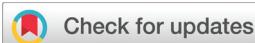


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Cite this: *Org. Chem. Front.*, 2017, **4**, 1736

The study of metal-free and palladium-catalysed synthesis of benzochromenes *via* direct C–H arylation using unactivated aryl benzyl ethers derived from essential oils as raw materials†

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The synthesis of 6H-benzo[c]chromenes from unactivated 2-bromo aryl benzyl ethers was studied through two approaches: (i) the transition-metal-free intramolecular dehydrohalide coupling *via* intramolecular homolytic aromatic substitution; and (ii) the intramolecular cyclization *via* direct C–H arylation catalysed by $\text{PdCl}_2(\text{MeCN})_2$. Having developed the most efficient method, a 17-membered chromene library was prepared in good yields and in shorter reaction times starting from commercially available phenol derivatives and phenol-rich essential oils (*Eugenia caryophyllus* and *Plectranthus amboinicus*) as raw materials, proving how sustainable and eco-friendly our protocol is. Additionally, the ruggedness of the optimized reaction conditions was evaluated with *N*-benzylanilines, giving the respective phenanthridone as an unexpected product, while the metal-free oxidation of the obtained 6H-benzo[c]chromenes was also performed to furnish the benzocoumarins.

Received 24th March 2017,
Accepted 19th May 2017

DOI: 10.1039/c7qo00232g
rsc.li/frontiers-organic

Introduction

The 6H-benzo[c]chromene ring has recently emerged as one of the most privileged scaffolds and an important substructure within the modern drug discovery field.^{1,2} This heteroaromatic system is present in many natural products, such as pulchrol **1** and pulchral **2**, both isolated from the plant *Bourreria pulchra* and possessing interesting antiprotozoal activities towards *Leishmania mexicana* and *Trypanosoma cruzi*, especially **1**.³ While the Δ^9 -tetrahydrocannabinol **3**, cannabinol **4** (*Cannabis sativa*) and the didehydroconicol **5** (*Aplidium aff. Densum*) displayed potent antibacterial and antimitotic activities.^{4,5} Moreover, synthetic benzo[c]chromenes like **6** and **7** have resulted to be selective progesterone receptor modulators (SPRMs) and potent agonists of the CB1, one of the G-protein-coupled receptors (GPCRs), respectively (Fig. 1).^{6,7}

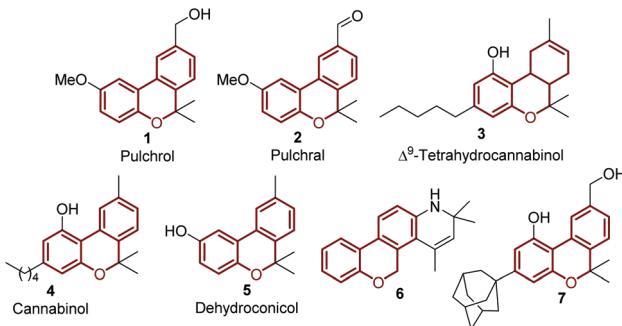


Fig. 1 Natural and synthetic products with the benzochromene moiety.

The interest and biological relevance for these structures have encouraged the development and study of novel strategies for the synthesis of benzo[c]chromenes. These methodologies can be divided into three different approaches. First, and with the pre-set biphenyl core, the intramolecular S_N2 reaction between phenols and fluorinated scaffolds promoted the formation of the middle ring (Path A).⁸ Second, the intramolecular Diels–Alder reaction, *via* a cascade pathway, between furan and unactivated alkenes under catalyst-free conditions resulted in the formation of the aromatic ring (Path B).⁹ Finally, the C–C coupling, which can be subcategorized into: the intramolecular biaryl formation ($\text{C}_{\text{Ar}}-\text{C}_{\text{Ar}}$), known as the Suzuki–Miyaura, Negishi, Heck, Kumada–Corriu and

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data and ¹H NMR, ¹³C NMR and DEPT-135 charts. See DOI: [10.1039/c7qo00232g](https://doi.org/10.1039/c7qo00232g)



Hiyama cross-coupling, involves the use of organometallics (B, Sn, Si, Zn, Mg, *etc.*) and halides or halide species in the presence of a transition metal (Path C);¹⁰ and these strategies for the aryl-aryl (C_{Ar}-C_{Ar}) bond formation characterized by the direct arylation mediated by metal-catalysed C-H activation, without the need of activating organometallic groups (Path D) (Fig. 2).¹¹

As was expected, the interest for developing more efficient and environmentally friendly protocols, based on the construction of new C-C bonds by coupling reactions, led to the known transition-metal-free strategies, where the use of expensive, sensitive and toxic transition-metal-catalyst and ligands was avoided, and a better insight into the possible reaction mechanisms is provided.¹²

The metal-free approach for the synthesis of benzochromenes from aryl benzyl ethers has been promoted by radical initiators such as azobisisobutyronitrile (AIBN) to give the desired product in low yields.¹³ This study proposed the formation of aryl radicals, which can be added to benzene derivatives through what is known as the homolytic aromatic substitution (HAS) reaction.¹⁴ However, the formation and handling of these aryl radicals species were extremely difficult until the use of mild and accessible potassium *tert*-butoxide (*t*-BuOK) that promoted the single electron transfer (SET) reaction with aryl halides to give aryl radicals.¹⁵ Nevertheless, the major drawbacks of the *t*-BuOK-mediated intramolecular arylation are: (i) the low yields obtained when unactivated aryl benzyl ethers are employed, (ii) the nature and reactivity of the aryl halide moiety (where iodines and bromides are more reactive than chlorides), and (iii) the low regioselectivity due to the kinetic *versus* thermodynamic radical intermediates formed during the reaction.¹⁶

