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Silver comes into play: Henry reaction and domino cycloisomerisation sequence catalysed by [Ag(ɪ)(Pc-L)] complexes†

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We report herein the synthesis of new pyridine-containing macrocyclic ligands (Pc-L) bearing a non-innocent pendant arm, by exploiting both chiral and functional properties of natural amino acids. The obtained macrocyclic ligands were employed to synthesize well-defined cationic silver(ɪ) complexes that were shown to be competent catalysts for the Henry (nitroaldol) reaction. Good to excellent yields and full selectivity in the β-nitroalcohol product were obtained starting from electron-poor aromatic aldehydes or other activated aldehydes such as furfural under mild reaction conditions. The straightforward synthesis of the macrocyclic ligands starting from cheap commercially available starting materials allowed the introduction of a suitable basic functionality into the ligand pendant arm, thus providing a bifunctional catalyst. Based on our previous experience in the [Ag(ɪ)(Pc-L)] catalysed domino addition/cycloisomerisation reaction of *o*-alkynylbenzaldehydes and nucleophiles, the synthesis of isochromenes coupling the Henry reaction and the cycloisomerisation in a single step was subsequently explored. Although with low selectivity, [Ag(ɪ)(Pc-L)] cationic complexes were able to promote such a cascade reaction and a possible mechanism based on experimental evidence has been proposed.

Introduction

Carbon–carbon bond forming reactions, due to their unique capability of generating molecular complexity, represent a powerful tool in the reserves of a synthetic chemist.[1,2] The last decade has witnessed considerable advances in the catalytic generation and enantioselective addition of carbon nucleophiles (*i.e.*, enolates[3] and nitronates[4]) to different types of electrophiles. In this context, nitroalkanes are important reagents not only due to their propensity to undergo easy α-dehydrogenation but also for their facile interconversion to other organic functional groups.[5,6] Even weak bases are capable of abstracting a proton in the α-position of a nitro group (pK_a ∼ 10) and the nucleophilic attack of the generated nitronate anion on a carbonyl compound to give a β-nitro alcohol is referred to as the Henry (or nitroaldol) reaction.[7] Although more than one century old, this reaction is still to be considered one of the most important examples of an atom-economical

transformation.[8–10] No need for a stoichiometric amount of a base, metal-catalysts,[11–15] enzymes[16,17] or organocatalysts[18–20] can efficiently promote the Henry reaction. Among the metal complexes commonly employed as catalysts, copper(ɪ)[21–30] and copper(ɪɪ)[11,31–44] complexes play a prominent role, whereas, to the best of our knowledge the activity of silver salts and complexes have rarely been tested. In several cases reported in the literature, the replacement of Cu with Zn gave comparable results but in some of them a reversed enantioselectivity was observed.[27,32,33,42,45] Cu-catalysed reactions are believed to proceed by a monometallic form of active species whereas there is strong evidence of the involvement of a multimetallic species as actual catalyst in Zn(ɪɪ) promoted Henry reactions.[26] Surprisingly, such a correlation in reactivity with silver has never been made and the few examples appeared in the literature report that silver salts either failed in promoting the reaction,[40,46] or gave very poor yields.[36,47]

In the past few years, our attention has turned to the introduction of a pyridine moiety into the skeleton of tetraazamacrocycles, with the aim to obtain ligands with increased conformational rigidity and different basicity.[48] The copper(ɪ) complexes of these 12-membered pyridine-containing ligands (Pc-L, Fig. 1) have been successfully employed as catalysts in the enantioselective cyclopropanation of alkenes.[49–52] The same Cu(ɪ)-catalysts have shown good activities in the Henry reaction.[22] Among coinage metals, reports on the catalytic activity of silver complexes are relatively sparse when compared to the

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† Electronic supplementary information (ESI) available: Yields and ^{1}H NMR tabulated spectra for all known compounds. Figures reporting full NMR spectra for all compounds. See DOI: 10.1039/c6ra22231e
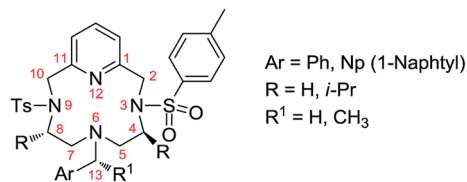
Fig. 1 Pyridine-containing ligand (Pc-L*) and numbering scheme adopted.

Fig. 2 Silver (1) and copper (2) PcL-complexes tested in the model Henry reaction.

more extensively studied copper and gold.[53–59] We have recently reported the full characterization of [silver(I)(pyridine-containing ligand)] complexes and their organometallic reactivity,[60] and we have demonstrated their catalytic activity in the regiospecific domino synthesis of 1-alkoxy-isochromenes under mild conditions[61] and in the microwave enhanced A³-coupling multicomponent reaction.[62] Compared with simple silver salts, the great advantages of [Ag(I)(Pc-L)] complexes are their solubility, their enhanced stability and the easiness of handling. Prompted by the interesting results above mentioned, we were intrigued to check if our well-defined silver(I) complexes were suitable catalysts also for the Henry reaction. As a result of this study, we were pleased to find that [Ag(I)(Pc-L)] complexes can actually activate the aldehyde toward the nitronate nucleophilic attack, in the first example of a silver mediated Henry reaction. Since the Henry reaction, especially in the asymmetric version, has provided a good platform for testing the dual activation of metal/base catalysts,[63] we have modified our ligands in order to attach in the proper position a suitable base to facilitate the reaction. Moreover, in connection with our ongoing interest in the study of domino nucleophilic addition/cyclization reaction involving alkynes characterized by the presence of a proximate nucleophile,[64–69] we envisaged to test the reaction on proper bifunctional substrates. Based on our experience, we chose the o-alkynylarylaldehydes with the ambition to join the Ag catalysed Henry reaction (by activation of the aldehyde moiety) to the Ag catalysed cycloisomerisation (by activation of the triple bond) with the aim to obtain in a cascade fashion new interesting O-heterocycles such as isochromenes.

Results and discussion

Silver catalysed Henry reaction

At first, we decided to test the ability of silver to promote the Henry reaction by using simple silver(I) salts such as Ag(OTf) or Ag(BF₄) and the Pc-L silver(I) complex 1[60] (already used in the A³-coupling study), and to compare their reactivity with those of the corresponding Pc-L copper(I) complex 2[50] (Fig. 2). As model reaction, we chose the condensation between 4-nitro-benzaldehyde 3a and nitromethane (Table 1). To promote the generation of the nitronate anion, a catalytic amount of trie-thylamine (TEA) – equal to the catalyst loading – was added to the reaction mixture.

Simple silver(I) salts gave results similar to those observed just in the presence of the base, the only difference being that in the latter case a number of by-products were observed (Table 1,
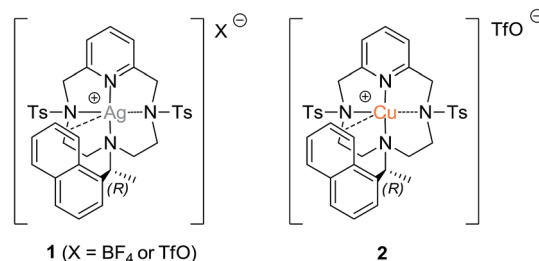
compare entries 1, 2 and 3). On the other hand, complex 1, which is fully soluble in chlorinated solvents, gave results comparable to those obtained with the related copper complex 2 (Table 1, entries 4 and 9). Under these conditions, the reaction gave identical results either employing the preformed complex 1 or the *in situ* formed 1 : 1 ligand/Ag(I) complex. We briefly investigated also the role of the counteranion, by changing from OTf⁻ to BF₄⁻, obtaining a slightly lower yield with the latter (Table 1, entry 5). However, when the same reaction was repeated in the presence of molecular sieves, a comparable conversion was again obtained (Table 1, entry 6). The use of a large excess of nitromethane (Table 1, entry 7) did not affect the reaction yield. We previously observed that the copper Pc-L complexes failed to catalyse the Henry reaction when it was performed in aromatic hydrocarbons and that Pc-L ligands alone, in the absence of any metal, are not suitable catalysts.[22]
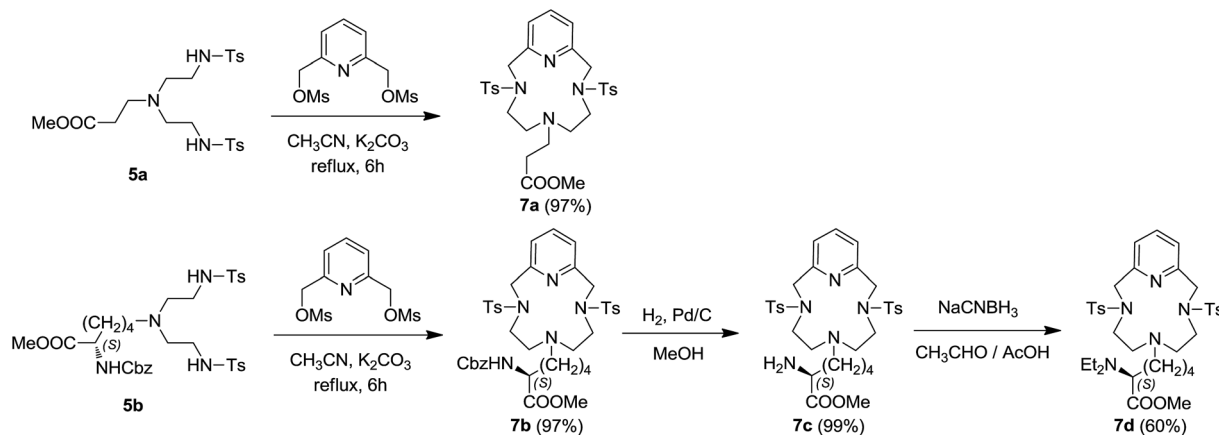
Table 1 Preliminary study of the silver(I) catalysed Henry reaction between 4-nitrobenzaldehyde 3a and nitromethane[a]

Entry	Cat.	X	Solv.	Base	Yield[b] (%)
1	Ag(OTf)		CH₂Cl₂	TEA	21
2[c]	Ag(BF₄)		CH₂Cl₂	Cs₂CO₃	25
3[d]	—		CH₂Cl₂	TEA	35
4	1-(13R)	OTf	CH₂Cl₂	TEA	84
5	1-(13R)	BF₄	CH₂Cl₂	TEA	75
6[e]	1-(13R)	BF₄	CH₂Cl₂	TEA	85
7	1-(13R)	OTf	CH₃NO₂	TEA	84
8	1-(13R)	OTf	Tol	TEA	60
9	2-(13R)	OTf	CH₂Cl₂	TEA	85

[a] Reactions were performed with [Ag(I)] (3.2×10^{-2} mmol) in the solvent (5 mL) at a cat./base/aldehyde/nitromethane ratio of 1 : 1 : 10 : 50 at rt for 20 h; lower catalyst loadings (1 mol%), resulted in very slow reactions. [b] Isolated yields based on initial 4-nitrobenzaldehyde; unreacted aldehyde accounted for the rest of the reaction mass balance. [c] $T = 30$ °C, $t = 6$ h. [d] Reaction conditions in the absence of metal catalyst: TEA/aldehyde/nitromethane ratio of 1 : 10 : 500 at rt for 20 h. Unreacted 4-nitrobenzaldehyde did not account for the rest of the reaction mass balance and some unidentified by-products derived from competitive side reactions were observed. [e] In the presence of molecular sieves (4 Å).

On contrary, the silver Pc-L complex **1** demonstrated to be effective also in toluene, giving the desired nitroalcohol **4a** in 60% yield (Table 1, entry 8). Finally, despite the presence of a defined stereocentre on the ligand, under all conditions tested we ever obtained the nitroalcohol **4a** as a racemic mixture.

Optimization of the silver(I) catalysts for the Henry reaction

Having in hand a quite active catalytic system, we were intrigued to further optimize the ligand features and then to explore the scope and limitations of the title reaction. The Pc-L's are easily constructed in good to excellent yields taking advantage of a 2 + 2 Richman–Atkins-type coupling,[70] which has been modified in order to improve chemical yields, as already reported.[50] In order to extend our method to the synthesis of Pc-L's bearing a non-innocent pendant arm on N6 (*i.e.*, a pendant with coordinating, basic or acidic functionalities), we envisioned that natural amino acids (*i.e.*, β-alanine and lysine) could be perfect nucleophilic reaction partners for the ring opening reaction with 2 moles of *N*-tosyl aziridine to give the corresponding 4-substituted 1,4,7-triazaheptanes **5a,b**, as depicted in Scheme 1.

In particular, β-alanine methyl ester hydrochloride and (*S*)-*N*(α)-Cbz-lysine methyl ester hydrochloride were quantitatively obtained by esterification of the corresponding amino acid with methanol in the presence of trimethylchlorosilane at room temperature.[71] Subsequent reaction with tosyl protected aziridine in a refluxing mixture of CH₃CN/toluene in the presence of TEA resulted in the formation of desired bis(sulfonamides) **5a–b** in quite fair yields, along with the corresponding mono

adducts **6a–b**. However, after chromatographic purification, isolated mono(sulfonamides) **6a–b** were easily converted to **5a–b** in very good yields (Scheme 1).

