

# Nitrogenated Azaphilone Derivatives through a Silver Catalysed Reaction of Imines of *ortho*-Alkynylbenzaldehydes

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This contribution is dedicated in memory of our mentor Professor José Barluenga who passed away on September 7<sup>th</sup>, 2016

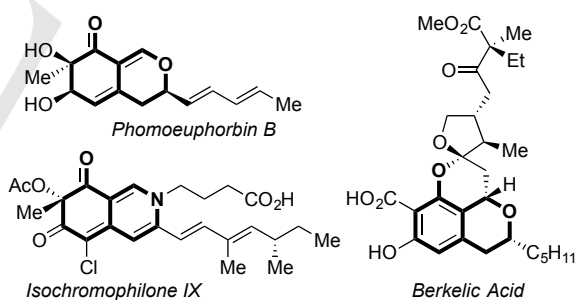
**Abstract:** Nitrogenated azaphilones are interesting natural products with wide range of applications whose structure is characterized by the presence of an isoquinolinone framework. Herein, we describe a new multicomponent silver-catalysed reaction that allows the transformation of simple imines derived from *ortho*-alkynylbenzaldehydes into complex nitrogenated azaphilone-type molecules in a straightforward way. This atom-economical process is high yielding, technically very simple and proceeds through a series of cascade processes that imply cycloisomerization and formal cross-coupling reactions. This conceptually new process formally supposes the synchronised catalytic generation and selective coupling of a nucleophile (isoquinolinone) and an electrophile (isoquinolinium). Some interesting colour properties of the synthesized azaphilone-type molecules are discussed.

Azaphilones are a family of natural products with significant pharmacological properties including, among many others, antimicrobial, antiviral, anticancer and anti-inflammatory activity.<sup>[1]</sup> Moreover, many azaphilonoid derivatives are coloured substances with potential utility as natural food colorants.<sup>[2]</sup> A common structural feature of azaphilones is an isochromene core (usually a isochromenone). Members of this family of natural products include structurally simple compounds such as phomoeuphorbin B or more complex molecules such as berkelic acid (Scheme 1a). In this context, we have been involved in recent years in the development of new reactions for the construction of molecules structurally related to azaphilones,<sup>[3]</sup> and also, in 2012 we reported a new total synthesis of (–)-berkelic acid.<sup>[4]</sup> At this point, the remarkable work developed by J. A. Porco and co-workers on the synthesis of azaphilones should be mentioned.<sup>[5]</sup> Following with our interest in this field, we focus our attention on the development of new methods for the synthesis of nitrogenated azaphilone-type products. The antibiotic isochromophilone IX (Scheme 1a) is a typical example of this kind of compounds that possess a isoquinolinone skeleton instead of the typical isochromenone one. Herein, we report a new silver-catalysed multicomponent coupling reaction for the synthesis of nitrogenated azaphilone derivatives.

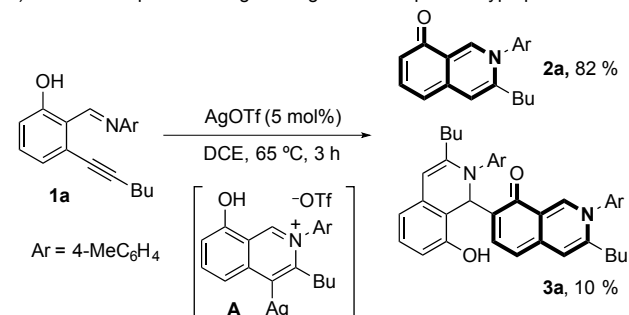
Initially, we thought that the most straightforward way to get nitrogenated azaphilone-type molecules would be the metal-catalysed cycloisomerization of imines derived from *ortho*-alkynylsalicylaldehydes.<sup>[6,7]</sup> To check this possibility, in our first experiment we treated the imine **1a** with 5 mol% of silver triflate (AgOTf) in 1,2-dichloroethane at 65 °C (Scheme 1b). Gratifyingly,