According to the statements described above and taking into account the current debate and discussion around the best synthetic choice between metal-free and transition-metal approaches for the synthesis of 6*H*-benzo[*c*]chromenes, which is supported and defended by the respective authors, our research was focused on: (i) establishing the optimal reaction conditions for the transition metal-free preparation of benzo[*c*]chromenes according to the variables: substrate, ligand,

solvent and yield, (ii) establishing the optimal reaction conditions for the palladium-catalysed synthesis of benzo[*c*]chromenes according to the variables: substrate, catalyst, ligand, base, additive, solvent, temperature and yield, (iii) with the established conditions in hand, preparing a 17-membered library of 6*H*-benzo[*c*]chromenes from unactivated aryl benzyl ethers, (iv) obtain the essential oils of *Eugenia caryophyllus* and *Plectranthus amboinicus* and use them as raw materials for the synthesis of 6*H*-benzo[*c*]chromenes under the established conditions, (v) evaluate the ruggedness of the optimized reaction conditions with nitrogen derivatives, like *N*-benzylanilines, and (vi) demonstrate the synthetic utility of the prepared 6*H*-benzo[*c*]chromenes as starting materials for the metal-free and efficient synthesis of the corresponding benzo[*c*]chromen-6-ones.

Results and discussion

Metal-free approach

With the knowledge that *t*-BuOK has recently promoted the synthesis of some 6*H*-benzo[*c*]chromenes from iodine and bromide aryl benzyl ethers,¹⁷ and inspired the synthesis of phenanthridines from *N*-(2-chloroaryl)benzoimines mediated by *t*-BuOK and ethylene glycol as a ligand,¹⁸ suggests that chlorine derivatives could favour the formation of aryl radical species during the reaction critical step,¹⁹ despite the low dissociation energy of the C-Cl bond.²⁰ Thus, we envisioned that chloride aryl benzyl ether **8a** could be a good substrate for the model HAS reaction. However, after performing the reaction with **8a**, *t*-BuOK (3 equiv.), ethylene glycol (10–40 mol%) and toluene as a solvent at 120 °C, the reaction did not give the desired product (Table 1, entries 1 and 2).

For the next experiments, the influence of another bidentate ligand such as phenanthroline (Phen) was examined. However, in the presence of several solvents (toluene, PEG-400 and [Bmim]PF₆), the reaction did not afford the corresponding 6*H*-benzo[*c*]chromene ring (Table 1, entries 3–6). Then, the efforts were focussed on the bromo aryl benzyl ether derivative **8b**, but when the reaction was performed using ethylene glycol (10–40 mol%) as a ligand and in toluene as a solvent, the formation of the desired product was not observed (Table 1, entries 7 and 8). Counting that the *t*-BuOK/Phen complex has promoted HAS transformations, this system was used under similar reaction conditions obtaining the expected product **9** in 46% yield, in contrast with the previous reports (73%)²¹ (Table 1, entry 9). Being conscious of the convenience of establishing, not only efficient, but more environmental transition-metal-free approaches in organic chemistry, the viability of the direct HAS reaction for the synthesis of 6*H*-benzo[*c*]chromene **9** was evaluated in different solvents. Despite the argument that affirmed the positive effect of an alcoholic medium during certain SET processes,²² the benign polyethylene glycol 400 (PEG-400) did not furnish benzo[*c*]chromene **9** (Table 1, entry 10), while propylene carbonate (PC) only gave the desired product in 13% yield (Table 1, entry 11). To our delight, the

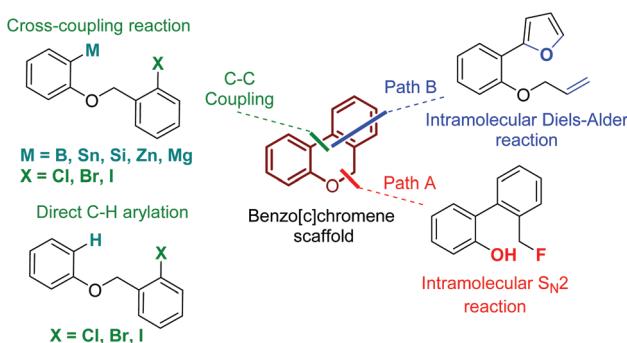


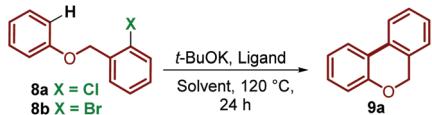
Fig. 2 Current strategies for the synthesis of a benzochromene scaffold.



Table 1 Synthesis of 6H-benzo[c]chromenes through the transition-metal-free approach^a

Entry	Substrate (X)	Ligand (mol%)	Solvent	Yield ^b (%)
1	Cl	Ethylene glycol (10)	Toluene	N.R. ^c
2	Cl	Ethylene glycol (40)	Toluene	N.R. ^c
3	Cl	Phen (40)	Toluene	N.R. ^c
4	Cl	Phen (40)	PEG-400	N.R. ^c
5	Cl	Phen (40)	[Bmim]PF ₆	N.R. ^c
6	Cl	Phen (40)	PEG-400/[Bmim]PF ₆ ^d	N.R. ^c
7	Br	Ethylene glycol (10)	Toluene	N.R. ^c
8	Br	Ethylene glycol (40)	Toluene	N.R. ^c
9	Br	Phen (40)	Toluene	46
10	Br	Phen (40)	PEG-400	N.R. ^c
11	Br	Phen (40)	PC	13
12	Br	Phen (40)	[Bmim]PF ₆	49
13	Br	Phen (40)	PEG-400/[Bmim]PF ₆ ^d	14
14	Br	NH ₂ CH ₂ CH ₂ NH ₂ (40)	[Bmim]PF ₆	9 ^e
15	Br	NH ₂ CH ₂ CH ₂ OH (40)	[Bmim]PF ₆	16 ^e
16	Br	TMEDA (40)	[Bmim]PF ₆	N.R. ^c
17	Br	L-Proline (40)	[Bmim]PF ₆	8 ^e

