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[Ag(PcL)]-Catalysed Domino Approach to 6-Substituted Benzoxazino Isoquinolines

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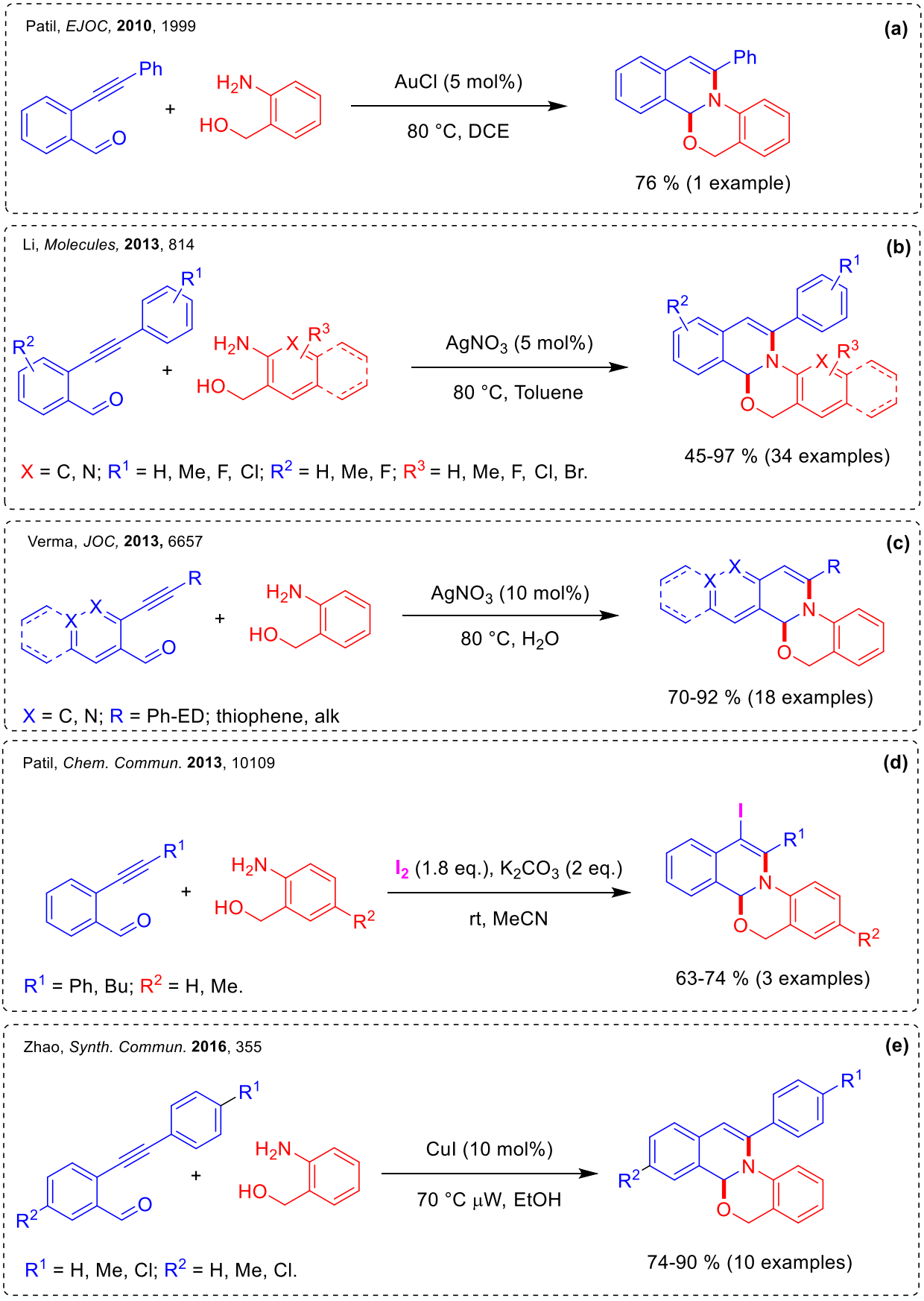
Abstract

In this paper, we describe a new silver catalysed domino approach to 6-substituted benzoxazino isoquinolines starting from 2-alkynylbenzaldehydes and 1-substituted-(2-aminophenyl)methanols. The strategy is characterized by good reaction yields, and can be performed at room temperature as well as under heating (conventional or dielectric) in different reaction times. Best results have been obtained by using silver complexes of macrocyclic pyridine-containing ligands (PcL) as catalysts. The stereoselectivity of the transformation has been investigated by using chiral reaction partners and chiral catalyst, but unfortunately, modest stereoselectivities has been achieved. On the other hand, this approach represents an alternative synthetic strategy for the preparation of 6-substituted benzoxazino isoquinolines, which are the key scaffold of some compounds endowed of biological activity.

Introduction

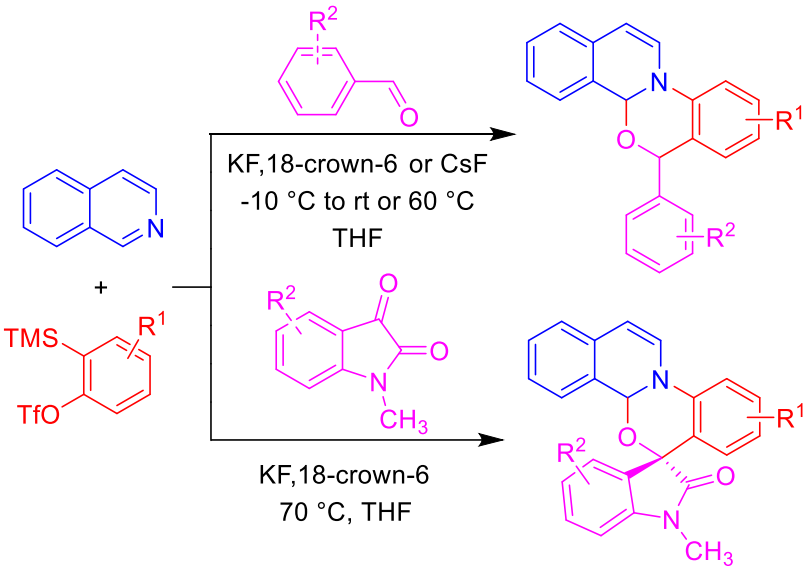
The "domino effect" is defined as the cumulative effect produced when one event triggers a chain of related events.[1] In analogy, in chemistry a domino reaction[2] is a sequence of reactions in which subsequent transformations are a consequence of the functionalities formed in the previous steps. In a typical domino reaction, a number of bond-forming transformations take place without change reaction conditions or add reagents and catalysts. *Everything fall–almost magically–in its place.* It is not surprising that in the last twenty-five years such approach fascinating many synthetic organic chemists. Domino transformations demonstrated to be especially useful and reliable strategies for the synthesis of heterocyclic compounds,[3] including polycyclic fused isoquinolines which display a broad spectrum of potential pharmacological applications against cancer,[4,5] for diabetes and obesity treatment,[5] as inhibitors of HIV-1,[6] and as PAF-receptor (Platelet Activating Factor receptor) antagonists,[7] just to cite some representative examples. In particular, 6-aryl-substituted 4b*H*,6*H*-benzo[4,5][1,3]oxazino[2,3-a]isoquinolines display interesting activities as antimalarial agents.[8]

One effective method to obtain benzoxazino isoquinolines is the domino reaction between a 2-alkynylbenzaldehyde and a 2-(hydroxymetyl)anilines in the presence of a suitable electrophilic reagent or catalyst. The very first example was reported in 2010 by Patil and co-workers. Within a more general study on cascade reaction of *o*-alkynylbenzaldehydes and aromatic amines containing tethered nucleophiles, the authors reported a single example of gold(I) chloride catalysed synthesis of 12-phenyl-benzoxazino isoquinoline at 80 °C in DCE[9] (Scheme 1, a). Li and co-workers in early 2013[10] widened the scope of the approach performing the reaction with silver nitrate as catalyst at 80°C in toluene, yielding the desired adducts in fair to very good yields (Scheme 1, b). A couple of month after, Verma and co-workers, independently reported a very similar $AgNO_3$-based approach, enhanced by the use of water as solvent, which needed a higher catalyst loading at the same temperature[11] (80 °C) (Scheme 1, c). In the same year, within a more extensive work on Electrophile Induced Branching Cascade approach (EIBC), Patil and co-workers prepared three benzoxazino isoquinolines at rt by using stoichiometric iodine as electrophile in the presence of K_2CO_3 in acetonitrile[12] (Scheme 1, d). More recently, a copper(I) iodide catalysed method under microwave irradiation (70 °C) has been also proposed[13] (Scheme 1, e).



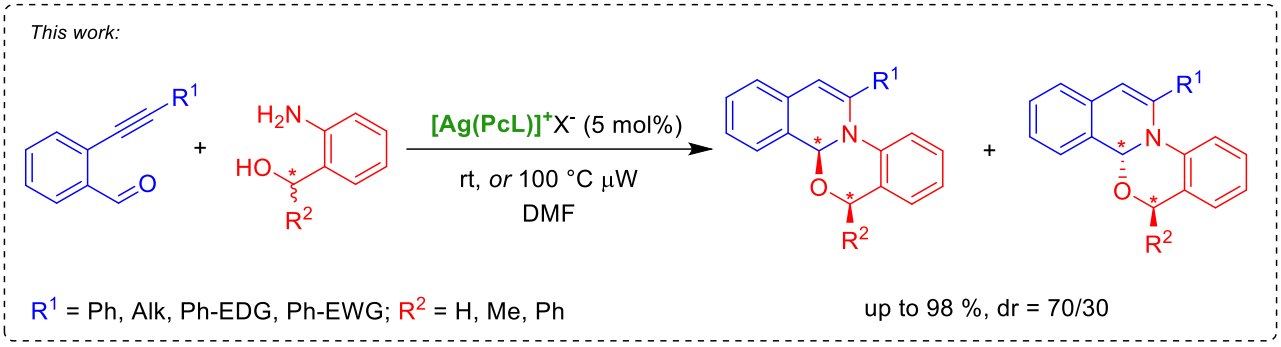
Scheme 1: Previous approaches to benzoxazino isoquinolines by domino reaction between a 2-alkynylbenzaldehydes and a 2-(hydroxymetyl)anilines.

