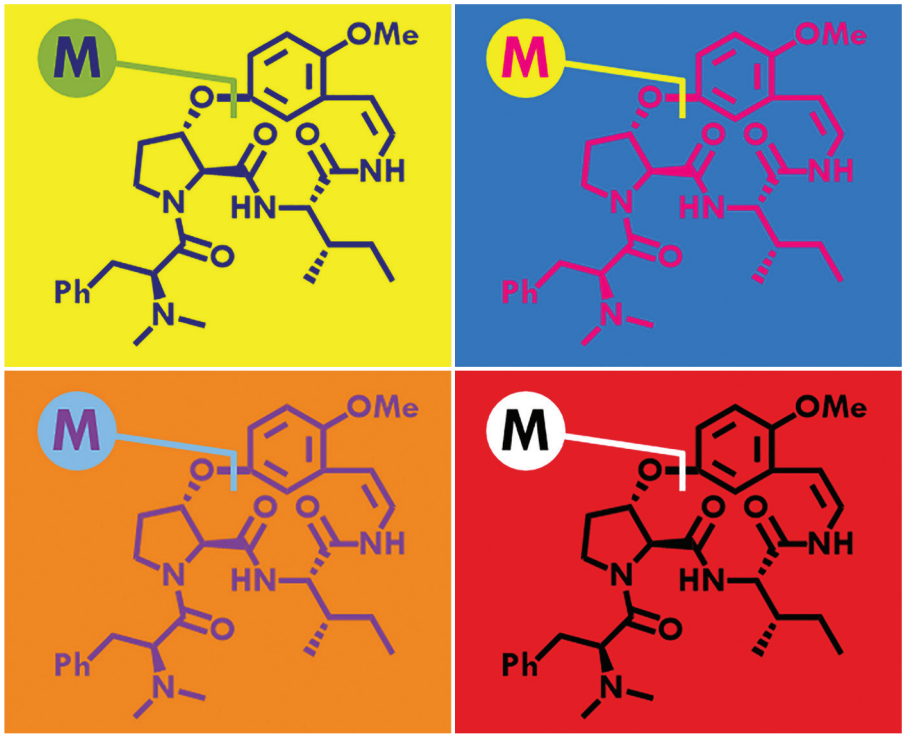
Volume 4 | Number 12 | December 2017



ORGANIC CHEMISTRY

FRONTIERS

Chinese Chemical Society
SIOC 1950
ROYAL SOCIETY OF CHEMISTRY
rsc.li/frontiers-organic

ORGANIC CHEMISTRY
FRONTIERS

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2017, **4**, 2480

Metal-mediated C–O bond forming reactions in natural product synthesis†

Gwilherm Evano, * Jianjun Wang and Antoine Nitelet

Received 1st August 2017,
Accepted 27th August 2017

DOI: 10.1039/c7qo00671c

rsc.li/frontiers-organic

Metal catalyzed reactions for the formation of C–O bonds have had a dramatic impact in natural product synthesis over the past few decades. Various metals have been reported to efficiently catalyze cross-coupling reactions for the formation of various C(sp^2)–O bonds from aryl/alkenyl halides or synthetic equivalents and phenols, aliphatic alcohols and water. The implementation of such reactions in natural product synthesis enabled the emergence of new bond disconnections, which notably resulted in remarkably efficient and short synthetic pathways. The use of these reactions for the formation of C–O bonds in natural product synthesis is overviewed in this critical review, with an emphasis on copper and palladium catalysts which are the most efficient ones to date.

Introduction

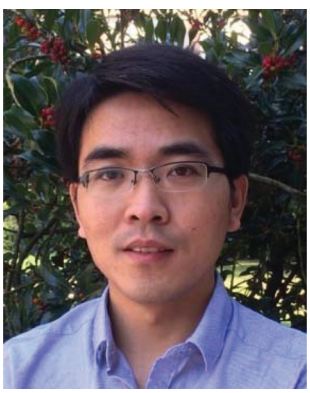
Natural products are at the core of organic synthesis and play a major and crucial role in many areas of chemistry. In addition to the excellent training they provide to the students and researchers working on natural product synthesis, an area in which they have to deal with a broad range of reactions that have to be performed on various scales, natural products are also key to the development of new drugs.[1] They indeed cover a broad part of the chemical space,[2] display a remarkable range of biological activities and are often excellent substrates for membrane transport proteins which enhances their bioavailability. Natural products are therefore a major source of inspiration for the pharmaceutical and agrochemical industries and recent advances in isolation, purification and characterization techniques have clearly facilitated their return to the front stage in drug discovery.

Laboratoire de Chimie Organique, Service de Chimie et PhysicoChimie Organiques, Université libre de Bruxelles (ULB), Avenue F. D. Roosevelt 50, CP160/06, 1050 Brussels, Belgium. E-mail: gevano@ulb.ac.be

†Dedicated to the memory of Prof. István E. Markó, a brilliant chemist and a passionate person who didn't leave anyone indifferent.

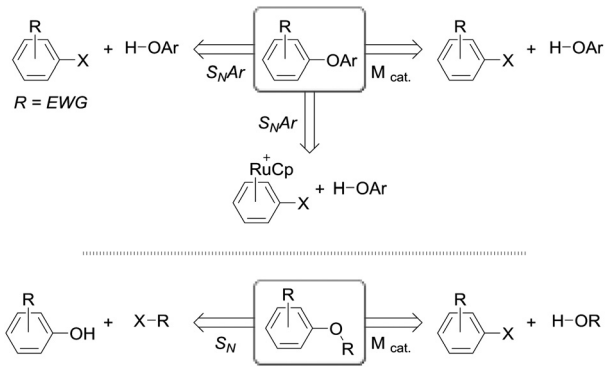
Gwilherm Evano

Gwilherm Evano was born in Paris in 1977 and studied chemistry at the Ecole Normale Supérieure. He received his PhD from the Université Pierre et Marie Curie in 2002 under the supervision of Profs François Couty and Claude Agami. After postdoctoral studies with Prof. James S. Panek at Boston University, he joined the CNRS as associate professor in 2004. He then moved to the Université libre de Bruxelles, where he became the head of the Laboratory of Organic Chemistry in 2012. His research program currently focuses on natural/bioactive product synthesis, copper catalysis, organometallic chemistry and on the chemistry of heteroatom-substituted alkynes and reactive intermediates.



Jianjun Wang

Jianjun Wang was born in Shandong (China) in 1986 and studied pharmacy at Jining Medical University. He obtained his master in phytochemistry from Minzu University of China under the supervision of Prof. Chunlin Long in 2013 and then moved to Belgium for his PhD as a Chinese Scholarship Council fellow. He has been working at the Université libre de Bruxelles under the supervision of Prof. Gwilherm Evano and his PhD work mostly focuses on total synthesis and copper catalysis.



Scheme 1 Classical and metal-based C(sp^2)–O bond disconnections.

They are also a unique source of inspiration for the development of new methods in chemical synthesis, some structural moieties found in natural products requiring the development of efficient tools for their installation. Moreover, natural product synthesis is most certainly the best arena to test the efficiency and functional group compatibility of synthetic methods. They are clearly pushed way beyond their limits when used for the synthesis of a given natural product and only the most robust processes will survive such a trial. Among all reactions that had a significant impact not only in natural product synthesis but also, in a broader sense, in chemical synthesis, metal-mediated processes for the formation of C(sp^2)–O bonds are of prime importance. They indeed provide an excellent alternative to the classical routes for the synthesis of aryl alkyl and diaryl ethers that were previously mostly prepared through the Williamson synthesis and S_NAr reactions, respectively (Scheme 1). Inspired by the pioneering studies reported by Fritz Ullmann in 1905,[3] recent advances in copper[4] and palladium[5] catalysis have enabled the development of a set of efficient processes for the arylation of phenols, aliphatic alcohols and water which are now commonly utilized both in academia and industry.[6] These reactions have also been integrated in various syntheses of natural products,[7] where their efficiency and robustness could be further demonstrated and which resulted in the emergence of new bond disconnections, which will be overviewed in this critical review. If the emphasis will be put on copper-mediated Ullmann-type reactions, which are by far the more utilized for the formation of C(sp^2)–O in natural product synthesis, palladium-mediated reactions will also be overviewed.

This review, which does not intend to be exhaustive but rather provides a comprehensive overview of the impact of metal-catalyzed C–O bond forming reactions in natural product synthesis, will be primarily classified according to the nature of the C–O bond formed (*i.e.* diaryl *vs.* aryl alkyl ethers) and the nature of the transformation (*i.e.* inter- *vs.* intra- molecular). Further subdivisions will be made accordingly regarding the metal used to mediate or catalyze the reaction.

The first section of this review article focuses on naturally occurring diaryl ethers, natural products for which the development of catalytic processes for the formation of C(sp^2)–O bonds clearly had the most significant impact.

Antoine Nitelet

Antoine Nitelet was born in 1990 in Charleroi (Belgium) and studied chemistry at the Université libre de Bruxelles. In 2012, he joined the group of Prof. Gwilherm Evano as a master's student and worked on the development of new copper-mediated transformations. After obtaining an F.R.I.A. fellowship in 2013, he pursued a Ph.D. in the same group. His research is focused on the development of copper-catalyzed transformations, notably the development of a vinylic version of the Finkelstein reaction and cross-coupling involving cyanamides, and their use in natural product synthesis.

Metal-mediated synthesis of naturally occurring diaryl ethers

Synthesis of naturally occurring diaryl ethers based on intermolecular Buchwald–Hartwig and Ullmann reactions

Diaryl ethers are structural moieties commonly found in a range of natural products displaying various biological activities.[7b] The most common ones include amino acid derivatives – which usually originate from the oxidative phenol coupling of aromatic aminoacids – the most iconic example being the glycopeptide antibiotic vancomycin, lignans/neolignans, chalcones and bisbibenzyls, cyclic diarylheptanoids and benzylisoquinoline alkaloids.

The combination of their interesting biological properties and their unique structures has attracted the attention of an important number of research groups. While classical methods for the installation of the diaryl ether core of such natural products mostly rely on nucleophilic aromatic substitution, which requires strongly activated aryl halide for the reaction to proceed, on the use of ruthenium arene complexes, or on the *de novo* construction of one of the aromatic rings, the development of efficient and robust processes for the arylation of phenols had a major impact on the synthesis of naturally occurring diaryl ethers. Indeed, such reactions, which can be efficiently catalyzed by palladium and copper complexes, enable an entirely new disconnection which in addition usually relies on the use of more readily available starting materials.

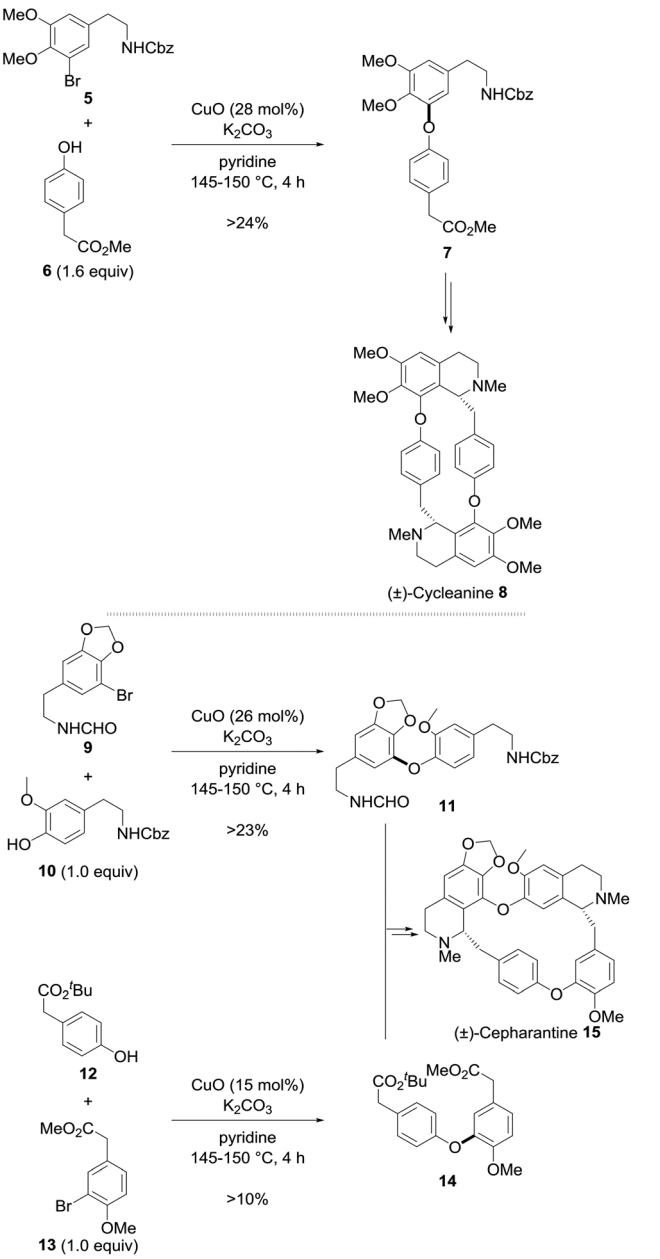
While both palladium and copper complexes can catalyze the cross-coupling between phenols and aryl halides, copper catalysis is usually preferred for the synthesis of naturally occurring diaryl ethers. There is actually, to the best of our knowledge, a single example of a Buchwald–Hartwig reaction

applied to the synthesis of such a natural product, gerfelin **4**.[8] This key step relies on the coupling of two rather simple substrates, phenol **1** and aryl triflate **2**, which was found to be best performed by using a combination of catalytic amounts of palladium(II) acetate and JohnPhos ((2-biphenyl)di-*tert*-butylphosphine) in the presence of potassium phosphate in toluene at 95 °C for 18 h (Scheme 2) to afford the corresponding diaryl ether **3**, a direct precursor of gerfelin **4**, in 60% yield. In sharp contrast, the use of triphenylphosphine as the ligand resulted in a dramatic drop in efficiency (1.7% yield) and reversing the polarity of the reagents by starting from aryl triflate **1′** and phenol **2′** failed to provide the desired product. This is actually quite representative of one of the greatest challenges lying in the use of such reactions for the synthesis of naturally occurring diaryl ethers where the identification of the most appropriate coupling partners is in most cases crucial.

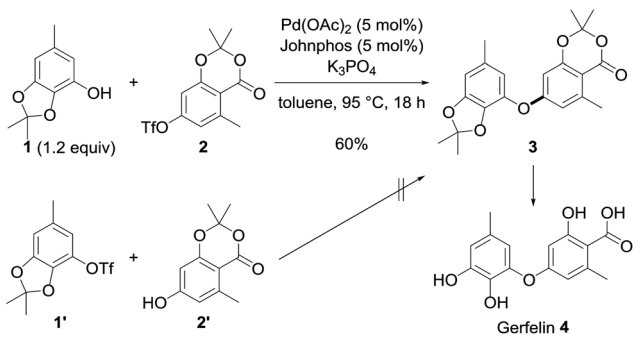
Apart from this isolated example, in which a copper catalyst couldn't have been used due to its inability to catalyze cross-coupling reactions involving aryl triflates, most other syntheses of natural diaryl ethers involve an Ullmann-type cross-coupling rather than a Buchwald–Hartwig reaction.