^a Reactions were performed on a 1 mmol scale using substrate **8** (1 mmol), *t*-BuOK (3 equiv.), ligand, solvent (0.2 M) in a sealed Schlenk tube under an argon atmosphere at 120 °C for 24 h. ^b Isolated yield after chromatographic purification (SiO₂). ^c N.R.: No reaction. ^d A mixture of PEG-400 and [Bmim]PF₆ (1:1) was used as a solvent. ^e Yields determined by ¹H-NMR spectroscopy using **8b** (0.2 mmol) in 0.4 mL of solvent and 1,3,5-trimethoxybenzene as an internal standard. PEG-400: Polyethylene glycol 400. [Bmim]PF₆: 1-Butyl-3-methylimidazolium hexafluorophosphate. PC: Propylene carbonate.



use of an ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim]PF₆), a kind of reaction medium less studied in this type of reaction, gave the highest yield (49%) among the tested conditions (Table 1, entry 12).

The negative effect of an alcoholic medium for this SET process was confirmed when a mixture of PEG-400 and [Bmim]PF₆ in a 1:1 ratio was used as a solvent, lowering dramatically the yield of **9** (Table 1, entry 13). Finally, being aware that the coordination of the ligand with the counteraction of *t*-BuOK plays an important role during the course of cross-coupling reactions,²³ other bidentate ligands were tested in order to promote the formation of five-membered ring species as catalytic systems. However, ethylenediamine and ethanolamine did not give good results, and *N,N,N',N'*-tetramethyl-ethylenediamine (TMEDA) also did not furnish the desired product (Table 1, entries 14–16). We evidenced that the nature of the groups attached to the nitrogen atom determines the reactivity of nitrogenated ligands, where tertiary aliphatic amines (–NRR') resulted to be ineffective, giving floppy complexes with the potassium ion, whereas secondary amines (–NHR) have demonstrated to be excellent ligands as long as there is no bulky substituent bonded to the nitrogen.²⁴ Although ethylene glycol did not afford the desired 6H-benzo

[c]chromene **9**, we evidenced that when a ligand with both primary amine and alcohol functionalities was used (ethanolamine), the yields slightly increase to 16%, putting in perspective the further development of ligands with secondary amine and primary alcohol functionalities. Nevertheless, when L-proline was employed the yields dramatically decrease, perhaps due to the presence of the carbonyl function that affected negatively the stability of the five-membered complex with the potassium ion (Table 1, entry 17).²⁵

Palladium-catalysed direct arylation through C–H activation

In spite of the efforts to perform and improve the reaction conditions for the HAS reaction based on the metal-free approach, the synthesis of 6H-benzo[c]chromene **9** did not give efficient results during our study. The moderate yields in which the desired product was obtained encourage our investigation to evaluate its synthesis *via* direct arylation processes from the respective aryl benzyl ethers through the C–H functionalization catalysed by Pd complexes.

The transition-metal approach for the formation of C–C bonds has become an attractive protocol for many areas of chemistry beyond the synthesis of natural and biologically active small molecules (SMs).²⁶ Undoubtedly, Fagnou's group has successfully developed the synthesis of diverse N- and O-heterocycles, including dibenzofurans, benzochromenes, dibenzooxepines, phenanthridines, phenanthridinones and carbazoles, *via* direct arylation reactions.^{27–29} However, this C–H functionalization required the study of several Pd catalysts, ligands, solvents, bases and additives in order to accomplish the synthesis of these derivatives; since the narrow substrate scope for which a developed protocol is successful and efficient, it fails or does not allow the C–C bond formation in substrates that differ from the halogen atom involved in the chemical transformation or with different electronic and steric nature. Additionally, some of these reaction conditions involve the use of expensive catalysts or ligands difficult to handle in order to enhance the reactivity and the yields of the desired product.

Aware of the unreactive or poorly reactive substrates that would be obtained from essential oils (EOs), we opted to screen diverse reaction conditions to prepare the corresponding 6H-benzo[c]chromene **9** having as a goal the use of more versatile and accessible substrates, catalysts, ligands, base additives and solvents to increase the substrate scope.

Thus, the Pd-catalysed direct arylation of chloride aryl benzyl ether **8a** was explored under various reaction conditions. First, the reaction between **8a** in the presence of the catalyst Pd(OAc)₂ (5 mol%)/PPh₃ (5 mol%) and base Cs₂CO₃ (2 equiv.) in DMF at 80 °C for 48 h, avoiding the use of any additive,³⁰ did not furnish the desired product (Table 2, entry 1). In order to examine the influence of pivalic acid (PivOH) as an additive and envisioned that a moderate electron-poor ligand could promote the formation of the respective 6H-benzo[c]chromene **9**, a second experiment was carried out between **8a**, Pd(OAc)₂ (5 mol%)/P(*p*-FC₆H₄)₃ (5 mol%), K₂CO₃ (2 equiv.), PivOH (30 mol%) in DMA at 120 °C for 24 h, but these reaction



Table 2 Screening of the optimal reaction conditions for the synthesis of benzo[c]chromene **9** from unactivated chloro- and bromo-aryl benzyl ethers **8**^a