All these methods are valuable, yields ranging from moderate to very good, but in general suffer for a relatively high catalyst loading (5-10 mol%) and none of them seems to well tolerate the presence of EW groups on the alkyne terminus. Moreover, no enantioselective examples of this transformation have been already reported, neither reactions involving the bidentate nucleophile partner (namely the (2-aminophenyl)methanol) substituted on benzylic carbon to obtain 6-substituted benzoxazino isoquinolines. This can be of particular interest, because, as mentioned above, some 6-aryl-substituted benzoxazino isoquinolines displayed an interesting antimalarial activity.[8] Usually this kind of benzoxazino isoquinolines are prepared by a different way, that is a multicomponent approach involving arynes, isoquinolines, and aldehydes that involves the formation of a 1,4-zwitterionic intermediate.[14] A similar approach allowed the synthesis of 6,6-spirobenzoxazino isoquinolines by using substituted isatins instead of aldehydes as carbonyl partner[15] (Scheme 2).



Scheme 2: Multicomponent approach to 6-substituted benzoxazino isoquinolines

Among the research interests of our group, the development of new and effective domino approaches for the synthesis of isoquinoline derivatives starting from γ-ketoalkynes[16] represent a topic since ever fascinated and attracted us.[17] Thus, in connection with our recent interest in silver catalysis,[18] and in the use of original PcL (pyridine containing ligands) as efficient metal ligands[19] we report here the results of our studies on [Ag(I)(PcL)] catalysed domino approach to 6-substituted benzoxazino isoquinolines, starting from 2-alkynylbenzaldehydes and 1-substituted (2-aminophenyl)methanols (Scheme 3).



Scheme 3: New domino approach to 6-substituted benzoxazino isoquinolines.

Results and discussion

The reaction between 2-[(4-tolyl)-ethynyl]benzaldehyde **1a** and 2-(hydroxymetyl)aniline **2a** was chosen to a preliminary study with the aim to optimize the reaction conditions. In particular we tested the activity of some [Ag(PcL)] complexes characterized by different electronic and steric properties (Figure 1). The result are summarized in Table 1.

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

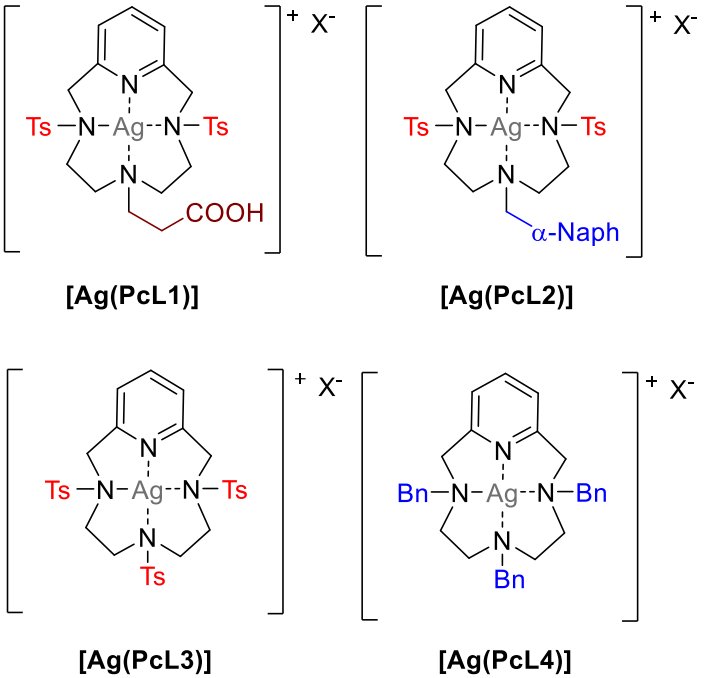
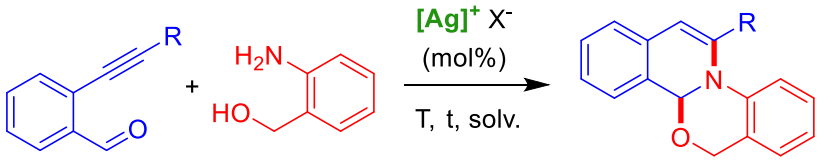


Table 1: Optimization of the reaction conditions.



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

1a: R = *p*-Tol
1b: R = *p*-MeO-Ph
1c: R = *n*-prop

3a: R = *p*-Tol
3b: R = *p*-MeO-Ph
3c: R = *n*-prop

Entry	1	$[Ag]^+$	X^-	(mol%)	Solvent	T (°C)	t (h)	3 (yield%) [a]	1 rec. (yield%)
1	**a**	Ag^+	TfO^-	10	DMF	60	3	**a**: 32	9[b]
2	**a**	$[Ag(PcL_1)]^+$	BF_4^-	10	DMF	60	3	**a**: 55	-[b]
3	**a**	$[Ag(PcL_2)]^+$	TfO^-	5	DMF	60	21	**a**: 82	-
4	**a**	$[Ag(PcL_2)]^+$	BF_4^-	5	DMF	80	7.5	**a**: 56	-[b]
5	**a**	$[Ag(PcL_3)]^+$	BF_4^-	5	DMF	60	72	**a**: 36	-[b]
6	**a**	$[Ag(PcL_4)]^+$	BF_4^-	5	DMF	60	44	**a**: 80	-
7	**a**	$[Ag(PcL_2)]^+$	BF_4^-	5	Toluene	80	7.5	**a**: 35	-[b]
8	**a**	$[Ag(PcL_2)]^+$	TfO^-	5	Toluene	40	48	**a**: 64	10
9	**a**	$[Ag(PcL_2)]^+$	TfO^-	5	DCE	40	48	**a**: (22)[c]	(58)[c]
10	**a**	$[Ag(PcL_2)]^+$	TfO^-	5	Dioxane	40	48	**a**: (18)[c]	(62)[c]
11	**a**	$[Ag(PcL_2)]^+$	TfO^-	5	Me-CN	40	48	**a**: (18)[c]	(45)[c]
12	**a**	$[Ag(PcL_2)]^+$	BF_4^-	5	Toluene	rt	120	**a**: 77	-
13	**b**	$[Ag(PcL_2)]^+$	TfO^-	5	DMF	60	25	**b**: 63	5
14	**c**	$[Ag(PcL_2)]^+$	TfO^-	5	DMF	60	19	**c**: 35	-[b]

[a] Isolated yields. [b] The NMR of the crude display the signals of unidentified by-products. [c] Yields estimated via ^1H NMR.

We chose DMF as solvent and 60 °C as starting reaction conditions; after a control experiment with a simple silver salt such as AgOTf (Table 1, entry 1), we started to test the activity of $[Ag(PcL)]^+$

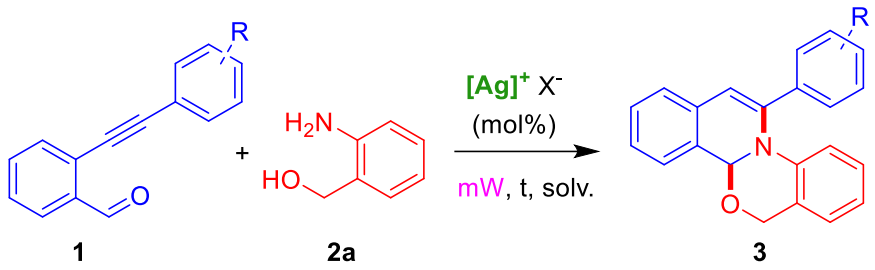
complexes. Among them, the complex $[Ag(PcL_2)]^+$ has already demonstrated to be effective in our previous study on silver catalysed A^3-coupling MCR.[18b] The reactions were normally stopped when the TLC analysis seemed to display the disappearance of the limiting starting material **2a**. $[Ag(PcL_1)]^+$ catalyst, characterized by the presence of a propionic acid pendant linked to the amino group of the macrocycle, gave promising result, although the ^1H NMR of the reaction crude displayed also the signals of unidentified by-products (Table 1, entry 2). A great improvement was observed when the reaction was performed with 5 mol% of $[Ag(PcL_2)]^+$ catalyst for a prolonged time (Table 1, entry 3), but an increase of temperature of 20 degrees and a reduction of reaction time gave slightly worse results (Table 1, entry 4). Electron-poor $[Ag(PcL_3)]^+$ complex gave worse results (Table 1, entry 5), while electron-rich $[Ag(PcL_4)]$ complex gave yields comparable to $[Ag(PcL_2)]^+$ (Table 1, entry 6). Then, we test some other solvents (Table 1, entries 7-12). When the reaction was performed at high temperature (80 °C for 7.5 h), toluene gave worse results compared to DMF (Table 1, compare entry 4 and entry 7). With in mind the idea to study also the stereoselective version of the approach, we performed the solvents screening at lower temperature. Under these conditions, only toluene gave results of a certain interest in terms of reaction yields, but only after prolonged reaction times (Table 1, entries 8 and 12).

