Silver Catalyzed Domino Approach to 1,3-Dicarbosubstituted Isochromenes

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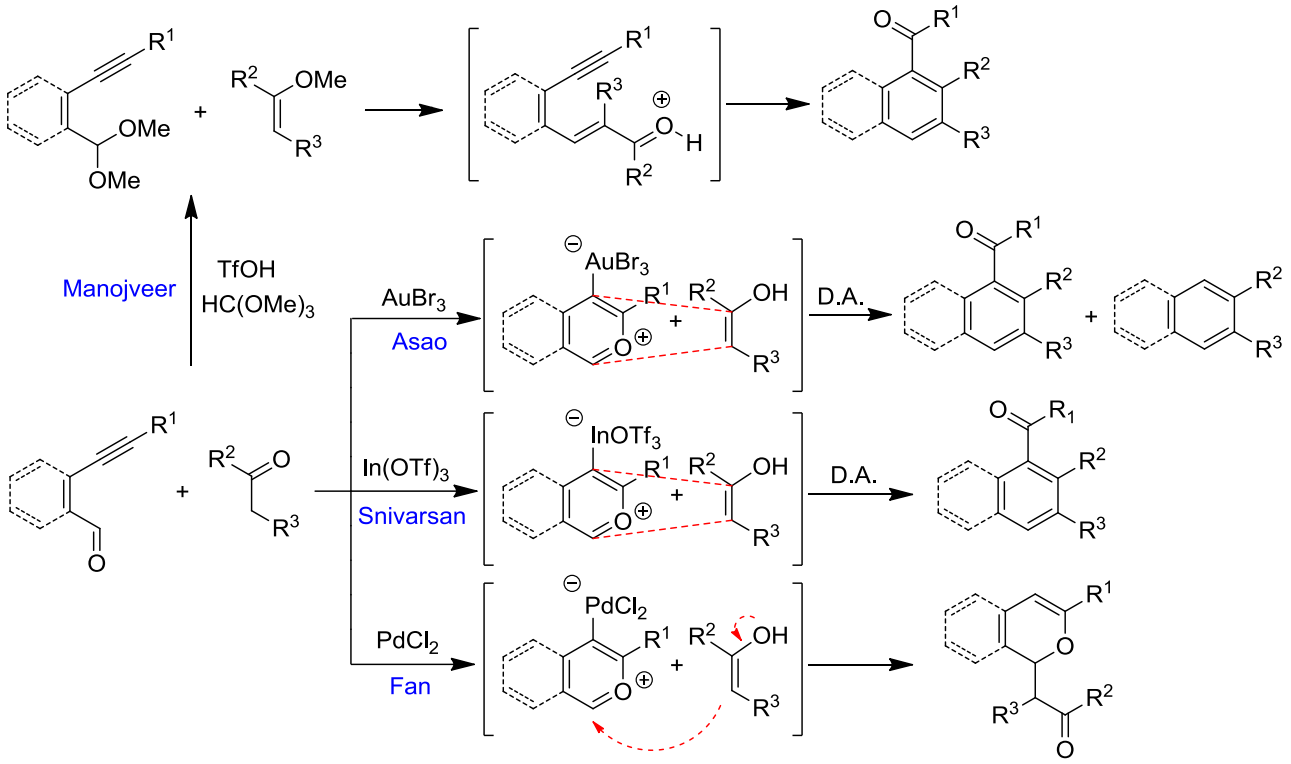
Abstract

In this paper, we report the first example of silver triflate-catalyzed synthesis of 1,3-dicarbosubstituted isochromene derivatives starting from 2-alkynyl(hetero)arylaldehydes and enolizable ketones. The reaction proceeds in a cascade fashion under mild heating with complete regioselectivity. The reaction yields range from moderate to good. In some cases, the reaction gives unexpected homodimeric products. Two competitive mechanistic paths for the formation of the desired isochromene derivatives and of the homodimeric products have been described.

Introduction

One of the most efficient methods for the synthesis of 1-substituted isochromenes (and related heteroaryl compounds such as pyrano[4,3-*b*]pyridines) is the metal-catalyzed regioselective domino cycloisomerization/nucleophilic addition reaction of a properly substituted 2-alkynyl(hetero)arylaldehyde in the presence of a suitable nucleophile.[1] The reactions with oxygen nucleophiles are the most studied and several metal catalysts, i.e., Pd(II),[2] Cu(I),[3] Ag(I),[4] Au(I)[5] and In(III),[6] demonstrated to be effective for the synthesis of 1-alkoxyisochromenes. Conversely, the reactions with carbon nucleophiles are relatively less investigated. One of the earlier examples has been reported by Asao and co-workers in 2005: the Japanese group investigated the reactivity of allyltrimethylsilane and trimethylsilylcyanide in the presence of a Pd(II)-Cu(II) bimetallic system.[7] Yao and Li in 2006[8] reported a gold(I) catalyzed domino approach involving terminal alkynes, whereas some examples of Rh(I) catalyzed reactions of methylene active compounds have been reported by Porco Jr. and co-workers in 2007 as part of a more extensive study on multidimensional reaction screening of *ortho*-alkynyl benzaldehydes.[9] The reactivity of indole as nucleophile has been explored by Tang and Li by means of Pd(II) catalysis[10] and by Peng, Wu and co-workers with Ag(I) as catalyst.[11] A broader investigation on the Ag(I) catalyzed reaction of 2-alkynyl(hetero)arylaldehydes in the presence of electron reach (hetero)aromatic compounds has been recently published by Belmont, Michelet and co-workers.[12]

Moreover, few different groups have investigated the reactivity of 2-alkynylbenzaldehydes and enolizable carbonyl compounds and the pattern of products obtained is different depending on the catalytic system used (Scheme 1). The Au(I)-catalyzed approach reported by Asao and Yamamoto[13] resulted in the formation of naphthylketone derivatives (beside the corresponding decarbonylated naphthalenes as by-products), through a inverse electron demand-type Diels-Alder reaction between the isochromenylium 4π system and enol 2π system derived from the tautomeric equilibria of the carbonyl compounds. Ten years later, Snivarsan[14] and co-workers increased the selectivity of this transformation by using a In(III) salt as catalyst, which produces the corresponding naphthylketones avoiding the formation of decarbonylation by-products. Manojveer and Malaburugan[15] have also obtained similar results in the presence of trimethyl orthoformate and a Brønsted acid such as triflic acid, but through a very different reaction mechanism: an in situ formed acetal assists the formation of a chalcone-type intermediate, which, after a *trans/cis* isomerization, undergoes, a methanol assisted annulation. Conversely, Cheng and Fan, within a more extensive work, were able to obtain selectively the 1-carbosubstituted isochromene derivatives, despite in fair yields, through an unprecedented cycloisomerization/addition path promoted by a simple Pd(II) salt.[16]



Scheme 1. Reactivity of 2-alkynylbenzaldehydes and enolizable carbonyl compounds.

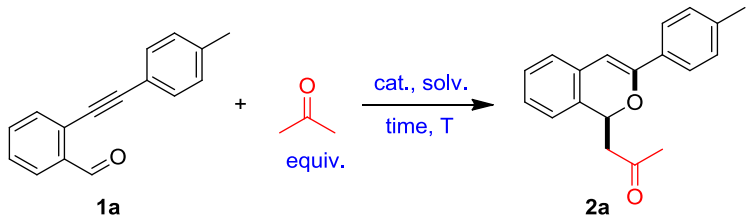
In connection with our ongoing interest in silver catalysis,[17] and in the development of domino approaches[18] for the synthesis of oxygen containing heterocycles[19] starting from alkyne derivatives,[20] we report here a AgOTf catalyzed cascade approach for the regioselective synthesis of isochromenes starting from 2-alkynyl(hetero)arylaldehydes and enolizable carbonyl compounds.

Results and discussion

The reaction between 2-[(4-tolyl)-ethynyl]benzaldehyde **1a** and acetone was chosen as model reaction to screen among different catalytic systems and to optimize the reaction conditions (Table 1). To obtain a reference product, first we performed the reaction under the conditions reported by Fan.[16] The model reaction performed in an excess of acetone as reagent/solvent, at 60 °C in the presence of 10 mol% of $PdCl_2$ proceeded fast to give the isochromene **2a** in good yield (Table 1, entry 1). Under the same reaction conditions, we replaced the palladium catalyst with silver triflate, and we were pleased to observe the selective formation of desired isochromene **2a** in a promising 45% yield (Table 1, entry 2). We tried to reduce the equivalents of acetone by performing the reaction in some different non-polar and polar solvents, but the results were rather unsatisfactory (Table 1, entries 3-5). Therefore, the use of an enolizable ketone as reagent/solvent seemed to be mandatory

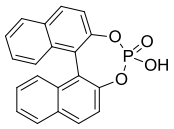
for our purpose. A reduction of the temperature resulted in a sluggish reaction (Table 1, entry 6), while higher reaction temperature gave **2a** in very good yield and in a reduced reaction time (Table 1, entry 7). The use of microwave heating resulted in lower yield and promoted the formation of some unidentified by-products (Table 1, entry 8). By changing the counter ion of the metal from triflate to a more bulky and charge delocalized anion as triflimidate,[21] the reaction became slower (Table 1, entry 9), whereas in the presence of $AgNO_3$ we obtained a complex mixture of by-products (Table 1, entry 10). We also tested the activity of a copper(I) salt, frequently used in domino cycloisomerization/addition reactions, but surprisingly, CuI hampered the reactivity (Table 1, entry 11). A more traditional Lewis acid such as $FeCl_3$ was unable to catalyze the reaction and a mixture of **1a** and some unidentified by-products was obtained (Table 1, entry 12). To confirm that the reaction needed a metal catalyst with a *well-biased* Lewis acidic character, we performed a reaction in the presence of a palladium complex such as $PdCl_2(PPh_3)_2$ and, as expected, the reaction failed, also after a prolonged reaction time, and the starting material was almost quantitatively recovered (Table 1, entry 13). Finally, to verify if the reaction could proceed under simple Brønsted acid catalysis, we performed a test in the presence of 1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, but also in this case the reaction resulted in a tarnish mixture of unidentified by-products (Table 1, entry 14).