Early studies based on the classical, ligandless version of the Ullmann reaction however highlighted the risks associated to this strategy which was found to be highly capricious and strongly dependent on the substitution pattern of both coupling partners.

A major breakthrough in this area was reported in 1965 by Tomita, Fujitani and Aoyagi who found that the efficiency of the Ullmann condensation reaction was greatly improved by using catalytic amounts of cupric oxide in the presence of potassium carbonate in pyridine.[9] The efficiency of this procedure was next highlighted by the total synthesis of racemic bis-benzyltetrahydroisoquinoline alkaloids cycleanine **8**[10] and cepharantine **15**[11] (Scheme 3). In the first case, the symmetrical nature of the target alkaloid **8** required an efficient preparation of its monomeric precursor **7** which could be readily obtained, although in a modest yield, by a modified Ullmann condensation from a brominated homoveratrylamine derivative **5** and methyl 2-(4-hydroxyphenyl)acetate **6**. In the second case, two Ullmann condensations were used to prepare the two main fragments **11** and **14** of (±)-cepharantine **15**, the first one from



Scheme 3 The Tomita–Fujitani–Aoyagi modification of the Ullmann condensation for the synthesis of naturally occurring diaryl ethers.

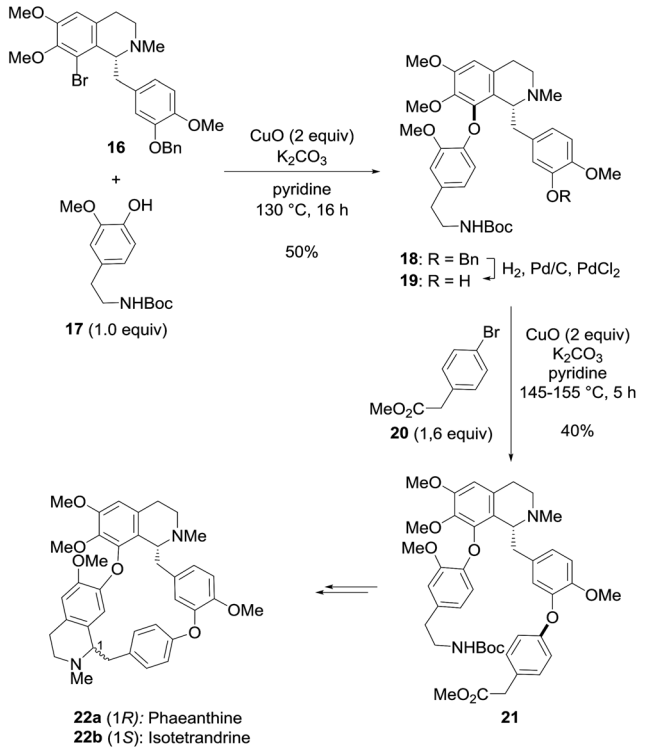


Scheme 2 The Buchwald–Hartwig etherification as a key step for the synthesis of gerfelin.

aryl bromide **9** and phenol **10**, the second one from phenol **12** and bromide **13**. Although these condensations were found to proceed in rather low yields, it should however be noted that equimolar amounts of each coupling partner could be used in these steps and that the first total synthesis of the target alkaloid could be achieved based on these copper-catalyzed etherifications. As an important note, the yields for all Ullmann condensations are actually higher than the ones indicated in Scheme 3 since the yields reported in the original publications include further functional group manipulations (*i.e.* saponification and esterification in the case of **7**, hydro-

lysis of the formamide in **11** and hydrolysis of the *tert*-butyl ester in **14**).

An impressive implementation of the Tomita–Fujitani–Aoyagi modification of the Ullmann condensation was reported later on by the Inubushi group who published in 1968 an efficient asymmetric synthesis of two diastereoisomeric bisbenzyltetrahydroisoquinoline alkaloids, phaeanthine **22a** and isotetrandrine **22b** (Scheme 4).[11b] In their synthesis, a first Ullmann condensation between brominated and benzylated (*R*)–laudanidine **16** and phenethylamine derivative **17** afforded an advanced precursor **18** which was subjected, after debenzylation of the phenol, to a second Ullmann condensation yielding acyclic precursor **21** which, after basic functional group modification and Bischler–Naperialski cyclization, gave the desired diastereoisomeric alkaloids.



Scheme 4 Application of the Tomita–Fujitani–Aoyagi modification of the Ullmann condensation for the synthesis of phaeanthine and isotetrandine.

These modified conditions for the Ullmann condensation were later on implemented by various research groups for the installation of the diaryl ether core of a range of natural products and are actually still worth considering in some cases. Representative natural products prepared using this procedure are shown in Fig. 1 and include cyclic isodityrosine natural products such as K-13 **23**[12] or OF4949-III **24**,[12–14] perrottetin E **25**,[15] the bisbibenzyl natural product marchantin I **26**,[16] ornatipolide **27**,[17] retipolide E **28**,[17] aspercyclide C **29**[18] and other members of this family of natural products[19] as well as combretastatin D1 **30**[20] and related natural products.[21] As an important note, the Ullmann condensation was conducted in all cases in the early stages of the total syntheses in order to avoid problems associated with functional group tolerance. Indeed, the rather harsh reaction conditions only enable the use of this procedure for the synthesis of rather simple diaryl ethers, which then serve as starting materials *en route* to the targeted natural products. The use of more complex starting materials requires the use of milder conditions which will be overviewed later on.

Another set of conditions that turned out to be remarkably efficient, although still relying on rather harsh conditions, was reported by the Boger group. By using the more soluble copper bromide dimethyl sulfide complex, they could indeed implement an Ullmann reaction from base-sensitive substrates in the context of the total synthesis of three cycloisodityrosine-

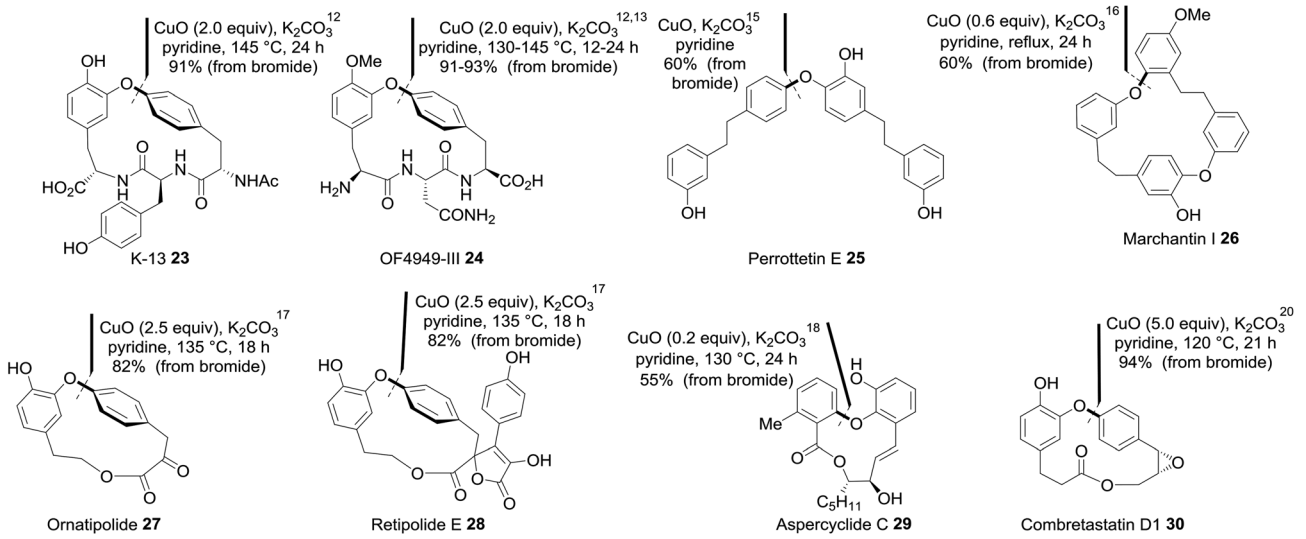
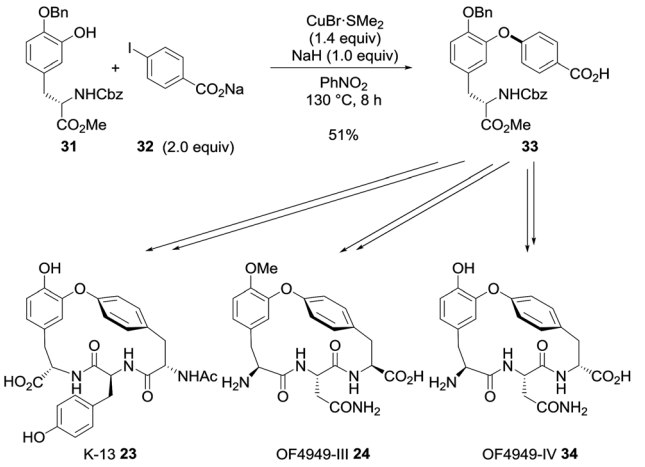
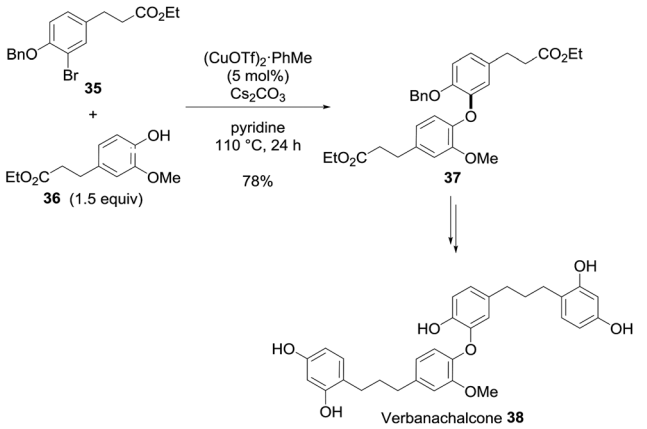


Fig. 1 Application of the Tomita–Fujitani–Aoyagi modification of the intermolecular Ullmann condensation in natural product synthesis.



Scheme 5 Boger's modification of the Ullmann condensation for the synthesis of cycloisodityrosine natural products.



Scheme 6 Buchwald's modification of the Ullmann condensation in Cuny's synthesis of verbanachalcone.

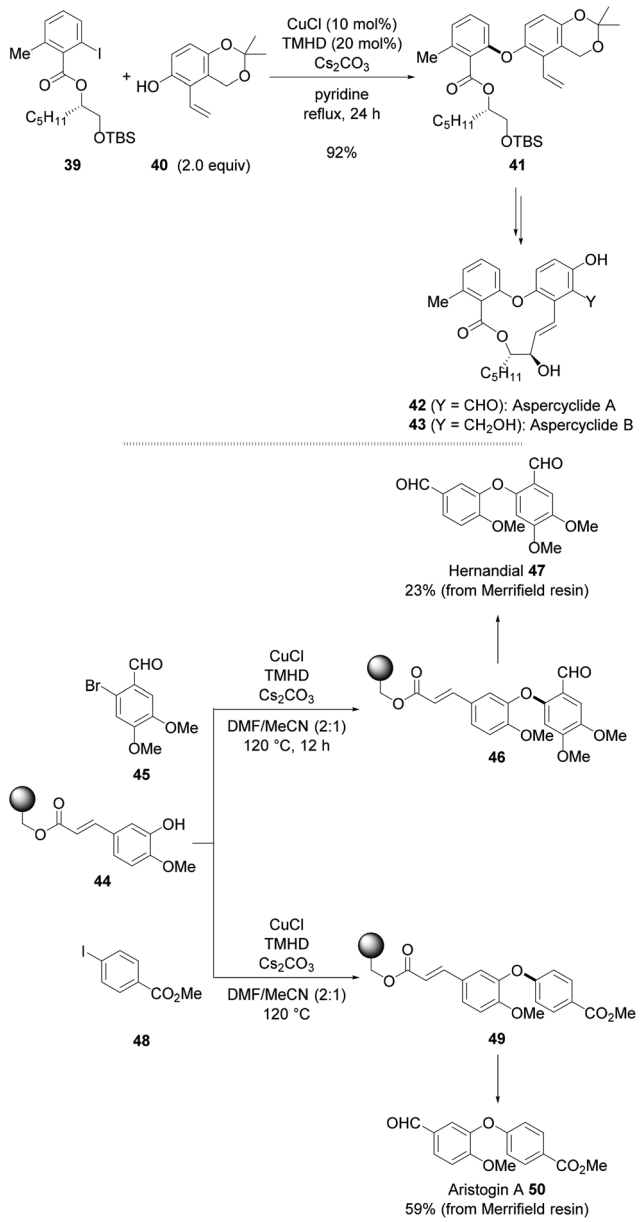
derived agents, K-13 **23**, OF4949-III **24** and OF4949-IV **34**, starting from the common intermediate **33** (Scheme 5).[22] This diaryl ether could be obtained with moderate efficiency by the Ullmann condensation of the L-DOPA derivative **31** with sodium *p*-iodobenzoate **32** upon treatment with sodium hydride and excess copper bromide dimethylsulfide at 130 °C in nitrobenzene. While these conditions allowed the coupling to proceed without racemization, which is in sharp contrast with results obtained with pyridine as the solvent, the scope of this reaction was however found to strongly depend on the nature of both reaction partners. Indeed, if the Ullmann condensation of electron-rich aryl iodides with unactivated phenols was shown to be successful for simple substrates and modestly successful for simple electron-rich aryl iodides bearing an *ortho* alkoxy group or for reactions involving a single functionalized tyrosine derivative, it unfortunately failed when applied to the coupling of two functionalized tyrosine or phenylalanine derivatives. Intramolecular applications of this procedure have had a deep impact in natural product synthesis and will be overviewed later on.

In 1997, Buchwald reported an efficient procedure for the copper-catalyzed coupling of phenols and aryl halides based on the use of catalytic amounts of $(CuOTf)_2$·PhH and ethyl acetate in the presence of cesium carbonate.[23] While the choice of the copper catalyst did not appear to be critical, $(CuOTf)_2$·PhH giving slightly accelerated reactions presumably due to its higher solubility in toluene compared to more standard sources of copper(I) such as cupric halides, a survey of reactions with a number of other bases confirmed that cesium carbonate, which is nowadays commonly used for such reactions, is responsible for the improved reaction conditions.

This had a quite significant impact for the synthesis of naturally occurring diaryl ethers and this procedure was notably used as a key step for the synthesis of verbanachalcone **38** by the Cuny group.[24] In this synthesis, the central diaryl ether core was assembled by coupling aryl bromide **35** with phenol **36** in the presence of cesium carbonate in pyridine (Scheme 6). As in many cases, model studies with simpler substrates however revealed that small changes in functional groups close to reacting centers could still have a dramatic impact on the reaction outcome.

