Article

# TRIFLIC ACID-PROMOTED REGIO AND STEREOSELECTIVE SYNTHESIS OF POLYFUNCTIONALIZED ENAMINONES FROM DIBENZYLIDENE KETONES AND ORGANIC AZIDES

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A stereoselective synthesis of α-aryl *Z* enaminones was developed by TfOH-promoted condensation of dibenzylidene ketones with organic azides. The cascade reactions involve the sequence of 1,3-dipolar cycloaddition of alkyl azides with the enone, aziridine formation, and 1,2-aryl migration via phenonium ion, whose stereochemical control by a strong N–H···O=C intramolecular hydrogen bond affords *Z* isomer exclusively. The readily available starting materials and ease of handling of TfOH are experimental advantages that give diversely substituted enaminones with total control of functionalization along the N–C=C–C=O conjugated system.

Keywords: alkyl azide; α-aryl enaminones; 1,2-aryl migration; cascade reactions; TfOH.

## INTRODUCTION

Enaminone presents the conjugated system N–C=C–C=O, which confers diverse reactive sites and many applications in organic synthesis[1-7] and medicinal chemistry.[8] There are a multitude of methodologies to obtain this class of compounds, and the simplest is the reaction of 1,3-dicarbonyl compounds with amines (Figure 1, type 1).[1,8] The access of type 1 enaminones was boosted by the substitution of 1,3-dicarbonyl compounds as starting materials to several other substrates such as phenacyl sulfoxides,[9] alkynyl derivatives,[10-13] vinyl azides,[14] among others.[15-17]

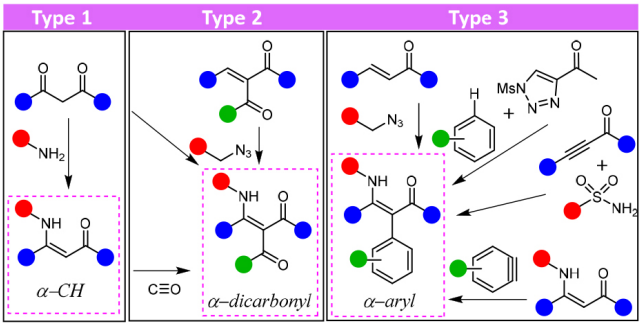


***Figure 1.*** *Selected routes to polyfunctionalized enaminones with structural diversity sites highlighted*

Synthetic approaches to α-substituted type 2[18-21] and type 3 enaminones,[22-26] functionalized with additional sites of structural diversity (highlighted in Figure 1 by colored circles), are scarce.[18-26] α-Aryl enaminones (type 3) are strategic in synthesizing indole derivatives,[1,2] however, the synthetic route is limited to a few reported methods.[22-26] Among these, the reaction of β-aryl enones and benzyl azide promoted by $BF_3{\cdot}OEt_2$ is the simplest one but provides a mixture of isomeric acyclic *E/Z* enaminones, corresponding to 1,2-aryl migration from β-aryl enone to α-aryl enaminone.[26] However, the Lewis acid $BF_3{\cdot}OEt_2$ as a promotor demands tedious manipulation before each enaminone preparation and during the reaction progress.

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Azides have been a successful building block to the nitrogenated group for enaminone synthesis,[14,15,18,20,26-30] and herein we amplify this strategy by the stereoselective synthesis of polyfunctionalized *Z* enaminones from dibenzylidene ketones with organic azides promoted by triflic acid (TfOH, trifluoromethanesulfonic acid) at room temperature. In addition, the simple reaction conditions associated with easy TfOH manipulation in comparison to other Lewis acid such as $BF_3{\cdot}OEt_2$[27] and substrates preparation open a way to introduce structural diversity along all components of enaminone's conjugated system type 3 (Figure 1).

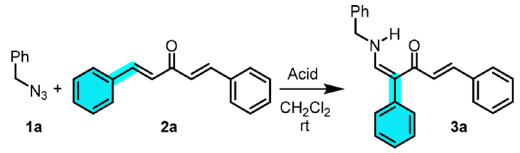
## RESULTS AND DISCUSSION

For the synthesis of substituted enaminones from dibenzylidene ketones and organic azides, the starting point was the conditions of our previous studies[26] concerning the use of $BF_3{\cdot}OEt_2$, which afforded a mixture of *E/Z* isomers. In the search for a practical promotor to develop a stereoselective synthesis of α-aryl substituted enaminones, benzyl azide **1a** and easily prepared dibenzalacetone **2a** were chosen as model substrates and different reaction parameters were investigated (Table 1).