Finally, under the best reaction condition (Table 1, entry 3), the reaction was performed on three different substrates (Table 1, entries 13-15). We were pleased to observed that an aromatic electron donating group on the alkyne end is well tolerated (Table 1, entry 13), whereas alkyl groups gave worse results (Table 1, entry 14), probably due to a low stability of the starting material.

This preliminary screening revealed some interesting features. First, electron-rich $[Ag(PcL)]^+$ complexes seem to be able to catalyse the reaction under conventional heating better than a simple silver salt such as AgOTf. Second, at rt and under conventional heating reaction times are long, also at relatively high temperatures. Third, DMF and toluene demonstrate to be the solvents of choice, in spite of their deep polarity differences.

To reduce reaction times and improve the efficiency of the approach we decided to switch from conventional to dielectric heating. The ability of microwaves to promote this kind of reaction has been already documented.[13] It is well known that the efficiency of dielectric heating is strongly related to the nature of the solvent,[20] so the highly polar DMF was selected as the solvent of choice to be used in these experiments, together with $[Ag(PcL_2)]^+$ complex as catalyst. The results are reported in Table 2.

Table 2: Optimization of the reaction conditions under microwave heating.



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

1a: R = *p*-Me
1d: R = *m*-CF_3

3a: R = *p*-Me
3d: R = *m*-CF_3

Entry	1	$[Ag]^+$	X^-	(mol%)	Solvent	T (°C)	t (h)	3 (yield%)[a]
1	**a**	$[Ag(PcL_2)]^+$	TfO^-	5	DMF	90	1	**a**: 69
2	**a**	$[Ag(PcL_2)]^+$	BF_4^-	5	DMF	100	1	**a**: 78
3	**a**	$[Ag(PcL_2)]^+$	BF_4^-	2	DMF	100	1	**a**: 62
4	**a**	$[Ag(PcL_2)]^+$	BF_4^-	2	DMF	100	2	**a**: 52
5	**a**	$[Ag(PcL_2)]^+$	BF_4^-	5	DMF	80	1	**a**: 53
6	**a**	$[Ag(PcL_2)]^+$	BF_4^-	5	DMF	80	2	**a**: 35
7	**a**	$[Ag(PcL_2)]^+$	BF_4^-	5	DMF	100	0.75	**a**: 65
8	**a**	$[Ag(PcL_2)]^+$	BF_4^-	5	Toluene	100	1	**a**: 45
9	**a**	Ag^+	BF_4^-	5	DMF	100	1	**a**: 76
10	**a**	Ag^+	NO_3^-	5	DMF	100	1	**a**: 75
11	**d**	$[Ag(PcL_2)]^+$	BF_4^-	5	DMF	100	1	**d**: 64
12	**d**	Ag^+	BF_4^-	5	DMF	100	1	**d:** 70

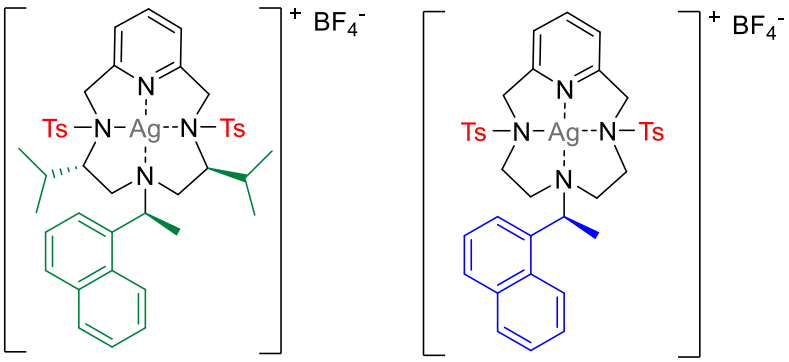
[a] Isolated yields.

When the model reaction was heated at 90° C for one hour under dielectric heating, the desired product was obtained in fair yields (Table 2, entry 1). Tetrafluoborate as counter-ion at 100° C for one hour seemed to be the best arrangement to our goal (Table 2, entry 2), as testified by the subsequent experiments (Table 2, entries 3-8). A halving of the catalyst loading (Table 2, entries 3 and 4), or a slight decrease of temperature, also under double reaction times (Table 2, entries 5 and

6) gave worse results, as well as a simple reduction of times under the best conditions (Table 2, entry 7). As expected, also the change of the solvent to less polar toluene, gave poor results (Table 2, entry 8). However, differently from what observed under conventional heating, two control experiments under the best microwave reaction conditions with simple silver salts, gave results comparable to those obtained with $[Ag(PcL_2)]^+$ complex (Table 2, entries 9 and 10) and a comparable behaviour was observed changing the nature of the substitution on alkynylbenzaldehyde (Table 2, entries 11 and 12).

In connection with the growing interest in the development of asymmetric silver catalysed transformation,[21] we decide to investigate also the possibility to induce enantioselectivity in this transformation by using some chiral $[Ag(PcL)^*]^+$ complexes (Figure 2).

Figure 2: Chiral $[Ag(PcL)^*]^+$ complexes tested in the study.

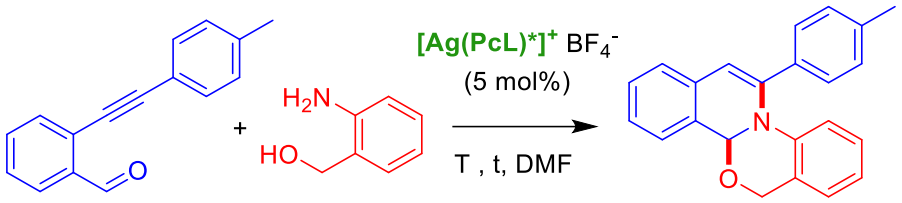


[Ag(PcL$_5$)*] **[Ag(PcL$_6$)*]**

We test two chiral silver complexes characterized by different stereospecific arrangements on the pyridine-containing macrocycle. One of them, i.e. $(PcL_6)^*$, has only a chiral pendant linked to the amine group in position 6, a (1-naphtalenyl)ethyl group in (*S*) configuration. The other, $(PcL_5)^*$ beside the chiral (1-naphtalenyl)ethyl group on the N-6 has two isopropyl group in (*S*)-configuration on the macrocycle in the positions 4 and 8, respectively (Figure 2).

The reaction with the chiral catalyst $[Ag(PcL_5)^*]^+$ at 60 °C gave good results in terms of yields but scarce enantioselectivity (Table 3, entry 1). The reduction of reaction temperature to 30 °C, beside a poor enantioselectivity, gave also low yield (Table 3, entry 2). The simplest catalyst $[Ag(PcL_6)^*]^+$ demonstrated to give comparable results to $[Ag(PcL_5)^*]^+$ in terms of yield and selectivity (Table 3, entry 3), so it was chosen for the prosecution of the study.

Table 3: Screening of the activity chiral [Ag(PcL)*] complexes on the model reaction.



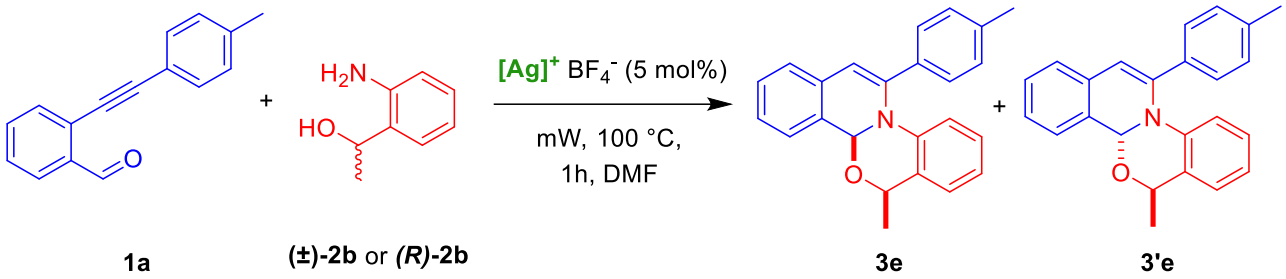
1a **2a** **3a**

Entry	[Ag(PcL)*]+	T (°C)	t (h)	3a (yield%)[a]	er[b]
1	[Ag(PcL5)*]+	60	26	80	53 : 47[b]
2	[Ag(PcL5)*]+	30	48	57	54 : 46[b]
3	[Ag(PcL6)*]+	rt	120	78	52 : 48[c]

[a] Isolated yields. [b] Determined by Chiral HPLC (Column: Phenomenex, Lux Amylose-2; eluent: *n*-hexane/isopropanol/diethylamine = 90:10:0.1). [c] Determined by Chiral HPLC (Column: Daicel, Chiracel AD, amylose; eluent: *n*-hexane/isopropanol/diethylamine = 75:25:0.1)

Due to above mentioned importance of 6-substituted benzoxazino isoquinolines,[8] we next focused our efforts to the synthesis of these interesting scaffolds, starting from 1-(2-aminophenyl)ethan-1-ol as racemate (**(±)-2b**) or as pure enantiomer (**(*R*)-2b**). The first was prepared by simple reduction of the corresponding 1-(2-aminophenyl)ethan-1-one with sodium borohydride in methanol in almost quantitative yields.[22] Enantiomeric pure (*R*)-1-(2-aminophenyl)ethan-1-one **(*R*)-2b** was prepared starting from the same starting material by enzymatic kinetic resolution of the corresponding *tert*-butyl 2-(1-hydroxyethyl)phenylcarbamate through a lipase-catalysed transesterification, as reported in the literature.[23] Reactions were conducted under the optimized reaction conditions under microwave heating using both racemic and enantiomeric pure **2b** and testing achiral and chiral [Ag(PcL)]+ complexes. Moreover, control reactions were also performed in the presence of simple silver salts. The results are reported in Table 4.

