

Synthesis of a New Bichalcone via Suzuki–Miyaura Coupling Reaction

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Abstract: Unlike the wide number of natural biflavonoids, natural bichalcones are a rare and even less studied class. Nevertheless, some of them have proved their interest in the fight against cancer through their cytotoxic activity against human tumor cell lines. The aim of this study was to synthesize a novel bichalcone: 3',3''',4,4',4'',4''',5',5'''-octamethoxy-2,3''-bichalcone **1**. The most efficient synthetic pathway was the Suzuki–Miyaura reaction between a boronated chalcone and a brominated one.

Keywords: bichalcones; Claisen–Schmidt condensation; Suzuki–Miyaura coupling

1. Introduction

Chalcones, with a 1,3-diarylprop-2-en-1-one skeleton, constitute a major group of natural compounds which display a wide range of biological activities, including anti-inflammatory, antimicrobial, antioxidant and anticancer properties [1]. Moreover, chalcones are the immediate precursors in the biosynthesis [2] and synthetic preparation of flavonoids [3,4], which are also known for their numerous beneficial effects [5].

Similar to flavonoids, biflavonoids are natural compounds which can be found in plants all around the world [6–8]. They possess many biological activities, such as antimicrobial [9], antitumor [10] and anti-inflammatory [11] properties, which are sometimes stronger than those of the corresponding monomers. This is also verified for synthetic biflavonoids [12]. Therefore, there is a renewed interest in the biological activities of this class, representing a library of structurally diverse molecules which remains to be fully investigated.

Unlike the wide number of natural biflavonoids, natural bichalcones are a rare and even less recognized class. In general, naturally occurring bichalcones carry a C–O–C linkage between the two chalcone units (biarylether type) [13]. But a C–C (biaryl type) linkage is found in the rhuschalcone VI (Figure 1), isolated from *Rhus pyroides*, a tree widely distributed in the eastern part of Bostwana and in South Africa, for example [14]. *Rhus pyroides* is a remarkable source of bioactive bichalcones since five other rhuschalcones (rhuschalcones I–V, Figure 1) have also been extracted from this tree. All these molecules have been tested in vitro for their cytotoxicity against a panel of 60 different human tumor cell lines; they showed selective activity against colon cancer cells, especially HT-29 and HCT-116 cell lines [14].



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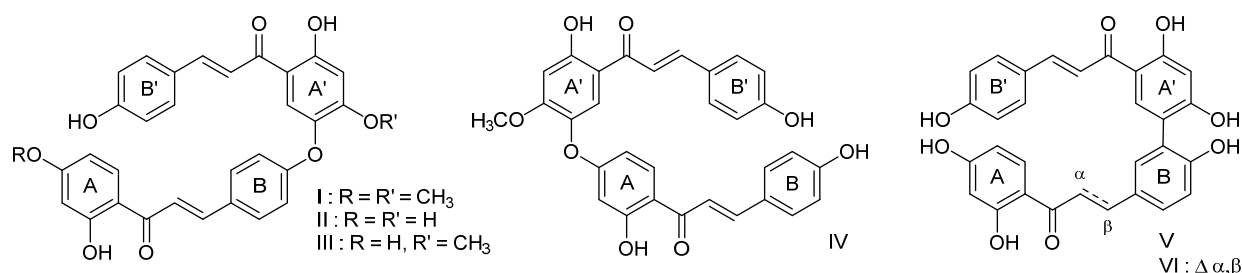


Figure 1. Structure of rhuschalcones I–VI [14].

Bichalcones can also be classified depending on which of the aromatic rings are joined together (aromatic rings in the 1,3-diarylprop-2-en-1-one structure are named as A and B). Thus, most bichalcones display a linkage of the A–B (e.g., rhuschalcone VI, Figure 1) or A–A type (e.g., rhuschalcone IV, Figure 1). The B–B type is also found but studies reporting these structures are much less common [13]. Considering the synthetic pathway of these bichalcones, the biaryl core is typically prepared via phenol coupling reaction [15], Ullmann condensation [7,16] and Suzuki–Miyaura coupling [17,18].

As part of an ongoing project on the design and synthesis of original antiproliferative chalcones, we became interested in the preparation of 3',3''',4,4',4'',4''',5',5'''-octamethoxy-2,3''-bichalcone **1** (Figure 2) with a biaryl type (C–C) linkage between the B rings of two chalcones. In addition to structural originality, our aim was to keep a trimethoxyphenyl moiety as A ring since this structural pattern is thought to be essential for the anticancer activity of chalcones [19,20].