Table 1. Optimization of the reaction conditions.



1a **2a**

Entry	Catalyst (10 mol-%)	Solvent	*T* (°C)	t (h)	2a (yield%)[a]	1a rec. (yield%)[a]
1	$PdCl_2$	Acetone (68 equiv.)	60	4	63	-
2	AgOTf	Acetone (68 equiv.)	60	12	45	-
3	AgOTf	Toluene:Acetone 9:1 (Acetone ~6 equiv.)	60	25	15[b]	-
4	AgOTf	DCE:Acetone 9:1 (Acetone ~6 equiv.)	60	25	10[b]	-
5	AgOTf	DMF:Acetone 9:1 (Acetone ~6 equiv.)	60	25	15[b]	30[b]

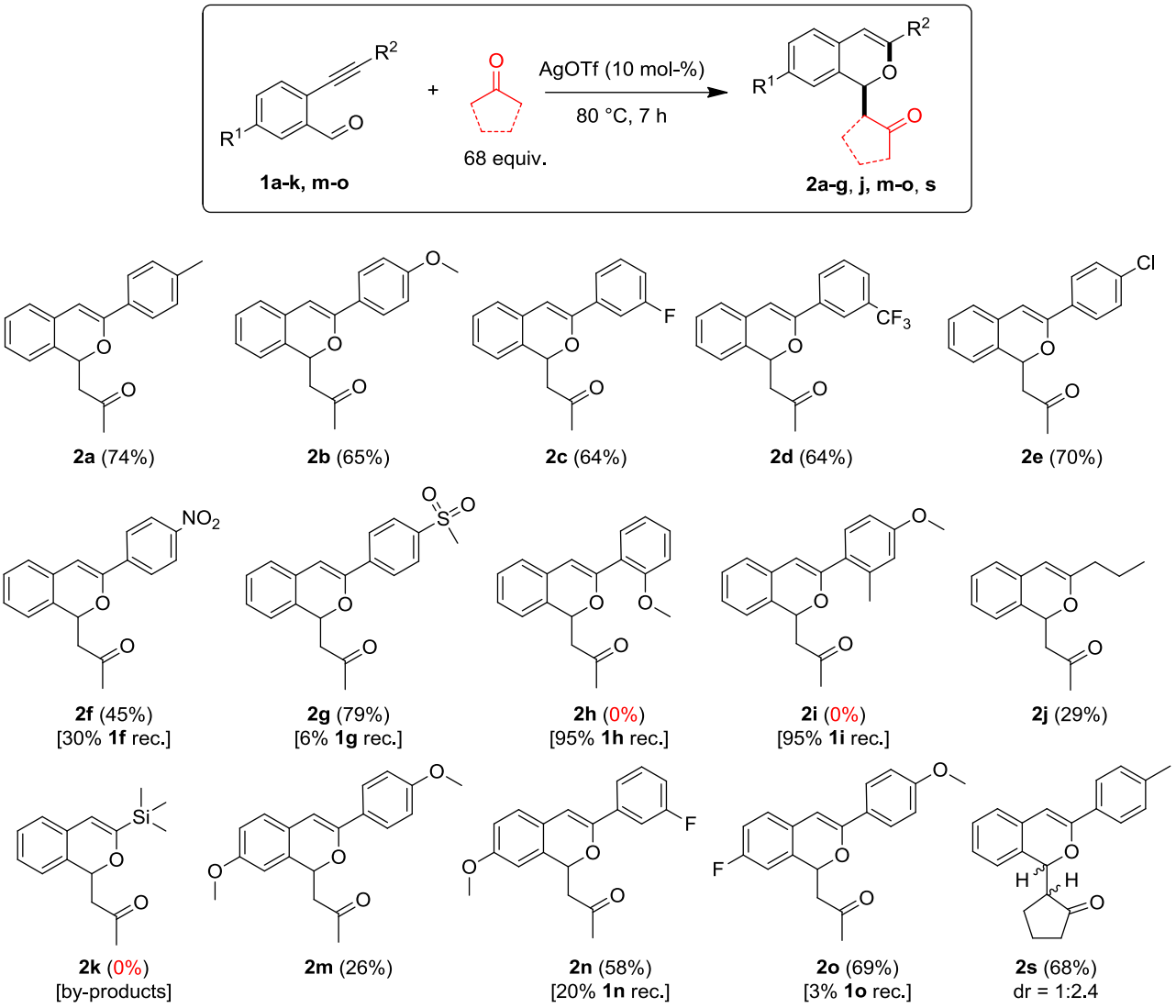
6	AgOTf	Acetone (68 equiv.)	r.t.	24	33[b]	-
7	AgOTf	Acetone (68 equiv.)	80	7	74	-
8	AgOTf	Acetone (68 equiv.)	100[c]	0.5	35[b]	5[b]
9	$AgNTf_2$	Acetone (68 equiv.)	80	7	42[b]	56[b]
10	$AgNO_3$	Acetone (68 equiv.)	80	3	-	-
11	CuI	Acetone (68 equiv.)	60	22	-	quant.[d]
12	$FeCl_3$	Acetone (68 equiv.)	60	29	-	30[b]
13	$PdCl_2(PPh_3)_2$	Acetone (68 equiv.)	60	27	-	quant.[d]
14		Acetone (68 equiv.)	60	24	-	40[b]

[a] Isolated yields. [b] Yields calculated via ^{1}H NMR using dimethyl terephthalate (DMT) as internal standard. [c] Under microwave heating. [d] Determined by TLC-analysis.

Under the best reaction conditions achieved (Table 1, entry 7), we tested scope and limitations of the approach. We selected some 2-alkynylbenzaldehydes characterized by the presence on the alkyne moieties of electron-donating (ED) or electron-withdrawing (EW) groups (**1a-l**), some 2-alkynylarylaldehydes with matching or mismatching electronic properties at their ends (**1m-p**), and a couple of 2-alkynylnicotinaldehydes bearing an EW or an ED group on the arylalkyne terminus (**1q,r**). The 2-alkynyl(hetero)arylaldehydes **1a-q** were synthesized by means of a typical Sonogashira coupling[22] in good to excellent yields starting from the proper 2-bromo(hetero)arylaldehydes and suitable terminal acetylenes (see Supporting Information).

The results of the scope and limitations study are depicted in Scheme 2. The approach gave in general the desired products in good yields. The reaction well tolerated the presence of electron-donating (**2a**,**b**) as well as electron-withdrawing groups (**2c-g**) in the *para* and *meta* positions of the aryl terminus of the alkyne moiety: only the presence of a nitro group (**2f**) adversely affected the reaction, while the substitution in the *ortho* position (**2h,i**) was not tolerated at all and the starting material was quantitatively recovered. Probably in these cases, the initial silver promoted formation of the isochromenylium intermediate is hampered for steric reasons, and in fact, we did not observed the formation of any degradation product (see below). Alkyl alkyne (**2j**) gave poor results, while the reaction of the trimethylsilylacetylene derivative (**2k**) gave a mixture of unidentified products. 2-Alkynylarylaldehydes with mismatching electronic properties at their ends gave better results with

respect to matching ones (compare the reaction yields of **2n,o** with respect to **2m**). We also tested the reaction of **1a** with a different ketone such as cyclopentanone, and a mixture of the two diastereoisomeric products in 1 : 2.4 ratio was obtained in 68% overall yield (**2s**).

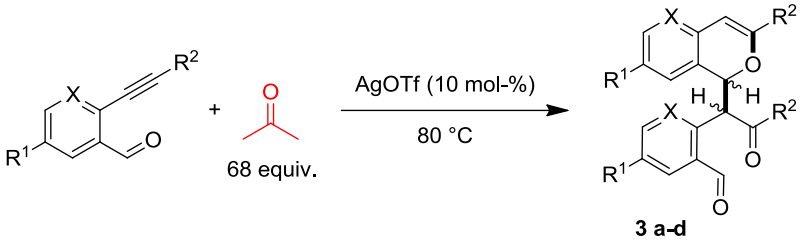


Scheme 2. Scope and limitations of the approach (isolated yields).

With the aim to verify the stability of isolated isochromenes **2** under different conditions, we made an additional experiment. We prepared three samples of the isochromene **2f** (20 mg, 0.065 mmol) in 1 mL of ethyl acetate, and in two of them 0.2 equiv of triethylamine and *p*-TSA, respectively, were added. Then, we followed the behaviour of the three sample by TLC analyses after 0,5, 1, 3, 24, 48, 72, and 96 hours. The results evidenced that **2f** is stable under neutral and basic conditions, whereas in the presence of *p*-TSA a number of unidentified breakdown products started to appear on the TLC plate after only 0.5 h, and approximately half of the isochromene **2f** was degraded after 96 h under these conditions (checked by TLC analysis).

