+): *m/z* (%) = 381.04 (20) $[M + Na]^+$, 358.89 (21) $[MH]^+$, 341.05 (50) $[MH - H_2O]^+$, 220.99 (85) [isochromenylium ion]$^+$. Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.85; H, 5.00; N, 7.86.

N-(2-nitrophenyl)-3-(p-tolyl)-1H-isochromen-1-amine **(3d)**: Purified by column chromatography on neutral alumina. Eluent for chromatography: hexane/EtOAc (98 : 2). Dark yellow solid. Yield: 56% (40 mg); mp 166-167 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 8.72 (d, *J* = 7.7 Hz, 1H), 7.92 (dd, *J* = 8.5,

1.6 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.33 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.11 (m, 1H overlapped with C_6D_6), 7.00 (m, 1H), 6.98 (s, 1H), 6.93 (m, 4H), 6.43 (d, *J* = 7.7 Hz, 1H), 6.37 (s, 1H), 6.26 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1H), 2.03 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 150.7 (C), 142.2 (C), 138.7 (C), 135.2 (CH), 133.9 (C), 132.0 (C), 131.1 (C), 129.4 (CH), 129.0 (CH), 126.9 (C), 126.7 (CH), 126.5 (CH), 125.3 (CH), 124.7 (CH), 124.5 (CH), 117.4 (CH), 115.4 (CH), 100.1 (CH), 80.7 (CH), 20.8 (CH_3). MS ESI(+): *m/z* (%) = 412.9 (100) $[M + MeOH + Na]^+$, 380.99 (85) $[M + Na]^+$, 358.99 (42) $[MH]^+$, 220.95 (85) [isochromenylium ion]$^+$. Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.89; H, 5.09; N, 7.89.

N-(2-fluorophenyl)-3-(p-tolyl)-1H-isochromen-1-amine **(3e)**: Purified by column chromatography on neutral alumina. Eluent for chromatography: hexane/EtOAc (98 : 2). White/gray solid. Yield: 81% (54 mg); mp 109-110 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.57 (d, *J* = 8.2, 2H), 7.30 (td, *J* = 8.3, 1.3 Hz, 1H), 7.10 (m, 1H), 7.00-6.87 (m, 6H), 6.78 (ddd, *J* = 11.4, 8.1, 1.2 Hz, 1H), 6.54 (m, 2H), 6.35 (s, 1H), 4.89 (m, 1H), 2.02 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 152.2 (d, J_1 = 239.3 Hz, CF), 151.2 (C), 138.6 (C), 133.4 (d, J_2 = 11.4 Hz, C-CF), 132.5 (C) , 131.5 (C), 129.2 (CH), 129.1 (CH), 127.9 (C), 126.5 (CH), 125.6 (CH), 125.4 (CH), 124.6 (d, J_4 = 3.5 Hz, CH), 124.3 (CH), 119.3 (d, J_3 = 7.0 Hz, CH), 115.1 (d, J_2 = 11.0 Hz, C-CF), 115.0 (d, J_3 = 5.3 Hz, CH), 99.7 (CH), 81.8 (CH), 20.9 (CH_3). MS ESI(+): *m/z* (%) = 331.93 (20) $[MH]^+$, 314.04 (100) $[MH - H_2O]^+$, 220.98 (35) [isochromenylium ion]$^+$. Anal. Calcd for $C_{22}H_{18}FNO$: C, 73.74; H, 5.48; N, 4.23. Found: C, 72.96; H, 5.49; N, 4.19.