Our previous work[26] and Gao and co-workers[15] study have concluded that $CH_2Cl_2$ is the best solvent for condensation of organic azides with α,β-unsaturated carbonyl compound. Thus, a $CH_2Cl_2$ solution of one and two equivalents of trifluoroacetic acid (TFA) as promotor was tested with two equivalents of **1a**. However, only starting materials were detected, even at long reaction times (entries 1 and 2, Table 1). A similar result was observed for sulfuric acid, sulfuric acid-supported silica gel (entries 3-5), and sulfamic acid (entries 6-7). The result was unsatisfactory when 1 equivalent of TfOH was tested (entry 8). However, when the amount of TfOH was increased, desirable enaminone **3a** was isolated (entries 9-12) except for 3 equivalents. The condition highlighted in entry 11 of Table 1 was the best one corresponding to the synthesis of polyfunctionalized enaminone from dibenzylidene ketones, because only one previous synthesis was reported,[26] but low yield and opposite *E* isomer as major product.

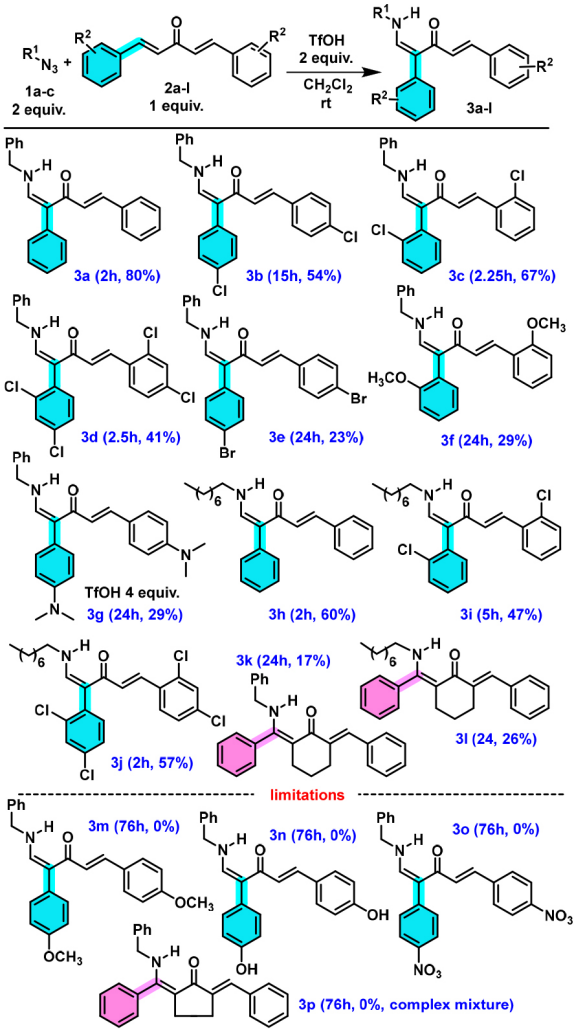
With optimal condition determined with TfOH as promotor, the scope of dibenzylidene ketones **2a**-**2o** and three organic azides **1a**-**1c** were evaluated, and the formation of enaminones **3a**-**3j** is presented in Scheme 1.

**Table 1.** Optimization of reaction conditions for the synthesis of α-phenyl enaminone **3a**




| Entry | Acid | Acid equiv. | **1a** equiv. | time / h | Yield / % |
|---|---|---|---|---|---|
| 1 | TFA | 1 | 2 | 76 | NR[a] |
| 2 | TFA | 2 | 2 | 76 | NR |
| 3 | $H_2SO_4$ | 1 | 2 | 76 | NR |
| 4 | $H_2SO_4$ | 2 | 2 | 76 | NR |
| 5 | $H_2SO_4$·$SiO_2$ | 2 | 2 | 76 | NR |
| 6 | $NH_3SO_3$ | 1 | 2 | 76 | NR |
| 7 | $NH_3SO_3$ | 2 | 2 | 76 | NR |
| 8 | TfOH | 1 | 2 | 76 | NR |
| 9 | TfOH | 1.5 | 1 | 48 | 47 |
| 10 | TfOH | 1.5 | 2 | 12 | 51 |
| 11 | TfOH | 2 | 2 | 2 | 80 |
| 12 | TfOH | 3 | 2 | 76 | CM[b] |

[a]No reaction, only starting materials detected by TLC; [b]complex mixture with incomplete reaction.