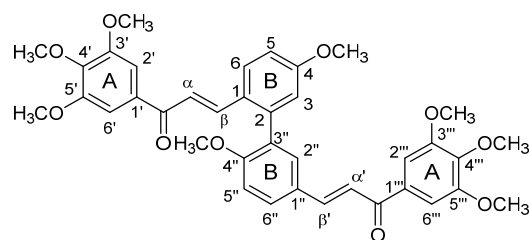


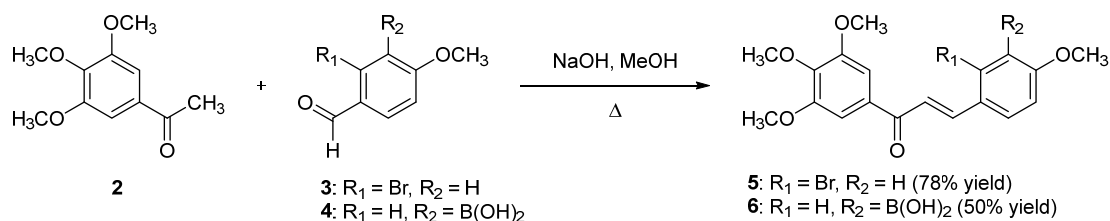
Figure 2. Structure of 3',3''',4,4',4'',4''',5',5'''-octamethoxy-2,3''-bichalcone **1**.

Among the various ways to perform C–C bond formation, we chose the Suzuki–Miyaura reaction. Indeed, this metal-catalyzed cross-coupling reaction between organic boron compounds and organic halides has emerged as one of the most interesting methods for the formation of carbon–carbon bonds under mild conditions and especially for the coupling of aryl–aryl moieties [21]. Pd-catalysts have been the mainstay for Suzuki–Miyaura cross-coupling for several decades. However, extensive studies of reaction parameters and catalyst systems have led to significant improvements for various chemical systems [22,23]. Thus, other metal catalysts, based on nickel, copper or iron for example, have been increasingly applied in Suzuki–Miyaura cross-coupling [24–26]. In the present paper, the preparation of bichalcone **1** through two synthetic pathways is described.