The following Richman–Atkins cyclisation with 2,6-pyridinedimethanol 2,6-dimesylate[61] yielded to the 12-membered macrocycles **7a–b** in excellent yields (Scheme 2). Catalytic hydrogenation of **7b** allowed the clean and quantitative removal of the Cbz amino-protecting group to afford **7c**, which was converted to macrocycle **7d**, containing a basic tertiary amine pendant arm, by reductive amination in presence of acetaldehyde and sodium cyanoborohydride (Scheme 2). To check the stability of the original stereocentre of the starting lysine under the reactions conditions, the optical rotation of the intermediates **5–7b** was measured after each reaction step. The values recorded are consistent with a complete retention of configuration, as confirmed *via* ¹⁹F NMR analysis of the Mosher's amide formation with ligand **7c** (see ESI†). To further confirm this data, ligand **7c** was reacted in deuterated chloroform with both enantiomers of the α-methoxyphenylacetic acid in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). In both cases, a single diastereoisomer was obtained (see Experimental section and ESI†).

Metal complex formation with ligands **7a–d** has been performed both with Ag(OTf) and Ag(BF₄), by treating at room temperature a solution of the ligand in dichloroethane (DCE) under nitrogen atmosphere (Scheme 3). After filtering off eventual uncomplexed metal salt, the colourless solution was concentrated, and the addition of *n*-hexane favoured the formation of a white precipitate of [Ag(Pc-L)] complex in good to

Scheme 1 Synthesis of amino acid derived 4 substituted 1,4,7-triazaheptanes **5a** and **5b**.

Scheme 2 Synthesis of Pc-L's **7a–d**.

Scheme 3 Synthesis of silver(I) complexes **8a–d**.

Table 2 The model Henry reaction catalysed by the active-pendant arm Ag(I) complexes **8a–d**[a]

Entry	Cat.	X	Base	Solv.	t (h)	T (°C)	Yield[b] **4a** (%)
1	**8a**	OTf	TEA	CH_2Cl_2	20	rt	60
2	**8a**	OTf	TEA	Tol	40	rt	15
3	**8a**	OTf	DiPEA	CH_2Cl_2	20	rt	53
4	**8a**	OTf	DMAP	CH_2Cl_2	20	rt	53
5	**8a**	OTf	Morpholine	CH_2Cl_2	20	rt	50
6	**8a**	OTf	K_2CO_3	CH_2Cl_2	20	rt	45
7	**8a**	OTf	Cs_2CO_3	CH_2Cl_2	20	rt	70
8	**8a**	BF_4	Cs_2CO_3	CH_2Cl_2	20	rt	70
9	**8b**	OTf	TEA	CH_2Cl_2	20	rt	67
10	**8b**	BF_4	TEA	CH_2Cl_2	20	rt	65
11	**8b**	BF_4	DiPEA	CH_2Cl_2	20	rt	75
12	**8b**	BF_4	Cs_2CO_3	CH_2Cl_2	20	rt	90
13	**8b**	BF_4	Cs_2CO_3	CH_2Cl_2	20	30	95
14	**8b**	BF_4	Cs_2CO_3	CH_2Cl_2	12	30	92
15	**8b**	BF_4	Cs_2CO_3	CH_2Cl_2	6	30	75
16	**8b**	BF_4	Cs_2CO_3	CH_2Cl_2	3	30	45
17	**8b**	OTf	—	CH_2Cl_2	20	rt	25
18	—	—	Cs_2CO_3	CH_2Cl_2	20	30	55
19[c]	**8c**	BF_4	—	CH_2Cl_2	20	rt	—
20[c]	**8c**	BF_4	—	$MeNO_2$	20	rt	—
21	**8c**	BF_4	—	MeOH	20	rt	—[d]
22	**8d**	BF_4	Cs_2CO_3	CH_2Cl_2	12	30	90
23	**8d**	BF_4	—	CH_2Cl_2	12	30	64

[a] Reactions were performed with [Ag(I)] (3.2×10^{-2} mmol) in the solvent (5 mL) at a cat./base/aldehyde/nitromethane ratio of 1 : 1 : 10 : 50 in the presence of molecular sieves (4 Å). [b] Yields based on initial 4-nitrobenzaldehyde calculated *via* ^{1}H NMR using 2,4-dinitrotoluene (DNT) as internal standard; unreacted aldehyde accounted for the rest of the reaction mass balance. [c] The metal complex **8c** is not soluble in the reaction medium: no reaction after 20 h as judged by TLC analysis. [d] Dimethyl acetal derived from the nucleophilic attack of MeO⁻ on the 4-nitrobenzaldehyde was recovered in 25% yield (see ESI).

excellent yields. All complexes have been isolated and fully characterised. They showed a remarkable stability both in solid and in solution phase and can be handled in air without decomposition even for a prolonged period.

The synthesis of these ligands is relatively simple and high-yielding. Moreover, the major advantage of this synthetic approach is that it allows an easy modification of a key moiety of the macrocycle, namely the *N*6 pendant, by exploiting both chiral and functional properties of the natural amino acids. The new Ag(I) complexes **8a–d**, where tested as catalysts in the model Henry reaction between 4-nitrobenzaldehyde **3a** and nitromethane. According to the best results obtained in the preliminary screening, the reactions where performed in CH_2Cl_2 with a ratio cat/base/aldehyde/CH_3NO_2 of 1 : 1 : 10 : 50. As during the optimization studies we noticed that adventitious traces of water

could in some cases affect the reproducibility of the results, all new reactions have been carried out in the presence of activated molecular sieves. The results are reported in Table 2.

Except for complex **8c**, which is the only one not soluble in dichloromethane, all other silver complexes gave the nitro-alcohol **4a** from moderate to very good yields in the model

reaction. Beside the desired nitroalcohol **4a** the starting aldehyde **3a** was the only product recovered at the end of the reaction, thus yields reported are coincident with conversions and a selectivity >99% was observed.

Silver complex **8a** (Table 2, entries 1–8), characterised by the presence of a slightly coordinating *N*6 pendant arm, gave on the whole results comparable to those observed by using complex **1**. Under the previously optimised reaction conditions, the reaction yield is slightly lower (cfr. Table 1, entry 4 and Table 2, entry 1). The use of a less polar solvent resulted in a drop of the reaction yield (Table 2, entry 2). Several bases were tested (Table 2, entries 3–7), and best results were obtained with cesium carbonate (Table 2, entry 7). The counter anion do not seem to influence the reaction yields (Table 2, entry 8), in agreement with the ^{1}H NMR spectra of the **8a-BF$_4$** and **8a-OTf** that do not show any apparent interaction between the counterion and the metal complex (see ESI†).

Complex **8b**, characterised by the presence of a Cbz-protected amino group on the *N*6 pendant arm, displayed a closely related behaviour regarding counter anion (Table 2, entries 9 and 10) and base (Table 2, entries 10–12) effects, but overall, the yields were higher. With catalyst **8b**, the best results were obtained in the presence of 1 eq. of Cs$_2$CO$_3$ in dichloromethane (Table 2, entries 12–14): after 20 h at rt, **4a** was formed in 90% yield (Table 2, entry 12); a rise in temperature to 30 °C resulted in an increase of yield to 95% (Table 2, entry 13), whereas a reduction of reaction time gave gradually worse results (Table 2, entries 14–16). As expected, in the absence of a base, poor results were obtained (Table 2, entry 17). It should be pointed out that Cs$_2$CO$_3$ alone is able to promote the Henry reaction, but under the same reaction conditions only a 55% of nitroalcohol **4a** was formed (Table 2, entry 18).

In order to avoid the addition of the base as co-catalyst, we tested complexes **8c** and **8d**, both containing a basic amine functionality on the *N*6 active-pendant arm.

As above pointed out, complex **8c** is insoluble in dichloromethane, as well as in nitromethane and failed to give any reaction in such heterogeneous system (Table 2, entries 19 and 20). When methanol was used as solvent, we observed the formation of the dimethyl acetal derived from the nucleophilic attack of MeO$^-$ on the 4-nitrobenzaldehyde in 25% yield (Table 2, entry 21).
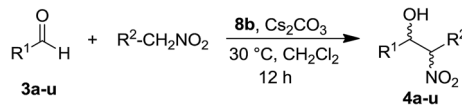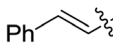
Under standard conditions, complex **8d**, which is fully soluble in dichloromethane, gave the Henry product **4a** in excellent yields (Table 2, entry 22). Moreover, we were pleased to observe that the presence of a tertiary amino group on the *N*6 active-pendant made this complex able to promote the formation of **4a** in 64% yields also without any basic co-catalyst in just 12 h at 30 °C (Table 2, entry 23). Unfortunately, again, despite the presence of a stereocentre in S configuration close to the amine, the enantioinduction in the product is very low (5% ee determined by chiral HPLC).

As already pointed out, the presence of NH$_2$ and/or COOH functional groups in the ligands could allow for the synthesis of di- or oligo-peptides embedding the metal complex. Hopefully, the chirality imposed by a more extended peptide structure to the whole catalytic system will provide a more stereoselective

transition state for the two incoming reaction partners. Current efforts in our laboratory are now devoted in this direction with the aim to improve the enantioselective outcome in this new silver catalysed Henry reaction.

We next explored scope and limitation of the approach (Table 3), employing complex **8b-BF$_4$** under the best reaction

Table 3 Scope and limitation of the Henry reaction catalysed by complex **8d-BF$_4$**^{a}

$$R^1\text{-CHO} + R^2\text{-CH}_2\text{NO}_2 \xrightarrow[\substack{30\ °C,\ CH_2Cl_2 \\ 12\ h}]{8b,\ Cs_2CO_3} R^1\text{-CH(OH)-CH(NO}_2)\text{-}R^2$$

3a-u → 4a-u

Entry	R^1	R^2	Product	syn/anti^b	Yield^c (%)
1	4-NO$_2$C$_6$H$_4$	H	**4a**	—	92 (90)
2	4-CNC$_6$H$_4$	H	**4b**	—	83 (80)
3	4-CF$_3$C$_6$H$_4$	H	**4c**	—	93 (92)
4	4-BrC$_6$H$_4$	H	**4d**	—	85 (82)
5	4-ClC$_6$H$_4$	H	**4e**	—	83 (80)
6	4-FC$_6$H$_4$	H	**4f**	—	70 (64)
7	C$_6$H$_5$	H	**4g**	—	60 (55)
8^d	4-MeC$_6$H$_4$	H	**4h**	—	15
9	4-Bu^{t}C$_6$H$_4$	H	—	—	n.d.
10	4-MeOC$_6$H$_4$	H	—	—	n.d.
11	4-Et$_2$NC$_6$H$_4$	H	—	—	n.d.
12	C$_6$F$_5$	H	**4i**	—	72 (68)
13	3,5-(CF$_3$)$_2$C$_6$H$_4$	H	**4j**	—	70 (66)
14	2-NO$_2$C$_6$H$_4$	H	**4k**	—	97 (95)
15	2-BrC$_6$H$_4$	H	**4l**	—	72 (65)
16	2,6-Cl$_2$C$_6$H$_4$	H	**4m**	—	70 (68)
17	2-MeOC$_6$H$_4$	H	**4n**	—	10
18	3-MeOC$_6$H$_4$	H	—	—	n.d.
19	Cy	H	—	—	n.d.
20	Ph-CH=CH- (cinnamyl)	H	—	—	n.d.
21	*N*-Me-pyrrolyl	H	—	—	n.d.
22	furyl	H	**4o**	—	65 (62)
23	thienyl	H	**4p**	—	10
24	4-NO$_2$C$_6$H$_4$	CH$_3$	**4q**	60 : 40	95 (90)
25^e	4-NO$_2$C$_6$H$_4$	CH$_3$	**4q**	60 : 40	90
26	2-NO$_2$C$_6$H$_4$	CH$_3$	**4r**	45 : 55	96 (93)
27	4-CF$_3$C$_6$H$_4$	CH$_3$	**4s**	51 : 49	93 (89)
28	4-ClC$_6$H$_4$	CH$_3$	**4t**	61 : 39	80 (75)
29	C$_6$H$_5$	CH$_3$	**4u**	55 : 45	75 (60)

^{a} Reactions were performed with [Ag(ı)] (3.2 × 10^{-2} mmol) in CH$_2$Cl$_2$ (5 mL) at a cat./Cs$_2$CO$_3$/aldehyde/nitromethane ratio of 1 : 1 : 10 : 50 in the presence of molecular sieves (4 Å) at 30 °C for 12 h. ^{b} *syn/anti* ratio determined by ^{1}H NMR. ^{c} Yields based on initial aldehyde calculated *via* ^{1}H NMR using 2,4-dinitrotoluene (DNT) as internal standard (isolated yields); unreacted aldehyde accounted for the rest of the reaction mass balance. ^{d} Reaction performed with complex **8a-BF$_4$** as catalyst. ^{e} Reaction performed with complex **8d-BF$_4$** as catalyst and in the absence of Cs$_2$CO$_3$.