As reported as early as in 1993 by Capdevielle in a remarkable publication entitled "Esters are effective co-catalysts in copper-catalyzed methanolysis of aryl bromides"[25] that unfortunately tends to be forgotten and already touched upon by the Buchwald group who noted in 1997 that the addition of catalytic amounts of ethyl acetate had a significant effect on the Ullmann condensation,[23] the use of ligands for copper has a dramatic impact on reaction rates and efficiency. In this perspective, Song at Merck reported in 2002 that the Ullmann condensation could be greatly accelerated by using 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) as a bidentate ligand for copper.[26] In combination with cupric chloride and cesium carbonate in NMP, the cross-coupling between a series of phenols and aryl iodides and bromides was found to be remarkably efficient. Due to its efficiency, this procedure was readily accepted by the synthetic community and implemented in various total syntheses. One of the first application of this procedure was reported in 2009 by the Fürstner group for the total synthesis of the aspercyclides A **42** and B **43** (Scheme 7).[19a] While the use of the Tomita–Fujitani–Aoyagi conditions was found to be efficient to install the diaryl ether core of the aspercyclides starting from simple substrates, the yields were found to be disappointingly low when moving to more complex and functionalized ones. In sharp contrast, using the Song modification enabled an especially clean reaction as highlighted by the excellent yield obtained for the coupling of **39** and **40**.

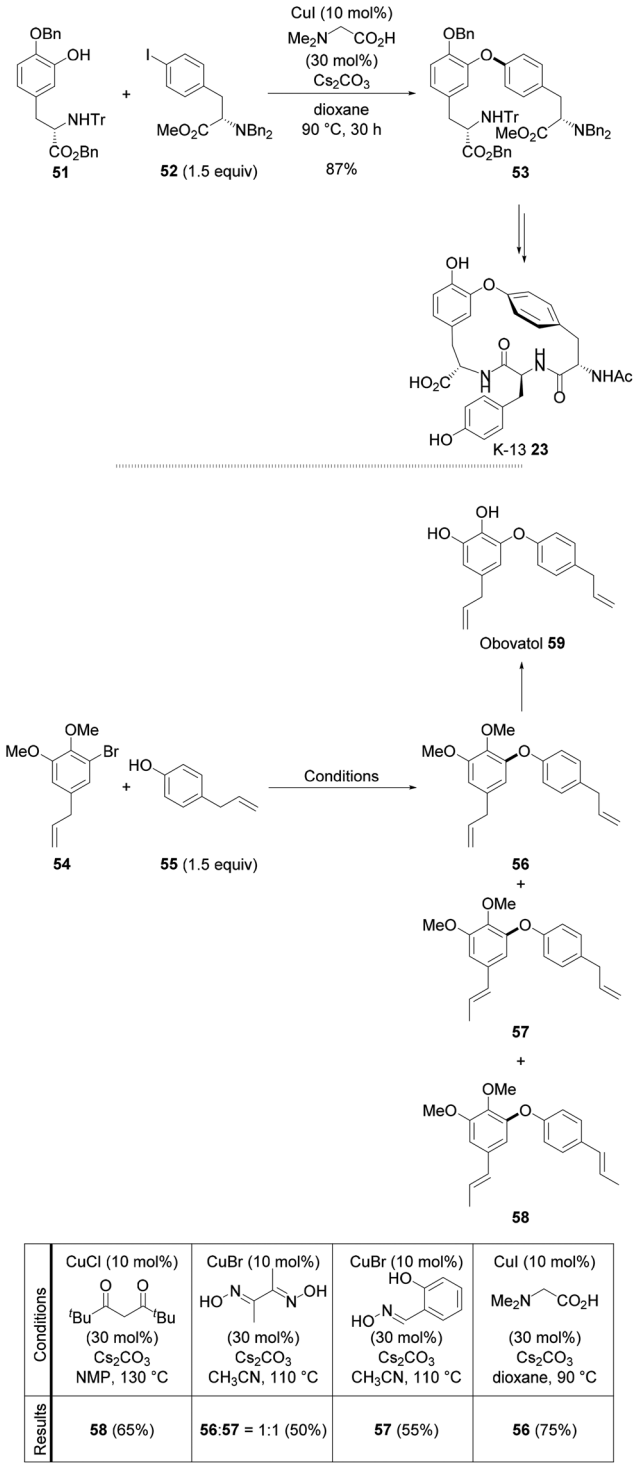
The same year, the Bräse group reported an interesting use of these conditions for the synthesis of various naturally occurring diaryl ethers relying on an Ullmann condensation on solid support.[27] Attaching the aryl halide or the phenol (such as in **44**) to a Merrifield resin and implementing the Song conditions turned out to be an interesting strategy that could be



Scheme 7 Song's modification of the Ullmann condensation in Fürstner's synthesis of aspercyclides A and B and in Bräse's synthesis of hernandial and aristogin A.

successfully implemented for the preparation of hernandial **47**, aristogin A (**50**), B, D, E and F as well as spiraformin A, the diaryl ethers being cleaved from the resin either by ozonolysis or methanolysis.

A probably even more efficient procedure that is still among the most reliable ones to date was reported in 2003 by the Ma group. As with the Buchwald and Song modifications, cesium carbonate is used as the base, the main difference actually lying in the nature of the ligand used for copper. *N*,*N*-Dimethylglycine indeed promoted the Ullmann condensation with a remarkable efficiency.[28] This procedure notably enables the long sought-after coupling of two epimerizable tyrosine derivatives, which was not possible before, as exemplified by the straightforward route developed for the preparation of K-13 **23** from advanced isodityrosine intermediate **53** readily obtained from **51** and **52** in 87% yield and without noticeable epimerization (Scheme 8).[29]



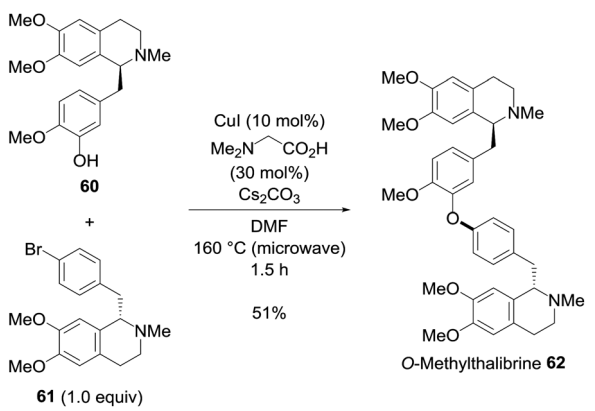
Scheme 8 Application of Ma's modification of the Ullmann condensation in the total synthesis of K-13 and obovatol.

The usefulness of this procedure was further highlighted by the Jung group in 2008.[30] Aiming at developing a concise synthesis of obovatol **59**, a structurally simple diaryl ether displaying a range of biological properties, they examined a series of conditions yielding its methylated derivative **56** without isomerisation of the double bonds to **57** or **58**. Among all the procedures screened, the conditions of the Ma group proved to be the only efficient ones, provided however that the reaction was run in dioxane since a complete isomerization to **57** was observed when switching to acetonitrile.

This procedure was recently utilized as a key step in the Opatz synthesis of bisbenzyltetrahydroisoquinoline alkaloids tetramethylmagnolamine and *O*-methylthalibrine **62**, the latter being summarized in Scheme 9.[31a] Among all the conditions screened for the final Ullmann-type coupling between advanced precursors **60** and **61**, used in a 1 : 1 ratio, it was found that the *N*,*N*-dimethylglycine ligand introduced by Ma was the most efficient one, the reaction being performed in this case in DMF under microwave heating at 160 °C for 1.5 hours, yielding the desired alkaloid **62** in 51% yield. Related alkaloids possessing a different linkage between the two benzyltetrahydroisoquinoline subunits such as nelumboferine were also prepared using a combination of $CuBr{\cdot}SMe_2$ and cesium carbonate in refluxing pyridine, although with less efficiency, the intermolecular Ullmann coupling proceeding in 34% yield only.[31b]

As evidenced with representative examples discussed in this section, the Ullmann condensation, which was originally plagued by harsh reaction conditions, has undergone nothing short of a revolution. The introduction of cesium carbonate and chelating ligands has enabled the development of an improved procedure operating with remarkable efficiency. This renaissance of the Ullmann reaction had a significant impact on natural product synthesis since other processes that were commonly used based on S_NAr or ruthenium arenes do not compete anymore with the Ullmann condensation.

The efficiency and robustness of this reaction has also prompted various research groups to study intramolecular variants of this reaction which were actually found to be quite efficient for the synthesis of macrocyclic, naturally occurring diaryl ethers. The most significant examples of this strategy will be overviewed in the next section of this review article. As in this section, most examples will be presented in a chronological order which is more suitable to fully comprehend the evolution of copper catalysis and its impact in total synthesis.



Scheme 9 Opatz' synthesis of *O*-methylthalibrine based on Ma's modification of the Ullmann condensation.

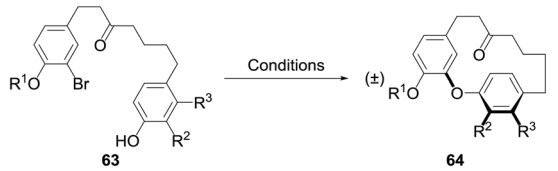
Synthesis of naturally occurring diaryl ethers based on intramolecular Ullmann reactions

Exactly the same trend can be observed retrospectively for the evolution of the procedures used for intramolecular Ullmann reactions. Indeed, while classical conditions could be used only for the macrocyclizations yielding simple macrocyclic diaryl ethers that are in most cases devoid of any functional groups, reports of more efficient procedures based on the use of cesium carbonate and/or chelating ligands have progressively led to the intramolecular Ullmann condensation being recognized as one of the most efficient entries to naturally occurring macrocyclic diaryl ethers. As a note, palladium-catalyzed reactions have not been used, to the best of our knowledge, for such reactions, which can be certainly attributed to the lower efficiency of the Buchwald–Hartwig reaction.

For the simplest substrates, the Tomita–Fujitani–Aoyagi conditions can be used to mediate the macrocyclization of acyclic precursors bearing both a phenol and an aryl halide such as **63** (Fig. 2). Such conditions have been indeed used for the total synthesis of a wide number of simple diaryl ether heptanoids such as those shown in Fig. 2.[32–36] The macrocycles **64** resulting from the macrocyclization possessing substituents at the *ortho* and *ortho*′ positions compared to the ether linkage are usually chiral due to the formation of atropoisomers during the intramolecular Ullmann condensation and are formed as racemic mixtures. By comparing the reaction conditions used for these macrocyclizations, the use of cesium carbonate seems to have a positive effect compared to potassium carbonate typically used for such reactions and high dilution conditions give better results.

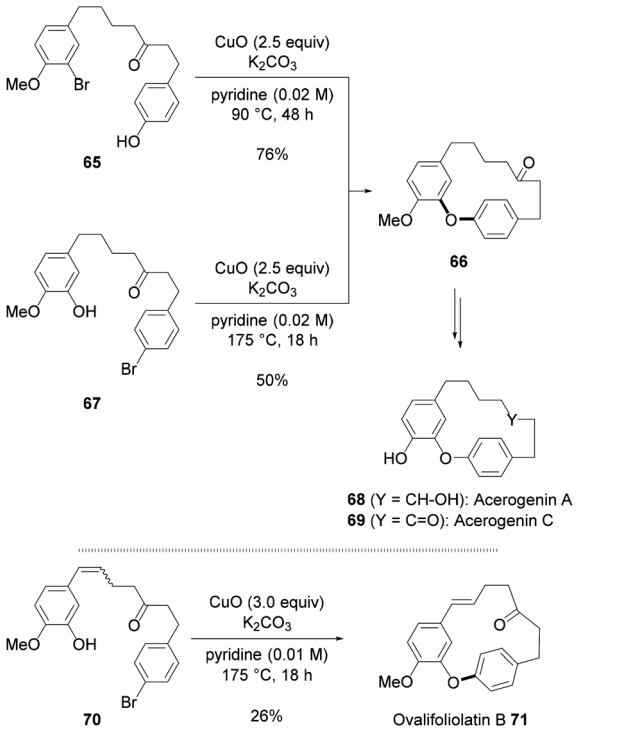
As in the case of intermolecular reactions, the disconnection of the $C(sp^2)$–O bond to be formed during the intramolecular Ullmann condensation can be of utmost importance, even if essentially dictated by the availability of the starting materials corresponding to the two possible disconnections. In the case of the total synthesis of the acerogenins A **68** and C **69**, both possibilities have been reported and are shown in Scheme 10.[32,37] In such a simple case and due to the modifications in the reaction conditions used, the difference in both pathways is however not striking. Finally, it ought to be mentioned that more strained diaryl ether heptanoids possessing an endocyclic double bond such as ovalifoliolatin B **71** can be prepared using this strategy, although with less efficiency.[37]

The efficiency of such conditions was further demonstrated in 2012 and 2013 by the Beaudry group who synthesized an impressive number of the garuganin **74**, **75**, **79**, **80** and garugamblin **76–78** diaryl ether heptanoids (Scheme 11).[38] The disconnection was chosen to position the phenol on the more electron-rich phenyl ring which was expected to give a

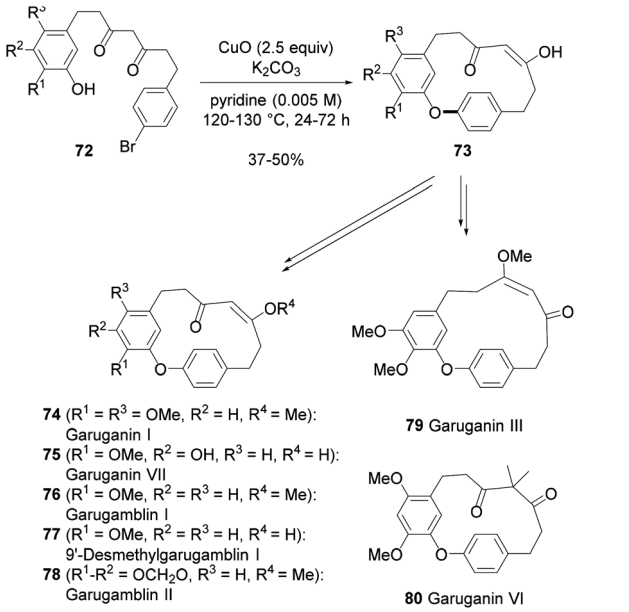


Substituents	Conditions	Yield	Precursor to
R^1 = Me R^2 = R^3 = H	CuO (2.5 equiv), K_2CO_3 pyridine (0.02 M) 90 °C, 48 h	49% [32]	Acerogenin L (R^1 = R^2 = R^3 = H)
R^1 = *i*Pr R^2 = R^3 = H	CuO (2.5 equiv), Cs_2CO_3 pyridine (0.007 M) reflux, 48 h	81% [33]	Acerogenin L (R^1 = R^2 = R^3 = H)
R^1 = Bn R^2 = OMe R^3 = H	CuO (2.5 equiv), K_2CO_3 pyridine (0.02 M) 90 °C, 48 h	52% [32]	(±)-Galeon (R^1 = R^3 = H, R^2 = OMe), (±)-Pterocarine = (±)-Engelhardione (R^1 = R^3 = H, R^2 = OH)
R^1 = *i*Pr R^2 = OMe R^3 = H	CuO (2.5 equiv), Cs_2CO_3 pyridine (0.007 M) reflux, 20 h	73% [33]	
R^1 = H R^2 = OMe R^3 = H	CuO (10.0 equiv), K_2CO_3 pyridine (0.1 M) 200 °C, 30 h	13% [34]	(±)-Galeon (R^1 = R^3 = H, R^2 = OMe) *directly obtained*
R^1 = Me R^2 = OMe R^3 = H	CuO (2.5 equiv), K_2CO_3 pyridine (0.02 M) 175 °C, 4.5 h	54% [35]	(±)-Pterocarine = (±)-Engelhardione (R^1 = R^3 = H, R^2 = OH)
	CuO (2.5 equiv), K_2CO_3 pyridine (0.01 M) 220 °C (microwave), 35 min	85% [36]	
	CuO (10.0 equiv), K_2CO_3 pyridine (0.1 M) 200 °C, 30 h	12% [34]	(±)-Platycarynol (R^1 = Me, R^2 = OMe, R^3 = H, alcohol instead of the ketone)
R^1 = *i*Pr R^2 = OMe R^3 = O*i*Pr	CuO (2.5 equiv), Cs_2CO_3 pyridine (0.007 M) reflux, 69 h	74% [33]	(±)-Myricatomentogenin (R^1 = H, R^2 = OMe, R^3 = OH)
R^1 = Me R^2 = OMe R^3 = O*i*Pr	CuO (2.5 equiv), Cs_2CO_3 pyridine (0.007 M) reflux, 48 h	63% [33]	(±)-Jugcathanin (R^1 = Me, R^2 = OMe, R^3 = OH)

Fig. 2 Naturally occurring macrocyclic diaryl ether heptanoids prepared through an intramolecular Ullmann condensation based on the Tomita–Fujitani–Aoyagi conditions.



