Review

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Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis

Gwilherm Evano,*,† Nicolas Blanchard,*,‡ and Mathieu Toumi†

Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles Saint Quentin en Yvelines, 45 avenue des Etats-Unis, 78035 Versailles Cedex, France, and Laboratoire de Chimie Organique, Bioorganique et Macromoléculaire, UMR CNRS 7015, ENSCMu, Université de Haute-Alsace, 3 rue A. Werner, 68093 Mulhouse Cedex, France

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* Authors to whom correspondence should be addressed (evano@chimie.uvsq.fr, nicolas.blanchard@uha.fr).
† Université de Versailles Saint Quentin en Yvelines.
‡ Université de Haute-Alsace.

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1. Introduction

Natural product synthesis is a highly demanding field in constant need of efficient transformations that allow either straightforward, scalable, and high-yielding preparation of starting materials or especially tolerant reactions that can be used in end game strategies on complex substrates to install a certain functional group with the utmost delicacy and surgical precision. Although many chemical transformations do perform well when applied to relatively simple, commercially available molecules, only a few of them can be used for the preparation of complex natural products in which they are clearly challenged and pushed way beyond their limits. The complex structures and functionalities of these targets ensure that only robust and selective methods come through such a trial. When successful, however, such reactions can enter the "hall of fame" of efficient procedures, and the use of reactions such as olefin metathesis, asymmetric hydrogenations, or oxidations in the context of natural product synthesis clearly helped demonstrate their efficiency, reliability, and generality.

Until the beginning of the 21st century, this was certainly not the case for copper-mediated C−N, C−O, and C−C bond formation reactions, first reported a hundred years ago in the pioneering and remarkable work of Ullmann and Goldberg. Even if these conceptual publications clearly are the basis of today's developments of copper-mediated reactions, and even if they found numerous industrial and academic applications, harsh reaction conditions and low substrate scope hampered their use in natural product synthesis. Using such reactions on complex substrates was a strategic decision that bore way too much risk, and even seemed somewhat counterintuitive: palladium-catalyzed transformations were preferred in most cases, and only smart adaptations of the classical reaction conditions or activation of the aryl halide were reported from time to time for the synthesis of complex targets.

This situation has come to an end with the development, in the past 10 years or so, of highly efficient catalytic systems that allow reactions to be conducted in milder conditions and with dramatically enhanced yields compared to classical procedures. The keys to the success of these improved conditions were the observation that simple organic derivatives could speed up cross-couplings and the introduction of new reaction partners such as organoboranes. This has allowed for the use of a wide range of substrates and mild reaction conditions together with the extension of these coupling reactions to the introduction of vinyl and alkyne functional groups. The synthetic potential of these transformations is now quite obvious, even if the golden age of copper-mediated cross-coupling reactions is probably just beginning. Their application in natural product synthesis has flourished recently: an array of copper-mediated procedures has been successfully employed to assemble many complex targets with new and efficient bond disconnections. They will occupy center stage in this review, which covers the literature up to February 2008.

Examples have been classified according to the nature of the bond (C−N, C−O, and C−C) formed in the copper-mediated process and are further subclassified by the nature of the two reaction partners. Additionally, an overview of the state-of-the-art procedures available for each bond formation has also been included together with a brief historical perspective: this first section is not intended to be exhaustive, and the reader is referred to excellent previous reviews for complete discussions of these areas.[1—6] In this section, recent developments are described and surveys of selected efficient and general procedures are shown in tables, which can be used as guides to search for "first-attempt" reaction conditions for a planned transformation. The spectacular achievements of these new methodologies in the context of natural product synthesis will then be described. Whenever possible, comparison with palladium-catalyzed transformations or alternative approaches will be presented.

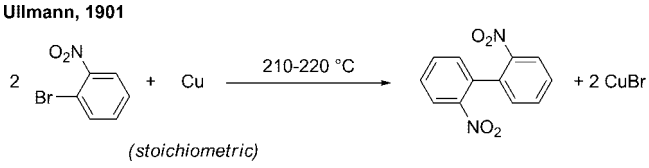
It should, however, be noted that reactions requiring the formation of discrete organometallic species before copper-mediated cross-coupling are beyond the scope of this review, as well as C−S bond formation procedures, which have found too few applications in natural product synthesis to date.

Gwilherm Evano studied chemistry at the Ecole Normale Supérieure in Paris (France) and received his Ph.D. from Université Pierre et Marie Curie in 2002 under the supervision of François Couty and Claude Agami. After postdoctoral study with James S. Panek at Boston University, working on the total synthesis of the ansamycin natural products Cytotrienin A and Reblastatin, he joined the CNRS as Chargé de Recherche at the University of Versailles in 2004. His research interests focus on asymmetric synthesis and reactivity of nitrogen heterocycles, copper-catalyzed cyclization reactions, and the total synthesis of natural products.

Nicolas Blanchard obtained his Ph.D. in 2000 from Paris VI University (France) under the supervision of Professor J. Cossy and Dr. C. Meyer, working on the total synthesis of the ionophoric antibiotic zincophorin. He then joined Professor W. R. Roush (University of Michigan) for a postdoctoral stay (2001−2002) as a Lavoisier fellow, working on the total synthesis of the plecomacrolide formamicin. In late 2002, he joined the CNRS as Chargé de Recherche in Professor Kouklovsky's laboratory (Orsay University, France). In 2006, he moved to the group of Prof. J. Eustache (Haute-Alsace University, France). His research interests focus on the synthesis of biologically relevant compounds using new methodologies including nitroso Diels−Alder cycloadditions and stereoselective metal-mediated transformations.