the expected isoquinolinone derivative **2a** was isolated in 82% yield. This compound is formed through a simple mechanism that implies the activation of the alkyne by the silver-catalyst and addition of the nitrogen of the imine to form the isoquinolinium intermediate **A** that after a simple formal intramolecular protodemetalation step delivers the product **2a**. Surprisingly, along with this product, we also observed the formation of an unexpected deep red coloured by-product whose structure corresponded to the dimer **3a** (10% yield). This molecule drew our attention not only because of its unusual structure comprising an isoquinolinyl-substituted isoquinolinone (isoquinoline-containing nitrogenated azaphilone derivative) but also because its formation was intriguing from the mechanistic point of view. Thus, we initiated a study in order to get this new type of products in a more efficient way. Also at the beginning, we thought that instead of getting “homodimeric” products such as **3a**, it would be much more interesting to get “heterodimeric” compounds where the isoquinoline part of the molecule (left hand part) was derived from a conventional benzaldehyde while the isoquinolinone part (right hand part) was derived from a salicylaldehyde.

a) Some azaphilone natural products



b) Our initial experiment to get nitrogenated azaphilone-type products

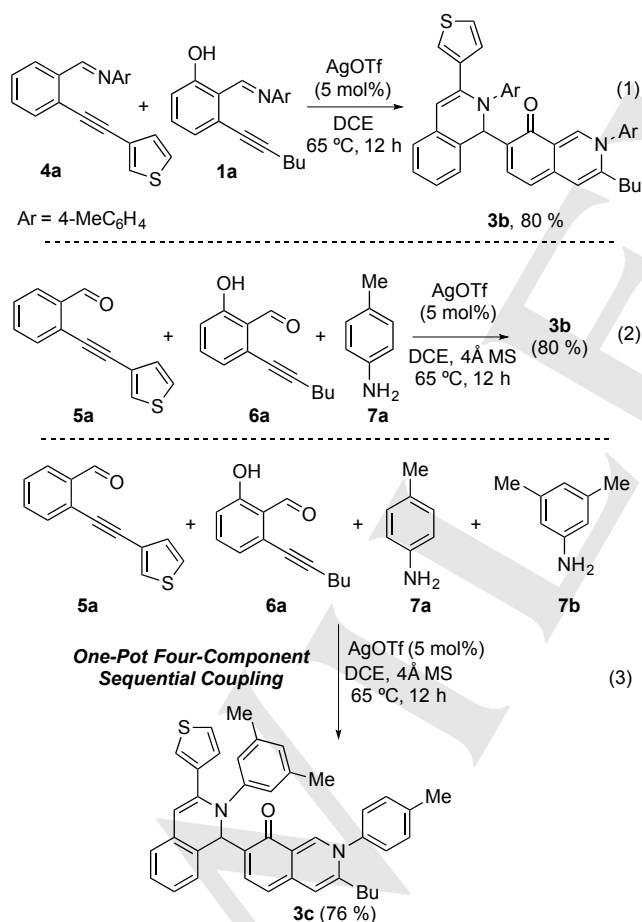


**Scheme 1.** Azaphilone natural products and our initial experiment.

With all this in mind, we tried the reaction of the two different imine derivatives **4a** and **1a** in the presence of 5 mol% of AgOTf

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in 1,2-dichloroethane (DCE) at 65 °C [Scheme 2, Eq. (1)]. Pleasantly, this reaction led to the formation of the heterodimer **3b** in 80% yield. It should be noted that although the monomer **2a** and the homodimer **3a** could have been obtained under these conditions, less than 5% of these products were observed in the crude of the reaction. In a subsequent experiment, we proved that the reaction could be performed directly from aldehydes **5a** and **6a** without the necessity of isolating the corresponding imines **1a** and **4a** [Scheme 2, Eq. (2)]. Thus, when aldehydes **5a** and **6a** were reacted with two equivalents of *p*-toluidine (**7a**) in the presence of 5 mol% of AgOTf in 1,2-dichloroethane at 65 °C for 12 hours, compound **3b** was isolated with the same yield (80 %) than the reaction carried out with preformed imines **1a** and **4a**. Finally, we targeted the most challenging reaction, the one-pot four-component coupling reaction of two different *ortho*-alkynylbenzaldehydes and two different anilines [Scheme 2, Eq. (3)]. In the event, sequential addition of *ortho*-alkynylbenzaldehyde **5a** and the aniline derivative **7b** along with the respective addition of *ortho*-alkynylsalicylaldehyde **6a**, *p*-toluidine (**7a**) and 5 mol% of AgOTf in 1,2-dichloroethane, resulted in the formation of the desired azaphilone derivative **3c** in 76% yield.