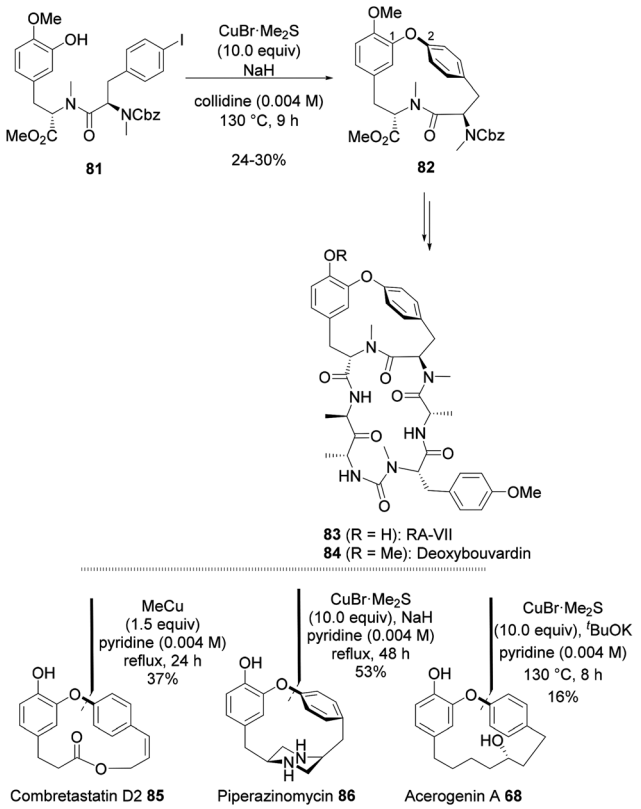
Scheme 10 Other diaryl ether heptanoids prepared through an intramolecular Ullmann condensation based on the Tomita–Fujitani–Aoyagi conditions.



Scheme 11 Beaudry's total syntheses of garuganin and garugamblin diaryl ether heptanoids through an intramolecular Ullmann condensation based on the Tomita–Fujitani–Aoyagi conditions.

smoother macrocyclization than the alternative approach that would rely on an electron-rich aryl bromide. This led to the identification of acyclic precursors **72** whose macrocyclization was accompanied by enolization of the diketone to form the vinylogous ester found within the ansa bridge of the garuganins and garugamblins. Based on these total syntheses, the chiral properties and free energies of activation for racemization of these natural products could be investigated and it was found that none of them were chiral, despite their reported specific rotation values.

The Boger group has been especially prolific in this area and has reported the total synthesis of a number of complex naturally occurring macrocyclic diaryl ethers using the conditions they previously developed for the intermolecular Ullmann condensation. Interestingly, while the intermolecular copper-mediated cross-coupling of two functionalized tyrosine or phenylalanine derivatives failed, the corresponding intramolecular reaction met with more success. The total syntheses of RA-VII **83** and deoxybouvardin **84**, potent antitumor antibiotics, shown in Scheme 12 are quite representative.[39] Examination of the two possible disconnections at the C^1–O or C^2–O bonds revealed that the latter would be more favourable than the former which would imply an electron-donating substituent *ortho* to the aryl iodide, which was confirmed by model studies. This led to the identification of the acyclic pre-



Scheme 12 Boger's total synthesis of RA-VII and deoxybouvardin based on an intramolecular Ullmann condensation and other natural products prepared using Boger's procedure.

cursor **81** possessing an aryl iodide, usually more reactive than the corresponding bromides in such reactions. The macrocyclization to **82** could be successfully implemented, although in modest yield, provided that the reaction was run under moderately dilute conditions and using collidine as the solvent instead of pyridine to suppress the epimerization.

The success met with this synthesis prompted the Boger group, as well as other research groups, to utilize this procedure for the preparation of other complex macrocyclic diaryl ethers such as bouvardin,[39] combretastatin D2 **85**,[40] piperazinomycin **86**[41] or acerogenin A **68**.[42] In all cases, the macrocyclization proceeded with moderate to reasonable efficiencies provided that the right C(sp^2)–O bond disconnection was selected. Recent advances in copper catalysis, that will be overviewed below, would however clearly allow revisiting these total syntheses since the yields might clearly be improved using ligand-assisted, copper-catalyzed processes for the key macrocyclizations.

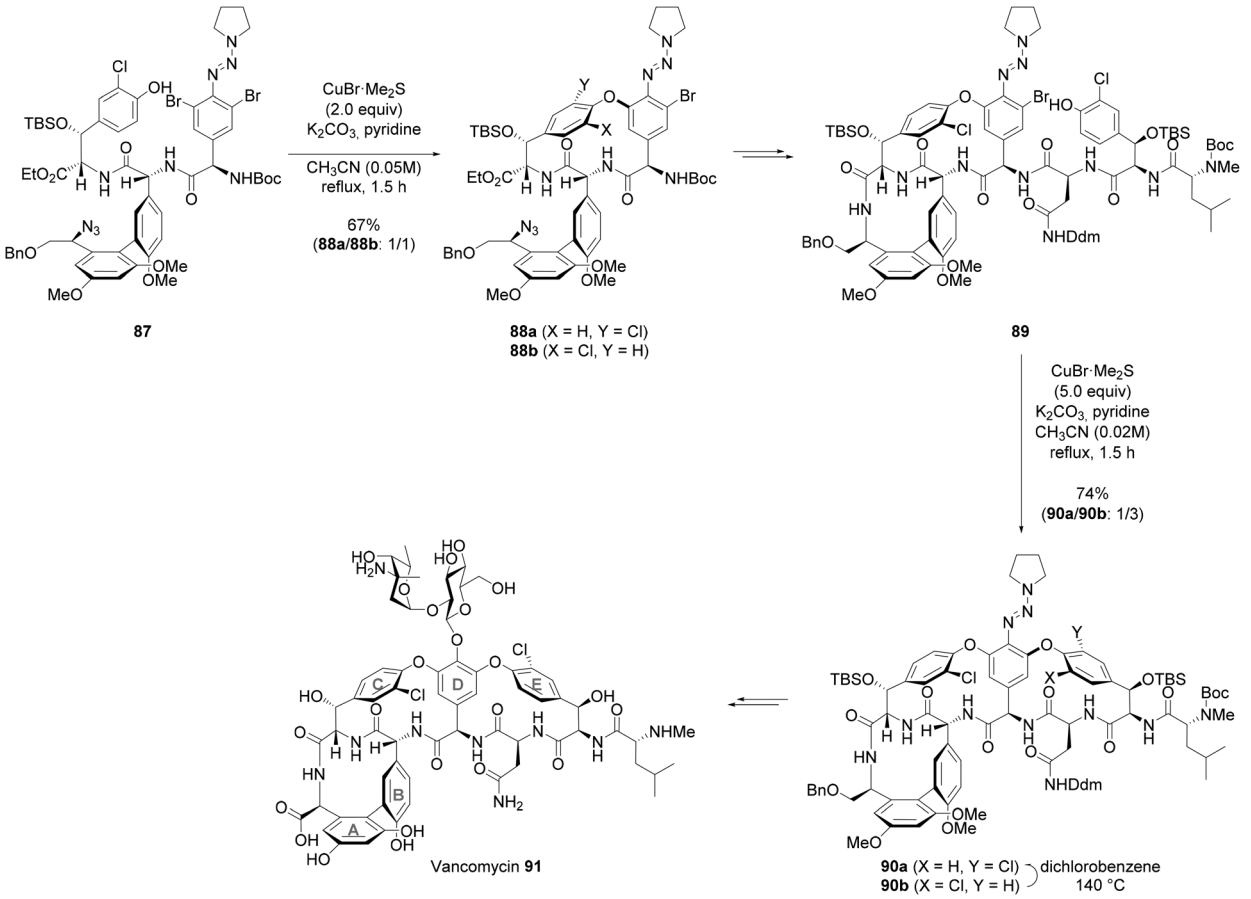
Indeed, despite its efficiency, Boger's procedure is still plagued with moderate yields and still rather harsh conditions. Its application to more complex substrates might therefore be challenging. While successfully applied to model systems *en route* to one of the most complex naturally occurring diaryl ether, vancomycin,[43] its use with real substrates, not model ones, for the total synthesis of such a challenging target has not been reported.

There are actually two options that can be considered when attempting to prepare such a complex and sensitive target by an intramolecular Ullmann condensation in order to step away from harsh reaction conditions. The first option has already been discussed in the previous section and relies on the use of a chelating ligand for copper that has enabled the development of remarkably efficient processes operating under milder conditions. These were however introduced only quite recently and were not available when vancomycin became a quite attractive synthetic target. The second option is based on the *ortho* effect that is quite marked in copper catalysis and that allows for the cross-coupling involving aryl halides possessing a chelating group in the *ortho* position to proceed remarkably easily. This effect, which was actually already touched upon by Ullmann himself who reported in 1903 the copper-mediated reaction between aniline and *ortho*-chloro-benzoic acid – the *ortho* carboxylic acid clearly being responsible for the success of the reaction[44] – was in fact key to the success of the remarkable total synthesis of vancomycin by the Nicolaou group.

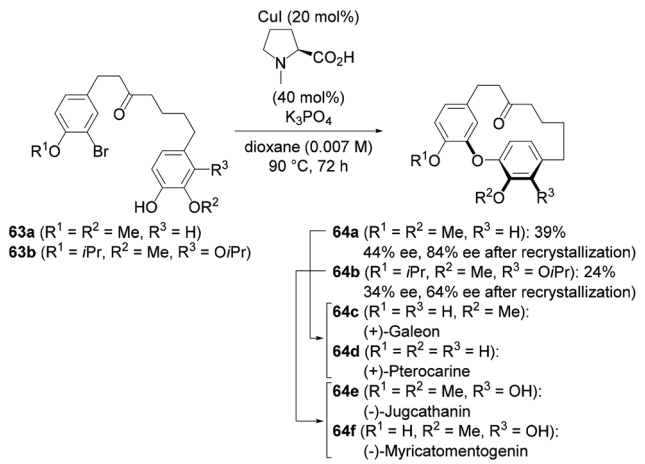
They indeed devised an efficient and especially elegant total synthesis of vancomycin **91** based on two intramolecular Ullmann condensations to build the AB-COD and DOE ring systems of the complex polycyclic target (Scheme 13).[45] With this goal in mind, and in order to facilitate these key steps for which the corresponding starting materials wouldn't survive harsh reaction conditions, an especially mild copper-mediated arylation reaction was designed based on the ingenious incorporation of a triazene unit in the starting material strategically placed *ortho* to the bromine: this internal helper auxiliary would serve as both a potential "electron sink" and to coordinate/stabilize the intermediate copper species. This strategy turned out to be remarkably efficient since both cyclizations (**87** → **88** and **89** → **90**) gave cyclized products in rather high yields for such a transformation and did not require the presence of strong bases or too high temperatures. As triazenes are easily prepared and converted to a variety of functional groups, including amines and iodides, this group could be utilized at the end of the synthesis for the stepwise installation of the phenol required to complete the synthesis of vancomycin.

As mentioned previously, ligands for copper have a dramatic effect on the efficiency of the Ullmann condensation. While various ligands have been reported for this transformation, aminoacids are among the most efficient ones. They are in addition readily available with high optical purities so that they can be used to catalyze enantioselective copper-mediated cross-coupling reactions, an area that is still in its infancy.

This was elegantly utilized by the Beaudry group in a remarkable asymmetric total synthesis of the diaryl ether heptanoids (+)-galeon **64c**, (+)-pterocarine **64d**, (−)-jugcathanin **64e** and (−)-myricatomentogenin **64f** (Scheme 14).[46] In continuation of their studies on the chirality of this family of natural products, they hypothesized that the use of chiral ligands such as amino acids could render the intramolecular Ullmann condensation enantioselective. After an extensive screening of ligands and reaction conditions, they eventually found that *N*-methyl-proline both facilitates the cyclization of



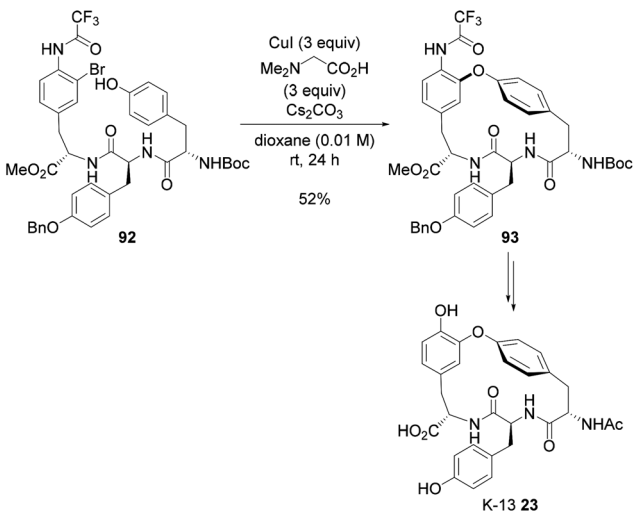
Scheme 13 Nicolaou's total synthesis of vancomycin based on consecutive intramolecular condensations accelerated by *ortho* effects.



Scheme 14 Beaudry's enantioselective intramolecular Ullmann condensation for the asymmetric synthesis of diaryl ether heptanoids.

acyclic precursors **63** and provides reasonable levels of enantioselectivity, which clearly opens new perspectives both in natural product synthesis and in copper catalysis.