It is worth to note that this domino approach displays some surprising results when four particular 2-alkynyl(hetero)arylaldehydes were used. In fact, the reaction of compounds **1l**, **1p**, **1q** and **1r** with acetone under the optimized conditions did not gave the expected products **2**, but led to the formation of the corresponding couples of homodimeric diastereoisomers **3a-d** (Table 2). All new compounds have been fully characterized by ^{1}H and ^{13}C NMR spectroscopies, and MS spectrometry.

Table 2. Formation of homodimeric diastereoisomers 3a-d.



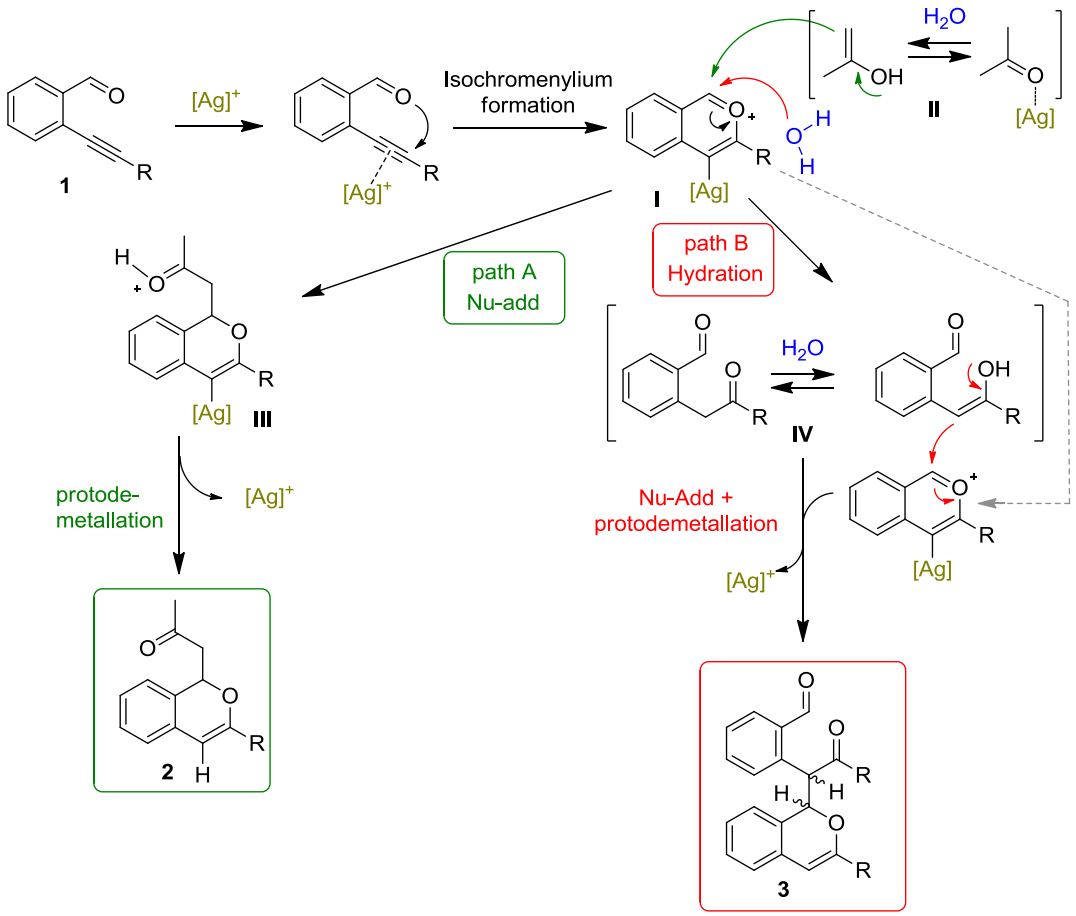
	X	R^1	R^2	t (h)	Yield (%)[a]	*dr*[b]	1 rec. (%)
1l	C	H	2-pyridinyl	24	**3a** 67	1 : 4.5	-
1p	C	F	3-CF_3-C_6H_4	6	**3b** 39	1.5 : 1	8
1q	N	H	4-MeO-C_6H_4	7	**3c** 90	1 : 1.4	-
1r	N	H	3-F-C_6H_4	2.5	**3d** 57	1 : 1.9	-

[a] Yields of pure isolated product. [b] Syn-anti ratio.

As previously observed[9,23] the formation of dimers **3** can been ascribed to a silver-catalyzed addition of water to the triple bond of the 2-alkynyl-(hetero)arylaldehyde **2**, or to the respective organosilver isochromenylium intermediate, thus generating a ketone which in the enol form attacks as a nucleophile a second electrophilic isochromenylium intermediate. Nevertheless, when we tried to perform the reaction in strongly anhydrous conditions (under a nitrogen atmosphere and in the presence of 4 Å molecular sieves), we observed that the reaction was totally hampered, and the starting material was almost quantitatively recovered. This behaviour confirms the presence of traces of water in the reaction mixture plays an essential role for the keto-enol tautomeric equilibria.[13]

Based on our findings and the previous literature, to explain the formation of isochromenes **2** and homodimers **3** we suggested the mechanism illustrated in Scheme 3. The coordination of the triple bond to AgOTf enhances the electrophilicity of alkyne, and the subsequent nucleophilic attack of the aldehyde oxygen to the electron-deficient alkyne would form the isochromenylium cation (**I**) (ate complex).[24] At the same time, the catalyst could coordinate to the carbonyl group of the enolizable ketone thus promoting, assisted by traces of water, the formation of the corresponding enol (**II**).[25] Then, following the path A, the enol (**II**) can attack the activate isochromenylium intermediate (**I**) to

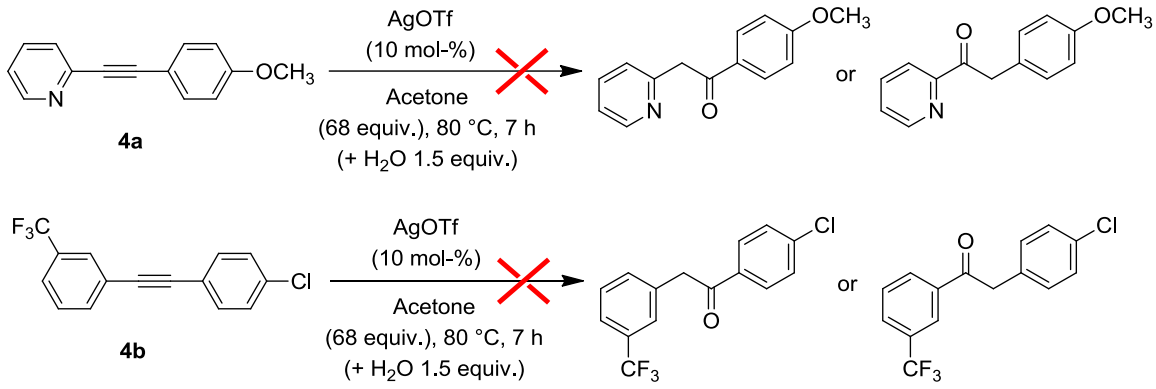
give the intermediate (**III**). A fast protodemetallation, maybe assisted by the acidic proton of the nucleophile,[12] leads to the 1-acylsubstituted-isochromene **2** and regenerates the catalyst. Alternatively, following path B, the isochromenylium (**I**) can be hydrated to give the ketoaldehyde (**IV**)[9,23] which then attacks as a nucleophile a second isochromenylium intermediate (**I**), yielding the dimeric compound **3**. Thus, in this cascade process the silver catalyst plays a double role: 1. as π-philic activator of the triple bond able to promote the formation of the isochromenylium intermediate (**I**) and 2. as σ-philic activator of the carbonyl oxygen, able to promote a fast keto-enolic equilibria in the ketone. And worth noting, both of them are *equally important* for the success of the transformation.



Scheme 3. Suggested reaction paths.

Regarding the hydration step, a possible formation of intermediate **IV** by direct silver catalyzed hydration of the triple bond was ruled out based on the results of the following experiments. When alkynes **4a** or **4b** (Scheme 4) were reacted in the presence of silver triflate under the standard reaction conditions, the corresponding possible hydration products were never observed. Also when the reaction was performed in the presence of 1.5 equiv. of water, the starting materials **4a,b** were

quantitatively recovered (Scheme 4). Moreover, a path involving hydration of the isochromenylium intermediate (**I**) well fits with the total regioselectivity observed in this process.



Scheme 4. Control experiments on direct Ag catalyzed hydration of alkynes.