Entry	Substrate (X)	Pd catalyst (mol %)	Ligand (mol %)	Base	Additive	Solvent	Temperature (°C)	Time (h)	Yield ^b (%)
1	Cl	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	—	DMF	80	48	N.R. ^c
2	Cl	Pd(OAc) ₂	P(<i>p</i> -FC ₆ H ₄) ₃	K ₂ CO ₃	PivOH	DMA	120	24	N.R. ^c
3	Cl	PdCl ₂	P(<i>p</i> -FC ₆ H ₄) ₃	K ₂ CO ₃	PivOH	DMA	120	24	N.R. ^c
4	Cl	PdCl ₂ (MeCN) ₂	P(<i>p</i> -FC ₆ H ₄) ₃	K ₂ CO ₃	PivOH	DMA	120	24	N.R. ^c
5	Br	Pd/C-Cu(OAc) ₂	—	K ₂ CO ₃	PivOH	DMA	120	24	N.R. ^c
6	Br	Pd(OAc) ₂	PPh ₃	Ag ₂ CO ₃	—	DMF	80	48	27
7	Br	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	—	DMF	80	48	11
8	Br	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	—	DMF	80	48	24
9	Br	Pd(OAc) ₂	P(<i>p</i> -FC ₆ H ₄) ₃	K ₂ CO ₃	PivOH	DMA	80	48	22
10	Br	Pd(OAc) ₂	P(<i>p</i> -FC ₆ H ₄) ₃	K ₂ CO ₃	PivOH	DMA	120	24	64
11	Br	PdCl ₂	P(<i>p</i> -FC ₆ H ₄) ₃	K ₂ CO ₃	PivOH	DMA	120	24	90
12	Br	PdCl ₂ (MeCN) ₂	P(<i>p</i> -FC ₆ H ₄) ₃	K ₂ CO ₃	PivOH	DMA	120	3	96
13	Br	PdCl ₂ (MeCN) ₂	PPh ₃	K ₂ CO ₃	PivOH	DMA	120	24	90
14	Br	PdCl ₂ (MeCN) ₂	PCy ₃	K ₂ CO ₃	PivOH	DMA	120	24	93
15	Br	PdCl ₂ (MeCN) ₂	dppe	K ₂ CO ₃	PivOH	DMA	120	24	87
16	Br	PdCl ₂ (MeCN) ₂	P(<i>p</i> -FC ₆ H ₄) ₃	K ₂ CO ₃	PivOH	DMA	120	24	96
17	Br	PdCl ₂ (MeCN) ₂	P(<i>p</i> -FC ₆ H ₄) ₃	K ₂ CO ₃	-	DMA	120	3	33

^a Reactions were performed on a 1 mmol scale using **8a–b** (1 mmol), Pd catalyst (5 mol%), ligand (5 mol%), base (3 equiv.), additive (30 mol%) and solvent (0.2 M) in a sealed Schlenk tube under an argon atmosphere to the indicated temperature and time until complete conversion of **8a–b**.

^b Isolated yield after chromatographic purification (SiO₂). ^c N.R.: No reaction.

conditions lead to the complete recovery of the starting material (Table 2, entry 2). A change of Pd-catalyst for others from Pd(OAc)₂ under the same parameters did not show any effect in the conversion of **8a** into **9** (Table 2, entries 3 and 4). From these results, we can infer that the conversion of chloride derivatives **8a** into the 6*H*-benzo[c]chromene **9** core cannot be achieved under the studied reaction conditions, since after the catalyst activation (Pd^(II) → Pd⁽⁰⁾), one of the crucial steps during the reaction mechanism is the oxidative addition of the Pd-complex to the C-Cl bond, a process that requires a higher dissociation energy of the C-X bond or a catalytic system that lowered the potential energy of the transition state (E^\ddagger).³¹ Based on these facts, Fagnou's group has reported some elegant studies where the direct arylation of a broad range of aryl chlorides has been realised by using N-heterocyclic carbene palladium catalysts or complex phosphine ligands.^{27,29}

According to the recent literature, the use of Pd/C, as a scalable and insensitive to air and moisture catalyst in some C–H functionalizations, can be enhanced beyond the common cross-coupling and hydrogenation reactions.³² Our efforts were focused on the ligand free dual catalytic system of heterogeneous Pd/C and CuSO₄ to promote the desired intramolecular arylation process of the bromo aryl benzyl ether **8b**, but unfortunately this experiments did not result in a detectable amount of the desired 6*H*-benzo[c]chromene **9** (Table 2, entry 5).

Being conscious of the fact that the bromo aryl benzyl ether **8b** will be a more suitable model substrate for our study, we evaluated the effect of different bases in the ligand and additive

free arylation reaction using Pd(OAc)₂ (5 mol%)/PPh₃ (5 mol%) in DMF at 80 °C, to afford **9a** in only 27% yield after 48 h when Ag₂CO₃ was used as a base (Table 2, entries 6–8). There is a current debate of the use and the role of an additive during this transformation, since some benzo[c]chromenes have been obtained with and without its use and as a challenge by reducing the number of species involved.^{28,29,33} Nevertheless, we observed that when PivOH was used as an additive, any representative effect was observed under the same reaction conditions (Table 2, entry 9).

Temperature is another decisive parameter, as we noticed, at 80 °C poorer conversion was accomplished, although it is also known that at higher temperatures (130 °C) the decomposition of substrates and products has a negative impact on the reaction;³⁴ a better yield (64%) was obtained when the reaction was performed at 120 °C for 24 h (Table 2, entry 10).

In an attempt to increase the yield of reaction, other accessible Pd-sources were further tested. Among the catalysts examined, PdCl₂(MeCN)₂ was the most effective, reaching a 100% conversion and giving **9a** in 96% isolated yield after 3 h, while PdCl₂ gave similar results but in prolonged reaction times (Table 2, entries 11 and 12).

Finally, another species that plays a critical role during the intramolecular direct arylation process is the phosphine ligand, whose electronic nature has an acceleration effect in the reaction. It has been established that highly electron-poor phosphines have a strong ability to coordinate to the Pd-center, increasing the reaction rate.³⁵ After having tested two phosphine ligands, we found that PPh₃, a similar ligand to



$\text{PdCl}_2(\text{MeCN})_2$ in terms of their electronic nature, and a more donating ligand like PCy_3 , gave good results affording **9a** in 90% and 93% yield, respectively, suggesting an almost null effect during the course of the reaction regarding the electronic nature of the ligand. However, when a bidentate phosphine like 1,2-bis(diphenylphosphino)ethane (dppe) was employed the yield decreased moderately to 88%, indicating a possible steric effect during the coordination with the Pd-atom that perhaps affects the approach of the two aromatic rings (Table 2, entries 13–15). In order to validate our established reaction conditions, two additional experiments revealed that at prolonged reaction times (24 h, 120 °C), the integrity of the formed product remains intact, while in the absence of PivOH the yield drastically decreased to 33% (Table 2, entries 16 and 17, respectively).