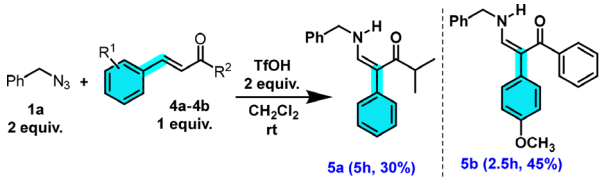



***Scheme 1.*** *Synthesis of polyfunctionalized Z enaminones via condensation of dibenzylidene ketones with organic azides*

While benzyl azide **1a** and octyl azide **1b** reacted, no reaction was observed with phenyl azide **1c** (**2a** was recovered). Nonetheless, contrary to the previous method with $BF_3$·$OEt_2$, *Z* isomers were exclusively formed, as shown by $^1$H nuclear magnetic resonance (NMR) analyses, which permitted the structural assignment of polyfunctionalized enaminones with one olefinic moiety on the right side and with the 1,2-aryl migration[26] in the left side of carbonyl group as indicated for **3a**-**3j**. These structural features of enaminones were deduced due to the disappearing of one olefinic $CH_\alpha$ from **2a**-**2g** and the presence of a $CH_\beta$-$NH$ $^3J$ coupling in **3a**-**3j** due to the incorporation of the $RCH_2NH$ moiety from azides **1a**-**1b**, besides the presence of typical H/H *trans* coupling constant integrated to only one olefinic group.

For all acyclic **2a**-**2g** tested substrates, regioselective α-aryl substituted enaminones were formed. Besides, despite two equivalents of organic azide being necessary in relation to dibenzylidene ketones **2a**-**2h**, only one olefinic moiety of **2a**-**2h** was transformed (Scheme 1). For 2,6-dibenzylidenecyclohexanone **2h** without α-hydrogen reacting with azides **1a**-**1b**, no 1,2-aryl migration[26] nor ring contraction/expansion was observed,[28] and β-aryl substituted *Z* enaminones **3k**-**3l** were formed. A mechanistic explanation of this dual behavior for acyclic dibenzylidene ketones **2a**-**2g** and cyclic **2h** is discussed later.

To compare the performance of the two acids (TfOH and $BF_3$·$OEt_2$), simple enones **4a**-**4b** were submitted to TfOH-promoted conditions, but the yields were inferior to those obtained with $BF_3$·$OEt_2$,[26] albeit enaminones **5a**-**5b** were still stereoselectivity formed (Scheme 2). However, for all benzylidene ketones, the easy handling of TfOH in comparison to $BF_3$·$OEt_2$ is an advantage to be considered in the overall experimental context, avoiding the previous tedious $BF_3$·$OEt_2$ purification with this Lewis acid before each novel synthetic run. Besides, the superacid TfOH has several characteristics that intensify its use in organic synthesis in relation to $BF_3$·$OEt_2$: it is inexpensive and insensitive to moisture and air.[27] Moreover, NMR analysis proved that TfOH afforded enaminones **3a**-**3j** and **5a**-**5b** as single isomers, revealing that this acid is adequate to the stereoselective synthesis of α-phenyl-substituted enaminones, in contrast to $BF_3$·$OEt_2$ that led to **5a**-**5b** as a mixture of *E*/*Z* isomers.[26] In this way, results of Schemes 1 and 2 indicate that TfOH-promoted synthesis is regio (exclusive acyclic α-aryl **3a**-**3j** or cyclic β-aryl **3k**-**3l** substituted enaminones) and stereoselective (only isomer *Z*) for all tested mono and dibenzylidene ketones.




***Scheme 2.*** *Synthesis of α-aryl enaminones via condensation of benzylidene-acetones with benzyl azide*

The scalability of the synthesis of enaminone **3a** was investigated, and it was increased from 1 to 10 mmol, as shown in Figure 2. A significant difference was noticed in yields from 1-2 to 5-10 mmol scales, with yield decreasing to approximately half, but no pronounceable difference was observed among 1-2 mmol or 5-10 mmol. However, the 1-2 mmol scale reaction time was 2 h, and 24 h was necessary for 5-10 mmol scale to complete the reaction. After purification by column chromatography, **3a** was obtained as a yellow oil, solidifying on standing (Figure 2). The decrease in yields by scale increase may be associated with inefficient mixing of the reaction media under magnetic stirring due to the formation of viscous liquid during the reaction progress.