Table 4: Reactions with 1-(2-aminophenyl)ethan-1-ol **2b**.



1a **(±)-2b** or ***(R)*-2b** **3e** **3'e**

Entry	2	$[Ag]^+$	Yield[a]	dr 3e:3'e[b]	er 3e[c]	er 3'e[c]
1	**(±)-2b**	Ag^+	80%	70 : 30	50 : 50	50 : 50
2	**(±)-2b**	$[Ag(PcL_2)]^+$	88%	71 : 29	50 : 50	48 : 52
3	**(±)-2b**	$[Ag(PcL_6)^*]^+$	98%	70 : 30	50 : 50	47 : 53
4	***(R)*-2b**	Ag^+	85%	76 : 34	1 : 99	10 : 90
5	***(R)*-2b**	$[Ag(PcL_2)]^+$	82%	72 : 28	1 : 99	9 : 91
6	***(R)*-2b**	$[Ag(PcL_6)^*]^+$	84%	72 : 28	1 : 99	9 : 91

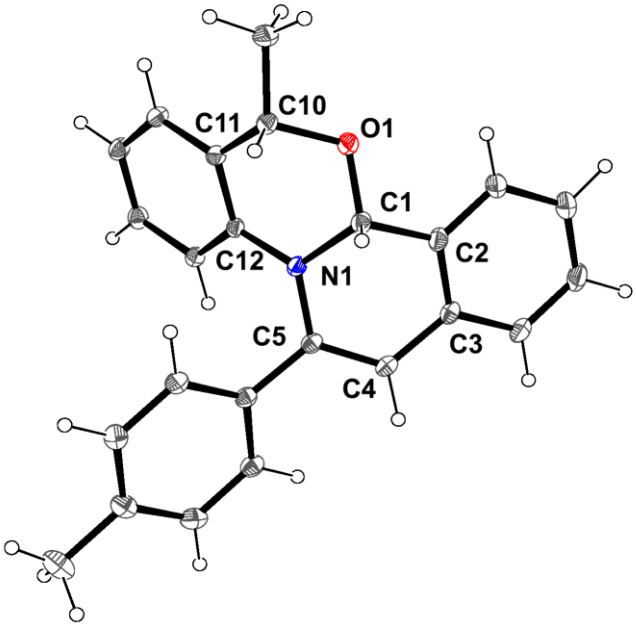
[a] Isolated yield by flash silica gel column chromatography *n*-hexane/AcOEt. [b] Calculated via ^{1}H NMR of the crude.
[c] Determined by Chiral HPLC (Column: Kromasil AmyCoat; eluent: *n*-hexane/isopropanol = 9:1).

In all the tests performed with 1-(2-aminophenyl)ethan-1-ol **2b**, the yields were comparable and slightly higher than those obtained in the previous experiments with 2-(hydroxymetyl)aniline **2a** (Table 4, entries 1-6). Irrespective to the catalyst used, the reactions performed with racemic **2b**, gave ever a mixture of the two possible diastereoisomers **3f** (*cis*) and **3'f** (*trans*) in a ratio of 70:30, both as racemates (Table 4, entries 1-3). This unequal distribution among *cis* and *trans* isomers reveals the existence of an energetic gap between the diastereoisomers and/or the corresponding transition states. Interestingly, the $[Ag(PcL)]^+$ complex gave higher yields than simple silver tetrafluoborate (Table 4, cfr entries 1 with 2,3), and in particular the chiral catalyst $[Ag(PcL_6)^*]^+$ gave the couple of diastereoisomers almost in quantitative yield (Table 4, entry 3).

When enantiopure **(*R*)-2b** was used, a comparable diastereoselectivity was observed (Table 4, entries 4-6), whereas the activity of the different catalysts in terms of yields was more homogeneous. Surprisingly, while the majority diastereoisomer **3e** was obtained in almost enantiopure form (ee = 99%), the minority ones **3'e** was obtained in 80% ee. This suggests that a partial racemization occurs specifically at the level of the high-energy transition state that bring to the formation of the minority diastereoisomer **3'e**.

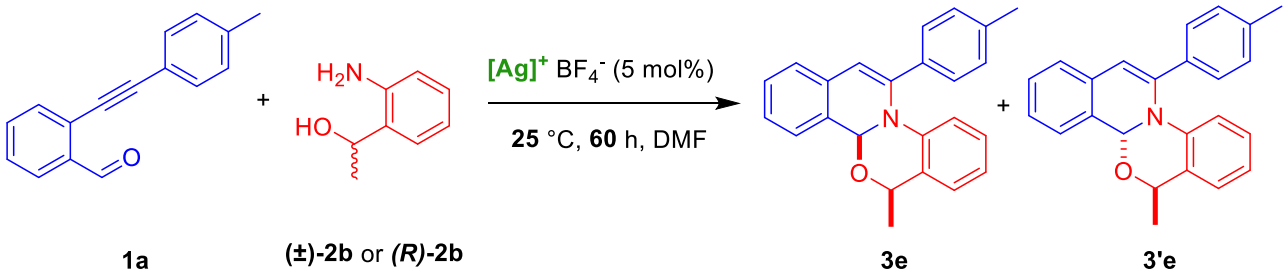
All new compounds have been fully characterized by ^{1}H and ^{13}C NMR spectroscopies, and MS spectrometry. The stereochemistry of diastereoisomeric products **3e** *(cis)* and **3'e** *(trans)* was assigned by NOESY experiments (see Supporting Information). Moreover, the structure of **3e** was confirmed by single crystal X-ray crystallography (Figure 3).

Figure 3: The molecular structure of compound **3e** showing the numbering schemes for some non-hydrogen atoms. Displacement ellipsoids are plotted at the 40% probability level.



Since in the experiments discussed above, the chiral catalyst failed to induce stereoselectivity, we decided to try the reactions at a lower temperature, with the aim to exclude and prevent whichever negative effect of the heat on diastereo- and enantio-selection. Thus, the reactions were repeated at rt for 60 hours. The results are reported in Table 5.

Table 5: Reactions with 1-(2-aminophenyl)ethan-1-ol **2b** at rt.



Entry	2	[Ag]$^+$	Yield[a]	dr 3e:3'e[b]	er 3e[c]	er 3'e[c]
1	**(±)-2b**	[Ag(PcL$_6$)*]$^+$	95%	77 : 23	49 : 51	53 : 47
2	**(*R*)-2b**	Ag$^+$	91%	88 : 12	1 : 99	15 : 85
3	**(*R*)-2b**	[Ag(PcL$_2$)]$^+$	93%	74 : 26	1 : 99	15 : 85
4	**(*R*)-2b**	[Ag(PcL$_6$)*]$^+$	99%	85 : 15	1 : 99	26 : 74

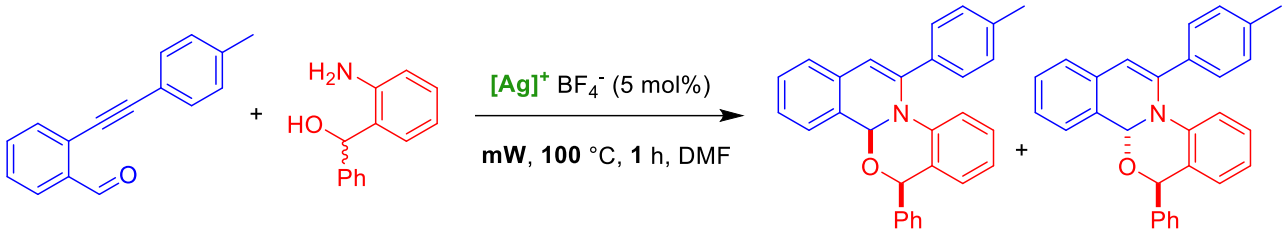
[a] Isolated yield by flash silica gel column chromatography *n*-hexane/AcOEt; [b] Calculated via ^{1}H NMR of the crude; [c] Determined by Chiral HPLC (Column: Kromasil AmyCoat; eluent: *n*-hexane/isopropanol = 9:1).

As already observed (see Table 4), in terms of yields [Ag(PcL)]$^+$ complexes gave in general slightly better results than simple silver salts, and in particular the chiral complex [Ag(PcL$_6$)*]$^+$ demonstrated once again to be the most effective (Table 5, entries 1 and 4). Unfortunately, the reduction of the reaction temperature did not give the desired improvement in terms of stereoselectivity. Interestingly, at room temperature, the formation of unfavoured diastereoisomers **3'e** seems to be a bit depressed (cfr. drs in Tables 4 and 5). This is in agreement with the previous observation that the energy of transition states of **3'e** is higher than for **3e**.

In the introduction, it has been underlined that 6-aryl-substituted oxazino isoquinolines displayed interesting activities as therapeutic agents, in particular versus malaria.[8] Thus, we performed our domino reaction with a new bidentate nucleophile partner, i.e. the (2-aminophenyl)(phenyl)methanol **2c**, prepared by conventional reduction of (2-aminophenyl)(phenyl)methanone with sodium borohydride.[21] Moreover, we reasoned that a bulkier group on the aminoalcohol could have a positive effect on the stereoselectivity of the transformation.