1-(2-((3-(4-methoxyphenyl)-1H-isochromen-1-yl)amino)phenyl)ethanone **(3f)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. White solid. Yield: 85% (63 mg); mp 150-152 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 10.03 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.25 (m, 2H), 7.09 (m, 2H), 6.96 (m, 2H), 6.63 (m, 3H), 6.51 (m, 1H), 6.32 (s, 1H), 3.17 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 200.2 (C), 160.3 (C), 151.0 (C), 148.3 (C), 134.3 (CH), 132.4 (CH), 131.8 (C), 129.0 (CH), 127.8 (C), 127.7 (C), 126.90 (CH), 126.2 (CH), 124.7 (CH), 124.1 (CH), 119.5 (C), 116.4 (CH), 113.71 (CH), 113.66 (CH), 99.3 (CH), 81.2 (CH), 54.4 (CH), 27.1 (CH). MS ESI(+): *m/z* (%) = 372.24 (24) $[MH]^+$, 371.26 (45) $[M]^+$, 370.30 (100) $[M - H]^+$, 352.29 (45) $[MH - H_2O]^+$, 237.15 (80) [isochromenylium ion]$^+$, 136.00 (5) [2-acethylanilinium ion]$^+$. Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.50; H, 5.64; N, 3.82.

1-(2-((3-(2-methoxyphenyl)-1H-isochromen-1-yl)amino)phenyl)ethanone **(3g)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. White solid. Yield: 95% (71 mg); mp 120-122 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 10.09 (d, *J* = 8.0 Hz, 1H), 7.91

(dd, *J* = 7.7, 1.7 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.26-7.10 (m, 3H, overlapped with C_6D_6), 7.05 (m, 2H), 6.98-6.91 (m, 2H), 6.92 (m, 1H), 6.78 (m, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.48 (t, *J* = 7.1 Hz, 1H), 6.41 (d, *J* = 7.9 Hz, 1H), 3.17 (s, 3H), 1.91 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 200.2 (C), 157.7 (C), 148.4 (C), 148.0 (C), 134.3 (CH), 132.3 (CH), 131.9 (C), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.2 (C), 126.6 (CH), 124.7 (CH), 124.6 (CH), 124.2 (C), 120.3 (CH), 119.3 (C), 116.3 (CH), 113.8 (CH), 111.0 (CH), 106.5 (CH), 80.9 (CH), 54.5 (CH_3), 27.2 (CH_3). MS ESI(+): *m/z* (%) = 372.02 (13) $[MH]^+$, 354.27 (100) $[MH - H_2O]^+$, 340.33 (15) $[MH - MeOH]^+$, 237.10 (30) [isochromenylium ion]$^+$. Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.57; H, 5.73; N, 3.78.

1-(2-((3-(3-(trifluoromethyl)phenyl)-1H-isochromen-1-yl)amino)phenyl) ethanone **(3h)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. White/gray solid. Yield: 86% (70 mg); mp 159-161 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 9.97 (d, *J* = 7.7 Hz, 1H), 8.02 (s, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.38 – 7.22 (m, 2H), 7.17 (m, 1H, overlapped with C_6D_6), 7.11 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.05 – 6.95 (m, 3H), 6.81 (t, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 6.56 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 6.28 (s, 1H), 1.91 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 200.4 (C), 148.9 (C), 147.7 (C), 136.0 (C), 134.4 (CH), 132.4 (CH), 130.6 (q, J_2 = 31.6 Hz, C-CF_3), 130.5 (C), 129.1 (CH), 128.6 (CH), 128.1 (CH), 127.1 (CH), 126.8 (C), 124.9 (CH), 124.8 (CH) ovelapped with 124.7 (q, J_3 = 3.9 Hz, CH), 124.5 (q, J_1 = 272.3 Hz, CF_3), 122.2 (q, J_3 = 3.9 Hz, CH) 119.4 (C), 116.8 (CH), 113.6 (CH), 102.2 (CH), 81.0 (CH), 27.1 (CH_3). MS ESI(+): *m/z* (%) = 409.71 (31) $[MH]^+$, 274.93 (100) [isochromenylium ion]$^+$. Anal. Calcd for $C_{24}H_{18}F_3NO_2$: C, 70.41; H, 4.43; N, 3.42. Found: C, 70.52; H, 4.48; N, 3.37.