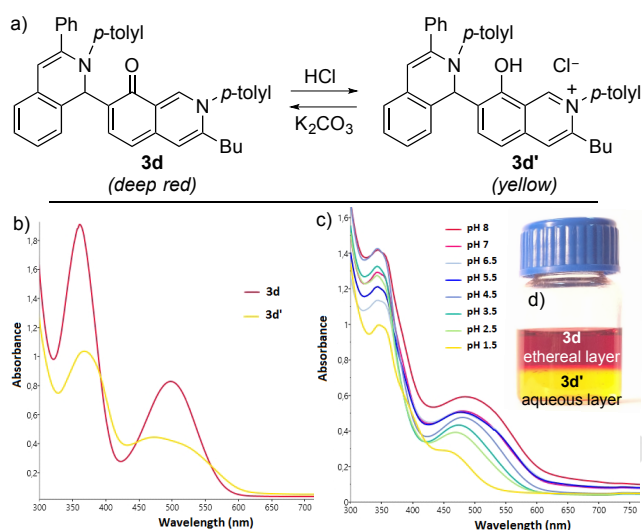
**Scheme 2.** Reaction of preformed or *in situ* formed imines derived from *ortho*-alkynylsalicylaldehydes and *ortho*-alkynylbenzaldehydes.

**Table 1.** Scope of the reaction of synthesis of azaphilone derivatives **3**.<sup>[a]</sup>

Ent	<b>3</b>	R <sup>1</sup>	R <sup>2</sup>	Ar <sup>1</sup>	Ar <sup>2</sup>	Yield (%) <sup>[b]</sup>
1	<b>3b</b>	Bu	3-Thienyl	<i>p</i> -tolyl	<i>p</i> -tolyl	80
2	<b>3c</b>	Bu	3-Thienyl	<i>p</i> -tolyl	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	76 <sup>[c]</sup>
3	<b>3d</b>	Bu	Ph	<i>p</i> -tolyl	<i>p</i> -tolyl	88
4	<b>3e</b>	Bu	Bu	<i>p</i> -tolyl	<i>p</i> -tolyl	63
5	<b>3f</b>	Bu	<i>c</i> -Pent	<i>p</i> -tolyl	<i>p</i> -tolyl	60
6	<b>3g</b>	Bu	<i>c</i> -Pr	<i>p</i> -tolyl	<i>p</i> -tolyl	54
7	<b>3h</b>	Bu	<i>p</i> -tolyl	<i>p</i> -tolyl	<i>p</i> -tolyl	89
8	<b>3i</b>	Bu	2-Thienyl	<i>p</i> -tolyl	<i>p</i> -tolyl	70
9	<b>3j</b>	Bu	3-Furyl	<i>p</i> -tolyl	<i>p</i> -tolyl	81
10	<b>3k</b>	Bu	Me-Ind <sup>[d]</sup>	<i>p</i> -tolyl	<i>p</i> -tolyl	77
11	<b>3l</b>	Bu	Bu	<i>p</i> -tolyl	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	70 <sup>[c]</sup>
12	<b>3m</b>	Bu	Ph	<i>p</i> -tolyl	4-MeOC <sub>6</sub> H <sub>4</sub>	72 <sup>[c]</sup>
13	<b>3n</b>	Bu	3-Thienyl	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	79
14	<b>3o</b>	Bu	Ph	4-BrC <sub>6</sub> H <sub>4</sub>	4-BrC <sub>6</sub> H <sub>4</sub>	72
15	<b>3p</b>	Bu	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	80
16	<b>3q</b>	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	3-Thienyl	<i>p</i> -tolyl	<i>p</i> -tolyl	75
17	<b>3r</b>	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	2-Thienyl	<i>p</i> -tolyl	<i>p</i> -tolyl	82
18	<b>3s</b>	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	Ph	<i>p</i> -tolyl	<i>p</i> -tolyl	84
19	<b>3t</b>	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	Bu	<i>p</i> -tolyl	<i>p</i> -tolyl	60
20	<b>3u</b>	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me	2-Thienyl	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	3,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	80
21	<b>3v</b>	Ph	3-Thienyl	<i>p</i> -tolyl	<i>p</i> -tolyl	85
22	<b>3w</b>	Ph	3-Thienyl	4-ClC <sub>6</sub> H <sub>4</sub>	<i>p</i> -tolyl	76 <sup>[c]</sup>
23	<b>3x</b>	Ph	<i>p</i> -tolyl	4-ClC <sub>6</sub> H <sub>4</sub>	4-BrC <sub>6</sub> H <sub>4</sub>	62 <sup>[c]</sup>
24	<b>3y</b>	<i>p</i> -tolyl	Ph	4-BrC <sub>6</sub> H <sub>4</sub>	<i>p</i> -tolyl	72 <sup>[c]</sup>
25	<b>3z</b>	<i>p</i> -tolyl	Ph	4-BrC <sub>6</sub> H <sub>4</sub>	4-MeOC <sub>6</sub> H <sub>4</sub>	67 <sup>[c]</sup>