The hydrolytic path B is competitive with the formation of the isochromenes **2** (path A), and the former is the preferred one when the substrate **1** has a pyridine moiety (**1l**,**q**,**r**) or when the alkyne is strongly electron-poor and little polarized (**1p**). The more pronounced nucleophilic character of nitrogen with respect to oxygen is well known as well as the complexation abilities of pyridine. Thus we argued that, probably, the pyridine nitrogen of compounds **1l**,**q**,**r** is able to coordinate to the silver atom so reducing its availability to promote the required enolization of acetone. This inevitably favours path B that implies a cascade addition reaction involving first a small nucleophile like adventitious water, and second an easily formable and more stable conjugated enol such as intermediate **IV**. On the other hand, when the alkyne is extremely electron-poor and little polarized, as in the case of alkynylaldehyde **1p**, the electrophilic properties of the resulting isochromenylium intermediate **I** are reduced. As a result, acetone is probably a too weak nucleophile to react with this isochromenylium intermediate **I**, and therefore path B results favoured also in this case.

Conclusions

In conclusion, we reported here a useful synthesis of 1,3-dicarbosubstituted isochromene derivatives starting from 2-alkynyl(hetero)arylaldehydes and enolizable ketones, by means of a silver(I) catalyzed domino approach. The importance to employ a silver catalyst with well-balanced *oxophilicity* and *alkynephilicity* features[26] such as silver triflate has been pointed out. In the majority of cases, the cascade reaction proceeded under relatively mild reaction condition and with absolute

regioselectivity, yielding the desired products in moderate to good yields. In the presence of 2-alkynyl(hetero)arylaldehydes characterized by the presence of a pyridine moiety or by a particular electronic distribution, the reaction produces diastereoisomeric couples of homodimeric products. The divergent formation of the 1-acylisochromenes and the alternative homodimeric products has been tentatively explained by some experiments and suggesting two conceivable competitive paths.

Experimental section

General experimental details

All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under inert atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Also 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 analysis were performed with 300 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), dt (double triplet), dd (double doublet), td (triple doublet), m (multiplet), br (broad), ps (pseudo). ^{13}C NMR analysis were performed with the same instruments at 74.45 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 a ICR-FTMS electrospray equipped instrument. The melting points are uncorrected. For the synthesis of starting materials sees Supporting Information.

General Procedure for the addition/cycloisomerization reactions of alkynylaldehydes 1. The catalyst AgOTf (10 mol%) was added to a stirred solution of the proper 2-alkynylbenzaldehydes **1a-r** (0.46 mmol) in acetone or cyclopentanone ([**1**] = 0.20 M), under a nitrogen atmosphere. The reaction mixture was stirred at 80 °C until no more starting product was detectable by TLC analysis. The reaction mixture was diluted with H_2O (25 mL) and extracted with ethyl acetate (3 × 15 mL). The

organic layer was dried with Na_2SO_4 and then evaporated to dryness under reduced pressure. The crude was purified by flash chromatography over a silica gel column yielding the corresponding product **2** or **3**.

1-(3-(p-tolyl)-1H-isochromen-1-yl)propan-2-one **(2a)**: Eluent for chromatography: hexane–EtOAc (95 : 5). Yellow solid. Yield: 74% (95 mg); mp 108-110 °C (lit.[16] 112-113 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.14–7.28 (m, 4H, H_{ar}), 7.10 (dd, *J* = 7.4, 1.2 Hz, 1H, H_{ar}), 7.06 (ddd, *J* = 7.4, 1.4, 0.7 Hz, 1H, H_{ar}), 6.41 (s, 1H, C_{sp2}-H), 5.85 (dd, *J* = 8.8, 4.6 Hz, 1H, CH-O), 3.30 (dd, *J* = 16.1, 8.8 Hz, 1H, CH_2), 2.78 (dd, *J* = 16.1, 4.6 Hz, 1H, CH_2), 2.37 (s, 3H, CH_3), 2.19 (s, 3H, CH_3). These data are in good agreement with literature values.[16]

1-(3-(4-methoxyphenyl)-1H-isochromen-1-yl)propan-2-one **(2b)**: Eluent for chromatography: hexane–EtOAc (95 : 5). Yellow-orange solid. Yield: 65% (88 mg); mp 103-105 °C (lit.[16] 118-119 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 9.0 Hz, 2H, H_{ar}), 7.21–7.27 (m, 1H, H_{ar}), 7.15 (td, *J* = 7.4, 1.4 Hz, 1H, H_{ar}), 7.09 (dd, *J* = 7.5, 1.0 Hz, 1H, H_{ar}), 7.05 (dd, *J* = 7.4, 0.6 Hz, 1H, H_{ar}), 6.90 (d, *J* = 9.0 Hz, 2H, H_{ar}), 6.34 (s, 1H, C_{sp2}-H), 5.83 (dd, *J* = 8.9, 4.5 Hz, 1H, CH-O), 3.83 (s, 3H, CH_3), 3.30 (dd, *J* = 16.1, 8.9 Hz, 1H, CH_2), 2.79 (dd, *J* = 16.1, 4.5 Hz, 1H, CH_2), 2.19 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 206.3 (C=O), 160.6 (C_q), 151.5 (C_q), 131.3 (C_q), 130.2 (C_q), 128.5 (CH_{ar}), 127.1 (C_q), 126.8 (CH_{ar}), 126.6 (CH_{ar}), 124.0 (CH_{ar}), 123.8 (CH_{ar}), 114.0 (CH_{ar}), 99.1 (CH), 74.3 (CH), 55.6 (CH_3), 47.4 (CH_2), 31.4 (CH_3). MS ESI(+): *m/z* (%) = 294.8 (100) $[M + 1]^+$, 317.0 $[M + Na]^+$ (65). These data are in good agreement with literature values.[16]

1-(3-(3-fluorophenyl)-1H-isochromen-1-yl)propan-2-one **(2c)**: Eluent for chromatography: hexane–EtOAc (95 : 5). Pale yellow solid. Yield: 64% (83 mg); mp 83-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (ddd, *J* = 7.9, 1.6, 1.0 Hz, 1H, H_{ar}), 7.39–7.28 (m, 2H, H_{ar}), 7.25 (dd, *J* = 7.4, 1.4 Hz, 1H, H_{ar}), 7.20 (td, *J* = 7.4, 1.5 Hz, 1H, H_{ar}), 7.12 (dd, *J* = 7.3, 1.2 Hz, 1H, H_{ar}), 7.10–6.98 (m, 2H, H_{ar}), 6.46 (s, 1H, C_{sp2}-H), 5.86 (dd, *J* = 8.6, 4.6 Hz, 1H, CH-O), 3.28 (dd, *J* = 16.2, 8.7 Hz, 1H, CH_2), 2.82 (dd, *J* = 16.2, 4.7 Hz, 1H, CH_2), 2.19 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 205.8 (C=O), 163.2 (d, $^1J_{C,F}$ = 245.2 Hz, CF), 150.2 (d, $^4J_{C,F}$ = 2.9 Hz, C_q), 136.8 (d, $^3J_{C,F}$ = 7.9 Hz, C_q), 130.6 (C_q), 130.5 (C_q), 130.1 (d, $^3J_{C,F}$ = 8.3 Hz, CH_{ar}), 128.6 (CH_{ar}), 127.4 (CH_{ar}), 124.6 (CH_{ar}), 123.9 (CH_{ar}), 120.8 (d, $^4J_{C,F}$ = 2.9 Hz, CH_{ar}), 115.9 (d, $^2J_{C,F}$ = 21.4 Hz, CH_{ar}), 112.1 (d, $^2J_{C,F}$ = 23.3 Hz, CH_{ar}), 101.7 (CH), 74.3 (CH), 47.5 (CH_2), 31.3 (CH_3). MS ESI(+): *m/z* (%) = 304.9 $[M + Na]^+$ (100), 225.1 (40) $[M – CH_2COCH_3]^+$. Anal. Calcd for $C_{18}H_{15}FO_2$: C, 76.58; H, 5.36. Found: C, 76.64; H, 5.32.

1-(3-(3-(trifluoromethyl)phenyl)-1H-isochromen-1-yl)propan-2-one **(2d)**: Eluent for chromatography: hexane–EtOAc (94 : 6). Pale yellow oil. Yield: 64% (98 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1H, H_{ar}), 7.84 (d, *J* = 7.8 Hz, 1H, H_{ar}), 7.58 (d, *J* = 7.7 Hz, 1H, H_{ar}), 7.49 (t, *J* =

7.8 Hz, 1H, H_{ar}), 7.25–7.30 (m, 1H, H_{ar}), 7.21 (td, *J* = 7.4, 1.6 Hz, 1H, H_{ar}), 7.14 (dd, *J* = 7.2, 1.4 Hz, 1H, H_{ar}), 7.08 (d, *J* = 7.3 Hz, 1H, H_{ar}), 6.52 (s, 1H, C_{sp2}-H), 5.88 (dd, *J* = 8.6, 4.7 Hz, 1H, CH-O), 3.28 (dd, *J* = 16.2, 8.8 Hz, 1H, CH_2), 2.85 (dd, *J* = 16.2, 4.7 Hz, 1H, CH_2), 2.19 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 205.8 (C=O), 150.0 (C_q), 135.3 (C_q), 131.1 (q, $^2J_{C,F}$ = 32.3 Hz, C-CF_3), 130.5 (C_q), 130.4 (C_q), 129.2 (CH_{ar}), 128.7 (CH_{ar}), 128.3 (q, $^4J_{C,F}$ = 1.1 Hz, CH_{ar}), 127.9 (q, $^1J_{C,F}$ = 272.5 Hz, CF_3), 127.6 (CH_{ar}), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz, CH_{ar}), 124.7 (CH_{ar}), 124.0 (CH_{ar}), 121.9 (q, $^3J_{C,F}$ = 3.8 Hz, CH_{ar}), 102.1 (CH), 74.4 (CH), 47.6 (CH_2), 31.2 (CH_3). MS ESI(+): *m/z* (%) = 387.0 $[M + Na + CH_3OH]^+$ (100). Anal. Calcd for $C_{19}H_{15}F_3O_2$: C, 68.67; H, 4.55. Found: C, 68.81; H, 4.58.