If you now combine this remarkable *ortho* effect and the ligand acceleration of the Ullmann condensation, the reaction becomes so facile that it does proceed readily at room temperature as demonstrated by the impressive total synthesis of K-13 **23** by the Ma group (Scheme 15).[47] Indeed, in continuation of their studies on the accelerating effect of amino acids in



Scheme 15 Total synthesis of K-13 by the Ma group: acceleration of the Ullmann condensation by combining ligand and *ortho* effects.

copper-catalyzed cross-coupling reactions, they reported an especially efficient intramolecular copper-catalyzed, ligand assisted Ullmann condensation facilitated by the trifluoroacetamide *ortho* to the aromatic bromide in **92**. The reaction proceeded at room temperature, which is quite rare for an Ullmann condensation, and afforded the corresponding precursor **93** of K-13 **23** in 52% yield.

The comparison of all syntheses of this natural product based on a copper-mediated approach (Fig. 1, Schemes 5, 8 and 15) is actually quite illustrative of the evolution of copper catalysis. Improved processes in copper-mediated transformations clearly led to more efficient synthetic routes and even to the emergence of new bond disconnections and paradigms in total synthesis.

Before concluding this section, it should be mentioned that intramolecular Ullmann-type reactions are not limited to the formation of large ring systems, as highlighted in Couture's total synthesis of aristoyagonine **95** based on Buchwald's modification of the Ullmann condensation (Scheme 16).[48] A notable feature of this cyclization is that the configuration of the alkene in the starting material is not crucial for the creation of the diaryl ether linkage ensuring the construction of the benzoxepine system.

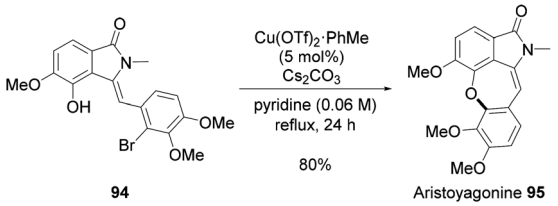
Symmetrical dimeric natural products possessing two diaryl ethers can also be prepared based on Ullmann-type reactions. The simplest option, which is also by far the most efficient and takes advantage of the symmetrical nature of the target, is based on a double Ullmann condensation. This copper-mediated cyclodimerization strategy will be overviewed in the next section.

Synthesis of dimeric naturally occurring diaryl ethers by copper-catalyzed cyclodimerization

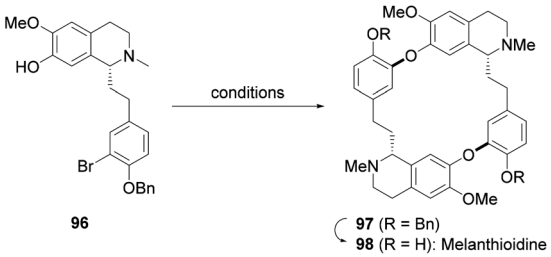
There is actually a single example of a natural product, melanthioidine **98**, prepared using this strategy. This dimeric diaryl ether phenethyltetrahydroisoquinoline alkaloid, isolated in 1962 from the leaves and corms of *Androcymbium melanthioides*, a perennial flowering plant that is extensively used in folk medicine for the treatment of many diseases, has a highly symmetrical structure that can be disconnected at two of its C(sp^2)–O bonds yielding a monomer that could be dimerized using a copper-mediated cyclodimerization.

While previous attempts at using this strategy proceeded with little efficiency and/or suffered either from the resolution of the monomer or the tedious separation of the diastereoisomeric macrocycles when such a step was not performed, we reported in 2016 an efficient procedure for this cyclodimerization from the readily available monomer **96**. Compared to other Ullmann condensations, finding the optimal copper-based system was not trivial since it has to promote both the inter- and intra- molecular reactions. Extensive screening of the reaction conditions revealed that the cyclodimerization was best performed using Boger's procedure, affording the desired macrocycle **97**, a direct precursor of melanthioidine **98**, in 35% yield (Fig. 3).[49]

A related strategy was explored by the Opatz group within the framework of their studies on the total synthesis of non-symmetrical bisbenzyltetrahydroisoquinoline curare alkaloids, curine **108** and tubocurine **109**.[50] If the non-symmetrical nature of the targets clearly renders a selective heterodimerization highly challenging, if not totally unreasonable, some levels of selectivity might however be reached as indicated by the reaction of **99** with **100** in the presence of $CuBr{\cdot}SMe_2$ and cesium carbonate in pyridine (Scheme 17). If a monocoupling yielding **101** was expected to be operative, the lability of the TIPS group under the reaction conditions led to the competitive formation of the macrocyclic heterodimer **102**. While of limited synthetic usefulness due to the moderate efficiency of the reaction and to the formation of mixtures of products including the monocoupled product **101** and the macrocycle

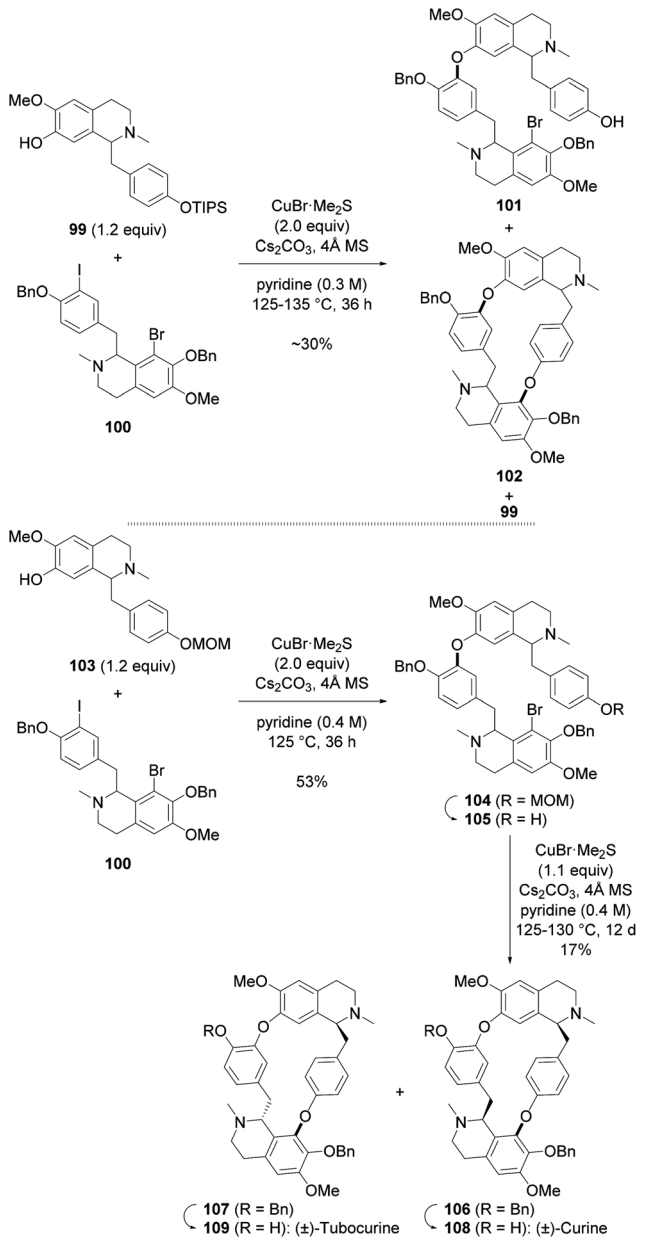


Scheme 16 Couture's total synthesis of aristoyagonine based on an intramolecular Ullmann condensation using Buchwald's conditions.



Conditions	Yield
$Cu(OTf)_2{\cdot}C_6H_6$ (0.1 equiv), Cs_2CO_3 pyridine (0.16 M), 110 °C, 24 h	8%
CuBr (0.1 equiv), picolinic acid (0.2 equiv) Cs_2CO_3, DMSO (0.16 M), 90 °C, 24 h	-
CuCl (0.2 equiv), TMHD (0.4 equiv) Cs_2CO_3, pyridine (0.16 M), 150 °C, 24 h	-
CuCl (1 equiv), TMHD (2 equiv) Cs_2CO_3, pyridine (0.16 M), 120 °C, 24 h	10%
CuCl (1 equiv), TMHD (2 equiv) Cs_2CO_3, pyridine (0.02 M), 120 °C, 24 h	-
Cu (3 equiv), K_2CO_3 pyridine (0.16 M), 150 °C, 24 h	15%
CuO (3 equiv), K_2CO_3 pyridine (0.16 M), 120 °C, 24 h	20%
$CuBr{\cdot}SMe_2$ (3 equiv), Cs_2CO_3 pyridine (0.16 M), 150 °C, 10 h	30%
$CuBr{\cdot}SMe_2$ (1 equiv), Cs_2CO_3 pyridine (0.16 M), 150 °C, 48 h	35%

Fig. 3 Total synthesis of melanthioidine by a copper-mediated cyclodimerization.



Scheme 17 Opatz's total synthesis of heterodimeric curare alkaloids tubocurine and curine featuring two consecutive inter- and intra-molecular Ullmann condensations.

102 – these two compounds being formed as mixtures of diastereoisomers – together with unreacted **99**, this reaction however shows that some levels of selectivity might be achieved by finely tuning the steric and electronic properties of both the phenol and the aryl halide. However, due to the impossible separation of all products formed, they resorted to a more classical strategy relying on two consecutive Ullmann condensations from **103** and **100**, an intermolecular one yielding **104** followed by deprotection and subsequent intramolecular coupling involving the newly deprotected phenol. This eventually led to the isolation, as racemic mixtures, of the two diastereoisomeric alkaloids curine **108** and tubocurine **109**.

In addition to the Buchwald–Hartwig reaction – that is only scarcely used for the synthesis of naturally occurring diaryl ethers – and the Ullmann condensation, another reaction has had a rather deep impact in this area, mostly due to its remarkably mild conditions. The use of the Chan–Lam–Evans reaction for the synthesis of natural diaryl ethers will be overviewed in the next section of this review article.

Synthesis of naturally occurring diaryl ethers based on the intermolecular Chan–Lam–Evans reaction

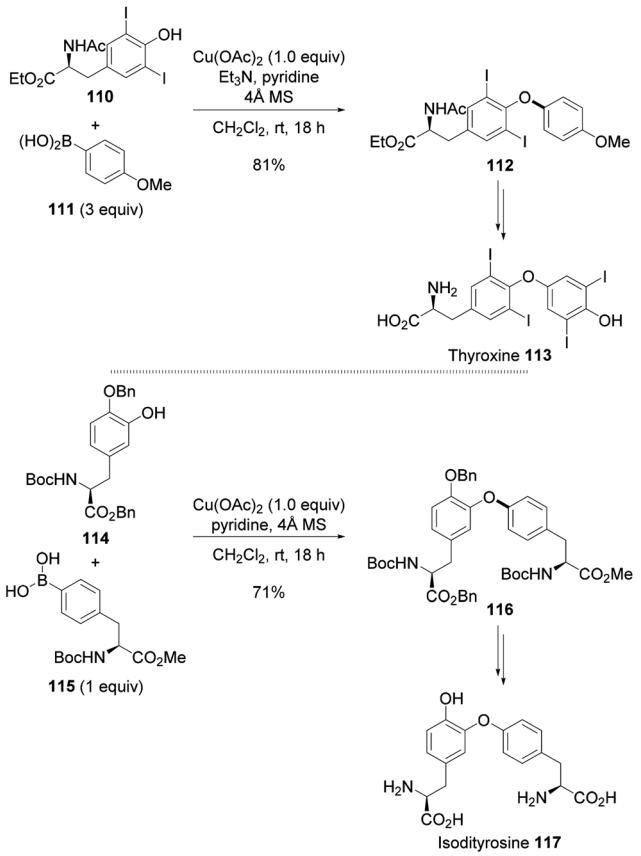
The Ullmann condensation still suffers from too harsh conditions. Except in rare cases, the reaction mixture needs to be heated for long periods in the presence of a base, which still represents a limitation when this reaction is used on complex and/or sensitive substrates. Before the renaissance of copper catalysis based on the introduction of chelating ligands for copper, a number of research groups have in fact devoted their attention to alternative reagents that could be used in place of the aryl halides used in the Ullmann condensation and that would enable the arylation of phenols under milder conditions.

This eventually led to the discovery, by Chan, Lam and Evans in 1998, that arylboronic acids were ideal reagents for such reactions.[51] This reaction, now commonly known as the Chan–Lam–Evans reaction, indeed usually proceed at room temperature in the presence of copper(II) salts – frequently used in stoichiometric amounts although the reaction can be catalytic in copper when performed under air or oxygen – and a mild base such as triethylamine or pyridine.[4b,52]

The mild conditions associated to this reaction inspired various research groups who implemented this process for the synthesis of a range of naturally occurring diaryl ethers. Among the first targets that were prepared by this Chan–Lam–Evans reaction, thyroxine **113**[53] and isodityrosine **117**[54] were readily identified, respectively, by the Evans and Jung groups, since they could be hardly prepared by an Ullmann condensation due to the sensitive nature of the precursors and/or the presence of aryl iodides that would not be compatible with such a reaction.

With this goal in mind, Evans reported in 1998 an efficient synthesis of thyroxine **113** from a precursor **112** that could be readily obtained, without epimerization in 81% yield by the arylation of the highly hindered phenol in **110** with boronic acid **111** at room temperature (Scheme 18). The total synthesis of isodityrosine, based on the cross-coupling of the L-DOPA derivative **114** with equimolar amounts of phenylalanine-derived arylboronic acid **115**, is equally impressive.

Other naturally occurring diaryl ethers prepared through an intermolecular Chan–Lam–Evans reaction are shown in Fig. 4. They include tejedine **118**,[55] combretastatin D2 **85**,[56] pulcherosine **119**[57] and rodgersinol **120**[58] and are representative of targets that can be prepared using this strategy. Since there's unfortunately nothing like an ideal reaction, the Chan–Lam–Evans reaction is actually quite sensitive to the nature of the substituents *ortho* to the boronic acid. This was recently exemplified by the Suh group who revisited their synthesis of



Scheme 18 Total syntheses of thyroxine and isodityrosine based on a Chan–Lam–Evans reaction.