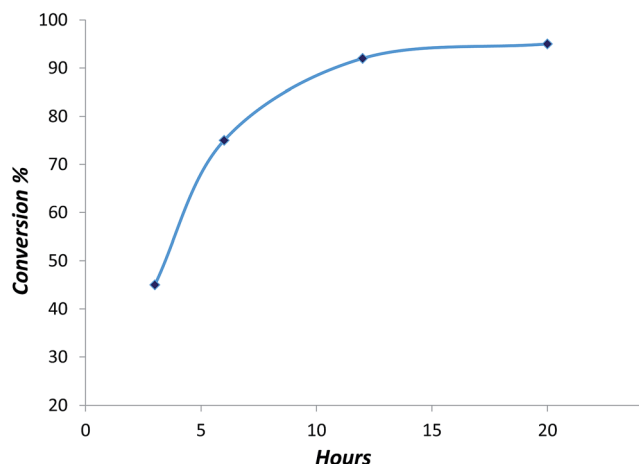**Fig. 3** Conversion of **3a** vs. time in the Henry reaction catalysed by **8b-BF₄**/Cs₂CO₃ in CH₂Cl₂ at 30 °C.

conditions (Table 2, entries 13 and 14). In particular, our interest was to verify the ability of our catalytic system to promote the reaction of aldehydes of different nature (aryl, heteroaryl and cycloalkyl) also in the presence of EW or ED groups on the aromatic ring. We decide to perform all reactions in CH₂Cl₂ at 30 °C and stop them after 12 h with the aim to compare the results obtained by changing the electrophilic properties of the aldehyde at fixed reaction time and temperature. It is well known that the Henry reaction is an equilibrium reaction and temperature plays an important role. The 12 h reaction time was decided based on a brief kinetic study performed on the model reaction (Table 2, entries 13–16), which displayed that a plateau in terms of % of conversion of the starting aldehyde is reached just after 12 h (Fig. 3).

Good results in terms of yields were obtained when one or more EWGs were present on the aryl ring (Table 3, entries 1–6 and 12–16). Although not linearly correlated with σ_{para} Hammett constants, yields between 83% and 93% were obtained with aromatic aldehydes having high positive values of *para* substituent constant (Table 3, entries 1–5). Slightly lower yields have been observed for *para*- and *per*-fluorobenzaldehydes (Table 3, entries 6 and 12), and neutral benzaldehyde (Table 3, entry 7). On the other hand, electron-rich aromatic aldehydes failed to give the Henry products (Table 3, entries 8–11). These latter results can be easily rationalised based on the less pronounced electrophilic character of the aldehyde. The presence of EW groups is well tolerated also in *meta* and *ortho* positions (Table 2, entries 13–16), suggesting that steric hindrance does not limit the transformation.

As observed for electron-rich benzaldehydes, no reaction was observed with aliphatic aldehydes (Table 3, entry 19) and with cinnamaldehyde (Table 3, entry 20). Among furan, tiophene and pyrrole carbaldehydes, a good reactivity was observed only in the case of furfural (Table 3, entry 22), the less "aromatic" among the five-membered heterocycles, in which, probably, the strong inductive EW effect of the oxygen atom plays a key role in the activation of the adjacent aldehyde functionality. On contrary, the reactions of thiophene-2-carbaldehyde and *N*-

methylpyrrole-2-carbaldehyde failed (Table 3, entries 21 and 23). In particular, the very poor yield obtained in the reaction of thiophene-2-carbaldehyde (Table 3, entry 23) can be also related to a plausible strong coordination of the sulphur atom to the metal centre that inhibits any catalytic activity, whilst in the case of *N*-methylpyrrole-2-carbaldehyde (Table 3, entry 21) only a mixture of unidentified by-products, probably derived from polymerization, were observed.

Next, we briefly explored the reactivity of some aromatic aldehydes with nitroethane, with a particular regard to the diastereoselective outcome of the reaction. In all cases, almost identical results were obtained switching the nitro partner from nitromethane to nitroethane, and all the reactions with electron poor aromatic aldehydes gave the corresponding Henry product in very good yields, although with very modest *syn/anti* ratio (Table 3, entries 24–29). Again, we were pleased to verify that complex **8d-BF₄** was able to catalyse the reaction between 4-nitrobenzaldehyde and nitroethane without the need of any additional base, yielding **4q** in a very satisfying 90% yield (Table 3, entry 25).

Taking into account that the indole nucleus is present in a large number of compounds of biological and/or pharmaceutical interest, we tested our approach also on isatine (Scheme 4).

The reaction with nitromethane gave the desired 3-hydroxy-3-(nitromethyl)-1,3-dihydro-2*H*-indol-2-one **9a** in 80% isolated yield[72] whereas the reaction with nitroethane gave a 6 : 4 diastereoisomeric mixture of **9b** with an overall yield of 97% (yield based on initial isatine calculated *via* ^{1}H NMR using 2,4-dinitrotoluene as internal standard, see Experimental section).[73] It should be emphasized that this transformation on isatine opens up new routes for the synthesis of a plethora of interesting oxindole alkaloids related molecules.[74]
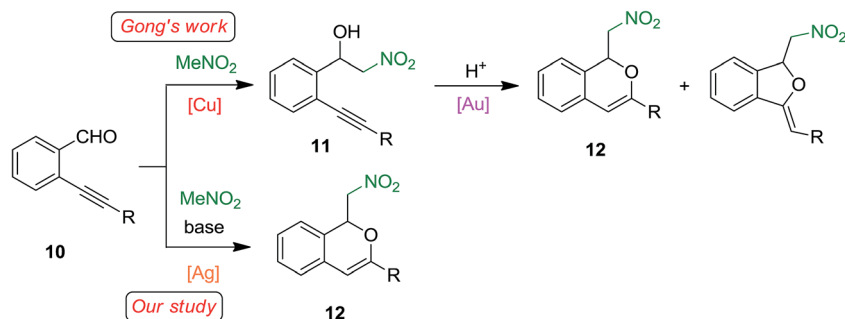
Silver catalysed domino Henry reaction/cycloisomerisation sequence

As mentioned above, we have recently reported that [silver(I)(Pc-L)] complexes are competent catalysts for the regioselective synthesis of 3-substituted-1-alkoxyisochromenes starting from 2-alkynylbenzaldehydes in the presence of alcohols as nucleophiles.[61] Having seen their ability in promoting the Henry reaction, we were thus intrigued to see if it was possible to combine in a single domino sequence the Henry reaction of 2-alkynylbenzaldehydes and the cycloisomerisation to yield isochromenes **12**. A two-step process that take advantage of a Cu(II)
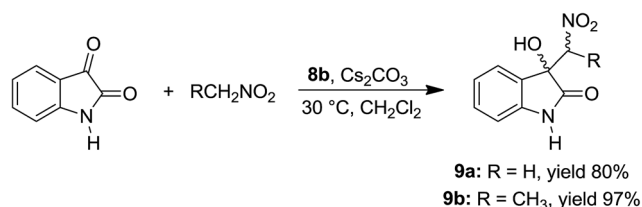
Scheme 4 **8b-BF₄** catalysed reaction of nitromethane and nitroethane with isatine.

9a: R = H, yield 80%
9b: R = CH₃, yield 97%

Scheme 5 Alternative domino silver(I) catalysed synthesis of 1-isochromenes.

catalysed Henry reaction followed by an Au(I) mediated cyclo-isomerisation[75] has recently been reported by Y. Gong and co-workers (Scheme 5).[39]

The reaction between 2-[(4-methoxyphenyl)-ethynyl] benzaldehyde **10a** and nitromethane was selected as model reaction for the optimization of reaction conditions. Firstly, we

Table 4 Study on the silver catalysed Henry reaction *versus* cycloisomerisation reaction[a]
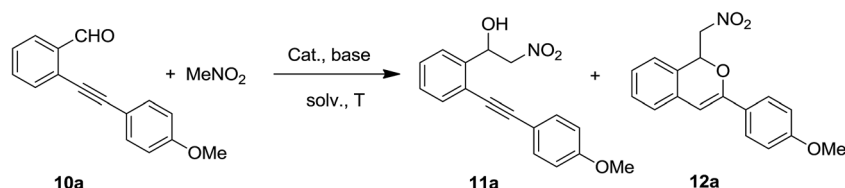
Entry	Catalyst	Base (equiv.)	MeNO$_2$ (equiv.)	Solvent	t (h)	T (°C)	Yield **11a**[b] (%)	Yield **12a**[b] (%)	Rec. **10a** (%)
1	**2**	TEA (1)	50	CH$_2$Cl$_2$	20	rt	(56)	—	(35)
2	**1-OTf**	TEA (1)	50	CH$_2$Cl$_2$	20	rt	(17)	(17)	(12)
3	**1-OTf**	TEA (1)	50	CH$_2$Cl$_2$	30	40	12	6	7
4	**1-OTf**	TEA (1)	50	CH$_2$Cl$_2$	30	60	11	4	4
5	**1-OTf**	TEA (5)	50	CH$_2$Cl$_2$	22	rt	45 (39)	—	11 (10)
6[c]	—	TEA[c]	[c]	CH$_2$Cl$_2$	22	rt	77	—	10
7	**1-OTf**	TEA (1)	50	Tol	20	30	30	8	11
8	**1-OTf**	TEA (1)	50	DMF	24	30	53	—	6
9	**1-OTf**	TEA (1)	50	THF	22	rt	46	2	21
10	**1-OTf**	TEA (1)	11	CH$_2$Cl$_2$	22	rt	3	—	5
11	**1-OTf**	TEA (1)	—	CH$_3$NO$_2$	20	rt	39	29	—
12	**AgOTf**	TEA (1)	—	CH$_3$NO$_2$	20	rt	—	15	15
13[d]	**1-OTf**	TEA (1)	500	CH$_2$Cl$_2$	22	rt	18	24	—
14[d]	**1-OTf**	TEA (1)	500	CH$_2$Cl$_2$	22	rt	25	33	—
15[d]	**1-NTf$_2$**	TEA (1)	500	CH$_2$Cl$_2$	22	rt	16	29	5
16[d]	**1-BF$_4$**	TEA (1)	500	CH$_2$Cl$_2$	22	rt	21 (18)	33 (30)	10 (9)
17[d,e]	**1-BF$_4$**	TEA (1)	500	CH$_2$Cl$_2$	22	rt	60 (57)	19 (17)	—
18[d,e]	**1-BF$_4$**	TEA (1)	500	CH$_3$CN	22	rt	96	—	—
19[d]	**1-BF$_4$**	DIPEA (1)	500	CH$_2$Cl$_2$	22	rt	36	27	—
20[d]	**1-BF$_4$**	DMAP (1)	500	CH$_2$Cl$_2$	22	rt	50	—	4
21[d]	**1-OTf**	DBU (1)	500	CH$_2$Cl$_2$	22	rt	11	4	16
22[d]	**1-BF$_4$**	NaHCO$_3$ (1)	500	CH$_2$Cl$_2$	22	rt	5	1	65
23[d]	**1-OTf**	Cs$_2$CO$_3$ (1)	500	CH$_2$Cl$_2$	22	rt	72	—	2
24[d]	**1-NTf$_2$**	K$_2$CO$_3$ (1)	500	CH$_2$Cl$_2$	22	rt	78	—	2
25[e]	**8b-BF$_4$**	TEA (1)	500	CH$_2$Cl$_2$	22	rt	57	15	8
26[e]	**8d**	—	500	CH$_2$Cl$_2$	22	rt	60	15	13

[a] Reactions were performed with [Ag(I)] (2.5 × 10⁻² mmol) in the solvent (1.25 mL) at a catalyst/aldehyde ratio of 1 : 10. [b] Yields based on initial **10a** calculated *via* ^{1}H NMR using 2,4-dinitrotoluene (DNT) as internal standard; isolated yields in brackets. Under these conditions, unreacted starting aldehyde did not always account for the rest of the reaction mass balance. In some cases, unidentified by-products derived from competitive side reactions were detected. [c] TEA (2.5 × 10⁻¹ mmol)/aldehyde/nitromethane ratio of 1 : 1 : 5. [d] Reaction performed with freshly distilled nitromethane. [e] In the presence of molecular sieves (4 Å).

compared the activity copper(I) catalyst **2** and silver(I) catalyst **1-OTf** (10 mol%) in dichloromethane in the presence of 5 equiv. of nitromethane and 10 mol% of TEA (Table 4, entries 1 and 2). This preliminary test interestingly revealed that while the copper complex **2** gave selectively the Henry reaction product **11a** in 56% yield, the silver complex **1-OTf** was able to promote the domino sequence, although with low selectivity, yielding the desired 1-isochromene **12a** and the nitroalcohol **11a** in equal amount, beside a 12% of unreacted aldehyde **10a** and a complex mixture of unidentified by-products. An increase of the reaction temperature resulted in lower yields and selectivity, with an increase of by-products formation (Table 4, entries 3 and 4). The addition of an excess of TEA resulted in the selective formation of the Henry product in 45% yield, but was detrimental for the formation of the desired product **12a** (Table 4, entry 5). As already stated above, while the Henry product can be formed also in the absence of the silver catalyst (although in poor yields), the presence of the metal is essential for the formation of the isochromene **12**. In fact, in the presence of 1 equiv. of TEA and without the metal catalyst, the nitroalcohol **11a** was selectively obtained in 77% yield (Table 4, entry 6).

The screening of solvent effect (Table 4, entries 7–9) revealed that polar aprotic solvents favour the formation of the nitroalcohol **11a**. The reduction of the equivalent of nitromethane was detrimental to the reaction outcome (Table 4, entry 10), whereas, when CH_3NO_2 was employed as a reagent/solvent, the formation of **11a** (39%) was accompanied by the formation of a discrete amount of isochromene **12a** (29%, Table 4, entry 11), suggesting that an excess of nitroalkane is able to promote both isochromene and nitroalcohol formation. Interestingly, when simple AgOTf salt was used no trace of Henry product **11a** was observed, and only a little amount of **12a** was obtained (Table 4, entry 12).

Thus, a 50 fold excess of the nitromethane (with respect to aldehyde **10a**) was used and this seems to favour the formation of the isochromene product, especially when freshly distilled nitromethane was used (Table 4, entries 13 and 14).