1-(3-(4-chlorophenyl)-1H-isochromen-1-yl)propan-2-one **(2e)**: Eluent for chromatography: hexane–EtOAc (98 : 2). Yellowish solid. Yield: 70% (96 mg); mp 77-78 °C (lit.[16] 89-90 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.9 Hz, 2H, H_{ar}), 7.34 (d, *J* = 8.9 Hz, 2H, H_{ar}), 7.26 (td, *J* = 7.4, 1.5 Hz, 1H, H_{ar}), 7.19 (td, *J* = 7.4, 1.5 Hz, 1H, H_{ar}), 7.11 (dd, *J* = 7.3, 1.4 Hz, 1H, H_{ar}), 7.06 (dd, *J* = 7.4, 0.7 Hz, 1H, H_{ar}), 6.43 (s, 1H, C_{sp2}-H), 5.85 (dd, *J* = 8.8, 4.4 Hz, 1H, CH-O), 3.28 (dd, *J* = 16.2, 8.8 Hz, 1H, CH_2), 2.80 (dd, *J* = 16.2, 4.4 Hz, 1H, CH_2), 2.19 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 206.0 (C=O), 150.4 (C_q), 134.9 (C_q), 132.9 (C_q), 130.7 (C_q), 130.4 (C_q), 128.9 (CH_{ar}), 128.6 (CH_{ar}), 127.3 (CH_{ar}), 126.5 (CH_{ar}), 124.5 (CH_{ar}), 123.9 (CH_{ar}), 101.1 (CH), 74.3 (CH), 47.5 (CH_2), 31.3 (CH_3). MS ESI(+): *m/z* (%) = 298.9 (100) $[M + H]^+$. These data are in good agreement with literature values.[16]

1-(3-(4-nitrophenyl)-1H-isochromen-1-yl)propan-2-one **(2f)**: Eluent for chromatography: hexane–EtOAc (95 : 5). Yellow solid. Yield: 45% (64 mg); mp 129-132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.8 Hz, 2H, H_{ar}), 7.79 (d, *J* = 8.8 Hz, 2H, H_{ar}), 7.33–7.20 (m, 2H, H_{ar}), 7.16 (d, *J* = 6.7 Hz, 1H, H_{ar}), 7.08 (d, *J* = 6.9 Hz, 1H, H_{ar}), 6.62 (s, 1H, C_{sp2}-H), 5.89 (dd, *J* = 8.8, 4.4 Hz, 1H, CH-O), 3.27 (dd, *J* = 16.5, 8.8 Hz, 1H, CH_2), 2.83 (dd, *J* = 16.5, 4.4 Hz, 1H, CH_2), 2.20 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 205.6 (C=O), 149.2 (C_q), 147.8 (C_q), 140.5 (C_q), 130.7 (C_q), 130.0 (C_q), 128.8 (CH_{ar}), 128.3 (CH_{ar}), 125.6 (CH_{ar}), 125.2 (CH_{ar}), 124.0 (CH_{ar}), 104.5 (CH), 74.3 (CH), 47.6 (CH_2), 31.2 (CH_3) (one CH_{ar} overlapped). MS ESI(+): *m/z* (%) = 252.0 (100) $[M - CH_2COCH_3]^+$. Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.81; H, 4.94; N, 4.47.

1-(3-(4-(methylsulfonyl)phenyl)-1H-isochromen-1-yl)propan-2-one **(2g)**: Eluent for chromatography: hexane–EtOAc (70 : 30). Pale yellow wax. Yield: 79% (124 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.6 Hz, 2H, H_{ar}), 7.83 (d, *J* = 8.6 Hz, 2H, H_{ar}), 7.33–7.19 (m, 2H, H_{ar}), 7.15 (dd, *J* = 7.1, 1.5 Hz, 1H, H_{ar}), 7.08 (d, *J* = 7.1 Hz, 1H, H_{ar}), 6.60 (s, 1H, C_{sp2}-H), 5.90 (dd, *J* = 8.8, 4.4 Hz, 1H, CH-O), 3.27 (dd, *J* = 16.2, 8.8 Hz, 1H, CH_2), 3.06 (s, 3H, CH_3), 2.83 (dd, *J* = 16.2, 4.4 Hz, 1H, CH_2), 2.20 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 205.6 (C=O), 149.4 (C_q),

140.3 (C_q), 139.7 (C_q), 130.7 (C_q), 130.1 (C_q), 128.8 (CH_{ar}), 128.1 (CH_{ar}), 127.8 (CH_{ar}), 125.7 (CH_{ar}), 125.0 (CH_{ar}), 124.0 (CH_{ar}), 103.9 (CH), 74.3 (CH), 47.6 (CH_2), 44.7 (CH_3), 31.2 (CH_3). MS ESI(+): *m/z* (%) = 342.9 $[M + H]^+$ (100), 365.2 $[M + Na]^+$ (40). Anal. Calcd for $C_{19}H_{18}O_4S$: C, 66.65; H, 5.30. Found: C, 66.78; H, 5.39.

1-(3-propyl-1H-isochromen-1-yl)propan-2-one **(2j)**: Eluent for chromatography: hexane–EtOAc (93 : 7). Yellow oil. Yield: 29% (31 mg). ^{1}H NMR (300 MHz, C_6D_6): δ = 7.01 (td, *J* = 7.5, 1.3 Hz, 1H, H_{ar}), 6.90 (td, *J* = 7.5, 1.3 Hz, 1H, H_{ar}), 6.79 (d, *J* = 7.5 Hz, 1H, H_{ar}), 6.70 (ddd, *J* = 6.9, 1.2, 0.6 Hz, 1H, H_{ar}), 5.64 (dd, *J* = 8.4, 4.9 Hz, 1H, CH-O), 5.45 (s, 1H, C_{sp2}-H), 2.79 (dd, *J* = 16.0, 8.4 Hz, 1H, CH_2), 2.28 (dd, *J* = 16.0, 4.9 Hz, 1H, CH_2), 1.98 (td, *J* = 7.2, 4.3 Hz, 2H, CH_2), 1.62 (s, 3H, CH_3), 1.45 (ddd, *J* = 15.0, 7.5, 3.0 Hz, 2H, CH_2), 0.80 (t, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (75.45 MHz, C_6D_6): δ = 203.4 (C=O), 156.2 (C_q), 131.3 (C_q), 129.9 (C_q), 126.0 (CH_{ar}), 123.9 (CH_{ar}), 123.1 (CH_{ar}), 100.8 (CH), 73.9 (CH), 47.5 (CH_2), 36.0 (CH_2), 30.0 (CH_3), 20.2 (CH_2), 13.6 (CH_3) (one CH_{ar} obscured). MS ESI(+): *m/z* (%) = 252.9 $[M + Na]^+$ (50). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.36; H, 7.91.

1-(7-methoxy-3-(4-methoxyphenyl)-1H-isochromen-1-yl)propan-2-one **(2m)**: Eluent for chromatography: hexane–EtOAc (80 : 20). Brownish wax. Yield: 26% (39 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.3 Hz, 2H, H_{ar}), 7.03 (d, *J* = 8.3 Hz, 1H, H_{ar}), 6.89 (d, *J* = 8.3 Hz, 2H, H_{ar}), 6.79 (dd, *J* = 8.3, 2.2 Hz, 1H, H_{ar}), 6.64 (d, *J* = 2.4 Hz, 1H, H_{ar}), 6.31 (s, 1H, C_{sp2}-H), 5.79 (dd, *J* = 8.8, 4.5 Hz, 1H, CH-O), 3.82 (d, *J* = 0.8 Hz, 3H, CH_3), 3.80 (d, *J* = 0.8 Hz, 3H, CH_3), 3.28 (dd, *J* = 16.1, 8.9 Hz, 1H, CH_2), 2.74 (dd, *J* = 16.1, 4.5 Hz, 1H, CH_2), 2.18 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 206.4 (C=O), 160.2 (C_q), 158.7 (C_q), 149.3 (C_q), 131.9 (C_q), 127.3 (C_q), 126.4 (CH_{ar}), 125.3 (CH_{ar}), 124.2 (C_q), 114.0 (CH_{ar}), 113.6 (CH_{ar}), 110.1 (CH_{ar}), 98.9 (CH), 74.2 (CH), 55.7 (CH_3), 55.5 (CH_3), 47.4 (CH_2), 31.4 (CH_3). MS ESI(+): *m/z* (%) = 325.1 $[M + H]^+$ (60). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.88; H, 6.17.