Having the optimized reaction conditions in hand, the versatility, scope and limitations of our protocol were broadened to other substrates with different functional groups (Table 3).

In general, the direct arylation reaction of aryl benzyl ethers **8a–p**, possessing different functional groups: aliphatic, hydroxy, methoxy and formyl proceeded smoothly and afforded the corresponding 6H-benzo[c]chromenes **9a–p** with great efficiency.

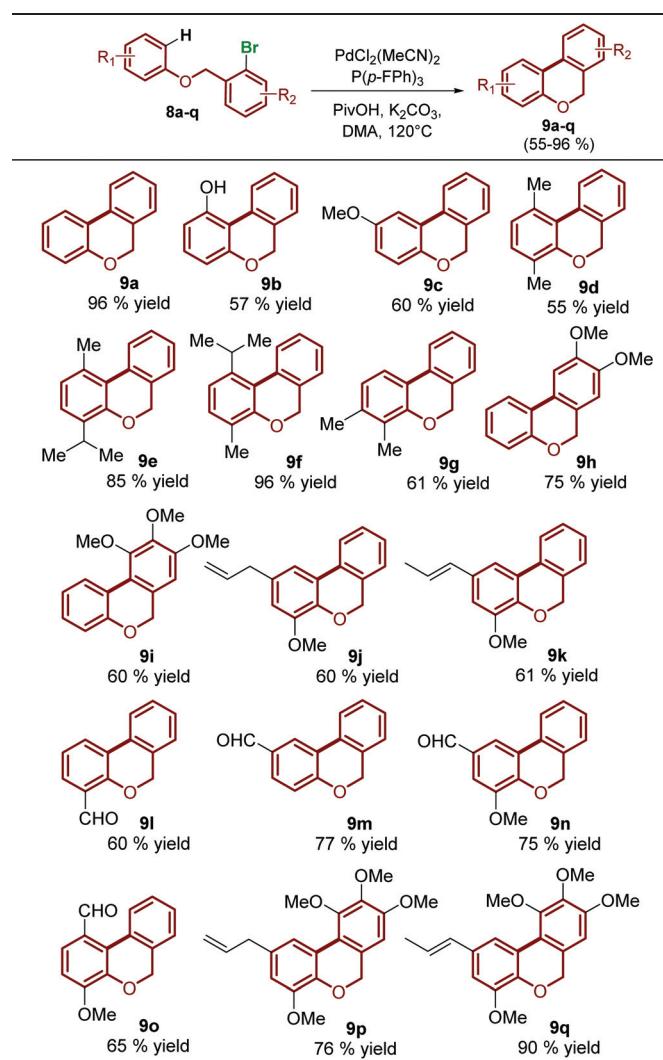
The simplest bromo aryl benzyl ether **8b** gave the higher yield for the respective 6H-benzo[c]chromenes **9a**, a comparable result with previous reports where more elaborated and complex ligands or higher temperatures were required.^{36,37} From the biological point of view, resorcinol has attracted attention as an interesting substrate for the arylation reaction, since a hydroxyl group could be easily inserted without any additional protection–deprotection steps in the benzo[c]chromene core. However, efforts for the construction of 1-hydroxy-6H-benzo[c]chromene **9b** under transition-metal-free and basic conditions with palladium catalysts present as the main drawback the poor control of the regioselectivity of the reaction.³⁸ We highlighted that although compound **9b** was generated in moderate yield (57%), under our standard reaction conditions, it was obtained as a single regioisomer.

Selected examples including alkyl substituents (methoxy, methyl and isopropyl) demonstrated to be reactive, furnishing the respective products next to the more encumbered position, **9c** (60%) **9d** (55%), **9e** (85%), **9f** (96%) and **9g** (61%) (Table 3).

In order to expand the structural diversity of the benzo[c]chromenes, the inclusion of various functional groups into the benzene ring fused with the chromene core has been a real challenge. However, a simple derivatization (bromination/reduction/bromination) of easily available benzaldehyde derivatives provided the corresponding aryl benzyl ethers that afforded 6H-benzo[c]chromenes **9h** and **9i** in good yields with two or three methoxy groups that did not affect the cyclization process due to a possible steric hindrance during the cyclization process (see the ESI†).

The scope of this C–H functionalization has been extended to study the tandem Heck/direct arylation reaction, but the process requires the incorporation of an additional halogen atom in the structure of **8** and the addition of styrene to the

Table 3 Synthesized 6H-benzo[c]chromenes **9a–n** under the optimized reaction conditions^{a,b}



^a Reactions were performed on a 1 mmol scale using **8a–o** (1 mmol), $\text{PdCl}_2(\text{MeCN})_2$ (5 mol%), $\text{P}(p\text{-FC}_6\text{H}_4)_3$ (5 mol%), K_2CO_3 (3 equiv.), PivOH (30 mol%) and DMA (0.2 M) in a sealed Schlenk tube under an argon atmosphere at 120 °C for 3 h. ^b Isolated yield after chromatographic purification (SiO_2).

reaction mixture.³⁹ Having in mind and envision further chemical transformations, a double bond can be easily inserted into the structure of the desired product in good yields by using eugenol and isoeugenol as starting materials, providing the corresponding benzo[c]chromenes **9j** and **9k**, while a formyl moiety, at different positions and with other functionalities, resulted to be a suitable group for these reactions without being affected by the reaction conditions, giving the desired products **9l–o** in good to excellent yields and encouraging the synthesis of more complex derivatives (Table 3).