The results of domino condensation of **1a** with **2c** are reported in Table 6.

Table 6: Reactions with (2-aminophenyl)(phenyl)methanol **2c**.



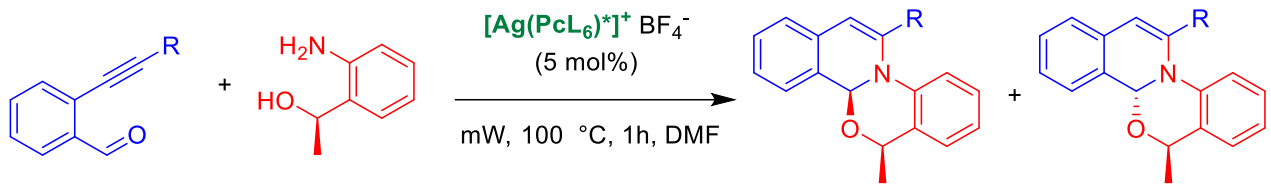
Entry	2	Catalyst	Yield[a]	dr 3f:3'f[b]	er 3f[c]	er 3'f [c]
1	**(±)-2c**	Ag^+	85%	69 : 31	50 : 50	50 : 50
2	**(±)-2c**	$[Ag(PcL_2)]^+$	83%	68 : 32	50 : 50	50 : 50
3	**(±)-2c**	$[Ag(PcL_6)^*]^+$	90%	69 : 31	50 : 50	49 : 51

[a] Isolated yield by flash silica gel column chromatography *n*-hexane/AcOEt; [b] Calculated via ^{1}H NMR of the crude; [c] Determined by Chiral HPLC (Column: Kromasil AmyCoat; eluent: *n*-hexane/isopropanol = 9:1).

With all the silver catalysts tested, the reactions under microwave heating gave the mixture of the two expected diastereoisomeric products in very good yields with a diastereoisomeric ratio near to 7 : 3. In agreement with the previous observations, the chiral $[Ag(PcL)]^+$ complex $[Ag(PcL_6)^*]^+$ gave the highest yield (Table 6, entry 3). However, the presence of the bulkier phenyl group on the nucleophile reaction partner, did not give any improvement in terms of diastereo- or enantio-selectivity. Also in this case the stereochemistry of diastereoisomeric products **3f** *(cis)* and **3'f** *(trans)* was assigned by NOESY experiments (see Supporting Information).

Finally, with the aim to briefly investigate the effect of the substitution at the alkyne terminus, we prepared four 2-alkynylbenzaldehydes characterized by the presence of EW, ED, and alkyl groups on the alkyne terminus. As for **1a**, 2-alkynylbenzaldehydes **1d-g** were synthesized by means of a typical Sonogashira coupling[24] in good to excellent yields starting from 2-bromobenzaldehyde and suitable terminal acetylenes. The results are described in Table 7. As expected, different substitution on alkyne terminus are well tolerated and the corresponding 6-substitued benzoxazino isoquinolines (**3g-j** and **3'g-j**) were obtained in very yield with diastereoisomeric ratios in agreement with the previous findings.

Table 7: Brief scope or the domino reaction.



1d-f **(*R*)-2b** **3g-j** **3'g-j**

1d: R = *m*-CF_3-Ph
1e: R = *p*-MeO-Ph
1f: R = *p*-Cl-Ph
1g: R = cyclopropyl

3g, 3'g: R = *m*-CF_3-Ph
3h, 3'h: R = *p*-MeO-Ph
3i, 3'i: R = *p*-Cl-Ph
3j, 3'j: R = cyclopropyl

Entry	1	R	Yield[a]	3	dr 3:3'[b]
1	**d**	*m*-CF_3-Ph	78%	**g**	72 : 28
2	**e**	*p*-MeO-Ph	66%	**h**	70 : 30
3	**f**	*p*-Cl-Ph	73%	**i**	73 : 27
4	**g**	cyclopropyl	80%	**j**	59 : 41

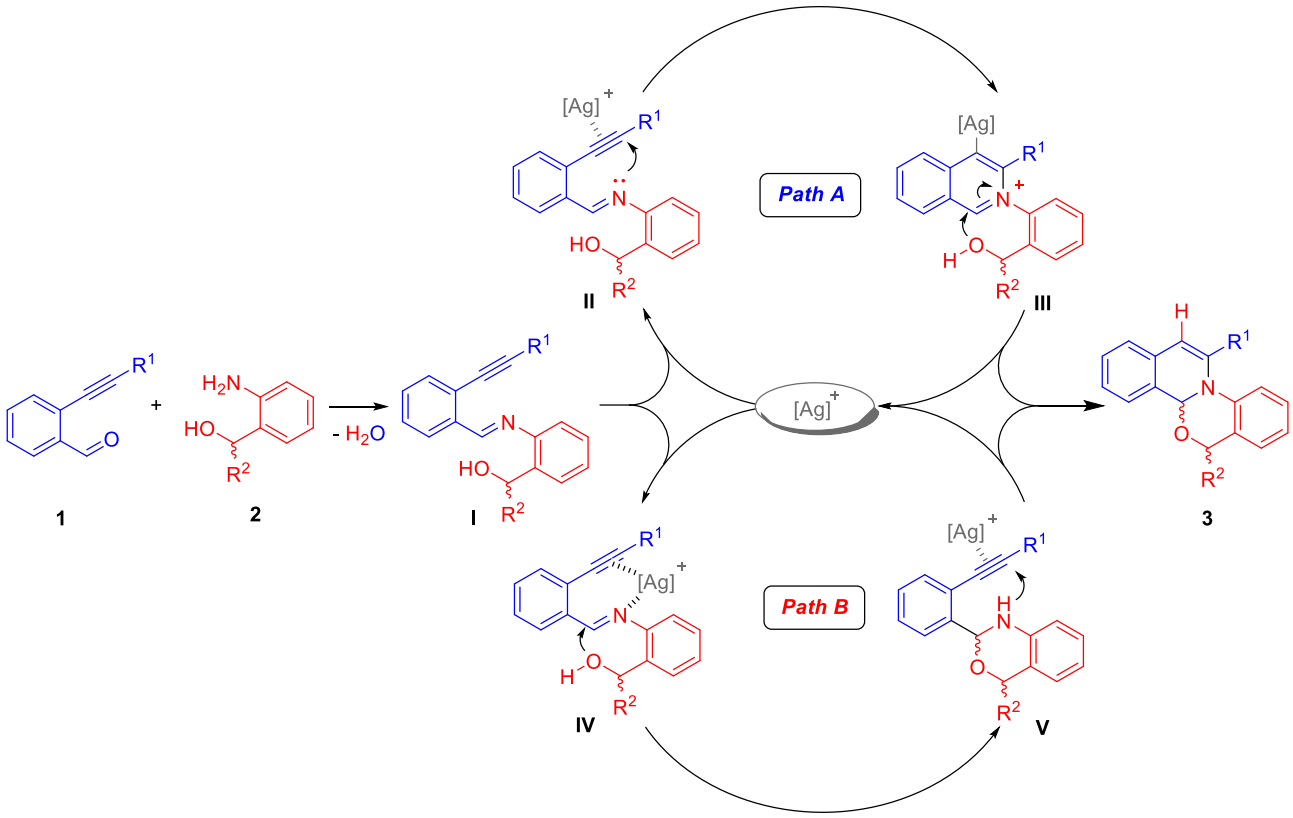
[a] Isolated yield by flash silica gel column chromatography *n*-hexane/AcOEt; [b] Calculated via ^{1}H NMR of the crude.

The stereochemistry of diastereoisomeric products **3g-j** *(cis)* and **3'g-j** *(trans)* was assigned by analogy with compounds **3e** and **3'e**.

According to literature findings[10,11,13] and based on our results, a plausible reaction mechanism is proposed as depicted in Scheme 1. The very first step is the condensation between the benzaldehydes **1** and γ-aminoalcohols **2** to give the imine intermediate **I**. This reaction is probably very fast due to the strong nucleophilicity of the electron-rich anilines. The transformation of the imine intermediate **I** into the final product **3** could occur through two different pathway-that are the real driving force of the transformation-involving two subsequent intramolecular cascade nucleophilic attacks, respectively pathway A and B (Scheme 1).

In path A, silver activates the triple bond, forming the intermediate **II**, which undergo the intramolecular nucleophilic attack from the nitrogen atom of the imine to give isoquinolines intermediate **III**. Then, the subsequent intramolecular attack of alcoholic oxygen on activated iminium group gave the final product **3**, whereas the protodemetallation restore the silver catalyst. Alternatively, path B involves the direct intramolecular addition of the alcoholic oxygen nucleophile to silver activated imine (intermediate **IV**) to give the benzoxazino intermediate **V**. The following intramolecular reaction of the nitrogen of the oxazine moiety to the silver activated triple bond

resulted in the formation of the product **3**, always after protodemetallation and regeneration of the catalyst (Scheme 4).



Scheme 4: Proposed mechanism.

Although path B cannot be ruled out, among the two possible pathways Path A seems to be more reliable on the basis of the following considerations: i) nitrogen is in general more nucleophile than oxygen; ii) a Path like A, in which the catalytic complex is far from the incoming stereocentre, justifies the absence of enantioselectivity observed also in the presence of hindered chiral silver catalysts such as $[Ag(PcL_6)^*]^+$ iii) under the optimized reaction conditions, intermediate V was never isolated or identified in the reaction crude.