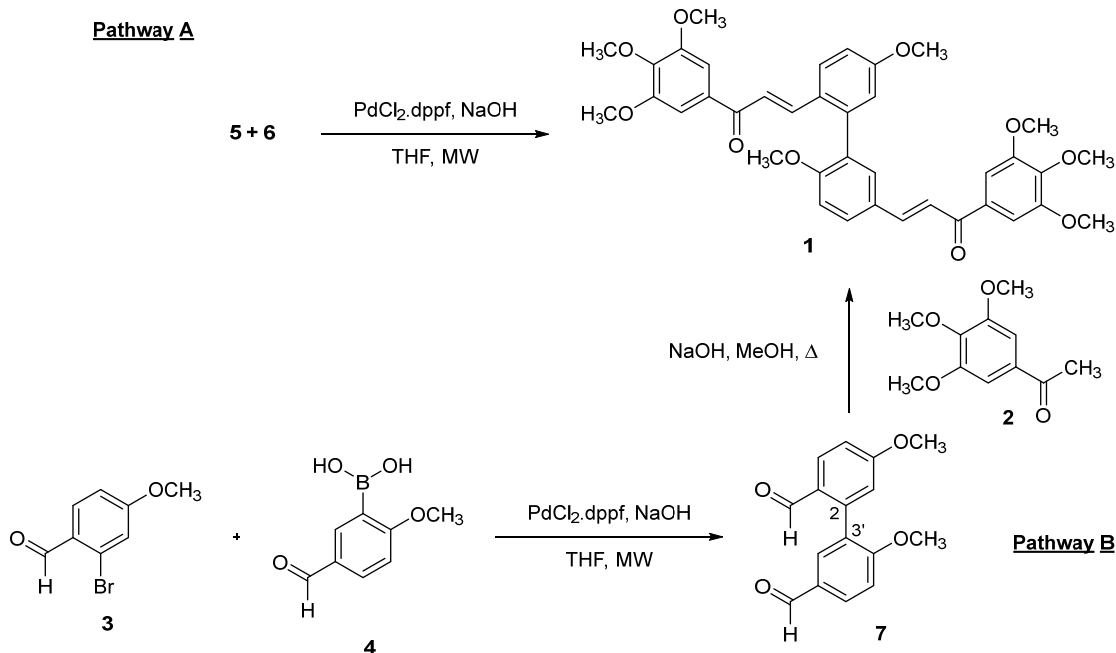
2. Results and Discussion

Two synthetic strategies were defined for the preparation of bichalcone **1**. Firstly, a brominated chalcone **5** and a boronated chalcone **6** were synthesized by a Claisen–Schmidt condensation (Scheme 1) to allow a Suzuki–Miyaura coupling between these two chalcones (Scheme 2, pathway A). The second pathway involved the synthesis of bis-benzaldehyde **7** through a Suzuki coupling reaction. This intermediate was then reacted with 3',4',5'-

trimethoxyacetophenone **2** according to the Claisen–Schmidt condensation (Scheme 2, pathway B).



Scheme 1. Synthesis of chalcones **5** and **6**.



Scheme 2. Synthetic strategies for the preparation of bichalcone **1**.

Considering the first synthetic strategy, the Claisen–Schmidt condensation was performed between 3',4',5'-trimethoxyacetophenone (1 eq) **2** and an appropriate benzaldehyde (1.2 eq), i.e., 2-bromo-4-methoxybenzaldehyde **3** and 5-formyl-2-methoxyphenylboronic acid **4** to give chalcones **5** and **6**, respectively (Scheme 1). All these reagents were commercially available. 2-bromo-3',4,4',5'-tetramethoxychalcone **5** was obtained in a 78% isolated yield and 3-borono-3',4,4',5'-tetramethoxychalcone **6** [27] was achieved in a moderate isolated yield (50%).

Then, on the basis of our previous results [28], the Suzuki coupling reaction (Scheme 2, pathway A) was performed between chalcones **5** and **6**, in tetrahydrofuran, in the presence of 0.2 eq of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (PdCl₂·dppf) as a catalyst and 3 eq of 3 M aqueous sodium hydroxide as a base, using a microwave irradiation at 120 °C (150 W, 2 × 10 min). A catalyst amount of 0.1 eq allowed the coupling reaction but the required reaction time had been increased to one hour. The bichalcone **1** was obtained in a 58% yield using 1.25 eq of chalcone **6**. The first experiment had shown that the yield was only 40% with 1.1 eq of chalcone **6**.

In the second pathway (Scheme 2, pathway B), bis-benzaldehyde **7** was synthesized through the Suzuki–Miyaura coupling reaction between 2-bromo-4-methoxybenzaldehyde **3** and 5-formyl-2-methoxyphenylboronic acid **4** with sodium hydroxide (3 eq). We explored

various Suzuki coupling conditions, as shown in Table 1, and the most efficient experiment led to bis-benzaldehyde 7 in 48% isolated yield with a reaction time of 50 min.

Table 1. Suzuki coupling conditions for the reaction between 2-bromo-4-methoxybenzaldehyde 3 (1 eq) and 5-formyl-2-methoxyphenylboronic acid 4.

Exp.	4	Catalyst	Time MW Heating	Yield
1	1.1 eq	PdCl ₂ -dppf 0.2 eq	2 × 10 min	30%
2	1.4 eq	PdCl ₂ -dppf 0.2 eq	2 × 10 min	38%
3	1.4 eq	PdCl ₂ -dppf 0.2 eq	5 × 10 min	48%
4	2.0 eq	PdCl ₂ -dppf 0.2 eq	5 × 10 min	35%
5	1.4 eq	Pd(PPh ₃) ₄ 0.2 eq	5 × 10 min	34%

An excess of phenylboronic acid 4 was required: the optimal quantity was found to be 1.4 equivalents. Using 2 eq of phenylboronic acid 4 led to a significant decrease in the yield as well as replacement of PdCl₂.dppf with tetrakis(triphenylphosphine)palladium (Pd(PPh₃)₄). Considering experiment 4, side products were observed, especially the 4-methoxybenzaldehyde, which was identified by NMR spectroscopy. Then, bis-benzaldehyde 7 was reacted with 3',4',5'-trimethoxyacetophenone 2 according to the Claisen–Schmidt condensation. The first experiment using 3 eq of acetophenone afforded bichalcone 1 but only in a 17% yield; therefore, the second experiment was performed with 4 eq of acetophenone 2. The desired product was isolated but the yield obtained (25%) remained unsatisfactory due to the formation of many by-products such as compounds 8 and 9 (Figure 3) which result from a mono-condensation between 3',4',5'-trimethoxyacetophenone 2 and the bis-benzaldehyde 7.