1-(2-((3-(4-chlorophenyl)-1H-isochromen-1-yl)amino)phenyl)ethanone **(3i)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. White solid. Yield: 54% (41 mg); mp 168-170 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 9.98 (d, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 8.6 Hz, 3H), 7.32 – 7.16 (m, 2H), 7.09 – 7.01 (m, 2H), 6.96 (t, *J* = 7.2 Hz, 4H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.54 – 6.46 (m, 1H), 6.21 (s, 1H), 1.90 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 200.3 (C), 149.6 (C), 148.0 (C), 134.3 (CH), 134.2 (C), 133.5 (C), 132.4 (CH), 131.0 (C), 129.0 (CH), 128.3 (CH), 126.8 (CH), 126.5 (CH), 124.8 (CH), 124.5 (CH), 119.5 (C), 116.6 (CH), 113.5 (CH), 101.2 (CH), 81.1 (CH), 27.1 (CH_3) one quaternary carbon obscured. MS ESI(+): *m/z* (%) = 376.33 (64) $[MH]^+$, 358.40 (100) $[MH - H_2O]^+$. Anal. Calcd for $C_{23}H_{18}ClNO_2$: C, 73.50; H, 4.83; N, 3.73. Found: C, 73.54; H, 4.79; N, 3.77.

1-(2-((3-(thiophen-3-yl)-1H-isochromen-1-yl)amino)phenyl)ethanone **(3j)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. White solid. Yield: 99%

(69 mg); mp > 260 (dec.) °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 10.02 (d, *J* = 7.7 Hz, 1H), 7.40 (m, 2H), 7.24 (m, 2H), 7.08 (m, 3H), 6.96 (m, 2H), 6.71 (dd, *J* = 5.1, 3.1 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.52 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 6.22 (s, 1H), 1.89 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 200.2 (C), 148.1 (C), 147.7 (C), 137.6 (C), 134.3 (CH), 132.4 (CH), 131.3 (C), 129.0 (C), 127.5 (C), 126.5 (CH), 125.5 (CH), 124.8 (CH), 124.3 (CH), 122.4 (CH), 119.4 (C), 116.5 (CH), 113.6 (CH), 100.7 (CH), 81.0 (CH), 27.1 (CH_3) two CH signals overlapped. MS ESI(+): *m/z* (%) = 346.37 (100) $[MH]^+$. Anal. Calcd for $C_{21}H_{17}NO_2S$: C, 72.60; H, 4.93; N, 4.03. Found: C, 72.47; H, 4.94; N, 4.09.

1-(2-((3-propyl-1H-isochromen-1-yl)amino)phenyl)ethanone **(3k)**: Purified by flash-column chromatography on silica gel. Eluent for chromatography: hexane/EtOAc/TEA (95:5:1). White vax. Yield: 62% (38 mg). ^{1}H NMR (300 MHz, C_6D_6): δ = 9.94 (d, *J* = 7.4 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.22 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 7.08 (td, *J* = 7.3, 1.6 Hz, 1H), 7.01 (d, *J* = 6.4 Hz, 1H), 6.95 (td, *J* = 7.3, 1.3 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.62 – 6.41 (m, 2H), 5.64 (s, 1H), 2.12 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.98 (s, 1H), 1.97 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.41 (sextet, *J* = 7.3 Hz, 2H), 0.71 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 200.3 (C), 154.7 (C), 148.3 (C), 134.3 (CH), 132.3 (CH), 131.2 (C), 128.9 (CH), 126.8 (C), 125.9 (CH), 124.9 (CH), 123.4 (CH), 119.2 (C), 116.3 (CH), 113.8 (CH), 101.0 (CH), 80.6 (CH), 35.9 (CH_2), 27.2 (CH_3), 20.1 (CH_2), 13.1 (CH_3). MS ESI(+): *m/z* (%) = 329.99 (60) $[M + Na]^+$, 290.04 (100) $[MH - H_2O]^+$. Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.16; H, 6.89; N, 4.56. Found: C, 78.01; H, 6.95; N, 4.50.