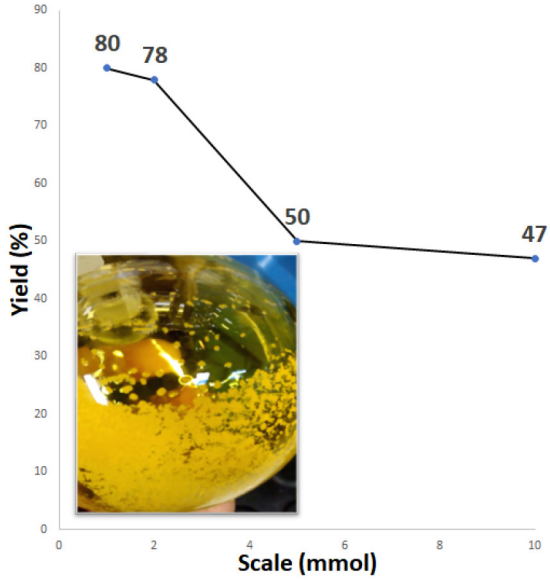
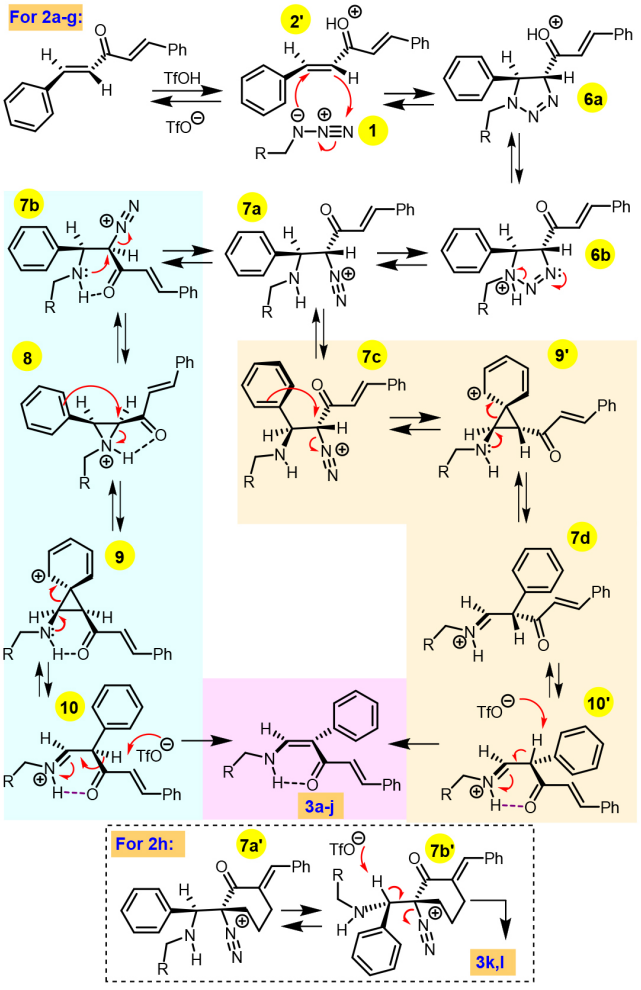



***Figure 2.*** *Dependence of yield with the reaction scale in synthesizing enaminone* ***3a*** *and its aspect after solidification*

To rationalize the regio and stereoselective formation of *Z* isomer for all obtained α-phenyl-substituted enaminone **3a**-**3j**, a mechanism pathway is proposed in Scheme 3, which was inspired by our previous synthesis of α-aryl enaminones through reactions of β-aryl enones with benzyl azide.[26] However, different intermediates were invoked to explain the observed stereoselective reaction. A 1,3-dipolar cycloaddition between alkyl azides **1** and one olefinic moiety of the protonated benzylideneacetone **2'** gives the dihydro triazole **6a** which, after proton shift to **6b**, suffers ring opening to the diazonium **7a**, which is in equilibrium with the rotamer **7b** (pathway highlighted in pale blue), wherein alkyl-$NH_2$ and $N_2^+$ are antiperiplanar. Favorable *3-exo-tet* ring closure by the alkylamino attack and molecular nitrogen extrusion forms protonated aziridine **8** stabilized by a strong N–H···O=C intramolecular hydrogen bond, which suffers ring opening and ring closure via phenonium ion **9**, preserving the hydrogen bond with nitrogen $RCH_2N$–H and carbonyl groups at the same face, driving to the observed regio and stereoselectivity. Aromatization of phenonium ion **9** is assisted by nitrogen electrons lone pair leading to the 1,2-aryl migration intermediate **10**, which thus yields *Z* enaminones **3a**-**3j** after hydrogen abstraction by triflate ion. When cyclic benzylidene ketone **2h** is the substrate (Scheme 3) the steric crowding by the bulky six-membered ring and absence of α-hydrogen prevents phenonium ion formation, and thus no 1,2-aryl migration is observed. The β-aryl *Z* enaminones **3k**-**3l** are formed by the same initial reaction pathway of acyclic **2a**-**2g** until corresponding intermediate **7a'**, which now is in equilibrium with rotamer **7b'**, wherein benzylic C–H and C–$N_2^+$ groups are antiperiplanar, which gives *Z* enaminones **3k**-**3l** after hydrogen abstraction by triflate ion (see box in Scheme 3).

Alternatively, it would be possible that, instead of the aziridinium ion formation (**7b** to **8**, Scheme 3), a direct attack of the phenyl ring on the diazonium might occur via **7c** (pathway highlighted in pale orange), which the phenyl ring is antiperiplanar to the diazonium. In this case, the phenonium ion **9'** would be directly formed, bypassing the formation of the aziridinium ion **8**. In this alternative pathway, aromatization of phenonium ion **9'** is assisted by nitrogen electrons lone pair leading to the 1,2-aryl migration intermediate **7d**, which rotate to more stable isomer **10'** due to the intramolecular H-bond. The hydrogen abstraction by triflate ion affords **3**. As one can see, the two possible pathways are degenerated route to the same compound.