[a] Conditions A: 4Å Molecular sieves, aldehydes **5** (1 equiv) and **6** (1 equiv), and aniline **7** (2 equiv) are reacted at room temperature in 1,2-dichloroethane for 8 h. Then, silver triflate (5 mol %) is added and the reaction heated at 65 °C for 12 h. [b] Based on **6**. [c] Conditions B: 4Å Molecular sieves, aldehyde **5** (1 equiv) and aniline **7** (1 equiv) are reacted at room temperature in 1,2-dichloroethane for 8 h. Then, silver triflate (5 mol %), aldehyde **6** (1 equiv) and aniline **7'** (1 equiv) are added (alternatively, the corresponding preformed imine **4** can be added) and the reaction heated at 65 °C for 12 h. [d] Me-Ind = 1-Methyl-1*H*-indol-3-yl.

In order to verify the possibility of synthesizing small libraries of nitrogenated azaphilone-type products **3** through the *one-pot four-component coupling process* above mentioned, a few *ortho*-alkynylbenzaldehydes **5**, *ortho*-alkynylsalicylaldehydes **6** and anilines **7** (**7'**) were combined to get the collection of products shown in Table 1.<sup>[8]</sup> The reaction seemed general in terms of the substitution of the *ortho*-alkynylbenzaldehydes **5** and the *ortho*-alkynylsalicylaldehydes **6**. Thus, aliphatic and aromatic substituents were allowed at the terminal position of the alkyne of both reagents ( $R^1$  and  $R^2$ ). Regarding the aniline counterparts **7**, the reaction also seems general and examples with anilines decorated with electron-donating or electron-withdrawing groups around the arene are reported. As shown, the yields were relatively high in all cases and formation of other plausible products similar to the monomer **2a** or the homodimer **3a** was almost negligible (< 5% in some particular cases).

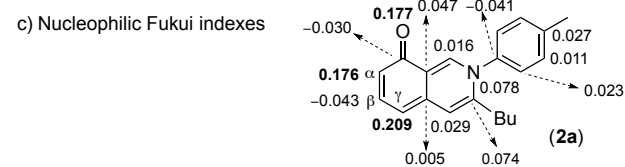
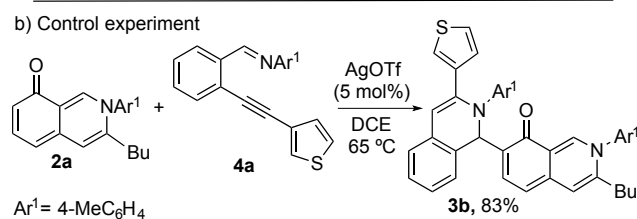
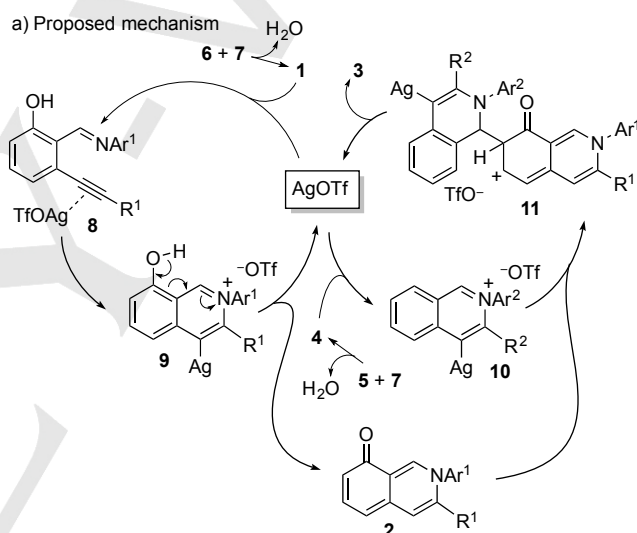


**Figure 1.** a) Interconversion between the neutral form **3d** and the salt **3d'**. b) Absorption spectra of compounds **3d** and **3d'** in ethanol (0.13 mM). c) Absorption spectra of **3d** (0.13 mM) in aqueous buffer (15% dimethyl sulfoxide) at the indicated pH values. d) A vial showing the distribution of **3d** / **3d'** between an organic etheral layer and an aqueous layer (pH 5.5).