1-(2-((3-cyclopropyl-1H-isochromen-1-yl)amino)phenyl)ethanone **(3l)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. White solid. Yield: 64% (39 mg); mp 120 °C^{1}H NMR (300 MHz, C_6D_6): δ = 9.90 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.19 (dd, *J* = 6.0, 1.3 Hz, 2H), 7.08 (td, *J* = 7.4, 1.5 Hz, 1H), 6.99 (d, *J* = 6.6 Hz, 1H), 6.94 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.51 (ddd, *J* = 8.1, 6.1, 2.2 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 1H), 5.79 (s, 1H), 1.94 (s, 3H), 1.31 (tt, *J* = 8.3, 5.0 Hz, 1H), 1.02 (dddd, *J* = 9.3, 6.0, 5.0, 3.6 Hz, 1H), 0.61 (dddd, *J* = 9.7, 6.2, 5.0, 3.5 Hz, 1H), 0.53 – 0.25 (m, 2H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 200.3 (C), 154.8 (C), 148.4 (C), 134.4 (CH), 132.5 (CH), 131.7 (C), 129.1 (CH), 127.3 (C), 125.6 (CH), 124.9 (CH), 123.1 (CH), 119.4 (C), 116.5 (CH), 113.7 (CH), 100.0 (CH), 80.8 (CH), 27.3 (CH_3), 14.5 (CH_3), 6.3 (CH_2), 4.3 (CH_2). MS ESI(+): *m/z* (%) = 306.07 (80) $[MH]^+$, 288.26 (100) $[MH - H_2O]^+$, 171.02 (90) [isochromenylium ion]$^+$. Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.56; H, 6.22; N, 4.52.

1-(2-((3-cyclopentyl-1H-isochromen-1-yl)amino)phenyl)ethanone **(3m)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. Light brown solid. Yield: 78% (52 mg); mp 119-121 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 9.91 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* =

8.4 Hz, 1H), 7.33 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.23 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.09 (td, *J* = 7.3, 1.5 Hz, 1H), 7.02 (d, *J* = 6.5 Hz, 1H), 6.97 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.53 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 5.73 (s, 1H), 2.53 (p, *J* = 7.8 Hz, 1H), 1.99 (s, 3H), 1.75 – 1.48 (m, 6H), 1.43 – 1.29 (m, 2H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 200.3 (C), 157.9 (C), 148.5 (C), 134.4 (CH), 132.5 (CH), 131.5 (C), 129.0 (CH), 126.0 (CH), 125.0 (CH), 123.70 (CH), 119.3 (C), 116.4 (CH), 114.0 (CH), 99.6 (CH), 80.8 (CH), 43.9 (CH_3), 30.6 (CH_2), 30. 5 (CH_2), 27.4 (CH), 25.8 (CH_2), 25.7 (CH_2) one quaternary carbon obscured. MS ESI(+): *m/z* (%) = 316.38 (100) $[MH - H_2O]^+$. Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.09; H, 7.01; N, 4.22.

3-(2-methoxyphenyl)-N-(2-nitrophenyl)-1H-isochromen-1-amine **(3n)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. Yellow solid. Yield: 46% (35 mg); mp 157-158 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 8.71 (d, *J* = 7.7 Hz, 1H), 7.92 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.80 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.13 – 6.90 (m, 7H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 2H), 6.25 (t, *J* = 7.4 Hz, 1H), 3.15 (s, 3H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 157.7 (C), 147.9 (C), 142.4 (C), 135.1 (CH), 133.8 (C), 131.4 (C), 129.5 (CH), 129.3 (CH), 128.6 (CH), 127.1 (C), 126.8 (CH), 126.4 (CH), 124.8 (CH), 124.6 (CH), 123.8 (C), 120.3 (CH), 117.2 (CH), 115.6 (CH), 111.1 (CH), 106.2 (CH), 80.5 (CH), 54.5 (CH_3). MS ESI(+): *m/z* (%) = 375.16 (20) $[MH]^+$, 357.31 (100) $[MH - H_2O]^+$. Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.67; H, 4.87; N, 7.55.