***Scheme 3.*** *Proposed pathways for forming polyfunctionalized Z enaminones with (**3a-3j**) and without (**3k-3l**) 1,2-aryl migration via condensation of dibenzylidene ketones with organic azides*

## CONCLUSIONS

Triflic acid was an efficient promotor of the regio and stereoselective synthesis of polyfunctionalized *Z* enaminones through the condensation of dibenzylidene ketones with organic azides. The readily available dibenzylidene ketones and the practical handling of TfOH are experimental advantages in the context of the cascade reactions sequence, which gives diversely substituted enaminones with total control of functionalization along the N–C=C–C=O conjugated system.

## EXPERIMENTAL

The reactions were monitored by thin-layer chromatography (TLC) and were performed on pre-coated plates of silica gel 60F254/0.2 mm supported on aluminum (Merck). Visualization in TLC was achieved using UV light (254 and 356 nm) or iodine. The obtained products were separated by column chromatography, which was carried out using Merck silica gel (60 mesh). The appropriate eluent mixtures are described in the following sections. NMR spectra were obtained on a Bruker Avance III spectrometer. The 500 MHz instrument was used for $^1$H NMR, and the 125 MHz instrument was used for $^{13}$C NMR in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard. Chemical shifts are expressed in ppm, and coupling constants are given in Hz. The $^1$H NMR data are described

as follows: chemical shift ($\delta$, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal), coupling constant (Hz). The $^{13}$C NMR data are described in terms of chemical shift ($\delta$, ppm). The melting points were determined using a Microquímica MQAPF 301 apparatus and are not corrected. Elemental analyses were performed on a PerkinElmer 2401 Elemental Analysis. Azides **1a**-**1b**,[29,30] dibenzylidene ketones **2a**-**2h**,[31-34] and enones **4a**-**4b**[35,36] were synthesized by known procedures. All reagents used were from Aldrich (purchased from representatives in the country; São Paulo, SP, Brazil), and the solvents were from Quimidrol (Joinville, Santa Catarina, Brazil). All equipment was purchased by representatives in the country (São Paulo, SP, Brazil). Caution: TfOH is a very strong acid and can cause severe burnings and is corrosive.[37] All reactions were performed with a recent opened bottle of TfOH.

**General procedure for the synthesis of enaminones**

To a solution of 1.0 mmol of benzylidene ketones **2a**-**2o** in 1.5 mL of $CH_2Cl_2$ under ice bath and under magnetic stirring, was slowly added 2.0 mmol of triflic acid dissolved in 1.5 mL of $CH_2Cl_2$. Then, 2.0 mmol of azide **1a**-**1c** was added. The mixture was stirred for 15 min and then removed from the ice bath and kept under magnetic stirring at room temperature for the indicated time in each case. At the end of the reaction, confirmed by TLC, the mixture was diluted in $CH_2Cl_2$, and the organic layer was washed with 20 mL of water, 20 mL of brine, dried with anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The obtained material was purified as indicated in each case.

*(1Z,4E)-1-(Benzylamino)-2,5-diphenylpenta-1,4-dien-3-one (**3a**)*

Following the general procedure using **2a** (234.9 mg, 1 mmol), benzyl azide **1a** (250 μL, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 2 h. Column chromatography purification (hexane/EtOAc 9:1) afforded **3a** (271 mg, 80%) as a yellow solid, mp 90-92 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.13 (s, 1 H), 7.57 (d, *J* 15.5 Hz, 1H), 7.33-7.19 (m, 15H), 7.03 (m, 1H), 6.82 (d, *J* 15.5 Hz, 1H), 4.45 (d, *J* 6 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.6, 139.3, 137.7, 136.0, 130.5, 129.3, 129.0, 128.8, 128.5, 128.1, 128.0, 127.4, 126.3, 53.1. Anal. calcd. for $C_{24}H_{21}NO$: C, 84.92%; H, 6.24%; N, 4.13%; found: C, 85.55%; H, 6.99%; N, 3.89%.

*Synthesis of enaminones **3a** in different scales*

Following the general procedure using **2a** (470 mg, 2 mmol), benzyl azide (516 mmL, 4 mmol), triflic acid (353 μL, 4 mmol), for 2 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3a** (530 mg, 78%) as a yellow solid, mp 90-92 °C.

Following the general procedure using **2a** (1.1720 g, 5 mmol), benzyl azide (1.3 mL, 10 mmol), triflic acid (882 μL, 10 mmol), for 24 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3a** (849 mg, 50%) as a yellow solid.