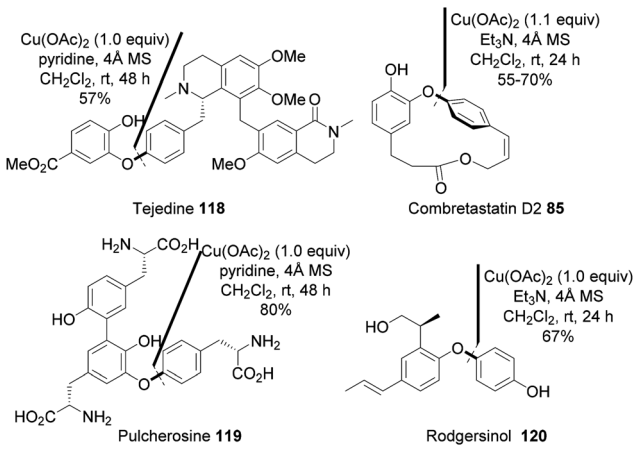
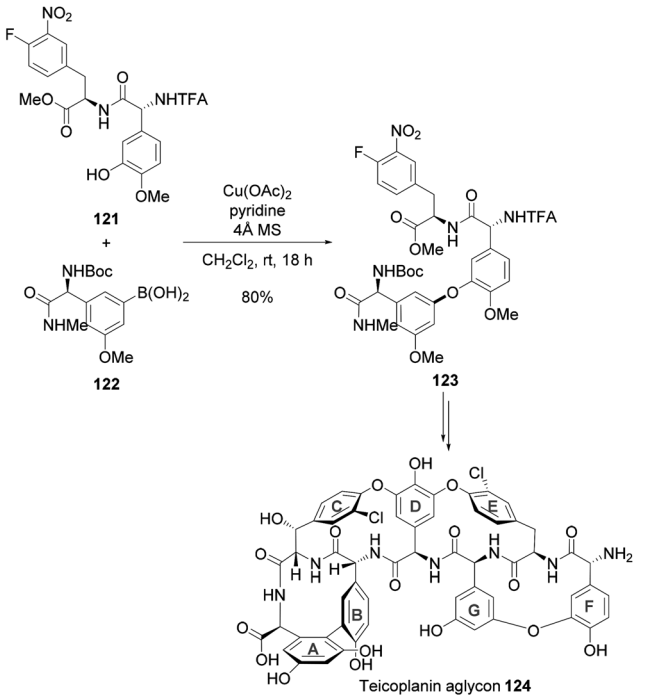


Fig. 4 Application of the intermolecular Chan–Lam–Evans reaction in natural product synthesis.

rodgersinol **120** and found that chelating groups such as an aldehyde or a ketone at this position totally inhibited the reaction while the presence of bulky substituents did not have a significant effect on the efficiency of the process.[59]

An ode to the efficiency of this reaction can be found in the stunning total synthesis of teicoplanin aglycon **124**, teicoplanin



Scheme 19 Evans' total synthesis of teicoplanin aglycon based on a Chan–Lam–Evans reaction.

being a member of the large family of glycopeptide antibiotics – among which vancomycin – and including three macrocyclic diaryl ether subunits, by the Evans group (Scheme 19).[60] One of the main issues associated with the total synthesis of teicoplanin is related to the presence of the arylglycine residue that is exceptionally prone to epimerization. While the method of choice for the construction of the diaryl ethers in the COD and DOE ring systems typically relies on nucleophilic aromatic substitutions, they envisioned that a Chan–Lam–Evans reaction could be operative. In addition to the mild reaction conditions that should be compatible with the sensitive arylglycine moiety, one of the main advantages of this approach compared to the one relying on a S_NAr reaction lies on the fact that it does not require the presence of strongly electron-withdrawing groups in one of the aryl rings for the reaction to proceed. Indeed, the condensation of arylglycineboronic acid **122** with the phenol group in dipeptide **121** under the conditions developed by the Evans group proceeded smoothly to provide the desired arylated product **123** in 80% yield.

As with the Ullmann condensation, it was quickly recognized that the intramolecular variant of the Chan–Lam–Evans reaction could provide excellent opportunities in natural product synthesis: representative examples will be overviewed in the next section.

Synthesis of naturally occurring diaryl ethers based on intramolecular Chan–Lam–Evans reactions

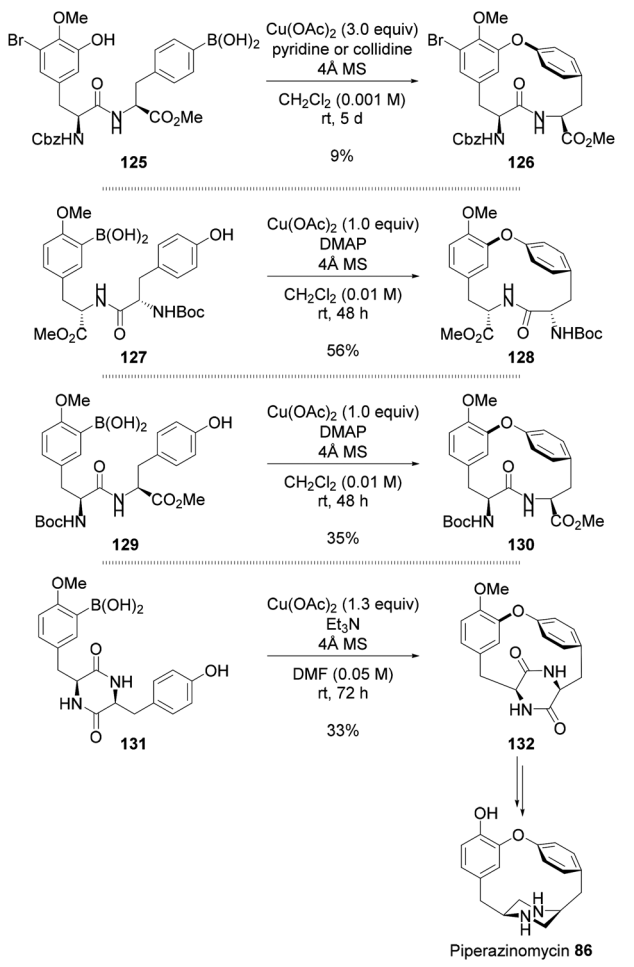
Although appealing, there are not that many examples of intramolecular Chan–Lam–Evans reactions for the synthesis of

diaryl ether-containing natural products, which might be connected with some difficulties associated to the use of boronic acids, or their surrogates.

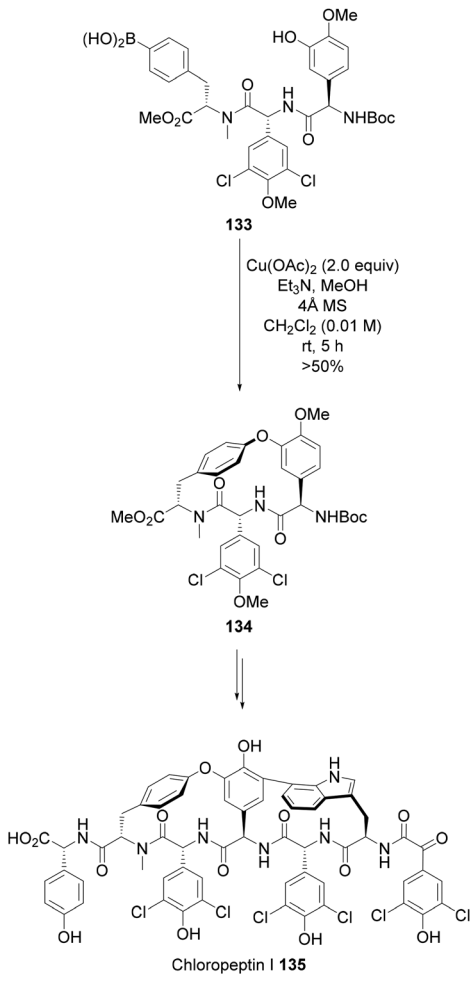
This reaction is actually for some reasons always associated to peptide-based macrocyclic diaryl ethers. It has for example been rather extensively investigated for the elaboration of the cycloisodityrosine subunits **126**,[61] **128**[62] and **130**[62] found in deoxybouvardin, RA-VII or RP 66453 as well as for the total synthesis of piperazinomycin **86**.[63] In all attempts, summarized in Scheme 20, the intramolecular Chan–Lam–Evans reaction was however found to be highly substrate-dependent, which can be attributed in some cases to competing protodeborylation or oxidation, especially when starting from arylboronic acids bearing an heteroatom at the *ortho* position, even if subtle changes in the nature of the base, solvent and concentration used for this kind of macrocyclization can have a dramatic impact.

The most impressive application of an intramolecular version of the Chan–Lam–Evans reaction can be found in Snapper and Hoveyda's total synthesis of the anti-HIV agent chloropeptin I **135** (Scheme 21).[64] In this synthesis, the macrocyclic diaryl ether ring system was formed using such a strategy which was however found to be rather challenging. Standard conditions resulted in low yields (15–20%), particularly when the reaction was carried out on a gram scale. Extensive optimization led to the identification that the use of 10 equivalents of methanol is crucial for the cyclization of **133**. The reaction was indeed much more sluggish without this additive (>24 h *vs.* 3–6 h), which was attributed to a possible increased solubility of the copper salt or to the *in situ* formation of the boron dimethyl ester. Moreover, the use of triethylamine (in place of pyridine) as base led to a notably more facile transformation, an effect that is often observed in the Chan–Lam–Evans coupling in which the nature of the base is crucial to reduce the amounts of deborylated or oxidized side-products.

As evidenced with all examples described up to this part of this review article, it should be clear that metal-mediated, especially copper-mediated, reactions for the arylation of phenols have had a deep impact in natural product synthesis. The Ullmann condensation, which can now be performed under relatively mild conditions and that has emerged as a



Scheme 20 Intramolecular Chan–Lam–Evans approaches to cycloisodityrosines and piperazinomycin.



Scheme 21 Snapper and Hoveyda' total synthesis of chloropeptin I based on an intramolecular Chan–Lam–Evans reaction.

robust synthetic tool, together with, to a lesser extent, the Chan–Lam–Evans reaction, have enabled new bond disconnections and have now quite replaced more classical approaches based on nucleophilic aromatic substitutions.

Together with the development of efficient processes operating under mild conditions, the renaissance of copper catalysis has also broadened the number of substrates that can be used for the formation of C–O bonds. Indeed, while the seminal contribution of Fritz Ullmann was restricted to the use of phenols as *O*-nucleophiles, alcohols can now be used and their arylation actually provides quite a convenient alternative to classical reactions such as the Williamson synthesis for the preparation or aryl alkyl ethers.

This also had an impact in total synthesis and representative examples will be overviewed in the next section.

Copper-mediated synthesis of naturally occurring aryl alkyl ethers

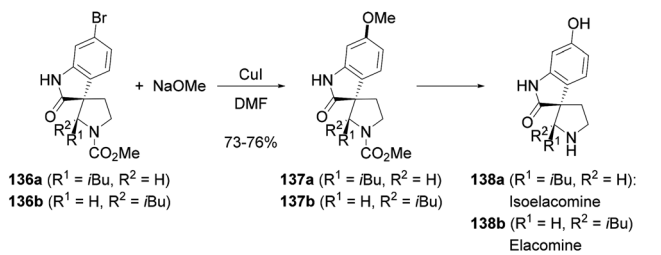
Synthesis of naturally occurring aryl alkyl ethers based on intermolecular Ullmann and Chan–Lam–Evans reactions

Aryl alkyl ethers can also be found in a variety of natural products. While their preparation classically relies on the Williamson and Mitsunobu reactions or on nucleophilic aromatic substitutions, recent advances in copper catalysis have enabled the development of robust systems for the arylation of aliphatic alcohols with aryl halides.

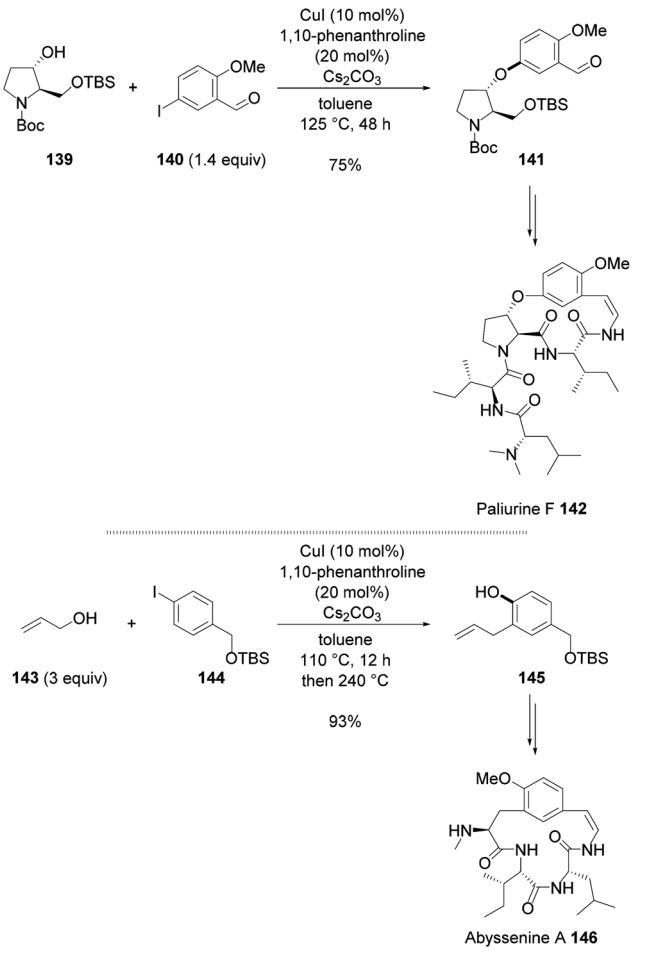
In addition to the fact that this reaction can be performed, in most cases, with catalytic amounts of copper complexes, it does provide an alternative disconnection to the aryl alkyl ether moiety compared to classical approaches ($C(sp^2)$–O *vs.* $C(sp^3)$–O). This strategy however has some inherent risks and is still only scarcely used for the synthesis of natural products containing an aryl alkyl ether moiety.

Indeed, while the Ullmann reaction had been used as early as in 1993 by Sharpless for the large scale arylation of the alcohol in dihydroquinine and dihydroquinidine, therefore demonstrating its synthetic potential with a rather complex substrate,[65] the first application of this strategy was only reported some 10 years later by the Horne group (Scheme 22).[66] Classical conditions based on the use of sodium methoxide and stoichiometric copper iodide in DMF were used to replace the bromide in diastereoisomeric spirocycles **136** by a methoxy group, providing, after deprotection, the desired alkaloids, namely isoelacomine **138a** and elacomine **138b**. Compared to alternative approaches with the phenol moiety, protected or not, of the target molecules that would have been included in the starting materials, the strategy utilized by the Horne group clearly benefits from readily available starting materials (tryptamine) and high overall efficiency (5 linear steps in total), the bromine in addition strongly accelerating the key step during which the spirocyclic system is formed.

In 2007, we reported the first example of an "aliphatic Ullmann condensation" involving a complex alcohol, that obviously couldn't be used in excess, in the context of the total synthesis of the cyclopeptide alkaloid paliurine F **142** (Scheme 23).[67] To install the aryl alkyl ether bond of paliurine F, the highly functionalized hydroxyprolinol **139** and aryl iodide **140** were coupled using a slight modification of Buchwald's procedure relying on the combination of 10 mol% CuI, 20 mol% 1,10-phenanthroline and cesium carbonate in toluene at 125 °C and using a moderate excess (1.4 equiv.) of



Scheme 22 Total syntheses of isoelacomine and elacomine based on an Ullmann reaction under classical conditions.