N-(2-nitrophenyl)-3-(thiophen-3-yl)-1H-isochromen-1-amine **(3o)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. Yellow solid. Yield: 64% (45 mg); mp 157-159 °C. ^{1}H NMR (300 MHz, C_6D_6): δ = 8.57 (d, *J* = 7.0 Hz, 1H), 7.91 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 7.12 – 7.05 (m, 1H), 7.03 (d, *J* = 4.1 Hz, 1H), 7.00 – 6.86 (m, 4H), 6.73 (dd, *J* = 5.1, 3.0 Hz, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 6.25 (t, *J* = 7.3 Hz, 1H), 6.17 (s, 1H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 147.8 (C), 142.6 (C), 137.7 (C), 135.7 (CH), 134.4 (C), 131.4 (C), 130.0 (CH), 127.4 (C), 127.3 (CH), 127.1 (CH), 126.4 (CH), 125.3 (CH), 125.2 (CH), 125.1 (CH), 123.0 (CH), 118.0 (CH), 115.8 (CH), 101.1 (CH), 81.1 (CH). MS ESI(+): *m/z* (%) = 349.31 (100) $[MH]^+$. Anal. Calcd for $C_{19}H_{13}N_2O_3S$: C, 65.13; H, 4.03; N, 8.00. Found: C, 65.26; H, 3.95; N, 7.94.

N-(4-nitrophenyl)-3-(thiophen-3-yl)-1H-isochromen-1-amine **(3p)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. Yellow solid. Yield: 48% (35 mg); mp 161-163 °C. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.17 (d, *J* = 9.1 Hz, 2H), 7.59 – 7.37 (m, 2H), 7.38 – 7.19 (m, 5H), 7.02 (d, *J* = 9.2 Hz, 2H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.47 (s, 1H), 5.36 (d, *J*

= 7.7 Hz, 1H). ^{13}C NMR (75.45 MHz, CD_2Cl_2): δ =150.3 (C), 147.0 (C), 140.0 (C), 136.9 (C), 130.6 (C) 129.7 (CH), 126.8 (CH), 126.6 (C) 126.3 (CH), 126.0 (CH), 125.5 (CH), 124.6 (CH) 124.5 (CH), 122.9 (CH),113.1 (CH), 100.2 (CH), 80.6 (CH). MS ESI(+): *m/z* (%) = 351.04 (70) $[MH]^+$, 213.04 (100) [isochromenylium ion]$^+$. Anal. Calcd for $C_{19}H_{13}N_2O_3S$: C, 65.13; H, 4.03; N, 8.00. Found: C, 65.32; H, 3.99; N, 8.04.

3-cyclopentyl-N-(2-nitrophenyl)-1H-isochromen-1-amine **(3q)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. Yellow wax. Yield: 34% (23 mg). ^{1}H NMR (300 MHz, C_6D_6): δ = 8.53 (d, *J* = 7.3 Hz, 1H), 7.97 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.09 (td, *J* = 7.5, 1.3 Hz, 1H), 7.02 – 6.91 (m, 2H), 6.86 (t, *J* = 6.9 Hz, 2H), 6.27 (ddd, *J* = 8.5, 5.3, 2.2 Hz, 2H), 5.67 (s, 1H), 2.46 (p, *J* = 7.7 Hz, 1H), 1.75 – 1.17 (m, 8H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 157.4 (C), 142.4 (C), 135.2 (CH), 133.9 (C), 131.1 (C), 129.5 (CH), 126.6 (CH), 126.5 (C), 126.3 (CH), 125.0 (CH), 124.0 (CH), 117.4 (CH), 115.7 (CH), 99.6 (CH), 80.3 (CH), 43.8 (CH), 30.5 (CH_2), 30.4 (CH_2), 25.7 (CH_2), 25.6 (CH_2). MS ESI(+): *m/z* (%) = 336.08 (100) $[M]^+$. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.54; H, 6.04; N, 8.40.