1-(3-(3-fluorophenyl)-7-methoxy-1H-isochromen-1-yl)propan-2-one **(2n)**: Eluent for chromatography: hexane–EtOAc (90 : 10). White solid. Yield: 58% (83 mg); mp 97-99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 8.1, 1.3 Hz, 1H, H_{ar}), 7.37–7.27 (m, 2H, H_{ar}), 7.06 (d, *J* = 8.4 Hz, 1H, H_{ar}), 6.99 (tdd, *J* = 8.3, 2.6, 1.0 Hz, 1H, H_{ar}), 6.80 (dd, *J* = 8.3, 2.6 Hz, 1H, H_{ar}), 6.65 (d, *J* = 2.5 Hz, 1H, H_{ar}), 6.43 (s, 1H, C_{sp2}-H), 5.81 (dd, *J* = 8.6, 4.6 Hz, 1H, CH-O), 3.81 (s, 3H, CH_3), 3.25 (dd, *J* = 16.2, 8.6 Hz, 1H, CH_2), 2.77 (dd, *J* = 16.2, 4.7 Hz, 1H, CH_2), 2.18 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 206.0 (C=O), 163.2 (d, $^1J_{C,F}$ = 245.0 Hz, CF), 159.3 (C_q), 148.1 (d, $^4J_{C,F}$ = 2.9 Hz, C_q), 137.0 (d, $^3J_{C,F}$ = 8.0 Hz, C_q), 132.3 (C_q), 130.1 (d, $^3J_{C,F}$ = 8.3 Hz, CH_{ar}), 125.9 (CH_{ar}), 123.4 (C_q), 120.4 (d, $^4J_{C,F}$ = 2.6 Hz, CH_{ar}), 115.4 (d, $^2J_{C,F}$ = 21.2 Hz, CH_{ar}), 113.7 (CH_{ar}), 111.7 (d,

$^{2}J_{C,F}$ = 23.2 Hz, CH_{ar}), 110.2 (CH_{ar}), 101.5 (CH), 74.2 (CH), 55.7 (CH_3), 47.5 (CH_2), 31.4 (CH_3). MS ESI(+): *m/z* (%) = 335.2 (100) $[M + Na]^+$. Anal. Calcd for $C_{19}H_{17}FO_3$: C, 73.06; H, 5.49. Found: C, 73.17; H, 5.51.

1-(7-fluoro-3-(4-methoxyphenyl)-1H-isochromen-1-yl)propan-2-one **(2o)**: Eluent for chromatography: hexane–EtOAc (90 : 10). Pale yellow solid. Yield: 69% (99 mg); mp 96-98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 9.0 Hz, 2H, H_{ar}), 7.05 (dd, *J* = 8.4, 5.5 Hz, 1H, H_{ar}), 6.95 (dd, *J* = 8.6, 2.5 Hz, 1H, H_{ar}), 6.90 (d, *J* = 9.0 Hz, 2H, H_{ar}), 6.80 (dd, *J* = 8.7, 2.5 Hz, 1H, H_{ar}), 6.31 (s, 1H, C_{sp2}-H), 5.78 (dd, *J* = 8.6, 4.7 Hz, 1H, CH-O), 3.83 (s, 3H, CH_3), 3.27 (dd, *J* = 16.3, 8.6 Hz, 1H, CH_2), 2.79 (dd, *J* = 16.3, 4.7 Hz, 1H, CH_2), 2.19 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 205.8 (C=O), 161.7 (d, $^{1}J_{C,F}$ = 245.0 Hz, CF), 160.6 (C_q), 150.9 (d, $^{6}J_{C,F}$ = 2.3 Hz, C_q), 132.2 (d, $^{3}J_{C,F}$ = 6.9 Hz, C_q), 127.5 (d, $^{4}J_{C,F}$ = 2.9 Hz, C_q), 126.9 (C_q), 126.7 (CH_{ar}), 125.4 (d, $^{3}J_{C,F}$ = 7.7 Hz, CH_{ar}), 115.2 (d, $^{2}J_{C,F}$ = 21.8 Hz, CH_{ar}), 114.1 (CH_{ar}), 111.3 (d, $^{2}J_{C,F}$ = 23.2 Hz, CH_{ar}), 98.4 (CH), 73.7 (CH), 55.6 (CH_3), 47.1 (CH_2), 31.4 (CH_3). ESI(+): *m/z* (%) = 335.3 (100) $[M + Na]^+$. Anal. Calcd for $C_{19}H_{17}FO_3$: C, 73.06; H, 5.49. Found: C, 73.21; H, 5.45.

2-(3-(p-tolyl)-1H-isochromen-1-yl)cyclopentanone **(2s)**: Eluent for chromatography: hexane–EtOAc (from 99 : 1 to 90 : 10).

Diast.1: fr.40-45. Yellow oil. Yield: 20% (28 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.31-7.17 (m, 3H, H_{ar}), 7.16-7.08 (m, 2H, H_{ar}), 6.96 (d, *J* = 7.0 Hz, 1H, H_{ar}), 6.32 (s, 1H, C_{sp2}-H), 5.87 (d, *J* = 4.6 Hz, 1H, CH-O), 2.85 (dd, *J* = 9.2, 4.6 Hz, 1H, CH-CO), 2.40 (s, 3H, CH_3), 2.33-2.22 (m, 1H, CH_2), 2.11-1.82 (m, 3H, CH_2), 1.72-1.61 (m, 2H, CH_2). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 217.7 (C=O), 152.1 (C_q), 139.0 (C_q), 131.72 (C_q), 131.66 (C_q), 129.1 (CH_{ar}), 128.3 (CH_{ar}), 128.0 (C_q), 126.4 (CH_{ar}), 125.1 (CH_{ar}), 124.9 (CH_{ar}), 123.7 (CH_{ar}), 99.5 (CH), 76.7 (CH), 55.2 (CH), 38.5 (CH_2), 25.4 (CH_2), 21.3 (CH_3), 20.5 (CH_2). ESI(+): *m/z* (%) = 327.0 (100) $[M + Na]^+$, 304.8 (60) $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.68; H, 6.66.

Diast.2: fr.50-55. Yellow wax. Yield: 48% (67 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.32-7.14 (m, 4H, H_{ar}), 7.12-7.07 (m, 2H, H_{ar}), 6.35 (s, 1H, C_{sp2}-H), 5.82 (d, *J* = 2.9 Hz, 1H, CH-O), 2.85 (dt, *J* = 9.3, 2.7 Hz, 1H, CH-CO), 2.52-2.17 (m, 4H, CH_2), 2.39 (s, 3H, CH_3), 2.14-2.00 (m, 1H, CH_2), 1.87-1.77 (m, 1H, CH_2). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 218.7 (C=O), 153.1 (C_q), 139.0 (C_q), 131.3 (C_q), 131.2 (C_q), 129.4 (C_q), 129.1 (CH_{ar}), 128.2 (CH_{ar}), 126.4 (CH_{ar}), 125.0 (CH_{ar}), 123.9 (CH_{ar}), 123.4 (CH_{ar}), 99.6 (CH), 76.9 (CH), 52.3 (CH), 39.4 (CH_2), 24.2 (CH_2), 21.3 (CH_3), 20.5 (CH_2). ESI(+): *m/z* (%) = 327.0 (50) $[M + Na]^+$, 304.9 (100) $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.75; H, 6.64.

2-(2-oxo-2-(pyridin-2-yl)-1-(3-(pyridin-2-yl)-1H-isochromen-1-yl)ethyl)benzaldehyde **(3a)**: Reaction time: 24 h. Eluent for chromatography: hexane–EtOAc (90 : 10 → 80 : 20).

Diast.1: fr.50-54. Pale green solid. Yield: 13% (13 mg); mp 130 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.65 (s, 1H, CHO), 8.52 (d, *J* = 4.7 Hz, 1H, H_{ar}), 8.38 (d, *J* = 4.7 Hz, 1H, H_{ar}), 7.93 (d, *J* = 7.7 Hz, 1H, H_{ar}), 7.81 (d, *J* = 8.4 Hz, 1H, H_{ar}), 7.76–7.53 (m, 4H, H_{ar}), 7.40–7.06 (m, 8H, H_{ar}), 7.03 (d, *J* = 10.3 Hz, 1H, H_{ar}), 6.44 (pst, 2H, CH). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 197.8 (C=O), 190.9 (CHO), 151.9 (C_q), 151.4 (C_q), 150.0 (C_q), 149.3 (CH_{ar}), 149.0 (CH_{ar}), 138.6 (C_q), 137.1 (CH_{ar}), 136.4 (CH_{ar}), 135.6 (C_q), 133.6 (CH_{ar}), 130.9 (C_q), 130.5 (C_q), 128.93 (CH_{ar}), 128.87 (CH_{ar}), 128.76 (CH_{ar}), 127.7 (CH_{ar}), 127.5 (CH_{ar}), 127.4 (CH_{ar}), 126.2 (CH_{ar}), 125.6 (CH_{ar}), 123.4 (CH_{ar}), 122.7 (CH_{ar}), 119.2 (CH_{ar}), 104.4 (CH), 78.5 (CH), 48.5 (CH). MS ESI(+): *m/z* (%) = 433.0 $[M + H]^+$ (100), 455.2 $[M + Na]^+$ (50). HRMS ESI $(M + H)^+$ calculated for $C_{28}H_{21}N_2O_3$ 433.1546, found 433.1549.