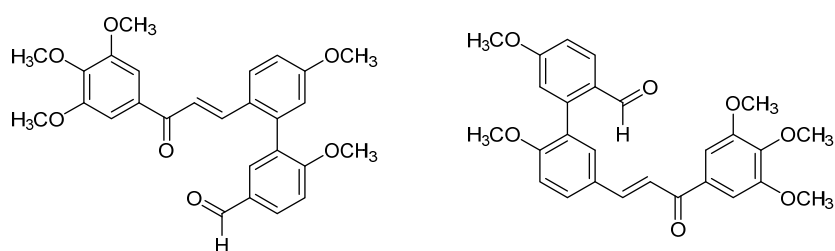


Figure 3. Structure of by-products 8 and 9.

3. Materials and Methods

3.1. General Chemistry

All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich, St. Louis, MO, USA), Alfa Aesar (Karlsruhe, Germany), VWR (Radnor, PA, USA), Acros Organics (Geel, Belgium) and Iris Biotech (Marktredwitz, Germany) and were used without further purification. Reactions were monitored by TLC (TLC Silica gel 60 F-254, Merck KGaA, Darmstadt, Germany). Microwave reactions were carried out into a Monowave 400 Anton Paar system (Les Ulis, France). Purifications by preparative TLC were performed on silica gel glass plates coated with 60 HF-254 (Merck, Darmstadt, Germany). Purifications by flash chromatography were achieved using CombiFlash Companion TS (Serlabo Technologies, Entraigues-sur-la-Sorgue, France) on normal phase disposable columns RediSep® RF (Tele-

dyne Isco, Lincoln, NE, USA). NMR spectra were recorded on Bruker 500 MHz Avance III HD spectrometer (Wissembourg, France), by the BISCem platform (US 42 INSERM/UAR 2015 CNRS/University of Limoges). Chemicals shifts (δ) are reported in ppm downfield from internal TMS standard. High-resolution mass spectra (HRMS) were performed on a Bruker maXis mass spectrometer (Wissembourg, France) by the ICOA platform (UMR 7311 CNRS/University of Orléans).

3.2. Synthesis of 2-Bromo-3',4,4',5'-tetramethoxychalcone 5

A total of 210 mg of 3',4',5'-trimethoxyacetophenone (1 mmol) and 258 mg of 2-bromobenzaldehyde (1.2 mmol, 1.2 eq) were dissolved in 20 mL of MeOH. A total of 200 mg of NaOH (5 mmol, 5 eq) previously dissolved in 2 mL of H₂O were added. The reaction mixture was heated at reflux for 2 h. After cooling, crystallization occurred; crystals were filtered off while 20 mL of water was added to the filtrate. Then, the aqueous phase was acidified to pH 3 using a 3 M solution of hydrochloric acid. A liquid–liquid extraction was performed with 3 $\times$ 20 mL of CH₂Cl₂. After drying over anhydrous sodium sulfate and filtration on a Büchner funnel, the organic phase was evaporated. The residue was purified through preparative TLC on silica gel using cyclohexane 80/ethyl acetate 20 as eluent. A global mass of 318 mg of 2-bromo-3',4,4',5'-tetramethoxychalcone was obtained (0.78 mmol, 78% isolated yield).

¹H NMR (500.15 MHz, CDCl₃, 25 °C) δ (ppm), 8.08 (1H, d, J = 15.7 Hz, H- β), 7.69 (1H, d, J = 8.8 Hz, H-6), 7.26 (2H, s, H-2' and H-6'), 7.26 (1H, d, J = 15.7 Hz, H- α) 7.18 (1H, d, J = 2.5 Hz, H-3), 6.92 (1H, dd, J = 8.8 Hz, J = 2.5 Hz, H-5), 3.95 (6H, s, (OCH₃)-3' and (OCH₃)-5'), 3.94 (3H, s, (OCH₃)-4'), 3.85 (3H, s, (OCH₃)-4). ¹³C NMR (125.04 MHz, CDCl₃, 25 °C) δ (ppm), 189.7 (CO), 161.6 (C-4), 153.2 (C-3' and C-5'), 142.9 (C- β), 142.5 (C-4'), 133.4 (C-1'), 128.7 (C-6), 127.4 (C-2), 127.0 (C-1), 122.9 (C- α), 118.3 (C-3), 114.5 (C-5), 106.3 (C-2' and C-6'), 61.0 ((OCH₃)-4'), 56.4 ((OCH₃)-3' and (OCH₃)-5'), 55.7 ((OCH₃)-4).