Among the counter anion tested, BF_4^- and OTf^- displayed very close results, while NTf_2^- led to slightly lower overall yields (Table 4, entries 14–16). It is interesting to note that the presence of 4 Å molecular sieves as water scavenger seems to speed up the formation of the Henry product to the detriment of isochromene (Table 4, entry 17), and this selectivity became specificity when the reaction was performed in acetonitrile (Table 4, entry 18).

We tried to improve the formation of the isochromene **12a** by using bases with different pK_b, ranging from organic to inorganic ones (Table 4 entries 19–24), but the more acceptable results remained those obtained with TEA or with the more sterically demanding diisopropylethyl amine (DiPEA) (Table 4, entry 19).

Finally, the use of the catalytic systems previously selected for the Henry approach, confirm their tendency to promote preferentially the formation of the corresponding nitroalcohol (Table 4, entries 25 and 26), also in the absence of the additional base (Table 4, entry 26).

With the aim to explain the behaviour observed, we made an additional experiment. Isolated **11a** was reacted in toluene at rt in the presence of 10 mol% of the silver(I) complex **1-OTf**. After 24 h no reaction occurred and the TLC analysis showed the presence of unreacted **11a**. Upon addition of 10 mol% of TEA the mixture was reacted for additional 24 h at rt, then the crude was analysed by ^{1}H NMR which reveals the presence of unreacted **11a** (44%) along with traces of 2-[(4-methoxyphenyl)-ethynyl]benzaldehyde **10a** ($\approx$5%), isochromene **11a** ($\approx$5%) and some unidentified by-products. This results suggest that the formation of the nitroalcohol **11a** (Path **B** in Scheme 6) and the cascade synthesis of isochromene **12a** (Path **A** in Scheme 6) are probably alternative and competitive pathways. According to reported metal catalysed domino synthesis of isochromenes in the presence of nucleophiles,[61,76] **12a** is most likely formed by nucleophilic attack of the nitronate anion on a preformed isochromenilium ion intermediate **I** (Path **A** in Scheme 6), while a subsequent silver catalysed cycloisomerisation of the nitroalcohol **11a** (Path **C**) seems to be most unlikely.[77] Endorsing this hypothesis, under our reaction conditions we never isolated or detected in the reactions crude the alternative isobenzofuran isomers obtained by Gong and co-workers[39] (see Scheme 5).

Up to now, any attempt to obtain in an exclusive fashion the desired isochromene **12a** meet with failure, thus we decided to briefly investigate the substrate effect under the best reaction condition achieved for the synthesis of isochromenes (Table 4, entry 16). The results are reported in Table 5.
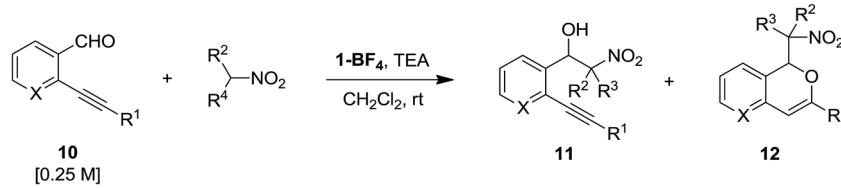
All tested o-alkynylarylaldehydes **10** were readily obtained in moderate to excellent yields by $PdCl_2(PPh_3)_2$ catalysed Sonogashira coupling reactions[78] starting from commercially available 2-bromo(hetero)arylaldehydes and terminal acetylenes (see Experimental section for details).

Compared to the model reaction (Table 5, entry 1) when nitroethane was used under standard conditions we observed
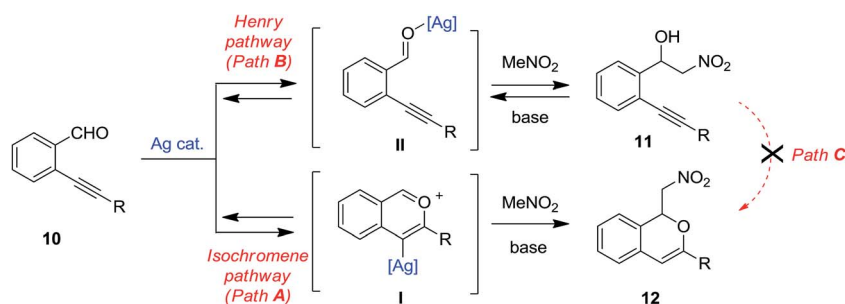
Scheme 6 Alternative/competitive pathways in the reaction of 2-alkynylarylalehydes and nitroalkanes.

Table 5 Substrate effect in the divergent silver catalysed Henry *versus* cycloisomerisation reaction[a]

| Entry	SM	R[1]	X	R[2]	R[3]	t (h)	Yield 11[b] (%)	Yield 12[b] (%)	Rec. SM (%)
1	**10a**	*p*-MeO-Ph	CH	H	H	22	**11a** 18	**12a** 30	9
2				Me	H	22	**11b** + **11b′** 70[c]	**12b** + **12b′** 7[d]	21
3				Me	Me	22	—	—	42[e]
4	**10b**	*p*-Me-Ph	CH	H	H	22	**11c** 32	**12c** 31	5
5[f]				H	H	22	**11c** 60	**12c** 5	9
6	**10c**	*p*-CF₃-Ph	CH	H	H	22	**11d** 45	**12d** traces	14
7	**10d**	Me₃Si	CH	H	H	22	**11e** 48	—	45
8[f]				H	H	22	**11e** 83	—	15
9	**10e**	*n*-Pr	CH	H	H	22	**11f** 15	**12f** 54	—
10	**10f**	*n*-Pr	N	H	H	1	**11g** 52	—	—
11	**10g**	*p*-MeO-Ph	N	H	H	22	**11h** 68	—	15
12[f]				H	H	22	**11h** 78	—	—

[a] Reactions were performed with [Ag(ɪ)] (2.5×10^{-2} mmol) in CH₂Cl₂ (1.25 mL) at a catalyst/TEA/aldehyde/nitromethane ratio of 1 : 1 : 10 : 500. [b] Isolated yields based on initial alkynylbenzaldehyde **10**. Under these conditions, unreacted starting aldehyde did not always account for the rest of the reaction mass balance. In some cases, unidentified by-products derived from competitive side reactions were detected. [c] Mixture of two diastereoisomers in 70 : 30 ratio. [d] Mixture of two diastereoisomers in 75 : 25 ratio calculated on the ¹H NMR. [e] In this case, the isocumarine **13** (29%) was recovered as major by-product. [f] In the presence of molecular sieves (4 Å).

the formation of only a small amount of distereoisomeric iso-chromenes **12b** and **12′b** (not separated), while the Henry products **11b** and **11′b** were recovered in 70 : 30 diastereoisomeric ratio in 70% overall yield (Table 5, entry 2). On the other hand, the reaction with bulkier 2-nitropropane gave the 3-(4-methoxyphenyl)isocumarine **13** (29%) as main reaction by-product, beside a huge amount of unreacted starting material (42%) (Table 5, entry 3). The formation of **13** probably derived from the oxidation of the aldehyde **10a** to a carboxylic acid, which was transformed by the alkaline reaction condition in a carboxylate nucleophile able to make an intramolecular attack to the silver(ɪ) activated triple bond[79] (Scheme 7).

The presence of a neutral aryl substituent on the alkynylbenzaldehyde **10b** gave an almost equal amount of nitroalcohol **11c**, and isochromene **12c**, (Table 5, entry 4). As already observed (Table 4, entries 16 and 17), the presence of traces of water seems to be important to promote the formation of the isochromene products **12**; when the reaction of **10b** was performed under strictly anhydrous conditions in the presence of 4

Å molecular sieves, the yield of **12c** fall down while the yield of **11c** doubled (Table 5, compare entries 4 and 5). The presence of EWG on the aryl moiety was not suitable for the formation of the isochromene **12d**, and the corresponding nitroalcohol **11d** was the main product obtained (Table 5, entry 6). In addition, trimethylsilyl substituted alkynylbenzaldehyde **10d**, gave exclusively the nitroaldol product **11e** (Table 5, entry 7), and when the reaction was conducted in the presence of a water scavenger, the yield of **11e** skyrocket to 83% (Table 5, entry 8). Alkyl substitution on the triple bond was the only substitution that lead a good selectivity in favour of the cyclic product (Table 5, entry 9). More basic and coordinating nicotinaldehyde derivatives **10g,h** yielded exclusively to the Henry products **10h** and **10i** (Table 5, entries 10 and 11). In the latter cases, the selectivity in favour of the Henry product could be explained by a speeding up of the nucleophilic attack of the nitronate anion to the aldehyde, promoted by the presence of an additional basic nitrogen on the pyridine moiety and by the EW activating effect of the electron-poor pyridine on the proximate aldehyde group.
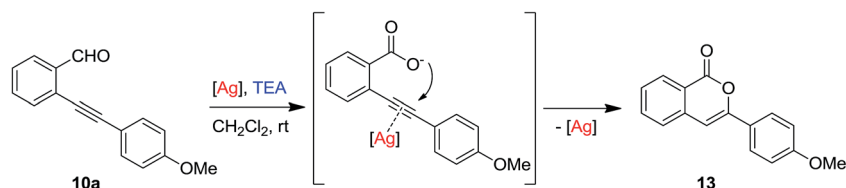
Scheme 7 Plausible path for the formation of isocumarine **13**.

Also in this case, the presence of molecular sieves resulted in higher yields of nitroalcohol **11i** (Table 5, entry 12).

Conclusions

The [Ag(I)(Pc-L)] complexes employed in the present study are suitable catalysts for the Henry reaction starting from various electron-poor aromatic aldehydes or other activated aldehydes such as furfural. Isatine can be converted into the corresponding nitroalcohol in excellent yields. Results obtained compares well with the state of the art and, at least compared to results obtained by us employing related copper(I) Pc-L complexes,[22] better yields in shorter reaction times could be obtained. Advantages of the silver catalysed nitro–aldol reaction are: (i) mild reaction conditions, (ii) good to excellent reaction yields, (iii) cleanness of the reaction and (iv) total selectivity in nitro-alcohol formation. All the silver(I) complexes reported are stable and can be handled in open-air atmosphere. Cs_2CO_3 demonstrated to be the base co-catalyst of choice in terms of reaction yields and reduced reaction times. Moreover, a careful design of the ligand has led to the synthesis of complex **8d**, which contains a suitable basic functionality embedded into the ligand pendant, thus providing a bifunctional catalyst. A major advantage is represented by the straightforward synthesis of ligand **7d** that is obtained in good overall yield starting from cheap starting materials. Further effort in our research group will be devoted to the structural modification of the ligand in order to control the enantioselectivity of this useful transformation.

Based on our experience in [Ag(I)(Pc-L)] catalysed domino addition/cycloisomerisation reaction of 2-alkynylbenzaldehydes and nucleophiles, we tried to find a new entry to isochromenes by coupling the Henry reaction and the cycloisomerisation in a single domino process. We have demonstrated that even though with strong limitations, this cascade reaction can occur and that the mechanism involves a preliminary metal catalysed cycloisomerisation of the 2-alkynylbenzaldehyde to form an isochromenilium intermediate, followed by the attack from the nucleophilic nitronate anion. A catalytic amount of base is necessary to generate enough nitronate anion in the reaction medium. Interestingly, this pathway seems to be alternative and competitive with the formation of the nitroalcohol *via* the Ag catalysed Henry reaction. Since in our reaction conditions the Henry reaction is in general faster, this results in a non-selective process, yielding a mixture of nitroalcohols **11** and isochromenes **12**. While is still possible to direct the reaction towards the nitroalcohol formation, a full selectivity toward the isochromene product has not yet been obtained.

Experimental procedures

General experimental details

All of the reactions that involved the use of reagents sensitive to oxygen or hydrolysis were carried out under an inert atmosphere. The glassware was previously dried in an oven at 110 °C and was set with cycles of vacuum and nitrogen. Also syringes, used to transfer reagents and solvents, were previously set

under a nitrogen atmosphere. The syntheses of the silver complexes were carried out under a nitrogen atmosphere by employing standard Schlenk techniques. All chemicals and solvents were commercially available and were used after distillation or treatment with drying agents. The chromatographic column separations were performed by a flash technique, using silica gel (pore size 60 Å, particle size 230–400 mesh, Merck grade 9385). For TLC, silica was used on TLC Alu foils with fluorescent indicator (254 nm) and the detection was performed by irradiation with UV light ($\lambda = 254$ nm or 366 nm). ^{1}H NMR analyses were performed with 200, 300, 400 or 600 MHz spectrometers at room temperature. The coupling constants (J) are expressed in hertz (Hz), and the chemical shifts (δ) in ppm. ^{13}C NMR analyses were performed with the same instruments at 75.5, 100 or 150 MHz, and attached proton test (APT) sequence was used to distinguish the methine and methyl carbon signals from those arising from methylene and quaternary carbon atoms. All ^{13}C NMR spectra were recorded with complete proton decoupling. The ^{1}H NMR signals of the ligand described in the following have been attributed by correlation spectroscopy (COSY) and nuclear Overhauser effect spectroscopy (NOESY) techniques. Assignments of the resonance in ^{13}C NMR were made using the APT pulse sequence and heteronuclear single quantum correlation (HSQC) and heteronuclear multiple bond correlation (HMBC) techniques. Low resolution MS spectra were recorded with instruments equipped with electron ionization (EI), ESI/ion trap (using a syringe pump device to directly inject sample solutions), or fast atom bombardment (FAB) (for Pc-L and metal complexes) sources. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown in brackets. UV-vis spectra of the ligand and its silver complexes were recorded in CH_2Cl_2. Elemental analyses were recorded in the analytical laboratories of Università degli Studi di Milano. Optical rotations were measured on a Perkin Elmer instruments model 343 plus; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Silver complex **1**,[60] *N*-tosyl-aziridine and copper complex **2**[50] and 2,6-pyridinedimethanol 2,6-dimesylate[61] were synthetized as previously reported.