Finally, we demonstrated the broad scope of the developed reaction conditions with the synthesis of multisubstituted benzo[c]chromenes **9p** and **9q** in good to excellent yields, 76% and 90% respectively, from bromo aryl benzyl ethers contain-



ing a Pd-sensitive double bond in one aromatic ring and some bulky substituents in the other ring without any negative effect on the reaction course (Table 3).

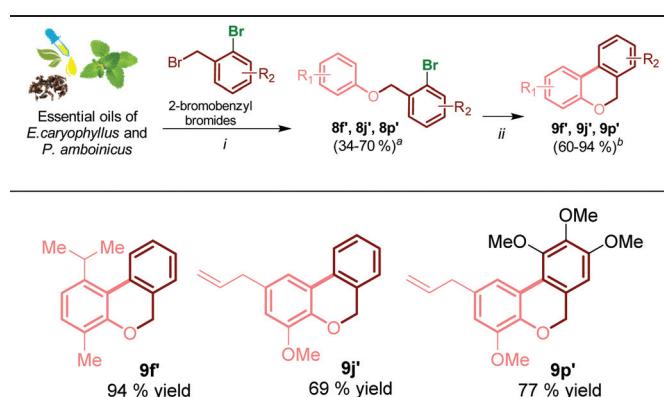
Prioritizing on the use of raw materials as precursors in organic synthesis and green methodologies, we have already published novel results on this topic in which the essential oil of anise, bud clove and palmarosa were used as starting materials for the synthesis of N- and O-heterocyclic compounds.⁴⁰

In this research work, we had the opportunity to work with the EOs of dried buds of *E. caryophyllus* and dried leaves of *P. amboinicus*. These concentrate mixtures of natural compounds were obtained through microwave-assisted hydrodistillation (MWHD) in 12.8% and 1% yields from *E. caryophyllus* and *P. amboinicus*, respectively.

The GC-MS analysis⁴¹ of the obtained EOs revealed that in *E. caryophyllus*, eugenol (71.8%) was the major component with eugenol acetate (18.4%) and *trans*- β -caryophyllene (7.5%), while in *P. amboinicus* carvacrol (67.1%) was identified as the main component with *trans*- β -caryophyllene (8.8%) and γ -terpinene (7.4%) (see the ESI† for details).

With the enriched EOs in phenolic compounds (eugenol and carvacrol), we turn our attention towards performing the *O*-alkylation reaction with two different 2-bromobenzyl bromides to furnish the bromo aryl benzyl ethers **8f** (34%), **8j'** (70%) and **8p'** (69%), which were used to accomplish the intramolecular direct arylation transformation in order to examine the scope of our developed protocol when these raw materials were employed (Table 4).

Table 4 Synthesis of 6H-benzo[c]chromenes using the EO of *Eugenia caryophyllus* (eugenol) and *Plectranthus amboinicus* (carvacrol) as raw materials



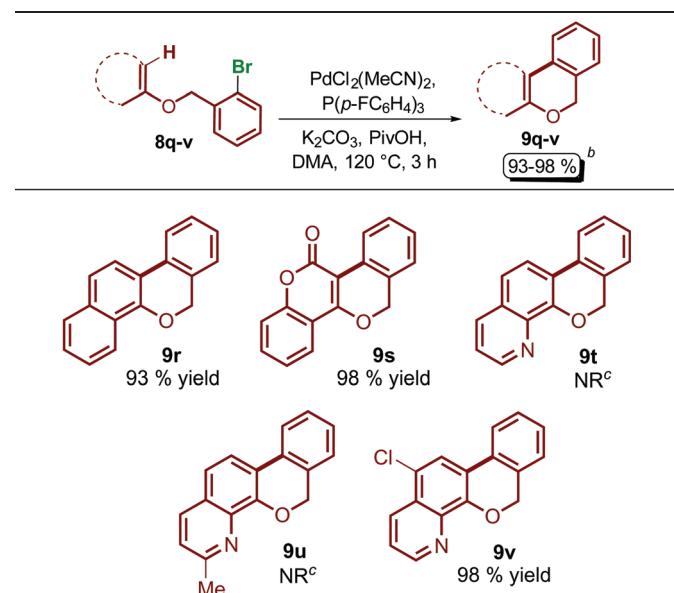
(i) Reactions were performed on a 1.5 mmol scale using 327 mg of EO *P. amboinicus* or 343 mg of EO *E. caryophyllus*, the respective benzyl bromide (3 mmol), K_2CO_3 (3 mmol), and NaI (0.75 mmol) in acetone (0.5 M) at 60 °C. ^aYields were calculated based on the 71.8% and 67.1% of the eugenol and carvacrol, respectively, present in the EOs and after chromatographic purification (SiO_2). (ii) Reactions were performed on a 1 mmol scale using **8f**, **8j'** and **8p'** (1 mmol), $PdCl_2(MeCN)_2$ (5 mol%), $P(p-FC_6H_4)_3$ (5 mol%), K_2CO_3 (3 equiv.), PivOH (30 mol%) and DMA (0.2 M) in a sealed Schlenk tube under an argon atmosphere at 120 °C for 3 h. ^bIsolated yield after chromatographic purification (SiO_2).

Gratifyingly, these reactions proceeded smoothly and gave in excellent selectivity and in good to excellent yields the benzo[c]chromenes **9f**, **9j'** and **9p'**. Although the yields of the direct C–H arylation, starting from the derivatives obtained from commercial or natural sources, were comparable, the global yield of the final product, thought to be the two synthetic-steps, decrease in comparison with the approach that employs commercial reagents. Nevertheless, the still attractive use of substrates obtained from natural sources, which combined with a good synthetic protocol, may contribute to the development of modern and sustainable organic chemistry, focusing the current efforts in the synthesis of novel compounds with a more complex molecular architecture.

Encouraged by the efficiency of the developed protocol during the synthesis of 6H-benzo[c]chromenes **9a–p**, and in order to continue demonstrating the scope and importance of these reaction conditions, that may apply to other heterocyclic phenolic molecules, the direct arylation process, under the optimized reaction conditions, has been achieved for molecules **8q–t** derived from naphthol, 4-hydroxy-coumarin and 8-hydroxyquinolines (see the ESI†) (Table 5).