TOF MS ES+: [M + H]⁺ for C₁₉H₂₀BrO₅; m/z 407.0489; found: m/z 407.0487.

3.3. Synthesis of 3-Borono-3',4,4',5'-tetramethoxychalcone 6

The synthetic pathway and structural analysis match the data described by Kong et al. [27].

3.4. Synthesis of 3',3''',4,4',4''',5',5'''-Octamethoxy-2,3''-bichalcone 1

A total of 102 mg of chalcone 5 (0.25 mmol) and 116 mg of chalcone 6 (0.32 mmol, 1.25 eq) were dissolved in 6 mL of tetrahydrofuran; 37 mg of PdCl₂-dppf (0.05 mmol, 0.2 eq) and 297 μ L of an aqueous solution (2.5 M) of sodium hydroxide (0.75 mmol, 3 eq) were added. The reaction was activated by microwave irradiation (120 °C, 150 W, 2 $\times$ 10 min). The solvent was then evaporated and the residue was taken up in 20 mL of H₂O. The aqueous phase was acidified to pH 6 using a 3 M solution of hydrochloric acid and extraction was carried out with 4 $\times$ 20 mL of dichloromethane. After drying over anhydrous sodium sulfate and filtration on a Büchner funnel, the organic phase was evaporated. The residue was purified with flash chromatography (dichloromethane 100% to dichloromethane 90/ethyl acetate 10) and 95 mg of pure bichalcone 1 were obtained (0.15 mol, 58% isolated yield).

¹H NMR (500.15 MHz, CDCl₃, 25 °C) δ (ppm), 7.84 (1H, d, J = 8.7 Hz, H-6), 7.81 (1H, d, J = 15.5 Hz, H- β'), 7.68 (1H, dd, J = 8.5 Hz, J = 1.9 Hz, H-6''), 7.62 (1H, d, J = 15.5 Hz, H- β), 7.53 (1H, d, J = 1.9 Hz, H-2''), 7.36 (1H, d, J = 15.5 Hz, H- α') 7.29 (1H, d, J = 15.5 Hz, H- α), 7.26 (2H, s, H-2''' and H-6'''), 7.18 (2H, s, H-2' and H-6'), 7.02 (2H, m, H-5 and H-5''), 6.86 (1H, d, J = 2.5 Hz, H-3), 3.94 (6H, s, 2xOCH₃), 3.93 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 3.89 (6H, s, 2xOCH₃), 3.88 (3H, s, OCH₃), 3.78 (3H, s, OCH₃). ¹³C NMR (125.04 MHz, CDCl₃, 25 °C) δ (ppm), 189.2 (CO), 188.9 (CO), 161.2 (C-4), 158.7 (C-4''), 153.2 (C-3''' and C-5'''),

153.1 (C-3' and C-5'), 144.2 (C-β'), 143.5 (C-β), 142.4 (C-4'''), 142.2 (C-4'), 141.3 (C-2), 133.8 (C-1'''), 133.7 (C-1'), 131.0 (C-2''), 130.8 (C-6''), 129.7 (C-3''), 128.2 (C-6), 127.8 (C-1''), 126.5 (C-1), 120.2 (C-α'), 119.9 (C-α), 116.1 (C-3), 114.2 (C-5), 111.5 (C-5''), 106.1 (C-2''' and C-6'''), 106.0 (C-2' and C-6'), 61.0 (2xOCH₃), 56.5 (2xOCH₃), 56.4 (2xOCH₃), 55.9 (OCH₃), 55.5 (OCH₃).

TOF MS ES+: [M + H]⁺ for C₃₈H₃₉O₁₀: *m/z* 655.2538; found: *m/z* 655.2540.