Synthesis of β-alanine methyl ester hydrochloride

TMS-Cl (8.7 mL, 68.6 mmol) was added dropwise to β-Ala (3.06 g, 34.3 mmol). Then MeOH (27.0 mL) was added slowly and the resulting solution was stirred for 24 h at rt. The solvent was evaporated to dryness leading to (**2**) (4.8 g, >99%) as a white solid. ^{1}H NMR (300 MHz, D_2O, δ) 3.81 (s, 3H, OCH_3), 3.36 (t, $J = 6.4$ Hz, 2H, CH_2), 2.89 (t, $J = 6.4$ Hz, 2H, CH_2). The spectral data are consistent with those previously reported.[71]

Synthesis of *N*(α)-Cbz-lysine methyl ester hydrochloride

TMS-Cl (0.9 mL, 7.0 mmol) was added dropwise to *N*(α)-Cbz-lysine (0.98 g, 3.0 mmol). Then MeOH (10.0 mL) was added slowly and the resulting solution was stirred for 24 h at rt. The solvent was evaporated to dryness leading to (**3**) (1.18 g, quantitative yield) as a colorless oil. ^{1}H NMR (300 MHz, D_2O, δ) 7.62–7.21 (m, 7H, H_{ar} and NH_2), 5.20 (s, 2H, CH_2), 4.28 (m, 1H, CH), 3.80 (s, 3H, OCH_3), 3.01 (m, 2H, CH_2), 2.39 (s, 1H, NH), 2.06–

1.63 (m, 4H, CH$_2$), 1.49 (m, 2H, CH$_2$). The spectral data are consistent with those previously reported.[80]

Synthesis of 5a and 6a

β-Alanine methyl ester hydrochloride (0.377 g, 2.7 mmol) was suspended in CH$_3$CN (10.0 mL). TEA (0.45 mL, 3.22 mmol) was added, the mixture was warmed at 60 °C and half of a solution of N-tosyl aziridine (1.33 g, 6.74 mmol in 10.0 mL of toluene) was added dropwise in 10 minutes. After one hour was added dropwise the second half of the solution and the mixture was left to react for 6 h at reflux temperature. The reaction solvent was evaporated to dryness and the crude was purified by flash chromatography (SiO$_2$, AcOEt/n-hexane 6 : 4 gradient to AcOEt/ MeOH 20%) yielding to **6a** (378 mg, yield 47%) and **5a** (402 mg, yield 30%).

5a. ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.77 (d, J = 8.2 Hz, 4H, H$_{ar}$), 7.30 (d, J = 8.2 Hz, 4H, H$_{ar}$), 5.50 (m, 2H, NH), 3.74 (s, 3H, OCH$_3$), 2.88 (m, 4H, CH$_2$), 2.57 (m, 2H, CH$_2$), 2.50–2.33 (m, 12H, CH$_3$ + CH$_2$). ^{13}C-NMR (75 MHz, CDCl$_3$, δ) 174.3 (CO), 143.4 (C$_{ar}$), 137.0 (C$_{ar}$), 129.9 (CH$_{ar}$), 127.4 (CH$_{ar}$), 53.2 (CH$_2$), 52.3 (OCH$_3$), 48.4 (CH$_2$), 40.7 (CH$_2$), 32.2 (CH$_2$), 21.6 (CH$_3$). MS (ESI): m/z (%) = 498.17 (100) [MH]$^+$. Anal. calcd for C$_{22}$H$_{31}$N$_3$O$_6$S$_2$: C, 53.10; H, 6.28; N, 8.44. Found: C, 53.25; H, 6.51; N, 8.53.

6a. ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.72 (d, J = 8.1 Hz, 2H, H$_{ar}$), 7.27 (d, J = 8.2 Hz, 2H, H$_{ar}$), 5.50 (m, 2H, NH), 3.65 (s, 3H, OCH$_3$), 2.95 (m, 2H, CH$_2$), 2.73 (t, J = 6.4 Hz, 2H, CH$_2$), 2.71 (m, 2H, CH$_2$), 2.42 (s, 3H, CH$_3$) overlapping with 2.41 (m, 2H, CH$_2$). MS (ESI): m/z (%) = 302.11 (100) [MH]$^+$. Anal. calcd for C$_{13}$H$_{20}$N$_2$O$_4$S: C, 51.98; H, 6.71; N, 9.33. Found: C, 51.89; H, 6.62; N, 9.11.

Synthesis of 5a from 6a

A solution of N-tosyl aziridine (278 mg, 1.45 mmol in 5.0 mL of toluene) was added dropwise to a solution of compound **6a** (364 mg, 1.21 mmol in 5.0 mL of toluene) at 60 °C. The mixture was left to react for 8 h at reflux temperature. The solvent was evaporated to dryness and the crude was purified by flash chromatography (SiO$_2$, AcOEt/n-hexane 7 : 3 gradient to AcOEt/ n-hexane 9 : 1) yielding to **5a** (503 mg, yield 84%) as a white foam. The spectral data are consistent with those reported above.

Synthesis of 5b and 6b

N(α)-Cbz-lysine methyl ester hydrochloride (0.608 g, 1.8 mmol) was suspended in CH$_3$CN (6.0 mL). TEA (0.37 mL, 2.7 mmol) was added, the mixture was warmed at 60 °C and half of a solution of N-tosyl aziridine (1.05 g, 5.35 mmol in 16.0 mL of toluene) was added dropwise in 10 min. After one hour was added dropwise the second half of the solution and the mixture was left to react for 6 h at reflux temperature. The reaction solvent was evaporated to dryness and the crude was purified by flash chromatography (SiO$_2$, AcOEt/n-hexane 6 : 4 gradient to AcOEt/MeOH 20%) yielding to (**6b**) (355 mg, yield 40%) and (**5b**) (552 mg, yield 45%).

5b. ^{1}H NMR (400 MHz, CDCl$_3$, δ) 7.75 (d, J = 8.2 Hz, 4H, H$_{ar}$), 7.35–7.28 (m, 9H, H$_{ar}$), 5.49 (d, J = 8.1 Hz, 1H, NH-Cbz), 5.12 (s,

2H, CH$_2$), 4.35 (m, 1H, CH), 3.73 (s, 3H, OCH$_3$), 2.93 (m, 4H, CH$_2$), 2.51 (m, 4H, CH$_2$), 2.41–2.31 (m, 8H, CH$_3$ + CH$_2$), 1.78 (m, 1H, CH$_2$), 1.64 (m, 1H, CH$_2$), 1.41 (m, 2H, CH$_2$), 1.33 (m, 2H, CH$_2$). ^{13}C-NMR (100 MHz, CDCl$_3$, δ) 173.0 (CO), 158.5 (CO), 143.6 (C$_{ar}$), 137.0 (C$_{ar}$), 136.4 (C$_{ar}$) 129.9 (CH$_{ar}$), 128.7 (CH$_{ar}$), 128.3 (CH$_{ar}$), 128.2 (CH$_{ar}$), 127.3 (CH$_{ar}$), 67.2 (CH$_2$), 60.5 (CH$_2$), 54.1 (CH$_2$), 53.7 (CH), 52.7 (OCH$_3$), 40.3 (CH$_2$), 32.5 (CH$_2$), 23.0 (CH$_2$), 21.7 (CH$_3$). MS (ESI): m/z (%) = 689.26 (100) [MH]$^+$. Anal. calcd for C$_{33}$H$_{44}$N$_4$O$_8$S$_2$: C, 57.54; H, 6.44; N, 8.13. Found: C, 57.10; H, 6.47; N, 8.24. [α]$_D^{20}$ = 5.60° (c 1.00 in CHCl$_3$).

6b. ^{1}H NMR (400 MHz, CDCl$_3$, δ) 7.76 (d, J = 8.2 Hz, 4H, H$_{ar}$), 7.40–7.28 (m, 7H, H$_{ar}$), 5.43 (d, J = 7.0 Hz, 1H, NH-Cbz), 5.10 (s, 2H, CH$_2$), 4.35 (m, 1H, CH), 3.74 (s, 3H, OCH$_3$), 3.03 (m, 2H, CH$_2$), 2.76 (m, 2H, CH$_2$), 2.55 (m, 2H, CH$_2$), 2.41 (s, 3H, CH$_3$), 1.78 (m, 1H, CH$_2$), 1.65 (m, 1H, CH$_2$), 1.51 (m, 2H, CH$_2$), 1.35 (m, 2H, CH$_2$). MS (ESI): m/z (%) = 492.21 (100) [MH]$^+$. Anal. calcd for C$_{24}$H$_{33}$N$_3$O$_6$S: C, 58.64; H, 6.77; N, 8.55. Found: C, 58.85; H, 6.74; N, 8.42.

Synthesis of 5b from 6b

A solution of N-tosyl aziridine (168 mg, 0.85 mmol in 4.0 mL of toluene) was added dropwise to a solution of compound **6b** (350 mg, 0.71 mmol in 4.0 mL of toluene) at 60 °C. The mixture was left to react for 8 h at reflux temperature. The solvent was evaporated to dryness and the crude was purified by flash chromatography (SiO$_2$, AcOEt/n-hexane 7 : 3 gradient to AcOEt/ n-hexane 9 : 1) yielding to **5b** (442 mg, yield 90%) as a white foam. The spectral data are consistent with those reported above.

Synthesis of 7a

Compound **5a** (201 mg, 0.40 mmol) was dissolved in anhydrous CH$_3$CN (12.0 mL). 2,6-Pyridinedimethanol 2,6-dimesylate (120 mg, 0.40 mmol) and K$_2$CO$_3$ (165 mg, 1.2) were added and the resulting mixture was left to react for 6 h at reflux temperature. The solvent was evaporated to dryness and the crude was suspended in 20 mL of water and extracted with AcOEt (3 × 10.0 mL). The organic phase was washed with brine (2 × 15.0 mL), treated with Na$_2$SO$_4$ and filtered. The solvent was evaporated to dryness yielding to **7a** (232 mg, yield 97%) as a light yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$, δ) 7.77–7.69 (m, 5H, H$_{ar}$), 7.37–7.29 (m, 6H, H$_{ar}$), 4.32 (s, 4H, CH$_2$), 3.64 (s, 3H, OCH$_3$), 3.10 (m, 4H, CH$_2$), 2.65 (m, 2H, CH$_2$), 2.44 (s, 6H, CH$_3$), 2.35–2.24 (m, 6H, CH$_2$). ^{13}C-NMR (100 MHz, CDCl$_3$, δ) 172.8 (CO), 155.2 (C$_{ar}$), 143.7 (C$_{ar}$), 138.9 (CH$_{ar}$), 130.0 (CH$_{ar}$), 127.3 (CH$_{ar}$), 124.2 (CH$_{ar}$), 54.7 (CH$_2$), 51.7 (CH$_2$), 51.3 (OCH$_3$), 51.1 (CH$_2$), 45.2 (CH$_2$), 34.0 (CH$_2$), 22.9 (CH$_2$), 21.7 (CH$_3$). MS (ESI): m/z (%) = 601.3 (100) [MH]$^+$. Anal. calcd for C$_{29}$H$_{36}$N$_4$O$_6$S$_2$: C, 57.98; H, 6.04; N, 9.33. Found: C, 57.62; H, 5.92; N, 9.12. UV/vis (5.2 × 10^{-5} mol L^{-1}, CH$_2$Cl$_2$ in 1 cm cuvettes): λ$_{max}$ [nm] = 234 nm. IR (ATR): 2949 cm^{-1} (w), 1733 cm^{-1} ($\nu_{C=O}$), 1157 cm^{-1}.