To our delight, selected ethers **8r** and **8s** underwent the pyran ring formation in excellent yields, furnishing the corresponding 6H-dibenzo[c,h]chromene **9r** and the isochromeno[4,3-c]coumarin **9s**. But surprisingly, the hydroxyquinoline derivatives **9t** and **9s** did not afford the desired product, maybe because of the poor activation of the benzene ring at C-7, while ether **8v** gave the respective 6H-isochromeno[4,3-h]-

Table 5 Synthesis of chromenes fused with other heterocyclic compounds **9q–s**^a



^a Reactions were performed on a 1 mmol scale using **8q–v** (1 mmol), $PdCl_2(MeCN)_2$ (5 mol%), $P(p-FC_6H_4)_3$ (5 mol%), K_2CO_3 (3 equiv.), PivOH (30 mol%) and DMA (0.2 M) in a sealed Schlenk tube under an argon atmosphere at 120 °C for 3 h. ^b Isolated yield after chromatographic purification (SiO_2). ^c NR: No reaction.



quinoline derivative **9v** in excellent yield. It is possible that the inductive effect of the chlorine atom located at position C-5 promotes the smooth intramolecular cyclization process at C-7, moreover, the higher yield led to conclude that the unreactive chloro substituent, under the optimized reaction conditions, does not interact with the Pd-catalyst and remains intact during the transformation (Table 5).

In line with Echavarren's, Maseras's and Fagnou's studies, where several reaction mechanisms for the intramolecular Pd-catalysed direct arylation have been proposed,⁴² a review of the most accepted pathway, with the strongest experimental support, is illustrated in Scheme 1.

This catalytic cycle involves the following sequence: first, the efficient oxidative insertion into the C-Br bond of **8a** by the Pd⁽⁰⁾ complex evidenced the role of the Pd catalyst and the selected ligand in the fast Pd^(II) reduction to Pd⁽⁰⁾ giving **10**. Second, an anion exchange that resulted in the liberation of bromide as KBr is promoted by the *in situ* formed potassium pivalate **12**, a highly soluble and bulky conjugate base, that resulted in **13**. Then, the main role and the importance of the electronic nature of the ligand are exhibited during the critical step of the reaction, the concerted metalation-deprotonation (CMD) process that activates the sp² position and results in intermediate **14**. During this transition state, the metalation is accelerated by using electron-poor ligands, while the deprotonation, the C-H cleavage, is promoted by the pivalate anion itself, which acts as an external base and results in the formation of PivOH. Finally, the catalyst is regenerated through a reductive elimination of **15** and the desired product **9a** is obtained (Scheme 1).

With the intention to demonstrate the robustness of the developed reaction conditions, the direct C-H arylation was extended to aniline derivatives. Two *N*-(2-bromobenzyl)anilines

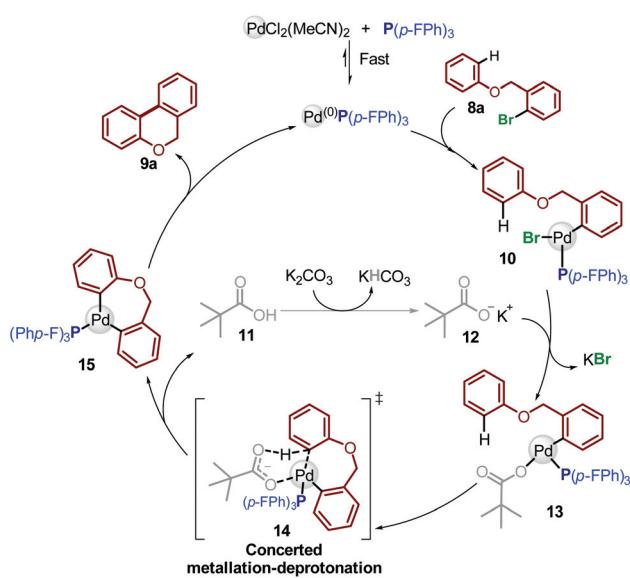
16a–b were prepared and subjected to the respective cyclization process. We found that the *N*-unprotected derivative **16a** did not give the desired product, but an interesting and surprising result was observed for the *N*-methyl derivative **16b**, when the unexpected phenanthridinone **17b'** was identified as the major product of this reaction and was isolated in 45% (Scheme 2).

Various synthetic protocols have been published for the preparation of phenanthridinones, including the intramolecular direct arylation *via* C-H activation from diverse aryl-substituted amide derivatives, which are commonly prepared in two-synthetic steps.⁴³ The result obtained from the *N*-methyl derivative **16b** represents a useful and atom-economical approach for the synthesis of phenanthridinones *via* the novel tandem C-H arylation/benzyllic oxidation reaction.

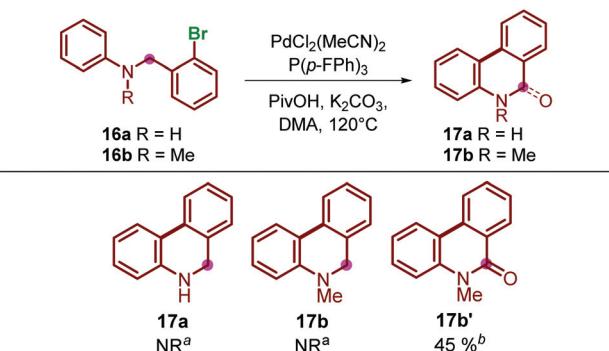
Inspired by compound **9r** and the results obtained above, we envisioned the usefulness of the synthesized benzo[c]chromenes **9** as interesting building blocks in the synthesis of the corresponding benzo[c]chromenones **18**. Therefore, the benzyllic oxidation was studied using *tert*-butyl hydroperoxide (TBHP) as an oxidant, and iodine (I₂) as a co-oxidant in the presence of pyridine (Py) at 80 °C for 24 hours (Scheme 3).