3.5. Synthesis of 4,4'-Dimethoxy-2,3'-bisbenzaldehyde 7

A total of 540 mg of 2-bromobenzaldehyde **3** (2.5 mmol) and 630 mg of 5-formyl-2-methoxyphenylboronic acid **4** (3.5 mmol, 1.4 eq) were dissolved in 20 mL of THF. Then, 366 mg of PdCl₂-dppf (0.5 mmol, 0.2 eq) and 3 mL of an aqueous solution (2.5 M) of sodium hydroxide (7.5 mmol, 3 eq) were added. The reaction was activated by microwave irradiation (120 °C, 150 W, 5 × 10 min). Then, the solvent was evaporated and the residue was taken up in 20 mL of H₂O. The aqueous phase was acidified to pH 6 using a 3 M solution of hydrochloric acid and extraction was carried out with 4 × 20 mL of dichloromethane. After drying over anhydrous sodium sulfate and filtration on a Büchner funnel, the organic phase was evaporated. The residue was purified with flash chromatography (dichloromethane 100% to dichloromethane 90/ethyl acetate 10) and 325 mg of pure bis-benzaldehyde **7** were obtained (1.2 mmol, 48% isolated yield).

¹H NMR (500.15 MHz, CDCl₃, 25 °C) δ (ppm), 9.96 (1H, s, CHO), 9.63 (1H, s, CHO), 7.99 (1H, d, *J* = 8.8 Hz, H-6), 7.97 (1H, dd, *J* = 8.5 Hz, *J* = 2.1 Hz, H-6'), 7.83 (1H, d, *J* = 2.1 Hz, H-2'), 7.10 (1H, d, *J* = 8.5 Hz, H-5'), 7.03 (1H, dd, *J* = 8.8 Hz, *J* = 2.5 Hz, H-5), 6.81 (1H, *J* = 2.5 Hz, H-3), 3.90 (3H, s, (OCH₃)-4'), 3.85 (3H, s, (OCH₃)-4). ¹³C NMR (125.04 MHz, CDCl₃, 25 °C) δ (ppm), 190.5 (CO) 190.4 (CO), 164.0 (C-4'), 161.6 (C-4), 142.6 (C-2), 132.8 (C-6'), 132.4 (C-2'), 130.0 (C-3'), 129.9 (C-6), 128.2 (C-1), 127.6 (C-1'), 116.1 (C-3), 114.1 (C-5), 110.7 (C-5'), 56.1 (OCH₃), 55.7 (OCH₃).

TOF MS ES+: [M + H]⁺ for C₁₆H₁₅O₄: *m/z* 271.0965; found: *m/z* 271.0964.

4. Conclusions

We described herein an efficient synthetic approach of a novel bichalcone. Indeed, the molecule synthesized in this work belongs to the B-B type with a C-C linkage (biaryl type), which is uncommon among natural or synthetic bichalcones. As key steps, we used Claisen-Schmidt condensation and a microwave-assisted Suzuki-Miyaura coupling. The most efficient synthetic pathway was the Suzuki-Miyaura reaction between a boronated chalcone and a brominated one. The second pathway based on the double aldol condensation between a bis-benzaldehyde and the 3',4',5'-trimethoxyacetophenone has to be improved, with varying reaction conditions. Finally, the developed synthetic methodology may find future applications in the synthesis of various original bichalcones to further study their anticancer activities.

Supplementary Materials: The following supporting information can be downloaded online, Figure S1: ¹H spectrum of chalcone **5**; Figure S2: ¹³C spectrum of chalcone **5**; Figure S3: ¹H spectrum of bichalcone **1**; Figure S4: ¹³C spectrum of bichalcone **1**; Figure S5: ¹H spectrum of bis-benzaldehyde **7**; Figure S6: ¹³C spectrum of bis-benzaldehyde **7**; Figure S7: HRMS spectrum of chalcone **5**; Figure S8: HRMS spectrum of bichalcone **1**; Figure S9: HRMS spectrum of bis-benzaldehyde **7**.

Author Contributions: Conceptualization, F.-X.T. and C.P.; methodology, F.-X.T. and C.P.; software, F.-X.T. and C.P.; validation, F.-X.T., Y.C. and C.P.; formal analysis, F.-X.T., Y.C. and C.P.; investigation, F.-X.T., A.L. and Y.C.; resources, C.F. and C.P.; writing—original draft preparation, F.-X.T. and C.P.; writing—review and editing, F.-X.T., Y.C., A.L., C.F. and C.P.; supervision, C.F. and C.P.; project administration, C.P.; funding acquisition, C.F. and C.P. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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