Diast.2: fr.63-73. Green solid. Yield: 54% (54 mg); mp 100 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.18 (s, 1H, CHO), 8.50 (d, *J* = 4.7 Hz, 1H, H_{ar}), 8.31 (d, *J* = 4.7 Hz, 1H, H_{ar}), 8.08 (d, *J* = 7.9 Hz, 1H, H_{ar}), 7.76–7.61 (m, 3H, H_{ar}), 7.53 (td, *J* = 7.6, 1.5 Hz, 1H, H_{ar}), 7.46 (td, *J* = 7.7, 1.7 Hz, 1H, H_{ar}), 7.37 (d, *J* = 7.9 Hz, 1H, H_{ar}), 7.35–7.09 (m, 6H, H_{ar}), 7.07 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H, H_{ar}), 6.75 (td, *J* = 7.3, 1.5 Hz, 1H, H_{ar}), 6.25 (d, *J* = 10.4 Hz, 1H, CH), 6.10 (d, *J* = 7.5 Hz, 1H, CH). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 198.5 (C=O), 190.6 (CHO), 152.5 (C_q), 152.0 (C_q), 149.5 (C_q), 149.3 (CH_{ar}), 137.0 (C_q), 136.9 (CH_{ar}), 136.7 (CH_{ar}), 135.5 (C_q), 133.6 (CH_{ar}), 130.4 (C_q), 129.1 (CH_{ar}), 128.9 (CH_{ar}), 128.8 (CH_{ar}), 128.1 (CH_{ar}), 127.9 (C_q), 127.4 (CH_{ar}), 126.5 (CH_{ar}), 125.7 (CH_{ar}), 125.3 (CH_{ar}), 123.2 (CH_{ar}), 122.4 (CH_{ar}), 119.3 (CH_{ar}), 103.2 (CH), 79.6 (CH), 45.1 (CH) (one CH_{ar} obscured). MS ESI(+): *m/z* (%) = 433.0 $[M + H]^+$ (100), 455.2 $[M + Na]^+$ (50). HRMS ESI $(M + H)^+$ calculated for $C_{28}H_{21}N_2O_3$ 433.1546, found 433.1541.

5-fluoro-2-(1-(7-fluoro-3-(3-(trifluoromethyl)phenyl)-1H-isochromen-1-yl)-2-oxo-2-(3-(trifluoromethyl)phenyl)ethyl)benzaldehyde **(3b)**: Reaction time: 6 h. Eluent for chromatography: hexane–EtOAc (70 : 30).

Diast.1: fr.19-24. Yellow solid. Yield: 23% (32 mg); mp 106-108 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.46 (s, 1H, CHO), 8.16 (s, 1H, H_{ar}), 8.04 (d, *J* = 7.9 Hz, 1H, H_{ar}), 7.94 (dd, *J* = 8.7, 5.1 Hz, 1H, H_{ar}), 7.67 (d, *J* = 7.8 Hz, 1H, H_{ar}), 7.56–7.33 (m, 5H, H_{ar}), 7.20–7.08 (m, 3H, H_{ar}), 7.02–6.86 (m, 3H, CH + H_{ar}), 6.68 (s, 1H, CH), 6.22 (d, *J* = 10.0 Hz, 1H, CH). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 197.2 (C=O), 192.0 (CHO), 162.5 (d, $^1J_{C,F}$ = 251.9 Hz, CF), 161.9 (d, $^1J_{C,F}$ = 247.6 Hz, CF), 148.5 (C_q), 137.0 (C_q), 136.2 (d, $^3J_{C,F}$ = 4.7 Hz, C_q), 134.4 (C_q), 132.1 (d, $^3J_{C,F}$ = 7.4 Hz, CH_{ar}), 131.9 (CH_{ar}), 131.5 (d, $^3J_{C,F}$ = 7.4 Hz, C_q), 131.5 (C_q), 131.5 (q, $^2J_{C,F}$ = 33.0 Hz, C-CF_3), 131.0 (q, $^2J_{C,F}$ = 33.0 Hz, C-CF_3), 130.2 (q, $^3J_{C,F}$ = 3.3 Hz, CH_{ar}), 129.5 (CH_{ar}), 128.8 (CH_{ar}), 127.5 (CH_{ar}), 126.7 (d, $^3J_{C,F}$ = 8.0

Hz, CH_{ar}), 126.2 (d, $^4J_{C,F}$ = 3.1 Hz, C_q), 125.9 (q, $^3J_{C,F}$ = 3.9 Hz, CH_{ar}), 125.5 (q, $^3J_{C,F}$ = 3.5 Hz, CH_{ar}), 123.7 (q, $^1J_{C,F}$ = 272.8 Hz, CF_3), 122.4 (d, $^2J_{C,F}$ = 21.7 Hz, CH_{ar}), 121.6 (d, $^2J_{C,F}$ = 21.1 Hz, CH_{ar}), 121.2 (q, $^3J_{C,F}$ = 3.8 Hz, CH_{ar}), 115.9 (d, $^2J_{C,F}$ = 22.0 Hz, CH_{ar}), 113.8 (d, $^2J_{C,F}$ = 23.4 Hz, CH_{ar}), 102.0 (CH), 79.4 (CH), 48.8 (CH) (one CF_3 obscured). MS ESI(+): *m/z* (%) = 603.3 $[M + H]^+$ (100). HRMS ESI $(M + H)^+$ calculated for $C_{32}H_{19}F_8O_3$ 603.1201, found 603.1205.

Diast.2: fr.26-33. Yellow wax. Yield: 16% (22 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.54 (s, 1H, CHO), 8.28 (s, 1H, H_{ar}), 8.11 (d, *J* = 7.8 Hz, 1H, H_{ar}), 7.91 (dd, *J* = 8.6, 5.2 Hz, 1H, H_{ar}), 7.62–7.65 (m, 3H, H_{ar}), 7.46–7.23 (m, 5H, H_{ar}), 7.11 (d, *J* = 9.9 Hz, 1H, H_{ar}), 7.07 (dd, *J* = 8.2, 5.2 Hz, 1H, H_{ar}), 6.87 (td, *J* = 8.5, 2.6 Hz, 1H, H_{ar}), 6.65 (s, 1H, CH), 6.08 (d, *J* = 9.7 Hz, 1H, CH), 5.79 (dd, *J* = 8.7, 2.5 Hz, 1H, CH). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 197.1 (C=O), 191.4 (CHO), 162.6 (d, $^1J_{C,F}$ = 252.2 Hz, CF), 161.1 (d, $^1J_{C,F}$ = 247.3 Hz, CF), 148.5 (C_q), 137.2 (C_q), 136.3 (d, $^3J_{C,F}$ = 5.4 Hz, C_q), 134.5 (C_q), 132.0 (d, $^3J_{C,F}$ = 7.4 Hz, CH_{ar}), 131.9 (CH_{ar}), 131.6 (q, $^2J_{C,F}$ = 32.6 Hz, C-CF_3), 131.0 (q, $^2J_{C,F}$ = 32.4 Hz, C-CF_3), 130.6 (d, $^4J_{C,F}$ = 3.4 Hz, C_q), 130.2 (q, $^3J_{C,F}$ = 3.1 Hz, CH_{ar}), 129.6 (CH_{ar}), 129.3 (d, $^3J_{C,F}$ = 7.2 Hz, C_q), 128.9 (CH_{ar}), 127.9 (CH_{ar}), 127.1 (d, $^4J_{C,F}$ = 3.1 Hz, C_q), 126.0 (d, $^3J_{C,F}$ = 7.7 Hz, CH_{ar}), 125.7 (q, $^3J_{C,F}$ = 4.0 Hz, CH_{ar}), 125.5 (q, $^3J_{C,F}$ = 3.4 Hz, CH_{ar}), 124.0 (q, $^1J_{C,F}$ = 272.8 Hz, CF_3), 123.6 (q, $^1J_{C,F}$ = 272.5 Hz, CF_3), 122.3 (d, $^2J_{C,F}$ = 21.8 Hz, CH_{ar}), 121.7 (q, $^3J_{C,F}$ = 4.0 Hz, CH_{ar}), 121.3 (d, $^2J_{C,F}$ = 21.2 Hz, CH_{ar}), 115.7 (d, $^2J_{C,F}$ = 21.8 Hz, CH_{ar}), 112.9 (d, $^2J_{C,F}$ = 23.2 Hz, CH_{ar}), 101.5 (CH), 80.3 (CH), 45.1 (CH). MS ESI(+): *m/z* (%) = 603.4 $[M + H]^+$ (100). HRMS ESI $(M + H)^+$ calculated for $C_{32}H_{19}F_8O_3$ 603.1201, found 603.1206.

2-(2-(4-methoxyphenyl)-1-(7-(4-methoxyphenyl)-5H-pyrano[4,3-b]pyridin-5-yl)-2-oxoethyl)-nicotinaldehyde **(3c)**: Reaction time: 7 h. Eluent for chromatography: hexane–EtOAc (70 : 30).