Regarding the colour of products **3**, some interesting photoactivity was observed (Figure 1). As previously noted, products **3** showed a deep red colour. Thus, the UV-visible absorption spectrum of compound **3d** is featured by an intense absorption band at the wavelength of 498 nm in the visible region (Figure 1b). Noteworthy, the red solution of compound **3d** changes to a yellow solution when treated with an acid. This change in colour is supposed to be due to the transformation of the red neutral species **3d** into the yellow salt **3d'** (Figure 1a) whose UV-visible absorption spectrum is also shown in Figure 1b. Interestingly, the characteristic red colour of **3d** could be recovered on treatment of the yellow solution of **3d'** with a base (Figure 1a). A gradual change of colour from red to yellow could also be observed when **3d** was dissolved in aqueous buffer solutions of decreasing pH values (Figure 1c). Interestingly, the equilibrium established between **3d** and **3d'** in aqueous solutions

and the different solubility of these two species in organic and aqueous solvents could be easily revealed when diethyl ether was added to the aqueous solution (pH 5.5) of **3d** / **3d'** (Figure 1d). As shown, the organic etheral layer acquires the typical red colour of species **3d** while the aqueous layer remains yellow due to the presence of species **3d'**. All this illustrates the potential of compounds **3** as dyes, pH-sensitive visible indicators and/or probes.

A plausible mechanism for the formation of nitrogenated azaphilone derivatives **3** is shown in Scheme 3a. Thus, the initial coordination of the catalyst to the triple bond of the imine **1**, derived from *ortho*-alkynylsalicylaldehyde **6**, generates the first intermediate **8**. This coordination favours the intramolecular addition of the nitrogen of the imine to the alkyne to form the isoquinolinium intermediate **9**. The subsequent formal intramolecular protodemetalation reaction regenerates the silver catalyst and delivers the isoquinolinone derivative **2**.



**Scheme 3.** Proposed mechanism for the formation of compounds **3**, some control experiments and nucleophilic Fukui Indexes  $f_k^-$  based on Natural Bond Orbital (NBO) population analysis (M06-2X/6-311G\*\*//b3lyp/6-31G\*)

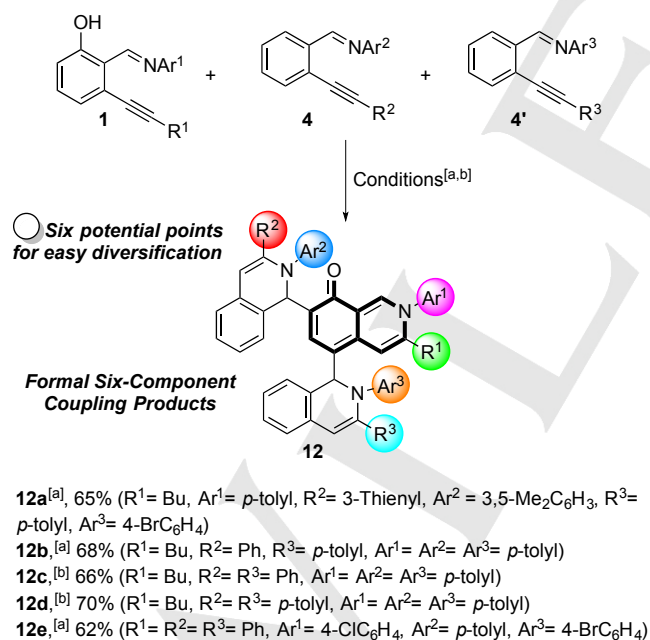
Following a similar process, the silver catalyst can also promote the cycloisomerization of imine **4**, derived from *ortho*-alkynylbenzaldehyde **5**, to form the new isoquinolinium