3-cyclopentyl-N-(4-nitrophenyl)-1H-isochromen-1-amine **(3r)**: Purified by trituration and sonication in diisopropyl ether (2 mL), then freeze (-18 °C) for 30 mins. Yellow wax. Yield: 45% (31 mg). ^{1}H NMR (300 MHz, C_6D_6): δ = 7.96 (d, J = 9.1 Hz, 2H), 7.12 (dd, J = 7.6, 1.3 Hz, 1H), 6.97 (td, J = 7.5, 1.3 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.76 – 6.67 (m, 1H), 6.09 (d, J = 9.2 Hz, 2H), 6.04 (d, J = 8.1 Hz, 1H), 5.67 (s, 1H), 4.36 (d, J = 8.1 Hz, 1H), 2.46 (p, J = 7.7 Hz, 1H), 1.71 – 1.28 (m, 8H). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 157.9 (C), 149.7 (C), 140.2 (C), 131.1 (C), 129.4 (CH), 126.1 (C), 125.9 (CH), 125.5 (CH), 125.4 (CH), 123.5 (CH), 112.7 (CH), 98.7 (CH), 80.1 (CH), 43.7 (2×CH_2), 30.4 (CH_2), 25.7 (CH_2), 25.5 (CH_2). MS ESI(+): *m/z* (%) = 335.70 (100) $[MH]^+$. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.47; H, 5.98; N, 8.38.