Synthesis of 7b

Compound **5b** (280 mg, 0.40 mmol) was dissolved in anhydrous CH$_3$CN (14.0 mL). 2,6-Pyridinedimethanol 2,6-dimesylate (123 mg, 0.42 mmol) and K$_2$CO$_3$ (184 mg, 1.3 mmol) were added and

the resulting mixture was left to react for 6 h at reflux temperature. The solvent was evaporated to dryness and the crude was suspended in 25 mL of water and extracted with AcOEt (3 × 15.0 mL). The organic phase was washed with brine (2 × 20.0 mL), treated with Na_2SO_4 and filtered. The solvent was evaporated to dryness yielding to **7b** (318 mg, 97%) as a light yellow solid. ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.73–7.69 (m, 5H, H$_{ar}$), 7.38–7.27 (m, 11H, H$_{ar}$), 5.29 (m, 1H, NH-Cbz), 5.11 (s, 2H, CH$_2$), 4.39–4.28 (m, 5H, CH and CH$_2$), 3.74 (s, 3H, OCH$_3$), 3.10 (m, 4H, CH$_2$), 2.44 (s, 6H, CH$_3$), 2.32–2.20 (m, 6H, CH$_2$), 1.79 (m, 1H, CH$_2$), 1.63 (m, 1H, CH$_2$), 1.36–1.16 (m, 4H, CH$_2$). ^{13}C-NMR (75 MHz, CDCl$_3$, δ) 173.1 (CO), 155.1 (C), 143.7 (C$_{ar}$), 138.9 (CH$_{ar}$), 136.2 (C$_{ar}$), 130.0 (CH$_{ar}$), 128.7 (CH$_{ar}$), 128.3 (CH$_{ar}$), 127.3 (CH$_{ar}$), 124.2 (CH$_{ar}$), 67.1 (CH$_2$), 55.2 (CH$_2$), 54.6 (CH$_2$), 54.0 (CH$_2$), 52.5 (OCH$_3$), 51.8 (CH$_2$), 44.8 (CH$_2$), 32.6 (CH$_2$), 27.78 (CH$_2$), 22.8 (CH$_2$), 21.7 (CH$_3$). MS (ESI): m/z (%) = 792.4 (100) [MH]$^+$. Anal. calcd for C$_{40}$H$_{49}$N$_5$O$_8$S$_2$: C, 60.66; H, 6.24; N, 8.84. Found: C, 60.28; H, 5.96; N, 8.60. $[\alpha]_D^{20} = 3.82°$ (c 1.00 in CHCl$_3$). UV/vis (5.0 × 10^{-5} mol L^{-1}, CH$_2$Cl$_2$ in 1 cm cuvettes): λ_{max} [nm] = 234 nm. IR (ATR): 3337 cm^{-1} (NH), 2932 (w), 1750 cm^{-1} ($\nu_{C=O}$), 1152 cm^{-1}.

Synthesis of 7c

Under H$_2$ atmosphere, compound **7b** (700 mg, 0.88 mmol) was dissolved in MeOH (15.0 mL). Pd/C (70 mg) was added and the resulting suspension was left to react for 24 h at rt. The suspension was filtered on celite layer and celite was washed with MeOH (3 × 5.0 mL). The solvent was evaporated to dryness yielding to **7c** (579 mg, 99%) as a pale yellow foam. ^{1}H NMR (300 MHz, CD$_3$OD, δ) 7.84 (d, J = 8.3 Hz, 4H, H$_{ar}$), 7.75 (pst, J = 7.7 Hz, 1H, H$_{ar}$), 7.75 (d, J = 8.3 Hz, 4H, H$_{ar}$), 7.26 (d, J = 7.7 Hz, 2H, H$_{ar}$), 4.59 (m, 2H, CH$_2$), 4.32 (m, 2H, CH$_2$), 4.15 (m, 1H, CH) overlapping with 4.7–4.13 (m, 2H, CH$_2$), 3.88 (s, 3H, OCH$_3$), 3.75 (m, 2H, CH$_2$), 3.70–3.48 (m, 4H, CH$_2$), 3.16 (m, 2H, CH$_2$), 2.45 (s, 6H, CH$_3$), 2.14 (m, 2H, CH$_2$), 1.97 (m, 2H, CH$_2$), 1.73–1.59 (m, 2H, CH$_2$). ^{13}C-NMR (75 MHz, CDCl$_3$, δ) 171.2 (CO), 159.3 (C$_{ar}$), 146.5 (C$_{ar}$), 140.3 (CH$_{ar}$), 134.7 (C$_{ar}$), 131.4 (CH$_{ar}$), 129.2 (CH$_{ar}$), 122.6 (CH$_{ar}$), 53.8 (OCH$_3$), 53.7 (CH), 53.4 (CH$_2$), 50.3 (CH$_2$), 46.7 (CH$_2$), 43.5 (CH$_2$), 31.1 (CH$_2$), 23.3 (CH$_2$), 21.5 (CH$_3$), 20.5 (CH$_2$). MS (ESI): m/z (%) = 658.3 (100) [MH]$^+$. Anal. calcd for C$_{32}$H$_{43}$N$_5$O$_6$S$_2$: C, 58.42; H, 6.59; N, 10.65. Found: C, 58.54; H, 6.50; N, 10.71.

Synthesis of 7d

Compound **7c** (579 mg, 0.88 mmol) was dissolved in AcOH (1.5 mL). NaCNBH$_3$ (166 mg, 2.65 mmol) was added and the mixture was left to stir 10 min at rt. Acetaldehyde (1.1 mL, 19.36 mmol) was added in 72 h in small amounts (4 eq. every 12 h). The solvent was evaporated to dryness, then brine (10.0 mL) was added and the solution was extracted with DCM (5 × 10.0 mL). The organic phase was treated with Na$_2$SO$_4$ and filtered. The solvent was evaporated to dryness yielding to **7d** (376 mg, yield 60%) as a light yellow foam. ^{1}H NMR (400 MHz, CDCl$_3$, δ) 7.72 (d, J = 8.2 Hz, 5H, H$_{Ar}$), 7.32 (t, J = 8.5 Hz, 6H, H$_{Ar}$), 4.34 (s, 4H, CH$_2$), 3.67 (s, 3H, OCH$_3$), 3.31 (t, J = 7.4 Hz, 1H, CH), 3.15–3.03 (m, 4H, CH$_2$), 2.70 (dq, J = 14.5, 7.2 Hz, 2H, CH$_2$), 2.51–2.40 (m, 8H, CH$_2$ + CH$_3$), 2.27 (dd, J = 16.6, 9.9 Hz, 6H, CH$_2$), 1.60 (ddd, J

= 15.6, 14.6, 9.2 Hz, 2H, CH$_2$), 1.31 (m, 2H, CH$_2$), 1.02 (t, J = 7.1 Hz, 6H, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$, δ) 174.2 (CO), 155.1 (C$_{Ar}$), 143.6 (C$_{Ar}$), 138.9 (CH$_{Ar}$), 136.2 (C$_{Ar}$), 130.0 (CH$_{Ar}$), 127.3 (CH$_{Ar}$), 124.2 (CH$_{Ar}$), 110.7 (CH), 63.2 (CH), 55.5 (CH$_2$), 54.8 (CH$_2$), 51.7 (CH$_2$), 51.1 (CH), 44.7 (CH$_2$), 29.9 (CH$_2$), 28.3 (CH$_2$), 24.1 (CH$_2$), 21.7 (CH$_3$), 14.1 (CH$_3$). MS (ESI): m/z (%) = 712.3 (100) [MH]$^+$. Anal. calcd for C$_{36}$H$_{51}$N$_5$O$_6$S$_2$: C, 60.56; H, 7.20; N, 9.81. Found: C, 60.22; H, 7.12; N, 10.02.

Reaction of ligand 7c with (R)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride

(R)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (17 mg, 0.067 mmol) was added to a solution of ligand **7c** (40 mg, 0.061 mmol) in CD$_3$COCD$_3$ (1.0 mL), in the presence of pyridine (14 mg, 0.18 mmol). The solution was stirred for 30 min, and then it was transferred into a NMR test tube. ^{19}F NMR (282 MHz, CDCl$_3$, δ) −71.24.

Reaction of ligand 7c with α-methoxyphenylacetic acid

To a solution of ligand **7c** (21 mg, 0.032 mmol) in CDCl$_3$ (1.0 mL) were added, in this order, (S)-(+) or (R)-(−)-α-methoxyphenylacetic acid (5 mg, 0.032 mmol), N,N′-dicyclohexylcarbodiimide (13 mg, 0.065 mmol) and 4-dimethylaminopyridine (3 mg, 0.022 mmol). The solution was stirred for 30 min, and then it was transferred into a NMR test tube.

General procedure for the synthesis of Ag(I) complexes

Under N$_2$, the ligand (0.39 mmol) was dissolved in anhydrous C$_2$H$_4$Cl$_2$ (10.0 mL), Ag(I) was added (0.39 mmol) as AgBF$_4$ or AgOTf and the mixture was left to react for 1 h at rt. The suspension was filtered under N$_2$, the solvent was concentrated to ∼1.0 mL and anhydrous n-hexane (10.0 mL) was added. The mixture was left for 10 min at rt, and then the solvent was evaporated to dryness. n-Hexane (10.0 mL) was added and the suspension was left under stirring over night at rt, then was opened at air and filtered yielding to the corresponding Ag(I) complex as a white powder.

8a-OTf. White powder: yield 89%; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.86 (t, J = 7.7 Hz, 1H, H$_{Ar}$), 7.76 (d, J = 8.2 Hz, 4H, H$_{Ar}$), 7.46 (d, J = 8.2 Hz, 4H, H$_{Ar}$), 7.31 (d, J = 7.7 Hz, 2H, H$_{Ar}$), 5.04 (d, J = 14.6 Hz, 2H, CH$_2$), 3.72 (s, 3H, OCH$_3$), 3.69 (d, J = 14.8 Hz, 2H, CH$_2$), 3.46 (m, 2H, CH$_2$), 3.04 (m, 2H, CH$_2$), 2.95–2.63 (m, 6H, CH$_2$), 2.48 (m, 8H, CH$_2$ + CH$_3$ overlapping), 2.19 (br, 2H, CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$, δ) 153.5 (C), 145.8 (C), 140.9 (CH$_{Ar}$), 130.7 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 125.5 (CH$_{Ar}$), 56.6 (CH$_2$), 53.4 (CH$_2$), 52.9 (CH$_3$), 48.9 (CH$_2$), 47.0 (CH$_2$), 31.9 (CH$_2$), 21.8 (CH$_3$). One quaternary carbon was not detected. MS (FAB): m/z (%) = 709 (100), 707 (97); 708 (31); 710 (30) [M − OTf]$^+$. Anal. calcd for C$_{30}$H$_{36}$AgF$_3$N$_4$O$_9$S$_3$: C, 42.01; H, 4.23; N, 6.53. Found: C, 42.13; H, 4.16; N, 6.49. UV/vis (5.0 × 10^{-5} mol L^{-1}, CH$_2$Cl$_2$ in 1 cm cuvettes): λ_{max} [nm] = 237, 264 nm. IR (ATR): 1728 cm^{-1} ($\nu_{C=O}$), 1155 cm^{-1}.

8a-BF$_4$. White powder: yield 93%; ^{1}H NMR (400 MHz, CDCl$_3$, δ) 7.91–7.70 (m, 5H, H$_{Ar}$), 7.45 (d, J = 7.8 Hz, 4H, H$_{Ar}$), 7.32–7.28 (m, 2H, H$_{Ar}$), 5.04 (d, J = 14.5 Hz, 2H, CH$_2$), 3.79 (s, 3H, OCH$_3$), 3.72–3.60 (m, 2H, CH$_2$), 3.50–3.43 (m, 2H, CH$_2$), 3.05 (m, 2H,

CH$_2$), 2.92–2.76 (m, 4H, CH$_2$), 2.72–2.58 (m, 2H, CH$_2$), 2.49 (m, 8H, CH$_2$ + CH$_3$ overlapping), 2.11 (m, 2H, CH$_2$). ^{13}C NMR (100 MHz, CDCl$_3$, δ) 145.8 (C$_{Ar}$), 140.7 (CH$_{Ar}$), 130.7 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 125.5 (CH$_{Ar}$), 56.6 (CH$_2$), 53.2 (CH$_2$), 52.8 (CH), 48.9 (CH$_2$), 46.9 (CH$_2$), 45.6 (CH$_2$), 21.8 (CH$_3$). One quaternary carbon was not detected. MS (FAB): m/z (%) = 709 (100), 707 (97); 708 (31); 710 (30) [M − BF$_4$]$^+$. Anal. calcd for C$_{29}$H$_{36}$-AgBF$_4$N$_4$O$_6$S$_2$: C, 43.79; H, 4.56; N, 7.04. Found: C, 43.89; H, 4.42; N, 6.62. UV/vis (5.0 × 10^{-5} mol L^{-1}, CH$_2$Cl$_2$ in 1 cm cuvettes): λ_{max} [nm] = 237, 264 nm. IR (ATR): 1727 cm^{-1} ($\nu_{C=O}$), 1161 cm^{-1}.

8b-OTf. White powder: yield 77%; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.85 (t, J = 7.7 Hz, 1H, H$_{Ar}$), 7.80–7.68 (m, 4H, H$_{Ar}$), 7.49–7.28 (m, 11H, H$_{Ar}$), 5.56 (m, 1H, NH), 5.17 (s, 2H, CH$_2$), 5.14–5.05 (m, 2H, CH$_2$), 4.52 (m, 1H, CH), 3.76 (s, 3H, OCH$_3$), 3.73–3.67 (m, 2H, CH$_2$), 3.48 (m, 2H, CH$_2$), 3.27 (m, 1H, CH$_2$), 3.03 (m, 1H, CH$_2$), 2.88–2.55 (m, 4H, CH$_2$), 2.51 (s, 6H, CH$_3$), 2.43 (m, 2H, CH$_2$), 2.17 (m, 2H, CH$_2$ overlapping with acetone), 1.95 (m, 1H, CH$_2$), 1.81 (m, 2H, CH$_2$), 1.59 (m, 2H, CH$_2$), 1.25 (m, 2H, CH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$, δ) 145.8 (C$_{Ar}$), 140.8 (CH$_{Ar}$), 130.6 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 125.3 (CH$_{Ar}$), 67.9 (CH$_2$), 56.6 (CH$_2$), 54.1 (CH$_2$), 53.7 (CH), 52.7 (OCH$_3$), 31.1 (CH$_2$), 30.0 (CH$_2$), 21.8 (CH$_3$). ^{13}C signals have been attributed by HSQC technique. Five quaternary carbons and three CH$_2$ were not located. MS (FAB): m/z (%) = 900 (100), 898 (94%); 901 (40%); 899 (40%) [M − OTf]$^+$. Anal. calcd for C$_{41}$H$_{49}$AgF$_3$N$_5$O$_{11}$S$_3$: C, 46.95; H, 4.71; N, 6.68. Found: C, 46.57; H, 4.35; N, 6.18. UV/vis (5.0 × 10^{-5} mol L^{-1}, CH$_2$Cl$_2$ in 1 cm cuvettes): λ_{max} [nm] = 237, 264 nm. IR (ATR): 1717 cm^{-1} ($\nu_{C=O}$), 1156 cm^{-1}.