Following the general procedure using **2a** (2.3654 mg, 10 mmol), benzyl azide (2.6 mL, 20 mmol), triflic acid (1.8 mL, 20 mmol), for 24 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3a** (1.5954 g, 47%) as a yellow solid.

*(1Z,4E)-1-(Benzylamino)-2,5-bis(4-chlorophenyl)penta-1,4-dien-3-one (**3b**)*

Following the general procedure using **2b** (304.5 mg, 1 mmol), benzyl azide **1a** (250 μL, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 15 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3b** (220.4 mg, 54%) as a yellow solid, mp 80-82 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.14 (m, 1H), 7.51 (d, *J* 15.5 Hz, 1H), 7.34-7.21 (m, 11H), 7.13-7.11 (m, 2H), 7.02 (m, 1H), 6.72 (d, *J* 15.5 Hz, 1H), 4.47 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.6, 138.3, 137.4, 135.3, 134.4, 131.8, 129.3, 129.1, 129.1, 128.7, 198.1, 127.4, 126.2, 53.2. Anal. calcd. for $C_{24}H_{19}Cl_2NO$: C, 70.60%; H, 4.69%; N, 3.43%; found: C, 70.99%; H, 5.02%; N, 3.21%.

*(1Z,4E)-1-(Benzylamino)-2,5-bis(2-chlorophenyl)penta-1,4-dien-3-one (**3c**)*

Following the general procedure using **2c** (303.6 mg, 1 mmol), benzyl azide **1a** (250 μL, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 2 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3c** (273 mg, 67%) as a yellow solid, mp 105-107 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.24 (m, 1H), 7.99 (d, *J* 16 Hz, 1H), 7.47-7.11 (m, 15H), 7.02 (d, *J* 13 Hz, 1H), 6.53 (d, *J* 16 Hz, 1 H), 4.50 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 186.3, 156.1, 137.7, 137.6, 136.1, 135.3, 135.1, 134.4, 133.7, 130.1, 130.0, 129.8, 129.1, 128.6, 128.2, 128.0, 127.7, 127.5, 127.0, 126.9, 108.5, 53.2. Anal. calcd. for $C_{24}H_{19}Cl_2NO$: C, 70.60%; H, 4.69%; N, 3.43%; found: C, 70.99%; H, 5.02%; N, 3.21%.

*(1Z,4E)-1-(Benzylamino)-2,5-bis(2,4-dichlorophenyl)penta-1,4-dien-3-one (**3d**)*

Following the general procedure using **2d** (372.7 mg, 1 mmol), benzil azyde **1a** (250 μL, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 2 h 30 min. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3d** (195.6 mg, 41%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.15-11.12 (m, 1H), 7.80 (d, *J* 15.5 Hz, 1H), 7.38 (m, 1H), 7.28-7.10 (m, 9H), 7.04-7.02 (m, 1H), 6.88 (d, *J* 12.5 Hz, 1H), 6.36 (d, *J* 5.5 Hz, 1H), 4.40 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 185.7, 156.1, 137.3, 136.8, 136.2, 135.6, 135.3, 134.4, 134.3, 133.7, 132.8, 129.9, 129.6, 129.1, 128.4, 128.1, 127.5, 127.4, 127.3, 107.3, 53.2. Anal. calcd. for $C_{24}H_{17}Cl_4NO$: C, 60.41%; H, 3.59%; N, 2.94%; found: C, 60.71%; H, 3.98%; N, 2.57%.

*(1Z,4E)-1-(Benzylamino)-2,5-bis(4-bromophenyl)penta-1,4-dien-3-one (**3e**)*

Following the general procedure using **2e** (395.0 mg, 1 mmol), benzyl azide **1a** (250 μL, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 24 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3e** (114.4 mg, 23%) as a yellow solid, mp 75.3-76.9 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.22-11.19 (m, 1H), 7.54-7.24 (m, 12H), 7.12-7.04 (m, 3H), 6.79 (d, *J* 15.5 Hz, 1H), 4.51 (d, *J* 6 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 186.3, 155.6, 138.4, 137.4, 134.8, 132.1, 132.0, 131.6, 129.5, 129.1, 128.1, 127.4, 126.4, 123.6, 120.4, 53.2. Anal. calcd. for $C_{24}H_{19}Br_2NO$: C, 57.97%; H, 3.85%; N, 2.82%; found: C, 60.13%; H, 4.21%; N, 2.42%.