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Keywords

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Notes and references

[1] J. D. Hepworth, B. M. Heron, *Progress Het. Chem.* **2003**, *15*, 360–384.
[2] *a*) D. Dey, B. Nag, P. Neogi, A. Sen, S. D. Sharma, B. Nag, US Patent US 6723736 B2, 2004; *b*) G. Attardo, T. Breining, J.-L. Kraus, T. Li, Y. St-Denis, W. Wang, Int. Patent WO 9512588 A1, 1995; *c*) W. Wang, T. Li, R. Milbum, J. Yates, E. Hinnant, M. J. Luzzio, S. A. Noble, G. Attardo, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1579–1584.
[3] *a*) J.-M. Gao, S.-X. Yang, J.-C Qin, *Chem. Rev.* **2013**, *113*, 4755–4811; *b*) T. Oja, P. San Martin Galindo, T. Taguchi, S. Manner, P. M. Vuorela, K. Ichinose, M. Metsä-Ketelä, A. Fallarero, *Antimicrob. Agents Chemother.* **2015**, *59*, 6046–6052; *c*) A. Shimbashi, S. Nishiyama, *Tetrahedron Lett.* **2007**, *48*, 1545–1548; *d*) S. Ankisetty, C. D. Amsler, J. B. Clintock, B. J. Baker, *J. Nat. Prod.* **2004**, *67*, 1172–1174; *e*) I.-S. Chen, I.-W. Tsai, C.-M. Teng, J.-J. Chen, Y.-L. Chang, F.-N. Ko, M. C. Lu, J. M. Pezzuto, *Phytochemistry,* **1997**, *46*, 525–529.
[4] For a couple of seminal works see: *a*) J. Barluenga, H. Vazquez-Villa, A. Ballesteros, J. M. Gonzalez, *J. Am. Chem. Soc*. **2003**, *125*, 9028–9029; *b*) D. Yue, N. Della Ca, R. C. Larock, *Org. Lett.* **2004**, *6*, 1581–1584.
[5] *a*) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127–2198; *b*) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3160.
[6] *a*) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2310; *b*) N. Asao, T. Nogami, K. Takahashi, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 764–765.
[7] N. T. Patil, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 5139–5142.
[8] *a*) G. Dyker, D. Hildebrandt, J. Liu, K. Merz, *Angew. Chem. Int. Ed.* **2003**, *42*, 4399–4402; *b*) X. Yao, C.-J. Li, *Org. Lett.* **2006**, *8*, 1953–1955.
[9] T. Godet, C. Vaxelaire, C. Michel, A. Milet, P. Belmont, *Chem. Eur. J.* **2007**, *13*, 5632–564.
[10] J. D. Tovar, T. M. Swager, *J. Org. Chem.* **1999**, *64*, 6499–6504.
[11] P. Belmont, in *Silver in Organic Chemistry* Ed. M. Harmata), John Wiley, Sons, Inc., Hoboken, 2010, pp 143–165; Chapter 5.
[12] For some early representative example see refs 4, 6b, 7
[13] For some early representative example, see ref 8b and A. B. Beeler, S. Su, C. A. Singleton, J. A. Porco Jr., *J. Am. Chem. Soc.* **2007**, *129*, 1413–1419.
[14] A. Arcadi, G. Abbiati, E. Rossi, *J. Organomet. Chem.* **2011**, *696*, 87–98.
[15] *a*) T. Sakamoto, A. Numata, Y. Kondo, *Chem. Pharm. Bull.* **2000**, *48*, 669–672; *b*) M. Alfonsi, M. Dell'Acqua, D. Facoetti, A. Arcadi, G. Abbiati, E. Rossi, *Eur. J. Org. Chem.* **2009**, 2852–2862.
[16] *a*) M. E. Domaradzki, Y. Long, Z. She, X. Liu, G. Zhang, Y. Chen, *J. Org. Chem.* **2015**, *80*, 11360–11368. *b*) V. Reddy, A. S. Jadhav, R.Vijaya Anand, *Org. Biomol. Chem*. **2015**, *13*, 3732–3741.
[17] *a*) N. Asao, K. Iso, Y. S. Salprima, *Org. Lett.* **2006**, *8*, 4149–4151; *b*) K. Gao, J. Wu, *J. Org. Chem.* **2007**, *72*, 8611–8613; *c*) Q. Ding, J. Wu, Lewis *Org. Lett.* **2007**, *9*, 4959–4962.
[18] *a*) N. T. Patil, A. K. Mutyala, P. G. V. V. Lakshmi, P. V. K. Raju, B. Sridhar, *Eur. J. Org. Chem.* 2010, 1999–2007, S1999/1–S1999/100; *b*) H. Waldmann, L. Eberhardt, K. Wittstein, K. Kumar, *Chem. Commun.* **2010**, *46*, 4622–4624; *c*) A. K. Verma, D. Choudhary, R. K. Saunthwal, V. Rustagi, M. Patel, R. K. Tiwari, *J. Org. Chem.* **2013**, *78*, 6657–6669.
[19] A. A. Ruch, F. Kong, V. N. Nesterov, LeGrande M. Slaughter, *Chem. Commun.* **2016**, *52*, 14133–14136.
[20] *a*) M. Dell'Acqua, B. Castano, C. Cecchini, T. Pedrazzini, V. Pirovano, E. Rossi, A. Caselli, G. Abbiati, *J. Org. Chem.* **2014**, *79*, 3494–3505; *b*) G. Tseberlidis, M. Dell'Acqua, D. Valcarenghi, E. Gallo, E. Rossi, G. Abbiati, A. Caselli, *RSC Adv.* **2016**, *6*, 97404–97419; *c*) M. Dell'Acqua, V. Pirovano, S. Peroni, G. Tseberlidis, D. Nava, E. Rossi, G. Abbiati, *Eur. J. Org. Chem.* **2017**, 1425–1433.
[21] *a*) G. Tseberlidis, D. Intrieri, A. Caselli, *Eur. J. Inorg. Chem.* **2017**, 3589–3603; *b*) T. Pedrazzini, P. Pirovano, M. Dell'Acqua, F. Ragaini, P. Illiano, P. Macchi, G. Abbiati, A. Caselli, *Eur. J. Inorg. Chem.* **2015**, 5089–5098.
[22] M. Trose, M. Dell'Acqua, T. Pedrazzini, V. Pirovano, E. Gallo, E. Rossi, A. Caselli, G. Abbiati, *J. Org. Chem.* **2014**, 79, 7311–7320.
[23] G. Tseberlidis, L. Demonti, V. Pirovano, M. Scavini, S. Cappelli, S. Rizzato, R. Vicente, A. Caselli, *ChemCatChem,* **2019**, *11*, 4907–4915.