intermediate **10**. Obviously, this intermediate cannot suffer a protodemetalation process similar to that observed in **9** due to the absence of the protic phenol functionality. However, the isoquinolinium intermediate **10** can react through a nucleophilic addition of the previously formed isoquinolinone **2**. This process would render the new intermediate **11**. A final rearomatization step and subsequent protodemetalation affords the final nitrogenated azaphilone derivatives **3** and releases the catalytic silver species. Globally, this process could be considered a self-relay one-pot catalytic reaction because one catalyst promotes two different reactions in a single flask. The role of isoquinolinone derivatives **2** as intermediates of the reaction is supported by an experiment performed with the isolated compound **2a** (Scheme 3b). As shown, when this isoquinolinone is reacted with imine **4a** under our conventional catalytic conditions, the expected heterodimer product **3b** was isolated in high yield (83 %).

One of the most appealing features of the reaction here described is the performance of isoquinolinone derivatives **2** as nucleophiles in their reaction with electrophilic species **10**. This is conceptually interesting because usually the cycloisomerization of imines derived from *ortho*-alkynylbenzaldehydes is a reaction that serves to generate electrophilic species (isoquinolinium **10**). However, here not only these electrophilic species are produced but also a nucleophile (isoquinolinone **2**) is generated. In other words, the silver-catalyst promotes the concomitant generation of a nucleophile and an electrophile by means of the same reaction, the cycloisomerization of *ortho*-alkynylbenzaldehydes.

As previously noted, although several conventional nucleophiles have been described as appropriate partners to react with electrophilic species **10**,<sup>[6]</sup> the behaviour of isoquinolinone derivatives **2** as nucleophiles was totally unanticipated. In order to get some information about which atoms in isoquinolinone derivatives **2** were prone to undergo a nucleophilic attack, we calculated the corresponding Fukui indexes on **2a** (Scheme 3c). As shown, the C $\alpha$  was predicted as one of the most nucleophilic sites of this molecule ( $\alpha$ ,  $\beta$ ,  $\gamma$  refers to the position with respect to the carbonyl). This is in agreement with our experiments as we always observed selective reactivity through this carbon. Interestingly, the C $\gamma$  was also predicted as a highly nucleophilic site (Scheme 3c). Accordingly, we reasoned that isoquinolinones **2** could behave as bis-nucleophiles reacting selectively through the  $\alpha$ -position with an imine **4** and further through the  $\gamma$ -position with another imine derivative **4'**. This reaction would render a multifunctional azaphilone derivative in an easy way and from simple and easily available starting materials. In order to verify this hypothesis, we sequentially reacted imine **1a** (the direct precursor of isoquinolinone **2a**) with the two different imines **4a** and **4b** under our conventional silver-catalysed conditions (Scheme 4). Delightfully, we were able to isolate the highly functionalized azaphilone-like "hetero-trimer" derivative **12a** in 65 % yield. In this process the isoquinolinone intermediate **2a** reacted through the  $\alpha$ - and  $\gamma$ -positions as planned (see Scheme 3c). Interestingly, this reaction could be considered a formal *one-pot six-components coupling process* where diversification can be easily achieved by simple changes in some of the starting materials. As a demonstration, compounds **12b-c**, which also featured a deep red colour, were straightforwardly synthesized (Scheme 4). The relative complexity of these products **12** if compared to the simplicity of the starting materials should be remarked. It should be also noted that this reaction is 100% atom economy (no by-products are produced) and the global process implies three cycloisomerizations and two formal cross-coupling reactions.

In summary, a new silver-catalysed reaction for the synthesis of nitrogenated azaphilone derivatives is described. The reaction implies the combination of two or three different imines derived from *ortho*-alkynylbenzaldehydes (one of them derived from salicylaldehyde) in a process with complete atom-economy. This work further demonstrates the power of silver-catalysed cycloisomerization reactions and in particular, the reaction here described represents the first example of a process where a nucleophile (an isoquinolinone derivative) and an electrophile (an isoquinolinium intermediate) are concurrently generated and subsequently coupled by means of the mentioned cycloisomerization reaction. The unanticipated behaviour of the in situ-formed isoquinolinones as nucleophiles should also be remarked because it opens the door for the development of new reactions of these isoquinolinones with other electrophilic partners. It should also be noted that the new reaction here described serves to synthesize natural product-like molecules with unusual structural motifs, difficult to get from conventional methods, and interesting in the context of medicinal chemistry. The potential utility of these nitrogenated azaphilone derivatives as dyes, indicators or colorimetric probes should also be mentioned. The easy generation of molecular diversity through the reaction here described offers a good opportunity to identify