*(1Z,4E)-1-(Benzylamino)-2,5-bis(2-methoxyphenyl)penta-1,4-dien-3-one (**3f**)*

Following the general procedure using **2f** (296.8 mg, 1 mmol), benzyl azide **1a** (250 μL, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 24 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3f** (115.8 mg, 29%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.12 (s, 1H), 7.91 (d, *J* 16 Hz, 1H), 7.38-7.17 (m, 9H), 7.01-6.92 (m, 3H), 6.85-6.82 (m, 2H), 6.77 (d, *J* 16 Hz, 1H), 4.48 (d, *J* 5.5 Hz, 2H), 3.76 (s, 2 × 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 153.8, 140.3, 138.9, 138.3, 132.2, 130.0, 129.8, 129.1, 125.0, 124.7, 123.8, 121.2, 119.3, 114.8, 114.5, 50.3, 33.6, 26.0, 25.3. Anal. calcd. for $C_{26}H_{25}NO_3$: C, 78.17%; H, 6.31%; N, 3.51%; found: C, 78.48%; H, 6.64%; N, 3.44%.

*(1Z,4E)-1-(Benzylamino)-2,5-bis(4-(dimethylamino)phenyl)penta-1,4-dien-3-one (**3g**)*

Following the general procedure using **2g** (320.8 mg, 1 mmol),

benzyl azide **1a** (250 μL, 2 mmol), triflic acid (353 μL, 4 mmol), for 48 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3g** (85.1 mg, 20%) as an orange solid, mp 90-92 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.02-10.99 (m, 1H), 7.56 (d, *J* 15.5 Hz, 1H), 7.37-7.28 (m, 7H), 7.15 (m, 2H), 6.98 (d, *J* 12.5 Hz, 1H), 6.79 (m, 1H), 6.73 (d, *J* 15.5 Hz, 1H), 6.62 (d, *J* 8.5 Hz, 1H), 4.47 (d, *J* 5 Hz, 2H), 2.99 (s, 6H), 2.97 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 188.2, 154.6, 151.3, 139.7, 138.3, 131.5, 129.7, 128.9, 127.7, 127.4, 124.4, 122.0, 112.1, 52.9, 40.4, 29.8. Anal. calcd. for $C_{28}H_{31}N_3O$: C, 78.17%; H, 6.31%; N, 3.51%; found: C, 79.29%; H, 6.79%; N, 3.19%.

*(1Z,4E)-1-(Octylamino)-2,5-diphenylpenta-1,4-dien-3-one (**3h**)*

Following the general procedure using **2a** (235.7 mg, 1 mmol), octyl azide **1b** (310.5 mg, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 2 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3h** (216 mg, 60%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.99 (s, 1H), 7.61 (d, *J* 15.5 Hz, 1H), 7.39-7.38 (m, 4H), 7.29-7.23 (m, 6H), 7.02 (m, 1H), 6.86 (d, *J* 15.5 Hz, 2H), 3.32-3.28 (q, *J* 6.5 Hz, 2H), 1.66-1.60 (m, 2H), 1.40-1.27 (m, 10H), 0.90-0.87 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.0, 138.7, 136.1, 130.4, 129.1, 128.6, 128.3, 127.9, 126.3, 126.0, 49.6, 31.8, 31.0, 29.2, 26.7, 22.6, 14.1. Anal. calcd. for $C_{25}H_{31}NO$: C, 83.06%; H, 8.64%; N, 3.87%; found: C, 83.16%; H, 8.88%; N, 3.88%.

*(1Z,4E)-2,5-Bis(2-chlorophenyl)-1-(octylamino)penta-1,4-dien-3-one (**3i**)*

Following the general procedure using **2c** (303.2 mg, 1 mmol), octyl azide **1b** (310.5 mg, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 5 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3i** (202.3 mg, 47%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.00 (m, 1H), 7.99 (d, *J* 15.5 Hz, 1H), 7.48-7.10 (m, 10H), 6.51 (d, *J* 15.5 Hz, 1H), 3.33 (m, 2H), 1.67-1.61 (q, *J* 6.5 Hz, 2H), 1.41-1.25 (m, 10H), 0.89-0.87 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 135.9, 135.0, 134.2, 133.7, 131.8, 130.0, 129.8, 127.6, 127.2, 126.9, 126.7, 49.7, 47.2, 31.8, 31.0, 29.2, 29.1, 26.6, 22.6, 14.1. Anal. calcd. for $C_{25}H_{29}Cl_2NO$: C, 69.76%; H, 6.79%; N, 3.25%; found: C, 69.86%; H, 7.17%; N, 2.78%.

*(1Z,4E)-2,5-Bis(2,4-dichlorophenyl)-1-(octylamino)penta-1,4-dien-3-one (**3j**)*

Following the general procedure using **2d** (372.0 mg, 1 mmol), octyl azide **1b** (310.5 mg, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 2 h. Flash column chromatography purification (hexane/EtOAc 8:2) afforded **3j** (284.6 mg, 57%) as a yellow solid, mp 49-50 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.98 (s, 1H), 7.55-7.42 (m, 5H), 7.26 (d, *J* 9 Hz, 2H), 7.10 (d, *J* 8 Hz, 2H), 6.77 (d, *J* 15.5 Hz, 1H), 3.33 (m, 2H), 1.66-1.61 (m, 2H), 1.38-1.11 (m, 12H), 0.90-0.87 (t, *J* 7 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 199.7, 163.6, 158.2, 144.1, 136.4, 130.6, 130.5, 130.2, 130.1, 129.7, 127.1, 125.1, 118.0, 114.5, 114.1, 113.9, 113.9,113.8, 55.6, 55.2, 48.4, 45.2, 44.7. Anal. calcd. for $C_{25}H_{27}Cl_4NO$: C, 60.14%; H, 5.45%; N, 2.81%; found: C, 59.89%; H, 5.39%; N, 2.88%.