These mild reaction conditions afforded the respective derivatives **18a–b** in good to excellent yields, including the corresponding 6*H*-benzo[c]chromen-6-one **18b**, which can be obtained from renewable starting materials. A preliminary study of the reaction mechanism allowed the isolation of the respective intermediate **A** as a stable solid after two hours in 60% yield. The role of TBHP and the possible determining step of the reaction would be established with further studies based on our results and the structural elucidation of the **A** species achieved by ¹H NMR spectroscopy (see the ESI†).

Finally, the discussion around the possibility of increasing the reactivity and the structural diversity of the final product by using 2-bromophenols as starting materials was examined and resolved. The respective *O*-benzyl derivative **20** was prepared through the selective *ortho*-bromination of thymol **19** in 65% yield,⁴⁴ and after the respective benzylation reaction,

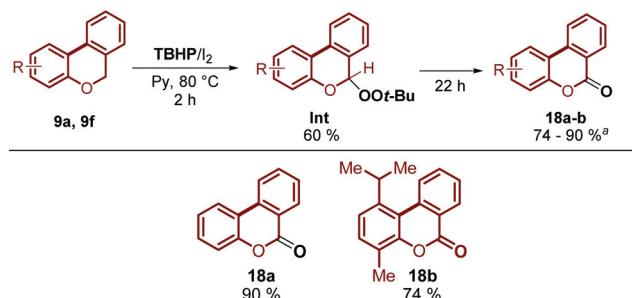


Scheme 1 Tentative mechanism for the direct arylation of bromo aryl benzyl ethers.

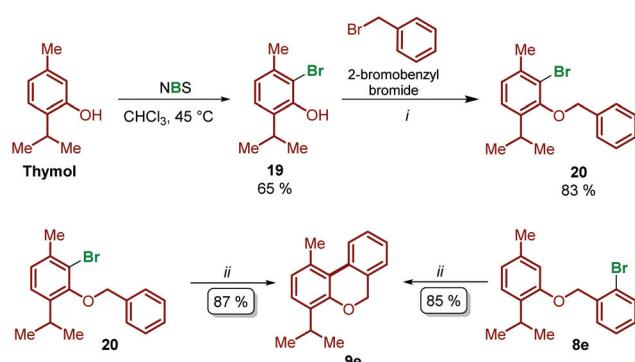


Scheme 2 Unexpected C-H arylation/benzyllic oxidation tandem process for the synthesis of phenanthridinone **17b'**. ^a Expected product, not identified. ^b Unexpected product.





Scheme 3 Synthesis of benzo[c]chromenones **18a–b** and isolation of the reaction intermediate. ^a Reactions were performed on a 1 mmol scale using substrate (1 mmol), I₂ (10 mol%), TBHP (4 equiv.) and pyridine (10 mol%) at 80 °C. ^b Isolated yield after SiO₂ column chromatography.



Scheme 4 Preparation of O-benzyl 2-bromophenol derivative **20** and its reactivity under the optimized reaction conditions in comparison with **9e**. (i) Reactions were performed on a 1 mmol scale using 1.5 mmol of **19**, benzyl bromide (3 mmol), K₂CO₃ (3 mmol), and NaI (0.75 mmol) in acetone (0.5 M) at 60 °C. (ii) Reactions were performed on a 1 mmol scale using **8f**, **8j**, and **8p'** (1 mmol), PdCl₂(MeCN)₂ (5 mol%), P(p-FC₆H₄)₃ (5 mol%), K₂CO₃ (3 equiv.), PivOH (30 mol%) and DMA (0.2 M) in a sealed Schlenk tube under an argon atmosphere at 120 °C for 3 h.

20 was subjected to the optimised reaction conditions to give the desired product in 87% yield (Scheme 4).

Although the yield of **9e**, starting from **20** (87%), was slightly higher than the one obtained from **8e** (85%), the broad scope of the developed reaction conditions was demonstrated since the electronic nature of the aromatic rings and the possible steric effects were not determinant during the transformation. Thereby, the protocol of choice will depend on the desired substitution pattern in the final product and the availability of the starting materials, since the bromination of phenols is not a very effective methodology and in some cases, the *meta*- and *para*- regioisomers are also obtained.

Conclusions

A robust and versatile synthetic protocol was developed to obtain a diverse library of 6*H*-benzo[c]chromenes by comparing the effectiveness of the transition metal-free and Pd-

catalysed approaches. The direct arylation reaction was chosen as the most effective methodology to prepare a 17-membered library of benzo[c]chromenes overcoming the major drawbacks of the known protocols that include the use of sensitive, expensive and complex catalysts, ligands and additives. Additionally, we demonstrated that these small molecules could be obtained from essential oils as raw materials or from other polycyclic derivatives including coumarins and quinolines.

In pursuit of finding more applications of our protocol, the replacement of *O*-benzyl ethers for *N*-benzyl anilines resulted in the unexpected formation of phenanthridinones, possibly through a tandem C–H arylation/benzyllic oxidation reaction, and after having performed the synthesis and preliminary studies for the preparation of benzochromenones, our efforts will be focused on gaining a comprehensive understanding of overall mechanisms, establishing the parameters involved during the *in situ* benzyllic oxidation process and the role of reactants and Pd-catalysts. Finally, the scope of these innovative processes will provide tools for the synthesis of bioactive natural and synthetic products.

Acknowledgements

VVK and FIZ dedicate this article to the memory of beloved Professor Anatoly T. Soldatenkov, Peoples' Friendship University of Russia, 1938–2016. We thank to Bio-Red-COCENIVAM-COLCIENCIAS under the project no. RC-0572-2012 for financial support. MCOV and CEPG thank the scholarship given by the doctoral program Colciencias-Conv. 617 and 727, respectively.

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