Conclusions

A new efficient synthetic [Ag(PcL)]-catalysed domino strategy has been developed which leads to the formation of 6-substituted benzoxazino isoquinolines with excellent yields starting from 2-alkynylbenzaldehydes and 1-substituted (2-aminophenyl)methanols. The approach has been optimized by a preliminary in-depth screening of the reaction conditions with 2-(*p*-

tolylethynyl)benzaldehyde and (2-aminophenyl)methanol as achiral model compounds. Best results have been obtained by using original silver complexes of macrocyclic pyridine-containing ligands (PcL) as catalysts. The reactions can be performed under conventional heating, under microwave irradiation, or at room temperature with comparable results in term of yields but very different reaction times. The use of a α-substituted *o*-aminobenzyl alcohol bring to the formation of two diastereoisomers characterized by different stability. In particular, the diastereoisomer in which the hydrogen in positions 4b and 6 are in a *cis* conformation (confirmed by NOE ^{1}H NMR experiments and single crystal X-ray crystallography) is the more stable and it is always isolated as major isomer. The formation of the disfavoured trans-diastereoisomer is improved by the reaction temperature, and this suggests the involvement of a higher-energy transition state. When the 1-substituted (2-aminophenyl)methanol is used as a racemate, the two diastereoisomeric products are obtained-as expected-in racemic form. Instead, when the starting material is enantiomerically pure, the *cis* diastereoisomer is obtained as almost pure enantiomer (ee = 99%), while the *trans* ones does not fully retain its configuration such as a sort of racemization occurred, most probably at the high energy transition state level. Unfortunately, in this transformation an adequate degree of enantioselection was not achieved in any case.

Nevertheless, this approach represents a new and alternative path for the synthesis of 6-substituted benzoxazino isoquinolines, which are important scaffolds in medicinal chemistry. The use of silver PcL complexes as catalysts bring some interesting improvements compared to the use of the simple silver salts. First, (PcL) ligands increase the solubility and the stability of the silver. Second, in some cases they improved reaction yields, as in the case of the chiral complex $[Ag(PcL_6)]^*$. Further studies will be now devoted to the elucidation of the reaction mechanism to gain some insight for a more accurate design of new chiral silver (PcL) complexes as effective stereoselective catalysts.

Experimental section

General experimental details

All the reactions, that involve the use of reagents sensitive to oxygen or hydrolysis, were carried out under a nitrogen atmosphere. The glassware was previously dried in an oven at 110 °C and set with cycles of vacuum and nitrogen. Syringes used to transfer reagents and solvents, were previously set under nitrogen atmosphere. All chemicals and solvents are commercially available and were used without further purification. The chromatographic column separations were performed by flash technique, using silica gel (pore size 60Å, particle size 230-400 mesh, Merck Grade 9385). For thin-layer chromatography (TLC), Silica on TLC Alu foils with fluorescent indicator (254 nm) was

employed and the detection was performed by irradiation with UV light (λ = 254 nm and/or 366 nm). Chiral HPLC analyses were performed with the following chiral columns: Phenomenex, Lux Amylose-2; (eluent: *n*-hexane/isopropanol/diethylamine = 90:10:0.1) or Column: Daicel, Chiracel AD, amylose; (eluent: *n*-hexane/isopropanol/diethylamine = 75:25:0.1) for **3a** and Kromasil, AmyCoat (eluent: *n*-hexane/isopropanol = 9:1) for **3e**, **3'e**, **3f** and **3'f**. ^{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 inject directly the sample solutions. The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown in brackets. Melting points are uncorrected. Alkynylbenzaldehydes **1a-f**,[18d] 1-(2-aminophenyl)ethan-1-one **(±)-2b**[21] and its enantiomeric pure form (*R*)-(2-aminophenyl)ethan-1-one **(*R*)-2b**[22] and (2-aminophenyl)(phenyl)methanol **(±)-2c**[21] are known compounds and have been prepared as described in the literature. The synthesis of complexes [Ag(PcL$_1$)],[18c] [Ag(PcL$_2$)],[18b] [Ag(PcL$_3$)],[18e] [Ag(PcL$_4$)],[18e] [Ag(PcL$_5$)],[19b] [Ag(PcL$_6$)],[19b] have been already described.

General procedure for the synthesis of benzoxazino isoquinolines 3. Method A–rt or thermal. To a N_2-flushed solution of the selected 2-alkynylbenzaldehyde **1** (0.317 mmol) and 2-aminobenzylalcohol **2** (0.380) in anhydrous DMF (1 mL), the [Ag(PcL)]$^{+}$X^{-} catalyst (5 mol%) was added. The mixture was stirred at room temperature or at 60 °C. The reaction mixture was poured into water (50 mL) and extracted twice with ethyl acetate (2 × 30 mL). The organic phase was washed twice with brine (30 mL) and water (30 mL). The organic phase was dried over sodium sulphate, filtered and concentrated to dryness to afford the reaction crude. This was purified by flash column chromatography over silica gel with mixtures of *n*-hexane/AcOEt/TEA as eluent. Some spectra show traces of the corresponding diastereoisomer, because they are very difficult to separate by column chromatography. For times, temperature and yields see the Table 1 in the main text.

Method B–microwave heating. In a microwave test tube, the selected 2-alkynylbenzaldehyde **1** (0.317 mmol) and 2-aminobenzylalcohol **2** (0.380) were dissolved in anhydrous DMF (1 mL), then the [Ag(PcL)]$^{+}$X^{-} catalyst (5 mol%) was added. The mixture was stirred at 100 °C under microwave

heating for 1 h. The reaction mixture was poured into water (50 mL) and extracted twice with ethyl acetate (2 × 30 mL). The organic phase was washed twice with brine (30 mL) and water (30 mL). The organic phase was dried over sodium sulphate, filtered and concentrated to dryness to afford the reaction crude. This was purified by flash column chromatography over silica gel with mixtures of *n*-hexane/AcOEt/TEA as eluent. Some spectra show traces of the corresponding diastereoisomer, because they are very difficult to separate by column chromatography.

12-(p-tolyl)-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3a)**: Method A (Table 1, entry 3). Reaction temperature: 60 °C. Eluent for chromatography: Hexane/EtOAc/TEA = 96:4:2.5. Yellow solid. Yield: 82% (84 mg); mp 152.3-154.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.20 (m, 2H), 7.08 (m, 5H), 6.92 (t, *J* = 7.1 Hz, 1H), 6.81 (t, *J* = 7.7 Hz, 1H), 6.25 (d, *J* = 8.0 Hz, 1H), 6.08 (s, 1H), 5.95 (s, 1H), 5.25 (d, *J* = 14.6 Hz, 1H), 5.09 (d, *J* = 14.6 Hz, 1H), 2.33 (s, 3H). The spectral data are in agreement with literature findings.[10]

12-(4-methoxyphenyl)-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3b)**: Method A (Table 1, entry 13). Reaction temperature: 60 °C. Eluent for chromatography: Hexane/EtOAc = 85:15. Yellow solid. Yield: 63% (68 mg); mp 158.1-162.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 7.5, 0.6 Hz, 1H), 7.32 (td, *J* = 7.4, 1.1 Hz, 1H), 7.23 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.19 (d, *J* = 3.4 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.92 (td, *J* = 7.4, 1.0 Hz, 1H), 6.83 (dd, *J* = 8.1, 0.7 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.25 (d, *J* = 8.1 Hz, 1H), 6.07 (s, 1H), 5.93 (s, 1H), 5.24 (d, *J* = 14.5 Hz, 1H), 5.08 (d, *J* = 14.5 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 159.4 (C), 140.6 (C), 139.9 (C), 132.9 (C), 129.8 (CH), 129.4 (C), 128.9 (CH), 128.4 (C), 127.0 (C), 126.6 (CH), 125.9 (CH), 125.8 (CH), 124.6 (CH), 124.2 (CH), 123.8 (CH), 122.3 (CH), 113.4 (CH), 105.3 (CH), 85.9 (CH), 67.9 (CH_2), 55.2 (CH_3). MS ESI(+): *m/z* (%) = 342.29 (100) $[M+H]^+$. Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 81.24; H, 5.68; N, 4.21.

12-propyl-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3c)**: Method A (Table 1, entry 15). Reaction temperature: 60 °C. Eluent for chromatography: Hexane/EtOAc/TEA = 95:5:2.5. Yellow oil. Yield: 35% (31 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.07 (m, 8H), 5.82 (s, 1H), 5.74 (s, 1H), 5.21 (d, *J* = 15.3 Hz, 1H), 4.99 (d, *J* = 15.3 Hz, 1H), 2.52 (ddd, *J* = 14.9, 8.9, 5.8 Hz, 1H), 2.37 (ddd, *J* = 15.4, 9.1, 6.8 Hz, 1H), 1.41–1.25 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 142.3 (C), 140.9 (C), 132.5 (C), 130.9 (C), 129.3 (CH), 127.7 (CH), 126.0 (CH), 125.4 (CH), 125.12 (CH), 125.07 (C), 124.97 (CH), 124.8 (CH), 123.7 (CH), 100.6 (CH), 84.9 (CH), 67.7 (CH_2), 34.9 (CH_2), 20.9 (CH_2), 13.7 (CH_3). MS ESI(+): *m/z* (%) = 278.25 (100) $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.39; H, 6.81; N, 4.99.