Scheme 23 Total syntheses of the cyclopeptide alkaloids paliurine F and abyssenine A based on Buchwald's procedure for the aliphatic Ullmann condensation.

the iodide **140**. Under these conditions, pyrrolidinyl-aryl ether **141**, which could not be obtained using a Buchwald–Hartwig reaction, was obtained in 75% yield. Compared to other strategies previously reported for the installation of this key structural element based on nucleophilic substitution, inter- or intramolecular aromatic nucleophilic substitution and the Mitsunobu reaction, the use of an aliphatic Ullmann reaction enabled the use of readily available starting materials and clearly shortened the overall synthesis. This strategy, which was implemented in the synthesis of other cyclopeptide alkaloids,[68] was next extended to the synthesis of the trisubstituted aromatic core of abyssenine A **146** in combination with a Claisen rearrangement.[69] The coupling of aryl iodide **144** and allyl alcohol followed by simply heating the intermediate allyl ether at 240 °C enabled a clean Ullmann coupling–Claisen rearrangement sequence to the trisubstituted aromatic core **145** of abyssenine A in excellent yield.

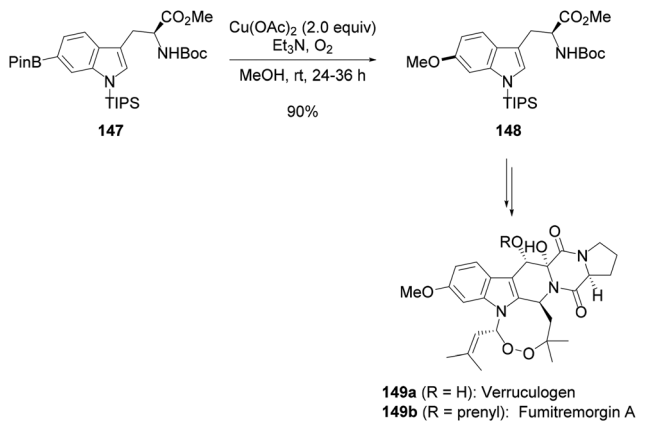
Concerning the Chan–Lam–Evans reaction involving aliphatic alcohols, it has only been scarcely used in natural product synthesis. The first report actually came from the Baran group in 2015 for the total syntheses of the bioactive alkaloids verruculogen **149a** and fumitremorgin A **149b** (Scheme 24).[70] An obvious straightforward route to construct the tricyclic piperidinoindole core of these complex targets would rely on a Pictet–Spengler reaction, which would in turn require starting from 6-methoxytryptophan **148** for which no short and scalable synthetic route was reported. This limitation was readily tackled by the Baran group which devised an especially straightforward and regioselective synthesis of this non-natural amino acid using a regioselective, iridium-catalyzed, ligand controlled borylation of protected tryptophan yielding **147** which was readily converted to the desired protected 6-methoxytryptophan **148** by a Chan–Lam–Evans reaction with methanol, therefore providing an efficient and scalable route to the preparation of the starting materials *en route* to the target natural products.

In addition to boronic acids, other arylmetal derivatives have been reported for the arylation of alcohols. They include arylbismuth, aryllead, arylstannanes, arylsiloxanes and aryliodonium derivatives.[4b] The use of an arylbismuth(v) reagent was key to the total synthesis of hirsutellone B **153**, a naturally occurring decahydrofluorene isolated from *Hirsutella nivea* BCC 2594 exhibiting strong antituberculosis activity, by the Nicolaou group (Scheme 25).[71] In this synthesis, an intermolecular arylation of the hindered secondary alcohol in **150** was performed using the Mukaiyama modification[72] of the Barton etherification,[73] a reaction that was found to proceed extremely well even with hindered alcohols, to install the aryl alkyl ether of the target molecule. The reaction of **150** with tetratolylbismuth fluoride **151** in the presence of catalytic amounts of cuprous acetate and methyldicyclohexylamine led to a smooth arylation occurring at room temperature, yielding the desired aryl alkyl ether **152** with a remarkable efficiency.

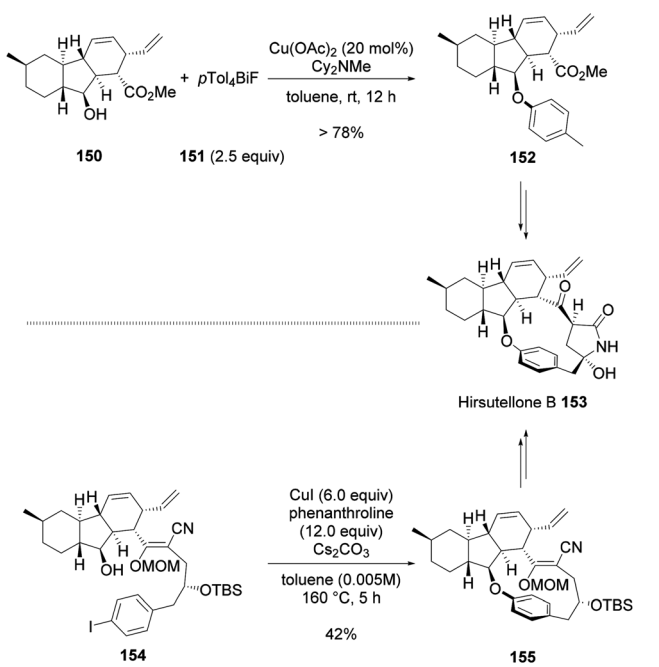
Intramolecular variants of the aliphatic Ullmann reaction have also been used for the synthesis of a couple of natural products, and notably for the total synthesis of hirsutellone B, that will now be described.

The intramolecular aliphatic Ullmann reaction in total synthesis

Such intramolecular variants indeed provide original bond disconnections in total synthesis and have been elegantly implemented by various research groups. One of the most spectacular examples was reported in 2011 by the Uchiro group which developed an alternate route to hirsutellone B relying on a spectacular and audacious intramolecular



Scheme 24 Baran's total syntheses of verruculogen and fumitremorgin A based on the synthesis of 6-methoxy-tryptophan by a Chan–Lam–Evans reaction.

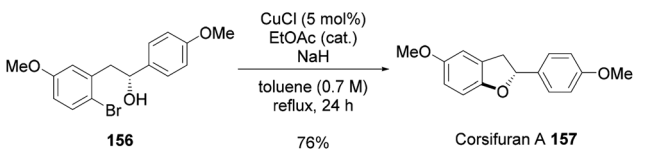


Scheme 25 Nicolaou's and Ushiro's total syntheses of hirsutellone B featuring intermolecular Barton and intramolecular Ullmann etherifications.

Ullmann condensation from the precursor **154** (Scheme 25).[74] The strained paracyclophane macrocycle was indeed installed, with good efficiency, especially when one keeps in mind the challenging nature of this macrocyclization, at the late stage of the synthesis using a modification of Buchwald's protocol. This vibrant example clearly highlights the impact of copper-mediated arylations in natural product synthesis and demonstrates that no one should be afraid of using such bond disconnections.

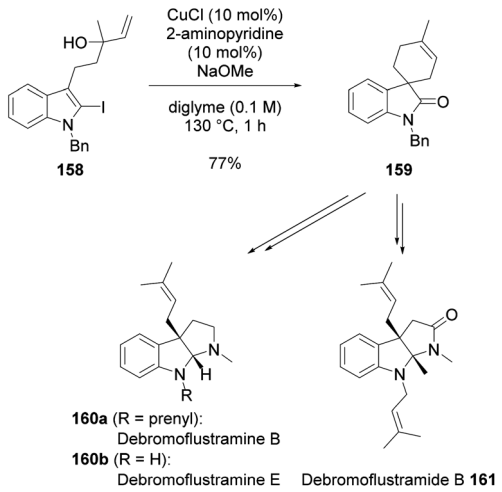
A simpler example of a related transformation was actually reported earlier by the Jones' group for the total synthesis of corsifuran A **157** (Scheme 26).[75] Aiming at developing an asymmetric route to this natural product whose configuration hadn't been determined, they envisioned using a metal-catalyzed cycloetherification from enantiomerically pure alcohol **156**. While the use of an intramolecular Buchwald–Hartwig reaction led to debromination and/or oxidation of the benzylic alcohol to the corresponding ketone, they eventually found that the cycloetherification could be promoted by using a combination of $Pd_2(dba)_3$, *t*-BuDavePhos (2-di-*tert*-butylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl) and sodium *tert*-butoxide in refluxing toluene. While a quantitative transformation could be obtained using these conditions, a racemization was found to occur by the reversible formation of a palladium hydride species formed by β-hydride elimination from the palladium(II) aryl alkoxide intermediate resulting from oxidative addition, yielding an important loss of stereochemical integrity (**157** isolated with 45% ee). This problem could be solved by switching to an intramolecular Ullmann condensation which smoothly provided the desired natural product with complete retention of the stereochemical information. Indeed, upon reaction with catalytic amounts of copper(I) chloride and ethyl acetate in the presence of sodium hydride, the desired corsifuran A **157** could be obtained in 76% yield and 100% ee.

The intramolecular Ullmann condensation involving aliphatic alcohols can in addition be used for the synthesis of natural products that do not contain an aryl ether. Kobayashi's total syntheses of debromoflustramines B **160a** and E **160b** and debromoflustramide B **161** is an interesting illustration of this strategy (Scheme 27).[76] The combination of an Ullmann coupling and a Claisen rearrangement, which we already discussed above for the total synthesis of abyssenine A, was found to provide an especially efficient entry to the debromoflustramines/amides from readily available starting materials. The intramolecular version of this reaction is quite spectacular and enables an easy access to the common intermediate in these syntheses, spiroxindole **159**, from the acyclic precursor



156 76% Corsifuran A **157**

Scheme 26 Jones' total syntheses of corsifuran A based on an intramolecular aliphatic Ullmann reaction.



Scheme 27 Kobayashi's total syntheses of debromoflustramines B and E and debromoflustramide B based on an intramolecular aliphatic Ullmann reaction/Claisen rearrangement sequence.

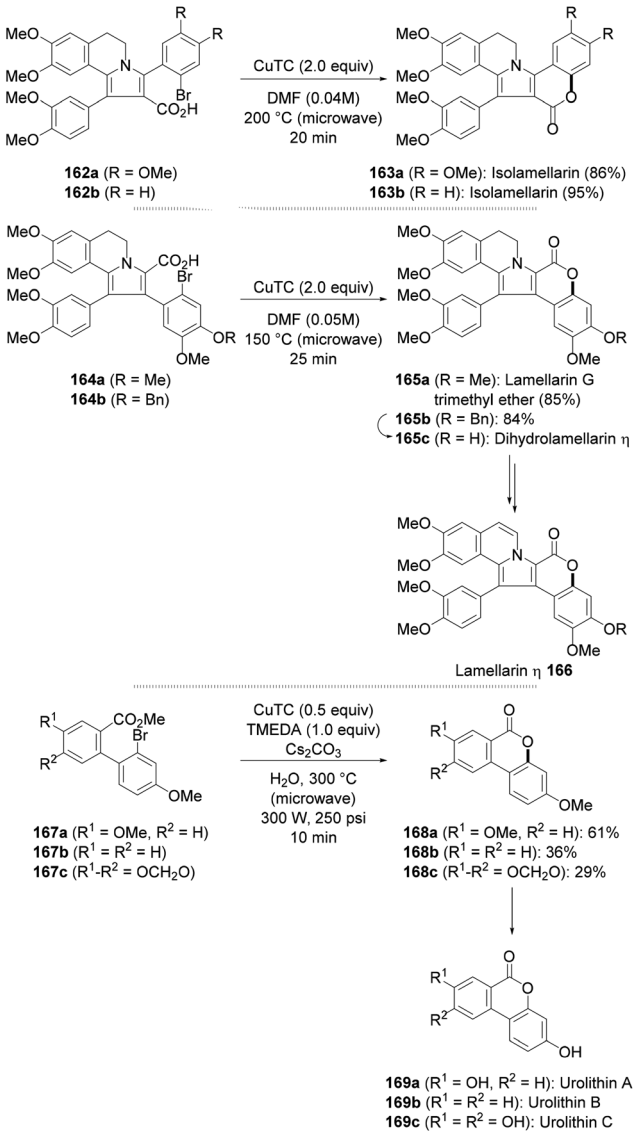
158. This reaction was efficiently catalyzed, in multigram quantities, by a combination of copper(I) chloride and 2-aminopyridine together with sodium methoxide as the base.

In addition to diaryl and aryl alkyl ethers, a metal-mediated reaction can also be used for the arylation of phenols to aryl esters. A single example of such a reaction in natural product synthesis has been reported to date and will be overviewed to close this review article.

Copper-mediated intramolecular arylation of carboxylic acids in total synthesis

While the intermolecular arylation of phenols with aryl halides is still an elusive transformation, its intramolecular variant was developed by Thasana who demonstrated its efficiency with the synthesis of isolamellarins **163** (Scheme 28).[77] Upon treatment with an excess of the Liebeskind catalyst CuTC in DMF at 200 °C under microwave irradiation, bromoaryl benzoic acids **162** cyclized to the desired polycyclic targets in excellent yields. As a note, an alternative procedure for the formation of the lactone ring based on a formal C–H activation from a debrominated analogue of **162** and using lead(IV) acetate also provided the isolamellarins, but in a disappointing yield (7%). The efficiency of this cyclization was further highlighted by the Opatz group starting from bromoaryl benzoic acids **164**, in which the bromoaryl and carboxylic moieties have switched places compared to the substrates **162** used in Thanasa's synthesis, whose cyclizations provided three other lamellarins, namely lamellarin G trimethyl ether **165a**, dihydrolamellarin η **165c** and lamellarin η **166**.[78]

The Thasana group reported some years later an improved substoichiometric procedure based on the use of a diamine ligand in subcritical water using microwave irradiations that



Scheme 28 Intramolecular arylation of carboxylic acids for the total synthesis of lamellarins and urolithins.

allowed for a remarkably fast cyclization, acyclic bromoesters **167** providing the corresponding benzochromenones **168**, direct precursors of the urolithins A–C **169** within 10 minutes and in moderate to good yields.[79]

Conclusions

If the reader arriving at the conclusion of this review article is not convinced that metal-, and especially copper- mediated reactions had a phenomenal impact in natural product synthesis, we'd have obviously done a poor job. The syntheses we have overviewed demonstrate the impact of these reactions in total synthesis: new bond disconnections have not only emerged for the formation of C(sp^2)–O bonds but have also changed the way chemists envision the installation of certain functional groups. This has actually some implications that go far beyond natural product chemistry since when a reaction has demonstrated its synthetic usefulness for the preparation of a range of natural products, it feels reasonable to say that it is a robust one that can be safely utilized on a broad range of substrates.

And indeed, beyond the applications of these metal-mediated reactions in total synthesis that we have overviewed, they also had a deep impact in many areas of science including medicinal chemistry, agrochemistry, and polymer and material sciences. Some limitations still remain to be overcome however. In order for palladium to compete with copper for the formation of C(sp^2)–O bonds, there is still a long way to go, notably to fully suppress competing β-hydride elimination that is too often observed when palladium-based catalytic systems are used on complex systems. As for copper, which has clearly been a real gold mine in natural product synthesis, the catalyst loadings are still too high in most cases and the reaction conditions often too harsh. The extension of the Ullmann condensation to the use of aryl chlorides and triflates would also represent a major step forward, even if significant progress has been recently made with the former.[80] Tackling these limitations would probably also have a significant impact in natural product synthesis and render this transformation even more attractive...