*(Z)-2-((Benzylamino)(phenyl)methylene)-6-((E)-benzylidene) cyclohexan-1-one (**3k**)*

Following the general procedure using **2h** (275.3 mg, 1 mmol), benzyl azide **1a** (250 μL, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 24 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3k** (64.5 mg, 17%) as a yellow solid, mp 142-144 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 13.19 (m, 1H), 7.82 (s, 1H), 7.53-7.26 (m, 16H), 4.29 (s, 2H), 2.82 (s, 2H), 2.14 (s, 2H), 1.69 (s, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 185.8, 166.6, 138.6, 137.7, 137.4, 134.3, 132.3, 130.1, 128.8, 128.3, 127.6, 127.5, 127.4, 127.2, 103.1, 48.9, 28.5, 28.1, 24.3. Anal. calcd. for $C_{27}H_{25}NO$: C, 85.45%; H, 6.64%; N, 3.69%; found: C, 85.49%; H, 6.69%; N, 3.46%.

*(Z)-2-((E)-Benzylidene)-6-((octylamino)(phenyl)methylene) cyclohexan-1-one (**3l**)*

Following the general procedure using **2h** (276.1 mg, 1 mmol), octyl azide **1b** (310.5 mg, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 24 h. Flash column chromatography purification (hexane/EtOAc 9:1) afforded **3l** (104.4 mg, 26%) as a yellow solid, mp 72-74 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 12.89 (m, 1H), 7.72 (m, 1H), 7.47-7.33 (m, 7H), 7.24-7.23 (m, 1H), 7.20-7.18 (m, 2H), 2.98-2.91 (m, 2H), 2.72-2.69 (m, 2H), 2.02-1.99 (m, 2H), 1.59-1.48 (m, 4 H), 1.30-1.18 (m, 10 H), 0.86 (t, *J* 7 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 184.9, 166.9, 137.9, 137.5, 137.0, 136.2, 136.0, 134.5, 131.4, 130.4, 129.9, 128.8, 128.6, 128.6, 128.4, 128.1, 127.3, 102.2, 45.1, 31.8, 30.7, 29.2, 29.1, 28.5, 28.4, 27.9, 26.8, 24.2, 22.6, 14.1. Anal. calcd. for $C_{28}H_{35}NO$: C, 85.45%; H, 6.64%; N, 3.69%; found: C, 85.85%; H, 6.89%; N, 3.34%.

*(Z)-1-(Benzylamino)-4-methyl-2-phenylpent-1-en-3-one (**5a**)*

Following the general procedure using **4a** (172.3 mg, 1 mmol), benzyl azide **1a** (250 μL, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 5 h. Flash column chromatography purification (hexane/EtOAc 8:2) afforded **5a** (83.8 mg, 30%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.63 (m, 1H), 7.43-7.22 (m, 11H), 6.89 (d, *J* 12.5 Hz, 1H), 4.44 (d, *J* 6 Hz, 2H), 2.92-2.82 (m, 1H), 1.03 (s, 3H), 1.02 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 204.0, 154.3, 140.4, 137.9, 130.8, 128.9, 128.4, 127.8, 127.5, 126.2, 109.8, 52.9, 35.5, 19.6.

*(Z)-3-(Benzylamino)-2-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (**5b**)*

Following the general procedure using **4b** (238.9 mg, 1 mmol), benzyl azide **1a** (250 μL, 2 mmol), triflic acid (176.5 μL, 2 mmol), for 2 h 30 min. Flash column chromatography purification (hexane/EtOAc 8:2) afforded **5b** (154 mg, 45%) as a yellow solid, mp 73.2-74.6 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.79 (m, 1H), 7.46 (m, 1H), 7.46-7.07 (m, 14H), 6.89 (m, 3H), 6.68 (m, 2H), 4.47 (m, 2H), 3.75 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 193.3, 157.7, 155.9, 152.8, 141.4, 137.8, 133.1, 131.8, 131.1, 129.8, 129.5, 129.0, 128.8, 127.9, 27.6, 127.4, 127.2, 55.3, 53.0.

## SUPPLEMENTARY MATERIAL

NMR spectra of all products can be found at http://quimicanova.sbq.org.br, as PDF file, with free access.

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