12-(3-(trifluoromethyl)phenyl)-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3d)**: Method B (Table 2, entry 11). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc/TEA = 96:4:1. Yellow solid. Yield: 64% (90 mg); mp 145.6-146.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (m, 2H), 7.44 (dd, *J* = 7.5, 0.6 Hz, 1H), 7.32 (m, 4H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H), 6.81 (t, *J* = 7.7 Hz, 1H), 6.16 (d, *J* = 8.1 Hz, 1H), 6.10 (s, 1H), 6.00 (s, 1H), 5.29 (d, *J* = 14.8 Hz, 1H), 5.12 (d, *J* = 14.8 Hz, 1H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 139.40 (C), 139.36 (C), 137.8 (C), 131.92 (C), 131.88 (CH), 130.6 (q, J^2 = 32.4 Hz, C-CF_3), 129.1 (CH), 128.7 (C), 128.4 (CH), 126.91 (CH), 126.89 (C), 126.5 (CH), 125.9 (CH), 125.3 (q, J^3 = 3.8 Hz, CH), 124.9 (CH), 124.71 (CH) overlapping with 124.66 (q, J^3 = 3.8 Hz, CH), 124.05 (q, J^1 = 272.5 Hz, CF_3) 123.7 (CH), 123.0 (CH), 106.6 (CH), 84.9 (CH), 68.0 (CH_2). MS ESI(+): *m/z* (%) = 380.28 (100) $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}F_3NO$: C, 72.82; H, 4.25; N, 3.69. Found: C, 72.99; H, 4.28; N, 3.61.

(Cis)-6-methyl-12-(p-tolyl)-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3e)**: Method A (Table 5, entry 4). Reaction temperature: 25 °C. Eluent for chromatography: Hexane/EtOAc/TEA = 95:5:1. Yellow solid. Yield: 85% (91 mg); mp 148.4-149.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.5 Hz, 1H), 7.34–7.20 (m, 2H), 7.20–7.03 (m, 6H), 6.93 (td, *J* = 7.5, 1.1 Hz, 1H), 6.81 (td, *J* = 7.8, 1.5 Hz, 1H), 6.24 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.14 (s, 1H), 5.96 (s, 1H), 5.39 (q, *J* = 6.5 Hz, 1H), 2.33 (s, 3H), 1.71 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 140.9 (C), 139.7 (C), 137.8 (C), 134.3 (C), 133.5 (C), 132.7 (C), 129.0 (CH), 128.9 (CH), 128.6 (CH), 127.3 (C), 126.7 (CH), 126.02 (CH), 125.99 (CH), 124.5 (CH), 124.4 (CH), 123.9 (CH), 122.5 (CH), 105.7 (CH), 85.2 (CH), 73.8 (CH), 22.0 (CH_3), 21.4 (CH_3). MS ESI(+): *m/z* (%) = 338.07 (100), 340.06 (96) $[M+H]^+$. Anal. Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13 Found: C, 84.24; H, 6.41; N, 4.08. Crystal data: $C_{24}H_{21}NO$, *M* = 1212.85, monoclinic a = 14.0503(6), b = 5.6227(3), c = 22.727(1) Å, β = 97.907(1)°, *V* = 1778.38(14) Å^3, *T* = 180 K, space group $P2_1/c$ (no. 14), *Z* = 4, 16557 reflections measured, 4171 unique (R_{int} = 0.0164), which were used in all calculations. The final agreement indices R_1 and wR_2 were 0.0406 and 0.1103 respectively for 3707 independent observed [$I > 2\sigma(I)$] absorption corrected data.

(Trans)-6-methyl-12-(p-tolyl)-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3'e)**: Method A (Table 5, entry 4). Reaction temperature: 25 °C. Eluent for chromatography: Hexane/EtOAc/TEA = 95:5:1. Yellow solid. Yield: 14% (16 mg); mp 68.5-69.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.5 Hz, 1H), 7.34–7.21 (m, 2H), 7.20–7.02 (m, 6H), 6.93 (td, *J* = 7.5, 1.1 Hz, 1H), 6.80 (td, *J* = 7.9, 1.0 Hz, 1H), 6.28 (d, *J* = 8.1 Hz, 1H), 6.06 (s, 1H), 5.90 (s, 1H), 5.20 (q, *J* = 6.5 Hz, 1H), 2.32 (s, 3H), 1.79 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 140.9 (C), 139.6 (C), 137.8 (C), 134.3 (C), 132.8 (C), 132.7 (C), 129.0 (CH), 128.8 (CH), 128.6 (CH), 127.1 (CH), 126.9 (C), 125.9

(CH), 125.8 (CH), 125.6 (CH), 124.4 (CH), 124.1 (CH), 122.6 (CH), 105.1 (CH), 80.6 (CH), 72.1 (CH), 22.2 (CH_3), 21.4 (CH_3). MS ESI(+): *m/z* (%) = 338.04 (25), 340.06 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13 Found: C, 84.72; H, 6.35; N, 4.15.

(Cis)-6-phenyl-12-(p-tolyl)-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3f)**: Method B (Table 6, entry 3). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = from 98:2 to 90:10. Yellow solid. Yield: 62% (79 mg); mp 94.9-96.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, *J* = 6.8 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.48–7.30 (m, 5H), 7.30–7.20 (m, 2H) overlapping with 7.26 (d, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.88–6.80 (m, 3H), 6.40 (s, 1H), 6.30 (s, 1H), 6.11 (s, 1H), 2.38 (s, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 141.1 (C), 140.6 (C), 139.7 (C), 138.0 (C), 134.0 (C), 132.8 (C), 132.2 (C), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.5 (C), 126.7 (CH), 126.3 (CH), 126.2 (CH), 126.2 (CH), 124.3 (CH), 123.5 (CH), 122.2 (CH), 106.5 (CH), 85.6 (CH), 80.5 (CH), 21.4 (CH_3). MS ESI(+): *m/z* (%) = 402.40 (100) $[M+H]^+$. Anal. Calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.77; N, 3.49 Found: C, 86.86; H, 5.85; N, 3.44.

(Trans)-6-phenyl-12-(p-tolyl)-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3'f)**: Method B (Table 6, entry 3). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = from 98:2 to 90:10. Yellow solid. Yield: 28% (35 mg); mp 101.2-102.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53–7.38 (m, 6H), 7.29 (dd, *J* = 6.5, 1.2 Hz, 2H), 7.17 (m, 6H), 6.94–6.87 (m, 2H), 6.35 (dd, *J* = 5.6, 3.7 Hz, 1H), 6.14 (s, 1H), 6.06 (s, 1H), 6.04 (s, 1H), 2.36 (s, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 141.1 (C), 140.4 (C), 139.6 (C), 137.9 (C), 134.2 (C), 132.7 (C), 129.0 (CH), 128.7 (CH), 128.7 (CH), 128.5 (C), 128.4 (CH), 128.3 (CH), 127.3 (CH), 126.8 (CH), 126.2 (CH), 126.0 (CH), 124.3 (CH), 122.9 (CH), 121.4 (CH), 107.3 (CH), 81.1 (CH), 77.7 (CH), 21.4 (CH_3), one C overlapped. MS ESI(+): *m/z* (%) = 402.45 (100) $[M+H]^+$. Anal. Calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.77; N, 3.49 Found: C, 86.92; H, 5.65; N, 3.56.

(Cis)-6-methyl-12-(3-(trifluoromethyl)phenyl)-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3g)**: Method B (Table 7, entry 1). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = 95:5. Yellow solid. Yield: 56% (70 mg); mp 54.2-56.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.48 (m, 2H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.38–7.23 (m, 5H), 7.21 (d, *J* = 7.4 Hz, 1H), 7.13 (dd, *J* = 7.6, 0.7 Hz, 1H), 6.97 (td, *J* = 7.5, 1.1 Hz, 1H), 6.81 (td, *J* = 7.7, 1.5 Hz, 1H), 6.16 (s, 1H), 6.01 (s, 1H), 5.43 (q, *J* = 6.2 Hz, 1H), 1.72 (d, *J* = 6.5 Hz, 3H).^{13}C NMR (75.45 MHz, $CDCl_3$): δ 139.4 (C), 139.2 (C), 138.0 (C), 133.7 (C), 132.1 (C), 131.9 (CH), 130.7 (q, J_2 = 32.3 Hz, C-CF_3), 129.2 (CH), 128.6 (CH), 127.3 (C), 127.0 (CH), 126.7 (CH), 126.2 (CH), 125.5 (q, J_3 = 3.8 Hz, CH), 124.9 (CH), 124.7 (CH) overlapping with 124.6 (q, J_3 = 3.8 Hz, CH), 124.1 (q, J_1 = 272.3 Hz, CF_3), 123.8 (CH), 123.2 (CH), 106.8 (CH), 85.1 (CH), 74.0 (CH), 22.0 (CH_3). MS ESI(+): *m/z* (%) = 394.28

(100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{18}F_3NO$: C, 73.27; H, 4.61; N, 3.56 Found: C, 73.05; H, 4.74; N, 3.64.

(Trans)-6-methyl-12-(3-(trifluoromethyl)phenyl)-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3'g)**: Method B (Table 7, entry 2). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = 95:5. Yellow solid. Yield: 22% (27 mg); mp 56.1-57.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54–7.46 (m, 2H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.36–7.18 (m, 5H), 7.15 (d, *J* = 7.7 Hz, 1H), 6.97 (td, *J* = 7.6, 1.1 Hz, 1H), 6.80 (t, *J* = 8.2 Hz, 1H), 6.18 (d, *J* = 8.1 Hz, 1H), 6.08 (s, 1H), 5.93 (s, 1H), 5.23 (q, *J* = 6.6 Hz, 1H), 1.79 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 139.5 (C), 139.2 (C), 138.1 (C), 133.2 (C), 132.2 (C), 132.0 (CH), 129.2 (CH), 128.5 (CH), 127.4 (CH), 126.9 (C), 126.5 (CH), 125.97 (CH), 125.95 (CH), 125.5 (q, J_3 = 3.8 Hz, CH), 124.7 (CH), 124.6 (q, J_3 = 3.8 Hz, CH), 124.1 (CH), 123.3 (CH), 106.1 (CH), 80.5 (CH), 72.1 (CH), 22.4 (CH_3), two C (C-CF_3 and CF_3) are not attributable. MS ESI(+): *m/z* (%) = 394.20 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{18}F_3NO$: C, 73.27; H, 4.61; N, 3.56 Found: C, 73.11; H, 4.69; N, 3.68.