**Scheme 4.** Synthesis of formal six-component coupling products **12**. [a] Conditions A: Imines **1** (1 equiv) and **4** (1 equiv), and silver triflate (5 mol%) are reacted in 1,2-dichloroethane at 65°C for 12 hours. Then, imine **4'** (2 equiv) is added and the mixture heated at 65°C for 8h. [b] Conditions B: Imines **1** (1 equiv) and **4** (3 equiv), and silver triflate (5 mol%) are reacted in 1,2-dichloroethane at 65°C for 12 hours.

new azaphilone-type molecules with potential application in some of the referred fields.

## Acknowledgements

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**Keywords:** azaphilones • cascade reactions • homogeneous catalysis • natural product analogues • silver

- [1] a) J.-M. Gao, S.-X. Yang, J.-C. Qin, *Chem. Rev.* **2013**, *113*, 4755-4811; b) N. Osmanova, W. Schultze, N. Ayoub, *Phytochem. Rev.* **2010**, *9*, 315-342.
- [2] S. A. S. Mapari, U. Thrane, A. S. Meyer, *Trends Biotechnol.* **2010**, *28*, 300-307.
- [3] a) T. Arto, F. J. Fañanás, F. Rodríguez, *Angew. Chem. Int. Ed.* **2016**, *55*, 7218-7221; *Angew. Chem.* **2016**, *128*, 7334-7337; b) T. Arto, P. Fernández, F. J. Fañanás, F. Rodríguez, *Chem. Commun.* **2016**, *52*, 13405-13408.
- [4] F. J. Fañanás, A. Mendoza, T. Arto, B. Temelli, F. Rodríguez, *Angew. Chem. Int. Ed.* **2012**, *51*, 4930-4933; *Angew. Chem.* **2012**, *124*, 5014-5017.
- [5] a) J. Zhu, A. R. Germain, J. A. Porco Jr., *Angew. Chem. Int. Ed.* **2004**, *43*, 1239-1243; *Angew. Chem.* **2004**, *116*, 1259-1263; b) J. Zhu, N. P. Grigoriadis, J. P. Lee, J. A. Porco Jr., *J. Am. Chem. Soc.* **2005**, *127*, 9342-9343; c) M. Achard, A. B. Beeler, J. A. Porco Jr., *ACS Comb. Sci.* **2012**, *14*, 236-244.
- [6] For some selected representative examples of reactions involving the cycloisomerization of imines derived from *ortho*-alkynylbenzaldehydes, see: a) Q. Huang, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 980-988; b) N. Asao, S. Yudha S., T. Nogami, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2005**, *43*, 5526-5528; *Angew. Chem.* **2005**, *117*, 5662-5664; c) S. Obika, H. Kono, Y. Yasui, R. Yanada, Y. Takemoto, *J. Org. Chem.* **2007**, *72*, 4462-4468; d) Q. Ding, J. Wu, *Org. Lett.* **2007**, *9*, 4959-4962; e) N. T. Patil, A. K. Mutyala, P. G. V. V. Lakshmi, P. V. K. Raju, B. Sridhar, *Eur. J. Org. Chem.* **2010**, 1999-2007; f) X. Yu, J. Wu, *J. Comb. Chem.* **2010**, *12*, 238-244; g) T. Xiao, P. Peng, Y. Xie, Z. Wang, L. Zhou, *Org. Lett.* **2015**, *17*, 4332-4335.
- [7] For an excellent account on the metal-catalysed reaction of *ortho*-alkynylbenzaldehydes, see: N. Asao, Y. Yamamoto in *Modern Gold Catalyzed Synthesis* (Eds.: A. S. K. Hashmi, F. D. Toste), Wiley-VCH Weinheim, **2012**, ch 3, p. 55.
- [8] In most cases, similar results were observed when tetrahydrofuran was used as solvent instead of 1,2-dichloroethane.

## Entry for the Table of Contents

## COMMUNICATION

**Colourful azaphilones:** Complex azaphilone derivatives with attractive colour properties are easily available from simple *o*-alkynylbenzaldehydes through a cascade silver-catalysed reaction that involves several cyclization and selective cross-coupling processes.



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