8b-BF$_4$. White powder: yield 94%; ^{1}H NMR (400 MHz, CDCl$_3$, δ) 7.86–7.62 (m, 5H, H$_{Ar}$), 7.49–7.27 (m, 11H, H$_{Ar}$), 5.68 (m, 1H, NH), 5.23–4.92 (m, 4H, CH$_2$), 4.48 (m, 1H, CH), 3.76–3.61 (s, 5H, CH$_2$ + OCH$_3$), 3.42 (m, 1H, CH$_2$), 3.27 (m, 1H, CH$_2$), 2.93 (m, 1H, CH$_2$), 2.80–2.54 (m, 4H, CH$_2$), 2.53–2.25 (m, 8H, CH$_2$ + CH$_3$), 2.06 (m, 1H, CH$_2$), 1.94 (m, 2H, CH$_2$), 1.77 (m, 2H, CH$_2$), 1.55 (m, 2H, CH$_2$), 1.25 (m, 2H, CH$_2$). ^{13}C NMR (100 MHz, CDCl$_3$, δ) 173.1 (CO), 157.3 (C$_{Ar}$), 156.6 (C$_{Ar}$), 153.7 (C$_{Ar}$), 145.8 (C$_{Ar}$), 140.6 (CH$_{Ar}$), 139.2 (CH$_{Ar}$), 136.6 (C$_{Ar}$), 130.7 (CH$_{Ar}$), 128.8 (CH$_{Ar}$), 128.6 (CH$_{Ar}$), 128.0 (CH$_{Ar}$), 125.2 (CH$_{Ar}$), 125.1 (CH$_{Ar}$), 121.6 (CH$_{Ar}$), 67.5 (CH$_2$), 56.6 (CH$_2$), 53.8 (CH), 52.7 (OCH$_3$), 23.1 (CH$_2$), 21.8 (CH$_3$). MS (FAB): m/z (%) = 900 (100), 898 (94); 901 (41); 899 (38) [M − BF$_4$]$^+$. Anal. calcd for C$_{40}$H$_{49}$AgBF$_4$N$_5$O$_8$S$_2$: C, 48.69; H, 5.01; N, 7.10. Found: C, 48.54; H, 5.16; N, 7.16. UV/vis (5.0 × 10^{-5} mol L^{-1}, CH$_2$Cl$_2$ in 1 cm cuvettes): λ_{max} [nm] = 237, 264 nm. IR (ATR): 1718 cm^{-1} ($\nu_{C=O}$), 1160 cm^{-1}.

8c-BF$_4$. Yellowish powder: yield 75%; ^{1}H NMR (300 MHz, CD$_3$OD, δ) 7.93–7.67 (m, 5H, H$_{Ar}$), 7.53–7.20 (m, 6H, H$_{Ar}$), 4.61 (d, J = 17.4 Hz, 2H, CH$_2$), 4.44–4.14 (m, 2H, CH$_2$), 4.06 (d, J = 17.1 Hz, 2H, CH$_2$), 3.81–3.53 (m, 4H, CH$_2$), 3.50–3.27 (m, 4H, CH$_2$), 3.20–2.91 (m, 3H, CH$_2$ + CH), 2.45 (s, 6H, CH$_3$), 2.23–1.77 (m, 4H, CH$_2$), 1.74–1.51 (m, 2H, CH$_2$). ^{13}C NMR (75 MHz, CD$_3$OD, δ) 159.3 (CO), 146.5 (C$_{Ar}$), 140.3 (C$_{Ar}$), 134.7 (C$_{Ar}$), 131.4 (CH$_{Ar}$), 131.0 (CH$_{Ar}$), 129.1 (CH$_{Ar}$), 128.2 (CH$_{Ar}$), 122.6 (CH$_{Ar}$), 67.8 (CH$_2$), 53.9 (CH), 53.7 (OCH$_3$), 53.4 (CH$_2$), 46.7 (CH$_2$), 43.6 (CH$_2$), 23.2 (CH$_2$), 21.5 (CH$_3$), 20.2 (CH$_2$). MS (FAB): m/z (%) = 766 (100); 764 (97%); 767 (40%); 765 (38%) [M −

BF$_4$]$^+$. Anal. calcd for C$_{32}$H$_{43}$AgBF$_4$N$_5$O$_6$S$_2$: C, 45.08; H, 5.08; N, 8.21. Found: C, 44.96; H, 5.42; N, 7.93.

8d-BF$_4$. White powder: yield 83%; ^{1}H NMR (600 MHz, CDCl$_3$, δ) 7.78 (br, 5H, H$_{Ar}$), 7.46 (br, 4H, H$_{Ar}$), 7.32–7.26 (m, 3H, H$_{Ar}$), 5.09 (d, J = 13.8 Hz, 2H, CH$_2$), 3.82–3.58 (m, 6H, CH$_2$), 3.20 (s, 1H, CH), 3.09–2.79 (m, 4H, CH$_2$), 2.70–2.54 (m, 6H, CH$_2$), 2.48 (s, 6H, CH$_3$), 2.23–2.05 (m, 2H, CH$_2$), 2.02–1.81 (m, 3H, CH$_2$), 1.75–1.45 (m, 2H, CH$_2$), 1.27 (br, 2H, CH$_2$), 1.15 (br, 6H, CH$_3$). ^{13}C NMR (151 MHz, CDCl$_3$, δ) 153.7 (C$_{Ar}$), 145.8 (C$_{Ar}$), 140.6 (CH$_{Ar}$), 130.7 (CH$_{Ar}$), 128.7 (CH$_{Ar}$), 128.6 (CH$_{Ar}$), 125.0 (CH$_{Ar}$), 56.5 (CH$_2$), 21.8 (CH$_3$). MS (FAB): m/z (%) = 822 (100); 820 (97%); 821 (40%); 823 (38%) [M − BF$_4$]$^+$; 714 (15%) [MH − AgBF$_4$]$^+$. Anal. calcd for C$_{36}$H$_{51}$AgBF$_4$N$_5$O$_6$S$_2$: C, 47.59; H, 5.66; N, 7.71. Found: C, 47.62; H, 5.32; N, 7.75.

General procedure for the Henry reaction

The reactions were performed under a nitrogen atmosphere. The catalyst (0.032 mmoles) was dissolved in dry CH$_2$Cl$_2$ (5.0 mL) at rt in a Schlenk flask equipped with a stirring bar (were indicated molecular sieves-4 Å were added, see Tables 1–3 captions). Reactants were then added in the following order: the proper aldehyde **3** (0.32 mmoles), the nitroalkane (1.6 mmoles), and finally the selected base (0.032 mmoles). The resulting mixture was stirred at 30 °C for 12 h, extracted three times with brine. The organic layer was dried over sodium sulphate, and the solvent was evaporated under reduced pressure. The reaction crude was purified by flash column chromatography over a silica gel column with gradients of n-hexane/ethyl acetate as eluent. Products **4h**, **4n** and **4p** (yields below 15%) were not isolated.

1-(3,5-Bis(trifluoromethyl)phenyl)-2-nitroethanol 4j. Yield 66% (64 mg); ^{1}H NMR (300 MHz, CDCl$_3$, δ) 7.94–7.89 (m, 3H, H$_{Ar}$), 5.64 (pst, J = 6.4 Hz, 1H, CH), 4.74–4.48 (m, 2H, CH$_2$), 3.32–3.06 (bs, 1H, OH). ^{13}C NMR (75 MHz, CDCl$_3$, δ) 140.7 (C$_{Ar}$), 132.70 (q, $^2J_{C,F}$ = 33.8 Hz), 126.4 (CH$_{Ar}$), 123.12 (q, $^1J_{C,F}$ = 272.8 Hz), 123.05 (hept, $^3J_{C,F}$ = 3.8 Hz, CH), 80.7 (CH$_2$), 69.8 (CH). Anal. calcd for C$_{10}$H$_7$F$_6$NO$_3$: C, 39.62; H, 2.33; N, 4.62. Found: C, 39.99; H, 2.60; N, 4.39.

General procedure for the synthesis of 2-alkynylbenzaldehydes 10a–e and 2-alkynylnicotinaldehydes 10f–g

To a solution of 2-bromobenzaldehyde or 2-bromonicotinaldehyde (3.24 mmol) in dry triethylamine (97.2 mmol), the appropriate alkyne (3.89 mmol) and *trans*-dichlorobis-(triphenylphosphine)palladium(ii) (2 mol%) were added, under a nitrogen atmosphere. The reaction was stirred at rt for 10 min, and then CuI (1 mol%) was added. The reaction mixture was stirred at 50 °C until no more starting product was detectable by TLC analysis (eluent: n-hexane/ethyl acetate). The solvent was then evaporated under reduced pressure and the crude material was purified by flash chromatography over a silica gel column with gradients of n-hexane/ethyl acetate as eluent. 2-Alkynylbenzaldehydes **10a**,[61] **b**,[61] **c**,[81] **d**,[61] and **e**,[61] and 2-alkynylnicotinaldehydes **f**[82] and **g**[83] are known compounds. They were

characterised by ^{1}H-NMR and spectral data are in good agreement with literature values.

General procedure for the reaction of 2-alkynylarylalehydes 10a–g with nitroalkanes

The reaction were performed in a 0.25 mmol scale under a nitrogen atmosphere. The catalyst **1-BF₄** (0.025 mmol) was dissolved in dry CH_2Cl_2 (1.25 mL) in a Schlenk test tube equipped with a stirring bar. The mixture was stirred at rt for 10 min. The proper 2-alkynylarylalehyde **10** (0.25 mmol), nitroalkane (12.5 mmol) and triethylamine (0.025 mmol) were added to the stirred solution, in this order. In some cases (see Table 5), 50 mg of 4 Å molecular sieves were added. The mixture was stirred at rt for 1–22 h (for reaction times see Table 5). The reaction mixture was diluted with CH_2Cl_2 (20.0 mL) and the organic layer was washed twice with brine (2 × 20.0 mL). The organic layer was dried over sodium sulphate, and the solvent was evaporated under reduced pressure. The reaction crude was purified by flash column chromatography over a silica gel column with gradients of *n*-hexane/ethyl acetate as eluent.

1-(2-((4-Methoxyphenyl)ethynyl)phenyl)-2-nitropropan-1-ol 11b. Yield 21% (16 mg); ^{1}H NMR (300 MHz, CDCl₃, δ) 7.60–7.52 (m, 3H, H$_{Ar}$), 7.51–7.46 (m, 1H, H$_{Ar}$), 7.43–7.34 (m, 2H, H$_{Ar}$), 6.95 (dd, J = 9.2, 2.3 Hz, 2H, H$_{Ar}$), 5.65 (d, J = 8.9 Hz, 1H, CH), 5.03 (dq, J = 8.8, 6.9 Hz, 1H, CH), 3.87 (s, 3H CH₃), 2.94 (s, 1H, OH), 1.45 (d, J = 6.9 Hz, 3H, CH₃). ^{13}C NMR (75 MHz, CDCl₃, δ) 160.2 (C$_{Ar}$), 139.6 (C$_{Ar}$), 133.1 (CH$_{Ar}$), 132.4 (CH$_{Ar}$), 128.8 (CH$_{Ar}$), 128.7 (CH$_{Ar}$), 127.0 (CH$_{Ar}$), 122.2 (C$_{Ar}$), 114.4 (C$_{Ar}$), 114.3 (CH$_{Ar}$), 95.9 (Csp), 88.4 (CH), 85.3 (Csp), 74.3 (CH), 55.4 (CH₃), 16.4 (CH₃). ESI-MS m/z (%): 334 [M + Na]$^+$ (100), 312 [M + H]$^+$ (80). Anal. calcd for C$_{18}$H$_{17}$NO₄: C, 69.44; H, 5.50; N, 4.50; found: C, 69.57; H, 5.53; N, 4.47.

11b′. Yield 49% (38 mg); ^{1}H NMR (300 MHz, CDCl₃, δ) 7.65 (d, J = 7.7 Hz, 1H, H$_{Ar}$), 7.54 (d, J = 8.9 Hz, 3H, H$_{Ar}$), 7.43–7.30 (m, 2H, H$_{Ar}$), 6.92 (dd, J = 8.8 Hz, 2H, H$_{Ar}$), 6.02 (d, J = 2.0 Hz, 1H, CH), 5.13 (dq, J = 6.9, 2.3 Hz, 1H, CH), 3.85 (s, 3H CH₃), 2.89 (s, 1H, OH), 1.45 (d, J = 6.9 Hz, 3H, CH₃). ^{13}C NMR (75 MHz, CDCl₃, δ) 160.3 (C$_{Ar}$), 139.9 (C$_{Ar}$), 133.4 (CH$_{Ar}$), 132.2 (CH$_{Ar}$), 128.6 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 126.3 (CH$_{Ar}$), 121.1 (C$_{Ar}$), 114.7 (C$_{Ar}$), 114.4 (CH$_{Ar}$), 96.8 (Csp), 85.4 (CH), 84.8 (Csp), 72.4 (CH), 55.6 (CH₃), 11.1 (CH₃). ESI-MS m/z (%): 334 [M + Na]$^+$ (100), 312 [M + H]$^+$ (80). Anal. calcd for C$_{18}$H$_{17}$NO₄: C, 69.44; H, 5.50; N, 4.50; found: C, 69.58; H, 5.48; N, 4.46.