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Université libre de Bruxelles (ULB). J. W. and A. N. acknowledge the Chinese Scholarship Council (CSC) and the Fonds pour la formation à la Recherche dans l'Industrie et dans l'Agriculture (F.R.I.A.) respectively for graduate fellowships.

Notes and references

1 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2016, **79**, 629.
2 M. Feher and J. Schmidt, *J. Chem. Inf. Comput. Sci.*, 2003, **43**, 218.
3 F. Ullmann and P. Sponagel, *Ber. Dtsch. Chem. Ges.*, 1905, **38**, 2211.
4 (*a*) A. Tlili and M. Taillefer, in *Copper-Mediated Cross-Coupling Reactions*, ed. G. Evano and N. Blanchard, John Wiley & Sons, Hoboken, 2013, pp. 41–111; (*b*) L. Neuville, in *Copper-Mediated Cross-Coupling Reactions*, ed. G. Evano and N. Blanchard, John Wiley & Sons, Hoboken, 2013, pp. 113–185.
5 (*a*) A. R. Muci and S. L. Buchwald, in *Practical Palladium Catalysts for C–N and C–O Bond Formation. Topics in Current Chemistry*, ed. N. Miyaura, Springer-Verlag, Berlin, 2001,

vol. 219, pp. 131–209; (*b*) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-I. Negishi, John-Wiley & Sons, New York, 2002, pp. 1097–1106.
6 For a review of metal-catalyzed etherifications, see: K. K. Krishnan, S. M. Ujwaldev, K. S. Sindhu and G. Anilkumar, *Tetrahedron*, 2016, **72**, 7393.
7 For general references on the use of metal-mediated reactions for the formation of C(sp^2)–O bonds in natural products, see: (*a*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (*b*) E. N. Pitsinos, V. P. Vidali and E. A. Couladouros, *Eur. J. Org. Chem.*, 2011, 1207; (*c*) D. Pappo, in *Copper-Mediated Cross-Coupling Reactions*, ed. G. Evano and N. Blanchard, John Wiley & Sons, Hoboken, 2013, pp. 643–682; (*d*) G. Evano, C. Theunissen and A. Pradal, *Nat. Prod. Rep.*, 2013, **30**, 1467.
8 M. S. Islam, M. Kitagawa, M. Imoto, T. Kitahara and H. Watanabe, *Biosci., Biotechnol., Biochem.*, 2006, **70**, 2523.
9 M. Tomita, K. Fujitani and Y. Aoyagi, *Chem. Pharm. Bull.*, 1965, **13**, 1341.
10 (*a*) M. Tomita, K. Fujitani and Y. Aoyagi, *Tetrahedron Lett.*, 1966, **7**, 4243; (*b*) M. Tomita, K. Fujitani and Y. Aoyagi, *Chem. Pharm. Bull.*, 1968, **16**, 62.
11 (*a*) Y. Inubushi, Y. Masaki, S. Matsumoto and F. Takami, *Tetrahedron Lett.*, 1968, **9**, 3399; (*b*) Y. Inubushi, Y. Masaki, S. Matsumoto and F. Takami, *J. Chem. Soc. C*, 1969, 1547.
12 D. A. Evans and J. A. Ellman, *J. Am. Chem. Soc.*, 1989, **111**, 1063.
13 U. Schmidt, D. Weller, A. Holder and A. Lieberknecht, *Tetrahedron Lett.*, 1988, **29**, 3227.
14 For the total synthesis of a related natural product, renieramide, see: B. Lygo and L. D. Humphreys, *Synlett*, 2004, 2809.
15 M. Toyota, M. Tori, K. Takikawa, Y. Shiobara, M. Kodama and Y. Asakawa, *Tetrahedron Lett.*, 1985, **26**, 6097.
16 T. Eicher, S. Fey, W. Puhl, E. Buchel and A. Speicher, *Eur. J. Org. Chem.*, 1998, 877.
17 A. Ingerl, K. Justus, V. Hellwig and W. Steglich, *Tetrahedron*, 2007, **63**, 6548.
18 A. Fürstner and C. Müller, *Chem. Commun.*, 2005, 5583.
19 (*a*) J. Pospíšil, C. Müller and A. Fürstner, *Chem. – Eur. J.*, 2009, **15**, 5956; (*b*) J. L. Carr, D. A. Offermann, M. D. Holdom, P. Dusart, A. J. P. White, A. J. Beavil, R. J. Leatherbarrow, S. D. Lindell, B. J. Sutton and A. C. Spivey, *Chem. Commun.*, 2010, **46**, 1824.
20 S. D. Rychnovsky and K. Hwang, *J. Org. Chem.*, 1994, **59**, 5414.
21 (*a*) E. A. Couladouros and I. C. Soufli, *Tetrahedron Lett.*, 1995, **36**, 9369; (*b*) K. K. Gangakhedkar, *Synth. Commun.*, 1996, **26**, 1887; (*c*) E. A. Couladouros, I. C. Soufli, V. I. Moutsos and R. K. Chadha, *Chem. – Eur. J.*, 1998, **4**, 33.
22 D. Boger and D. Yohannes, *J. Org. Chem.*, 1990, **55**, 6000.
23 J.-F. Marcoux, S. Doye and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 10539.
24 X. Xing, D. Padmanaban, L.-A. Yeh and G. D. Cuny, *Tetrahedron*, 2002, **58**, 7903.
25 P. Capdevielle and M. Maumy, *Tetrahedron Lett.*, 1993, **34**, 1007.
26 E. Buck, Z. J. Song, D. Tschaen, P. G. Dormer, R. P. Volante and P. J. Reider, *Org. Lett.*, 2002, **4**, 1623.
27 N. Jung and S. Bräse, *Eur. J. Org. Chem.*, 2009, 4494.
28 D. Ma and Q. Cai, *Org. Lett.*, 2003, **5**, 3799.
29 Q. Cai, G. He and D. Ma, *J. Org. Chem.*, 2006, **71**, 5268.
30 J.-H. Kwak, J.-K. In, M.-S. Lee, E.-H. Choi, H. Lee, J. T. Hong, Y.-P. Yun, S. J. Lee, S.-Y. Seo, Y.-G. Suh and J.-K. Jung, *Arch. Pharmacal Res.*, 2008, **31**, 1559.
31 (*a*) N. Blank and T. Opatz, *J. Org. Chem.*, 2011, **76**, 9777; (*b*) K. Nishimura, S. Horii, T. Tanahashi, Y. Sugimoto and J. Yamada, *Chem. Pharm. Bull.*, 2013, **61**, 59.
32 B.-S. Jeong, Q. Wang, J. K. Son and Y. Jahng, *Eur. J. Org. Chem.*, 2007, 1338.
33 M. Q. Salih and C. M. Beaudry, *Org. Lett.*, 2012, **14**, 4026.
34 V. C. Bryant, G. D. K. Kumar, A. M. Nyong and A. Natarajan, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 245.
35 L. Shen and D. Sun, *Tetrahedron Lett.*, 2011, **52**, 4570.
36 L. Shen, C. J. Simmons and D. Sun, *Tetrahedron Lett.*, 2012, **53**, 4173.
37 G. D. K. Kumar and A. Natarajan, *Tetrahedron Lett.*, 2008, **49**, 2103.
38 (*a*) Z.-Q. Zhu, M. Q. Salih, E. Fynn, A. D. Bain and C. M. Beaudry, *J. Org. Chem.*, 2013, **78**, 2881; (*b*) Z.-Q. Zhu and C. M. Beaudry, *J. Org. Chem.*, 2013, **78**, 3336.
39 (*a*) D. L. Boger and D. Yohannes, *J. Am. Chem. Soc.*, 1991, **113**, 1427; (*b*) D. L. Boger, D. Yohannes, J. Zhou and M. A. Patane, *J. Am. Chem. Soc.*, 1993, **115**, 3420; (*c*) D. L. Boger, M. A. Patane and J. Zhou, *J. Am. Chem. Soc.*, 1994, **116**, 8544.
40 D. L. Boger, S. M. Sakya and D. Yohannes, *J. Org. Chem.*, 1991, **56**, 4204. Also see: G. R. Pettit, P. D. Quistorf, J. A. Fry, D. L. Herald, E. Hamel and J.-C. Chapuis, *J. Nat. Prod.*, 2009, **72**, 876.
41 D. L. Boger and J. Zhou, *J. Am. Chem. Soc.*, 1993, **115**, 11426.
42 G. M. Keserii, M. Nógrádi and A. Szöllösy, *Eur. J. Org. Chem.*, 1998, 521.
43 D. L. Boger, Y. Nomoto and B. R. Teegarden, *J. Org. Chem.*, 1993, **58**, 1425.
44 F. Ullmann, *Ber. Dtsch. Chem. Ges.*, 1903, **36**, 2382.
45 (*a*) K. C. Nicolaou, H. Li, C. N. C. Boddy, J. M. Ramanjulu, T.-Y. Yue, S. Natarajan, X.-J. Chu, S. Bräse and F. Rübsam, *Chem. – Eur. J.*, 1999, **5**, 2584; (*b*) K. C. Nicolaou, C. N. C. Boddy, H. Li, A. E. Koumbis, R. Hughues, S. Natarajan, N. F. Jain, J. M. Ramanjulu, S. Bräse and M. E. Solomon, *Chem. – Eur. J.*, 1999, **5**, 2602; (*c*) K. C. Nicolaou, A. E. Koumbis, M. Takayanagi, S. Natarajan, N. F. Jain, T. Bando, H. Li and R. Hughues, *Chem. – Eur. J.*, 1999, **5**, 2622; (*d*) K. C. Nicolaou, H. J. Mitchell, N. F. Jain, T. Bando, R. Hughes, N. Winssinger, S. Natarajan and A. E. Koumbis, *Chem. – Eur. J.*, 1999, **5**, 2648.
46 M. Q. Salih and C. M. Beaudry, *Org. Lett.*, 2013, **15**, 4540.

47 Q. Cai, B. Zou and D. Ma, *Angew. Chem., Int. Ed.*, 2006, **45**, 1276.
48 A. Moreau, A. Couture, E. Deniau and P. Grandclaudon, *J. Org. Chem.*, 2004, **69**, 4527.
49 J. Wang and G. Evano, *Org. Lett.*, 2016, **18**, 3542.
50 N. Otto, D. Ferenc and T. Opatz, *J. Org. Chem.*, 2017, **82**, 1205.
51 (*a*) D. M. T. Chan, K. L. Monaco, R.-P. Wang and M. P. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933; (*b*) D. A. Evans, J. L. Katz and T. R. West, *Tetrahedron Lett.*, 1998, **39**, 2937; (*c*) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941.
52 J. X. Qiao and P. Y. S. Lam, *Synthesis*, 2011, 829.
53 D. A. Evans, J. L. Katz and T. R. West, *Tetrahedron Lett.*, 1998, **39**, 2937.
54 M. E. Jung and T. I. Lazarova, *J. Org. Chem.*, 1999, **64**, 2976.
55 Y.-C. Wang and P. E. Georghiou, *Org. Lett.*, 2002, **4**, 2675.
56 D. Cousin, J. Mann, M. Nieuwenhuyzen and H. van der Berg, *Org. Biomol. Chem.*, 2006, **4**, 54.
57 O. Skaff, K. A. Jolliffe and C. A. Hutton, *J. Org. Chem.*, 2005, **70**, 7353.
58 S.-Y. Seo, J.-W. Jung, J.-K. Jung, N.-J. Kim, Y.-W. Chin, J. Kim and Y.-G. Suh, *J. Org. Chem.*, 2007, **72**, 666.
59 J.-W. Jung, J. Jang, S.-Y. Seo, J.-K. Jung and Y.-G. Suh, *Tetrahedron*, 2010, **66**, 6826.
60 D. A. Evans, J. L. Katz, G. S. Peterson and T. Hintermann, *J. Am. Chem. Soc.*, 2001, **123**, 12411.
61 P. J. Kreitsky and D. L. Boger, *Tetrahedron Lett.*, 2002, **43**, 407.
62 Y. Hitotsuyanagi, H. Ishikawa, S. Naito and K. Takeya, *Tetrahedron Lett.*, 2003, **44**, 5901.
63 S. Gosh, A. S. Kumar, G. N. Mehta, R. Soundararajan and S. Sen, *ARKIVOC*, 2009, **vii**, 72.
64 H. B. Deng, J. K. Jung, T. Liu, K. W. Kuntz, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, 9032.
65 W. Amberg, Y. L. Bennani, R. K. Chadha, G. A. Crispino, W. D. Davis, J. Hartung, K. S. Jeong, Y. Ogino, T. Shibata and K. B. Sharpless, *J. Org. Chem.*, 1993, **58**, 844.
66 F. Y. Miyake, K. Yakushijin and D. A. Horne, *Org. Lett.*, 2004, **6**, 711.
67 M. Toumi, F. Couty and G. Evano, *Angew. Chem., Int. Ed.*, 2007, **46**, 572.
68 (*a*) M. Toumi, F. Couty and G. Evano, *Synlett*, 2008, 29; (*b*) M. Toumi, V. Rincheval, A. Young, D. Gergeres, E. Turos, F. Couty, B. Mignotte and G. Evano, *Eur. J. Org. Chem.*, 2009, 3368; (*c*) G. Evano, M. Toumi and A. Coste, *Chem. Commun.*, 2009, 4166.
69 M. Toumi, F. Couty and G. Evano, *J. Org. Chem.*, 2007, **72**, 9003.
70 Y. Feng, D. Holte, J. Zoller, S. Umemiya, L. R. Simke and P. S. Baran, *J. Am. Chem. Soc.*, 2015, **137**, 10160.
71 K. C. Nicolaou, D. Sarlah, T. R. Wu and W. Zhan, *Angew. Chem., Int. Ed.*, 2009, **48**, 6870.
72 T. Mukaiyama, N. Sakurai and K. Ikegai, *Chem. Lett.*, 2006, **35**, 1140.
73 R. A. Abramovitch, D. H. R. Barton and K. P. Finet, *Tetrahedron*, 1988, **44**, 3039.
74 H. Uchiro, R. Kato, Y. Arai, M. Hasegawa and Y. Kobayakawa, *Org. Lett.*, 2011, **13**, 6268.
75 H. Adams, N. J. Gilmore, S. Jones, M. P. Muldowney, S. H. von Reuss and R. Vemula, *Org. Lett.*, 2008, **10**, 1457.
76 H. Miyamoto, Y. Okawa, A. Nakazaki and S. Kobayashi, *Tetrahedron Lett.*, 2007, **48**, 1805.
77 N. Thasana, R. Worayuthakarn, P. Kradanrat, E. Hohn, L. Young and S. Ruchirawat, *J. Org. Chem.*, 2007, **72**, 9379.
78 D. Imbri, J. Tauber and T. Opatz, *Chem. – Eur. J.*, 2013, **19**, 15080.
79 P. Nealmongkol, K. Tangdenpaisal, S. Sitthimonchai, S. Ruchirawat and N. Thasana, *Tetrahedron*, 2013, **69**, 9277.
80 M. Fan, W. Zhou, Y. Jiang and D. Ma, *Angew. Chem., Int. Ed.*, 2016, **55**, 6211.