Diast.1: fr.16-28. Ochre solid. Yield: 38% (43 mg); mp 130-134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.79 (s, 1H, CHO), 8.84 (d, *J* = 4.5 Hz, 1H, H_{ar}), 8.37 (d, *J* = 4.8 Hz, 1H, H_{ar}), 7.87 (d, *J* = 7.9 Hz, 1H, H_{ar}), 7.83 (d, *J* = 8.8 Hz, 2H, H_{ar}), 7.70 (d, *J* = 7.4 Hz, 1H, H_{ar}), 7.39 (dd, *J* = 7.6, 4.8 Hz, 1H, H_{ar}), 7.06 (d, *J* = 8.5 Hz, 2H, H_{ar}), 6.97 (dd, *J* = 7.2, 5.1 Hz, 1H, H_{ar}), 6.82–6.60 (m, 7H, H_{ar} + CH), 3.80 (s, 3H, CH_3), 3.73 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 193.9 (C=O), 191.1 (CHO), 163.9 (C_q), 161.0 (C_q), 156.5 (C_q), 155.8 (C_q), 153.8 (CH_{ar}), 150.6 (C_q), 149.3 (CH_{ar}), 141.1 (CH_{ar}), 134.7 (CH_{ar}), 131.2 (CH_{ar}), 130.8 (C_q), 129.8 (C_q), 126.8 (CH_{ar}), 125.6 (C_q), 124.8 (C_q), 122.7 (CH_{ar}), 121.0 (CH_{ar}), 114.0 (CH_{ar}), 113.7 (CH_{ar}), 100.6 (C_{sp2}-H), 79.1 (CH), 55.6 (CH_3), 55.5 (CH_3), 53.0 (CH). MS ESI(+): *m/z* (%) = 493.1 $[M + H]^+$ (100). HRMS ESI $(M + H)^+$ calculated for $C_{30}H_{25}N_2O_5$ 493.1758, found 493.1763.

Diast.2: fr.48-91. Dark orange solid. Yield: 52% (59 mg); mp 101-103 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.74 (s, 1H, CHO), 8.75 (dd, *J* = 4.8, 1.8 Hz, 1H, H_{ar}), 8.24 (dd, *J* = 4.9, 1.3 Hz, 1H, H_{ar}),

7.91 (d, J = 8.9 Hz, 2H, H_{ar}), 7.81 (dd, J = 7.8, 1.8 Hz, 1H, H_{ar}), 7.54 (d, J = 8.9 Hz, 2H, H_{ar}), 7.31 (dd, J = 7.7, 4.8 Hz, 1H, H_{ar}), 6.85 (d, J = 9.1 Hz, 1H, H_{ar}), 6.77 (d, J = 8.9 Hz, 2H, H_{ar}), 6.74 (d, J = 8.9 Hz, 2H, H_{ar}), 6.64 (m, 2H, H_{ar}), 6.57 (dd, J = 7.5, 4.9 Hz, 1H, CH), 6.39 (d, J = 7.0 Hz, 1H, CH), 3.76 (s, 3H, CH_3), 3.72 (s, 3H, CH_3). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 193.4 (C=O), 190.5 (CHO), 163.8 (C_q), 161.1 (C_q), 156.5 (C_q), 155.6 (C_q), 153.3 (CH_{ar}), 151.3 (C_q), 149.1 (CH_{ar}), 141.1 (CH_{ar}), 132.6 (CH_{ar}), 131.2 (CH_{ar}), 130.3 (C_q), 130.1 (C_q), 127.7 (CH_{ar}), 126.2 (C_q), 123.0 (CH_{ar}), 122.9 (C_q), 119.7 (CH_{ar}), 114.1 (CH_{ar}), 114.0 (CH_{ar}), 99.9 (C_{sp2}-H), 78.6 (CH), 55.6 (CH_3), 55.5 (CH_3), 50.6 (CH). MS ESI(+): *m/z* (%) = 493.3 $[M + H]^+$ (100). HRMS ESI $(M + H)^+$ calculated for $C_{30}H_{25}N_2O_5$ 493.1758, found 493.1754.

2-(2-(3-fluorophenyl)-1-(7-(3-fluorophenyl)-5H-pyrano[4,3-b]pyridin-5-yl)-2-oxoethyl)nicotinaldehyde **(3d)**: Reaction time: 3 h. Eluent for chromatography: hexane–EtOAc (70 : 30).

Diast.1: fr.13-15. Dark orange solid. Yield: 20% (22 mg); mp 90-93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.67 (s, 1H, CHO), 8.83 (dd, J = 4.8, 1.8 Hz, 1H, H_{ar}), 7.88 (dd, J = 7.8, 1.8 Hz, 1H, H_{ar}), 7.77 (d, J = 7.6 Hz, 1H, H_{ar}), 7.61 (td, J = 7.7, 1.4 Hz, 1H, H_{ar}), 7.56 (ddd, J = 9.7, 2.5, 1.7 Hz, 1H, H_{ar}), 7.45 (dd, J = 7.8, 4.8 Hz, 1H, H_{ar}), 7.28–7.17 (m, 3H, H_{ar}), 7.15–7.04 (m, 3H, H_{ar}), 6.99 (td, J = 8.2, 2.6 Hz, 1H, H_{ar}), 6.83 (m, 2H, CH + H_{ar}), 6.70–6.56 (m, 2H, CH). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 194.5 (C=O), 191.5 (CHO), 162.9 (d, $^1J_{C,F}$ = 248.5 Hz, CF), 162.8 (d, $^1J_{C,F}$ = 245.6 Hz, CF), 155.4 (C_q), 154.6 (C_q), 153.8 (CH_{ar}), 149.8 (C_q), 149.3 (CH_{ar}), 142.3 (CH_{ar}), 138.7 (d, $^3J_{C,F}$ = 6.3 Hz, C_q), 135.4 (d, $^3J_{C,F}$ = 8.0 Hz, C_q), 135.1 (CH_{ar}), 130.6 (C_q), 130.5 (d, $^3J_{C,F}$ = 7.7 Hz, CH_{ar}), 130.0 (d, $^3J_{C,F}$ = 8.0 Hz, CH_{ar}), 125.1 (C_q), 125.4 (d, $^4J_{C,F}$ = 2.9 Hz, CH_{ar}), 123.2 (CH_{ar}), 121.9 (CH_{ar}), 120.9 (d, $^4J_{C,F}$ = 2.9 Hz, CH_{ar}), 120.7 (d, $^2J_{C,F}$ = 21.6 Hz, CH_{ar}), 116.7 (d, $^2J_{C,F}$ = 21.3 Hz, CH_{ar}), 115.5 (d, $^2J_{C,F}$ = 22.7 Hz, CH_{ar}), 112.0 (d, $^2J_{C,F}$ = 23.7 Hz, CH_{ar}), 103.1 (CH), 79.0 (CH), 53.8 (CH). MS ESI(+): *m/z* (%) = 469.1 (100) $[M + H]^+$. HRMS ESI $(M + H)^+$ calculated for $C_{28}H_{19}N_2F_2O_3$ 469.1358, found 469.1355.

Diast.2: fr.29-51. Pale orange solid. Yield: 37% (40 mg); mp 108-111 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.67 (s, 1H, CHO), 8.74 (dd, J = 4.8, 1.8 Hz, 1H, H_{ar}), 8.28 (dd, J = 4.9, 1.5 Hz, 1H, H_{ar}), 7.83 (dd, J = 7.8, 1.8 Hz, 1H, H_{ar}), 7.65 (t, J = 8.5 Hz, 2H, H_{ar}), 7.43–7.33 (m, 2H, H_{ar}), 7.30–7.17 (m, 3H, H_{ar}), 7.07 (td, J = 7.5, 1.8 Hz, 1H, H_{ar}), 6.98 (td, J = 8.3, 2.1 Hz, 1H, H_{ar}), 6.91 (d, J = 9.0 Hz, 1H, H_{ar}), 6.76 (s, 1H, CH), 6.63 (d, J = 7.6 Hz, 1H, CH), 6.61 (d, J = 8.9 Hz, 1H, H_{ar}), 6.38 (d, J = 7.6 Hz, 1H, CH). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ = 193.8 (C=O), 190.9 (CHO), 163.00 (d, $^1J_{C,F}$ = 245.3 Hz, CF), 162.98 (d, $^1J_{C,F}$ = 248.5 Hz, CF), 154.7 (C_q), 153.3 (CH_{ar}), 150.7 (C_q), 149.6 (CH_{ar}), 142.1 (CH_{ar}), 138.9 (d, $^3J_{C,F}$ = 6.3 Hz, C_q), 135.8 (d, $^3J_{C,F}$ = 8.0 Hz, C_q), 132.5 (CH_{ar}), 130.5 (d, $^3J_{C,F}$

= 7.6 Hz, CH_{ar}), 130.2 (d, $^3J_{C,F}$ = 8.3 Hz, CH_{ar}), 130.2 (C_q), 124.5 (d, $^4J_{C,F}$ = 2.9 Hz, CH_{ar}), 123.3 (CH_{ar}), 123.0 (C_q), 121.5 (d, $^4J_{C,F}$ = 2.8 Hz, CH_{ar}), 120.5 (d, $^2J_{C,F}$ = 18.6 Hz, CH_{ar}), 120.4 (CH_{ar}), 116.8 (d, $^2J_{C,F}$ = 21.3 Hz, CH_{ar}), 115.6 (d, $^2J_{C,F}$ = 22.6 Hz, CH_{ar}), 112.7 (d, $^2J_{C,F}$ = 23.5 Hz, CH_{ar}), 102.8 (CH), 78.6 (CH), 51.4 (CH) (one C_q obscured). MS ESI(+): *m/z* (%) = 469.3 (100) $[M + H]^+$. HRMS ESI $(M + H)^+$ calculated for $C_{28}H_{19}N_2F_2O_3$ 469.1358, found 469.1353.

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