3-(4-Methoxyphenyl)-1-(1-nitroethyl)-1*H*-isochromene 12b + 12b′ (in 75 : 25 ratio). Yield 7% (6 mg); ^{1}H NMR (300 MHz, CDCl₃, δ) 7.64 (d, J = 9.0 Hz, 2H, H$_{Ar}$), 7.57 (d, J = 9.0 Hz, 2H, H$_{Ar}$), 7.36–7.11 (m, 4 + 4H, H$_{Ar}$), 6.94–6.89 (m, 2 + 2H, H$_{Ar}$), 6.39 (s, 1H, H$_{Ar}$), 6.30 (s, 1H, H$_{Ar}$), 5.90 (d, J = 5.9 Hz, 1H, –CH–O), 5.68 (d, J = 9.7 Hz, 1H, –CH–O), 5.09 (dq, J = 9.7, 6.8 Hz, 1H, –CH–NO₂), 4.93 (dq, J = 6.7, 5.9 Hz, 1H, –CH–NO₂), 3.85 (s, 3H, CH₃–O), 3.83 (s, 3H, CH₃–O), 1.66 (d, J = 6.7 Hz, 3H, CH₃), 1.39 (d, J = 6.8 Hz, 3H, CH₃). ^{13}C NMR (75 MHz, CDCl₃, δ) 160.9 (C$_{Ar}$), 160.8 (C$_{Ar}$), 151.4 (C$_q$), 151.0 (C$_q$), 131.4 (C$_{Ar}$), 131.1 (C$_{Ar}$), 129.8 (CH$_{Ar}$), 129.5 (CH$_{Ar}$), 127.1 (CH$_{Ar}$), 126.9 (CH$_{Ar}$), 126.6 (CH$_{Ar}$), 126.5 (CH$_{Ar}$), 126.4 (CH$_{Ar}$), 126.1 (C$_{Ar}$), 125.7 (C$_{Ar}$), 125.0 (CH$_{Ar}$), 124.53 (C$_{Ar}$), 124.48 (C$_{Ar}$), 124.42 (CH$_{Ar}$), 114.2 (CH$_{Ar}$), 114.1 (CH$_{Ar}$), 98.7 (CH$_{Ar}$), 98.6 (CH$_{Ar}$), 85.7 (CH), 82.3 (CH), 79.5 (CH), 78.8 (CH), 55.56 (CH₃–O), 55.54 (CH₃–O), 16.22 (CH₃),

13.94 (CH₃) (one quaternary carbon of the minority compound **12b′** obscured). ESI-MS m/z (%): 312 [M + H]$^+$ (100).

2-Nitro-1-(2-((4-(trifluoromethyl)phenyl)ethynyl)phenyl)ethanol 11d. Yield 45% (38 mg); ^{1}H NMR (300 MHz, CDCl₃, δ) 7.71–7.65 (m, 5H, H$_{Ar}$), 7.59 (td, J = 7.4, 1.4 Hz, 1H, H$_{Ar}$), 7.47 (td, J = 7.4, 1.4 Hz, 1H, H$_{Ar}$), 7.37 (td, J = 7.7, 1.4 Hz, 1H, H$_{Ar}$), 6.03 (dd, J = 9.6, 1.4 Hz, 1H, CH), 4.79 (dd, J = 12.9, 2.5 Hz, 1H, CH₂), 4.54 (dd, J = 12.9, 9.9 Hz, 1H, CH₂), 2.98 (s, 1H, OH). ^{13}C NMR (75 MHz, CDCl₃, δ) 140.1 (C$_{Ar}$), 132.7 (CH$_{Ar}$), 132.1 (CH$_{Ar}$), 130.8 (q, $^2J_{C,F}$ = 33.0 Hz), 130.0 (CH$_{Ar}$), 128.8 (CH$_{Ar}$), 126.3 (q, $^5J_{C,F}$ = 1.7 Hz), 126.0 (CH$_{Ar}$), 125.7 (q, $^3J_{C,F}$ = 3.8 Hz), 124.0 (q, $^1J_{C,F}$ = 272.0 Hz), 120.1 (C$_{Ar}$), 94.9 (Csp), 87.9 (Csp), 80.7 (CH₂), 69.8 (CH). ESI-MS m/z (%): 380 [M + EtOH − H]$^+$ (55), 334 [M − H]$^+$ (100), 287 [M − NO₂ – H]$^+$ (50). Anal. calcd for C$_{17}$H$_{12}$F₃NO₃: C, 60.90; H, 3.61; N, 4.18; found: C, 60.78; H, 3.58; N, 4.14.

2-Nitro-1-(2-((trimethylsilyl)ethynyl)phenyl)ethanol 11e. Yield 48% (32 mg) Table 5, entry 7; yield 83% (55 mg) Table 5, entry 8; ^{1}H NMR (300 MHz, CDCl₃, δ) 7.63 (d, J = 7.7 Hz, 1H, H$_{Ar}$), 7.47 (dd, J = 7.7, 1.4 Hz, 1H, H$_{Ar}$), 7.40 (td, J = 7.4, 1.4 Hz, 1H, H$_{Ar}$), 7.29 (td, J = 7.7, 1.4 Hz, 1H, H$_{Ar}$), 5.87 (dd, J = 9.6, 1.9 Hz, 1H, CH), 4.75 (dd, J = 13.2, 2.5 Hz, 1H, CH₂), 4.47 (dd, J = 13.2, 9.9 Hz, 1H, CH₂), 3.03 (s, 1H, OH), 0.26 (s, 9H, CH₃). ^{13}C NMR (75 MHz, CDCl₃, δ) 140.1 (C$_{Ar}$), 132.5 (CH$_{Ar}$), 129.3 (CH$_{Ar}$), 128.3 (CH$_{Ar}$), 125.6 (CH$_{Ar}$), 120.4 (C$_{Ar}$), 102.2 (Csp), 101.2 (Csp), 80.0 (CH₂), 69.5 (CH), 0.0 (CH₃). ESI-MS m/z (%): 308 [M + EtOH − H]$^+$ (23), 262 [M − H]$^+$ (100). Anal. calcd for C$_{13}$H$_{17}$NO₃Si: C, 59.29; H, 6.51; N, 5.32; found: C, 59.10; H, 6.58; N, 5.33.

2-Nitro-1-(2-(pent-1-yn-1-yl)phenyl)ethanol 11f. Yield 15% (9 mg); ^{1}H NMR (300 MHz, CDCl₃, δ) 7.60 (d, J = 7.6 Hz, 1H, H$_{Ar}$), 7.45–7.28 (m, 3H, H$_{Ar}$), 5.88 (d, J = 9.4 Hz, 1H, CH), 4.76 (d, J = 13.0 Hz, 1H, CH₂), 4.52 (dd, J = 13.2, 9.7 Hz, 1H, CH₂), 2.95 (d, J = 4.3 Hz, 1H, OH), 2.47 (t, J = 7.0 Hz, 2H, CH₂), 1.68 (hex, J = 7.2 Hz, 2H, CH₂), 1.10 (t, J = 7.3 Hz, 3H, CH₃). ^{13}C NMR (75 MHz, CDCl₃, δ) 139.4 (C$_{Ar}$), 132.4 (CH$_{Ar}$), 128.33 (CH$_{Ar}$), 128.30 (CH$_{Ar}$), 125.5 (CH$_{Ar}$), 121.4 (C$_{Ar}$), 97.8 (Csp), 80.2 (CH₂), 77.3 (Csp), 69.6 (CH), 22.1 (CH₂), 21.5 (CH₂), 13.6 (CH₃). ESI-MS m/z (%): 256 [M + Na]$^+$ (100), 234 [M + H]$^+$ (25). Anal. calcd for C$_{13}$H$_{15}$NO₃: C, 66.94; H, 6.48; N, 6.00; found: C, 67.14; H, 6.53; N, 5.96.

1-(Nitromethyl)-3-propyl-1*H*-isochromene 12f. Yield 54% (31 mg); ^{1}H NMR (300 MHz, CDCl₃, δ) 7.28 (td, J = 7.5, 1.3 Hz, 1H, H$_{Ar}$), 7.37 (td, J = 7.5, 1.3 Hz, 1H, H$_{Ar}$), 7.39 (d, J = 7.5 Hz, 1H, H$_{Ar}$), 7.01 (d, J = 7.3 Hz, 1H, H$_{Ar}$), 5.97 (dd, J = 10.2, 3.2 Hz, 1H, CH), 5.71 (s, 1H, Csp²–H), 4.91 (dd, J = 12.2, 10.2 Hz, 1H, CH₂), 4.30 (dd, J = 12.2, 3.4 Hz, 1H, CH₂), 2.19 (dt, J = 7.2, 1.8 Hz, 2H, CH₂), 1.59 (hex, J = 7.4 Hz, 2H, CH₂), 0.98 (t, J = 7.4 Hz, 3H, CH₃). ^{13}C NMR (75 MHz, CDCl₃, δ) 155.0 (C$_q$), 130.8 (C$_{Ar}$), 129.4 (CH$_{Ar}$), 126.5 (CH$_{Ar}$), 124.39 (C$_{Ar}$), 124.36 (CH$_{Ar}$), 123.6 (CH$_{Ar}$), 100.4 (CH), 76.7 (CH₂), 74.5 (CH), 35.6 (CH₂), 19.7 (CH₂), 13.7 (CH₃). ESI-MS m/z (%): 256 [M + Na]$^+$ (100). Anal. calcd for C$_{13}$H$_{15}$NO₃: C, 66.94; H, 6.48; N, 6.00; found: C, 67.08; H, 6.54; N, 5.97.

2-Nitro-1-(2-(pent-1-yn-1-yl)pyridin-3-yl)ethanol 11g. Yield 52% (30 mg); ^{1}H NMR (300 MHz, CDCl₃, δ) 8.46 (dd, J = 4.9, 1.6 Hz, 1H, H$_{Ar}$), 7.98 (dd, J = 8.0, 1.6 Hz, 1H, H$_{Ar}$), 7.28 (t, J = 4.9 Hz, 1H, H$_{Ar}$), 5.86 (ddd, J = 9.6, 4.4, 2.2 Hz, 1H, CH), 4.77 (dd, J = 13.2, 2.5 Hz, 1H, CH₂), 4.44 (dd, J = 13.2, 9.6 Hz, 1H, CH₂),

4.15 (d, J = 4.4 Hz, 1H, OH), 2.44 (t, J = 7.2 Hz, 2H, CH$_2$), 1.64 (hex, J = 7.2 Hz, 2H, CH$_2$), 1.02 (t, J = 7.4 Hz, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$, δ) 149.6 (CH$_{Ar}$), 141.1 (C$_{Ar}$), 136.4 (C$_{Ar}$), 134.2 (CH$_{Ar}$), 123.1 (CH$_{Ar}$), 98.7 (Csp), 80.2 (CH$_2$), 77.5 (Csp), 68.3 (CH), 22.0 (CH$_2$), 21.6 (CH$_2$), 13.9 (CH$_3$). ESI-MS m/z (%): 235 [M + H]$^+$ (100). Anal. calcd for C$_{12}$H$_{14}$N$_2$O$_3$: C, 61.53; H, 6.02; N, 11.96; found: C, 61.75; H, 6.04; N, 11.79.

1-(2-((4-Methoxyphenyl)ethynyl)pyridin-3-yl)-2-nitroethanol 11h. Yield 68% (51 mg) Table 5, entry 11; yield 78% (58 mg) Table 5, entry 12; ^{1}H NMR (300 MHz, CDCl$_3$, δ) 8.41 (d, J = 4.2 Hz, 1H, H$_{Ar}$), 8.03 (d, J = 7.8 Hz, 1H, H$_{Ar}$), 7.45 (d, J = 8.5 Hz, 2H, H$_{Ar}$), 7.24 (dd, J = 7.7, 4.9 Hz, 1H, H$_{Ar}$), 6.83 (d, J = 8.5 Hz, 2H, H$_{Ar}$), 6.01 (d, J = 9.5, 1H, CH), 5.10 (s, 1H, OH), 4.82 (d, J = 12.5, 1H, CH$_2$), 4.47 (dd, J = 12.5, 10.4 Hz, 1H, CH$_2$), 3.82 (s, 3H, CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$, δ) 160.7 (C$_{Ar}$), 149.2 (CH$_{Ar}$), 140.5 (C$_{Ar}$), 136.6 (C$_{Ar}$), 134.2 (CH$_{Ar}$), 133.8 (CH$_{Ar}$), 123.0 (CH$_{Ar}$), 114.3 (CH$_{Ar}$), 113.1 (C$_{Ar}$), 97.1 (Csp), 84.0 (Csp), 80.2 (CH$_2$), 68.2 (CH), 55.3 (CH$_3$). ESI-MS m/z (%): 299 [M + H]$^+$ (100). Anal. calcd for C$_{16}$H$_{14}$N$_2$O$_4$: C, 64.42; H, 4.73; N, 9.39; found: C, 64.50; H, 4.74; N, 9.43.

Acknowledgements

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