(Cis)-12-(4-methoxyphenyl)-6-methyl-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3h)**: Method B (Table 7, entry 2). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = 90:10. Yellow solid. Yield: 46% (52 mg); mp 150-152 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 1H), 7.31 (td, *J* = 7.4, 1.4 Hz, 1H), 7.23 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 3H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.94 (td, *J* = 7.5, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.26 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.14 (s, 1H), 5.95 (s, 1H), 5.39 (q, *J* = 6.5 Hz, 1H, 3.80 (s, 2H), 1.72 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (C), 140.5 (C), 139.5 (C), 133.3 (C), 132.6 (C), 129.7 (CH), 129.5 (C), 128.8 (CH), 127.2 (C), 126.5 (CH), 125.9 (CH), 125.8 (CH), 124.3 (CH), 124.1 (CH), 123.7 (CH), 122.3 (CH), 113.5 (CH), 105.3 (CH), 85.1 (CH), 73.6 (CH), 55.2 (CH_3), 21.8 (CH_3). MS ESI(+): *m/z* (%) = 356.45 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94 Found: C, 80.88; H, 5.79; N, 3.81.

(Trans)-12-(4-methoxyphenyl)-6-methyl-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3'h)**: Method B (Table 7, entry 2). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = 90:10. Yellow solid. Yield: 19% (21 mg). mp 98-101°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.4 Hz, 1H), 7.31 (dt, *J* = 7.5, 3.7 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.20 – 7.05 (m, 5H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.28 (d, *J* = 8.2 Hz, 1H), 6.06 (s, 1H), 5.89 (s, 1H), 5.20 (q, *J* = 6.6 Hz, 1H), 3.79 (s, 3H), 1.78 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (C), 140.5 (C), 139.5 (C), 132.7 (C), 132.6 (C), 129.8 (CH), 129.6 (C), 128.7 (CH), 126.9 (C), 126.8 (CH), 125.7 (CH), 125.6 (CH), 125.3 (CH), 124.1 (CH), 123.8 (CH), 122.3 (CH), 113.4 (CH), 104.8 (CH), 80.6 (CH), 71.8 (CH), 55.2 (CH_3), 21.9 (CH_3). MS

ESI(+): *m/z* (%) = 356.32 (100) $[M+H]^+$. Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94 Found: C, 81.24; H, 5.90; N, 4.09.

(Cis)-12-(4-chlorophenyl)-6-methyl-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3i)**: Method B (Table 7, entry 2). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = from 100:0 to 70:30. Brownish wax. Yield: 53% (60 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.5 Hz, 1H), 7.32 (td, *J* = 7.4, 1.4 Hz, 1H), 7.24 (d, *J* = 1.4 Hz, 1H), 7.20 (d, *J* = 9.0 Hz, 3H), 7.16 (s, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.95 (td, *J* = 7.5, 1.0 Hz, 1H), 6.84 (dd, *J* = 11.2, 4.2 Hz, 1H), 6.20 (d, *J* = 8.1 Hz, 1H), 6.13 (s, 1H), 5.96 (s, 1H), 5.39 (q, *J* = 6.5 Hz, 1H), 1.70 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5 (C), 139.2 (C), 135.5 (C), 133.7 (C), 133.4 (C), 132.1 (C), 129.7 (2CH), 128.9 (CH), 128.3 (2CH), 127.3 (C), 126.6 (CH), 126.3 (CH), 126.0 (CH), 124.5 (CH), 124.4 (CH), 123.6 (CH), 122.6 (CH), 106.3 (CH), 85.0 (CH), 73.7 (CH), 21.7 (CH_3). MS ESI(+): *m/z* (%) = 360.64 (100) $[M+H]^+$. Anal. Calcd for $C_{23}H_{18}ClNO$: C, 76.77; H, 5.04; N, 3.89 Found: C, 76.94; H, 5.12; N, 3.75.

(Trans)-12-(4-chlorophenyl)-6-methyl-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3'i)**: Method B (Table 7, entry 2). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = from 10:0 to 7:3. Brownish wax. Yield: 20 % (23 mg).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.26 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.19 (m, 3H), 7.13 (m, 3H), 6.96 (td, *J* = 7.5, 1.2 Hz, 1H), 6.83 (td, *J* = 7.9, 1.1 Hz, 1H), 6.24 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.06 (s, 1H), 5.89 (s, 1H), 5.20 (q, *J* = 6.7 Hz, 1H), 1.78 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR, MS and elemental analysis have not been performed because the product contains a not negligible amount of the diastereoisomer **3i**.

(Cis)-12-cyclopropyl-6-methyl-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3j)**: Method B (Table 7, entry 4). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = from 9:1 to 7:3. Yellow oil. Yield: 47% (43 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.39 (m, 1H), 7.34–7.25 (m, 2H), 7.25–7.08 (m, 5H), 5.91 (s, 1H), 5.67 (s, 1H), 5.40 (q, *J* = 6.5 Hz, 1H), 1.66–1.43 (m, 2H) overlapping with 1.51 (d, *J* = 6.5 Hz, 3H), 0.98–0.77 (m, 2H), 0.65–0.57 (m, 1H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 144.0 (C), 140.7 (C), 135.8 (C), 132.6 (C), 129.2 (CH), 127.8 (CH), 126.2 (CH), 125.9 (CH), 125.7 (CH), 125.4 (C), 125.2 (CH), 124.8 (CH), 123.9 (CH), 98.2 (CH), 85.2 (CH), 74.2 (CH), 23.9 (CH), 14.6 (CH_3), 9.9 (CH_2), 6.2 (CH_2). MS ESI(+): *m/z* (%) = 290.15 (100) $[M+H]^+$. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84 Found: C, 82.88; H, 6.60; N, 4.91.

(Trans)-12-cyclopropyl-6-methyl-4bH,6H-benzo[4,5][1,3]oxazino[2,3-a]isoquinoline **(3'j)**: Method B (Table 7, entry 4). Reaction temperature: 100 °C. Eluent for chromatography: Hexane/EtOAc = from 9:1 to 7:3. Yellow oil. Yield: 33% (30 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.5 Hz,

1H), 7.34–7.13 (m, 6H), 7.10 (d, J = 7.6 Hz, 1H), 5.86 (s, 1H), 5.63 (s, 1H), 5.03 (q, J = 6.6 Hz, 1H), 1.70 (d, J = 6.6 Hz, 3H), 1.52 (tt, J = 5.8, 4.7 Hz, 1H), 0.97–0.74 (m, 2H), 0.66–0.51 (m, 2H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 143.7 (C), 140.8 (C), 135.2 (C), 132.7 (C), 129.2 (CH), 127.9 (CH), 126.2 (CH), 126.0 (CH), 125.9 (CH), 125.2 (C), 125.2 (CH), 124.6 (CH), 123.9 (CH), 97.9 (CH), 80.9 (CH), 71.6 (CH), 23.0 (CH), 14.7 (CH_3), 10.3 (CH_2), 6.1 (CH_2). MS ESI(+): *m/z* (%) = 290.15 (100) $[M+H]^+$. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84 Found: C, 82.95; H, 6.51; N, 4.88.

Chrystal data: Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 1989682). A copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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Keywords

Alkynes, Pyridine containing ligands, Silver, Domino reactions, Microwaves, Polycyclic N-O Heterocycles

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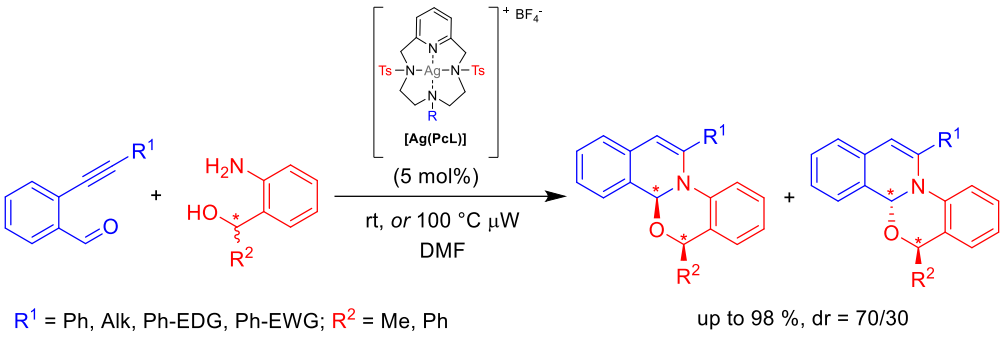

6-Substituted benzoxazino isoquinoline nucleus, a key skeleton in some biological active molecules, can be prepared by a silver catalysed domino approach starting from 2-alkynylbenzaldehydes and 1-substituted (2-aminophenyl)methanols. The silver(I) complexes of macrocyclic pyridine-containing ligands (PcL) demonstrated to be the catalysts of choice.

Key Topic

Domino Addition/Cycloisomerization