Mathieu Toumi obtained his B.A. degree from the University of Versailles and is currently engaged in Ph.D. research under the supervision of François Couty and Gwilherm Evano at the Lavoisier Institute. His work has focused on the development of copper-mediated cyclization reactions with application in total synthesis of several alkaloids.

Scheme 1. Ullmann Reaction: Synthesis of Biaryls



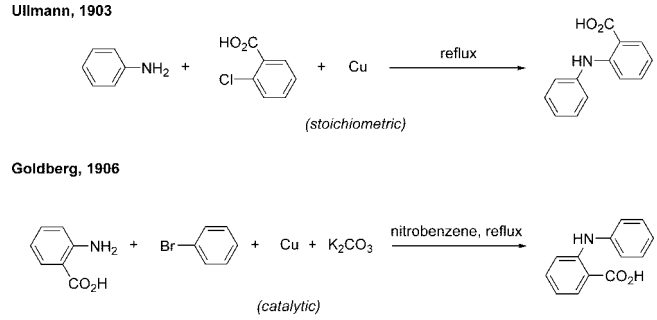
2. Background: Copper-Mediated Coupling Reactions

2.1. Ullmann, Goldberg, and Hurtley Coupling Reactions

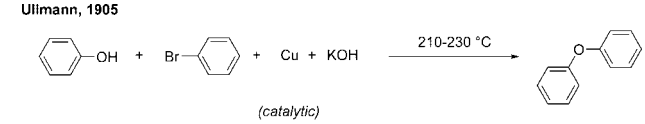
The foundations of modern copper-mediated chemistry lie in the pioneering and remarkable work of Fritz Ullmann and Irma Goldberg. It all started in 1901 when Ullmann reported that "Erhitzt man o-Bromnitrobenzol mit fein vertheiltem Kupferpulver, so bemerkt man, dass letzteres seinen Glanz verliert und in eine matte graue Masse verwandelt wird. Bei Aufarbeitung des Reactionsproductes zeigte sich nun, dass das Kupfer zum grössten Theil in Cuprobromid und das Bromnitrobenzol in eine bromfreie Substanz verwandelt worden ist, welche sich bei näherer Untersuchung identisch, mit der von Tauber auf andere Weise dargestellten 2.2′-Dinitrobiphenyl erwies." (If one heats *o*-bromonitrobenzene with fine spreaded Cu powder, one recognizes that the last one is losing its shine and turns into a mattegray mass. After purification of the reaction products, it appears that copper has turned into a copper bromide and that the bromonitrobenzene has turned into a brome-free substance, which, on a closer look, turns out to be identical with the 2,2-dinitrobiphenyl synthesized in a different way by Tauber.)[7] Two molecules of *o*-bromonitrobenzene could be coupled in the presence of metallic copper to give the corresponding biaryl: the Ullmann reaction was born (Scheme 1).

Two years later, Ullmann reported that aniline reacted with 2-chlorobenzoic acid in the presence of 1 equiv of copper to give 2-phenylaminobenzoic acid,[8] a reaction that was shown to be catalytic by Goldberg in 1906 starting from the potassium salt of 2-aminobenzoic acid (Scheme 2).[9] It is quite amazing to note, a century later, that the ortho-effect that still has a deep impact on copper-mediated transformations was already touched upon.

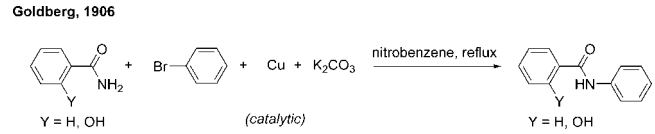
Scheme 2. Ullmann Condensation Reaction: Synthesis of Diarylamines



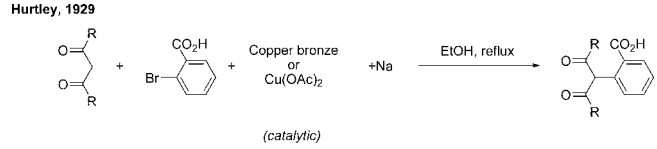
Scheme 3. Ullmann Condensation Reaction: Synthesis of Diarylethers



Scheme 4. Goldberg Condensation Reaction: Synthesis of Arylamides



Scheme 5. Hurtley Reaction: Arylation of CH-Acid Derivatives



Ullmann next extended the reaction to the preparation of diphenyl ether by reaction of potassium phenoxide and bromobenzene and demonstrated the considerable effect of catalytic amounts of copper on the rate of the reaction (Scheme 3).[10] A year later, the first copper-catalyzed arylation of amides was successfully reported by Goldberg, who managed to condense bromobenzene with benzamide and salicylamide (Scheme 4).[9]

Some 20 years later, another exceptional contribution was reported by William R. H. Hurtley: under the catalytic influence of copper−bronze or copper acetate, the halogen atom in *o*-bromobenzoic acid is easily substituted by sodium salts of diketones and malonates (Scheme 5).[11] Here again, the ortho-effect had a dramatic influence because "the halogen atom in *o*-bromobenzoic acid is much more reactive".

These pioneering contributions clearly paved the way for the development of copper-mediated coupling reactions and are the basis of today's developments. Since the early work of Ullmann, Goldberg, and Hurtley, an array of copper sources, ligands, and preformed catalysts have been introduced and used for the development of milder and general procedures.

2.2. Available Copper-Based Systems

This "Copper Catalysis Toolbox", so named by Kunz and co-workers,[2] is now relatively consistent, even if less developed than the corresponding palladium one. As a general trend, copper-catalyzed cross-coupling reactions are

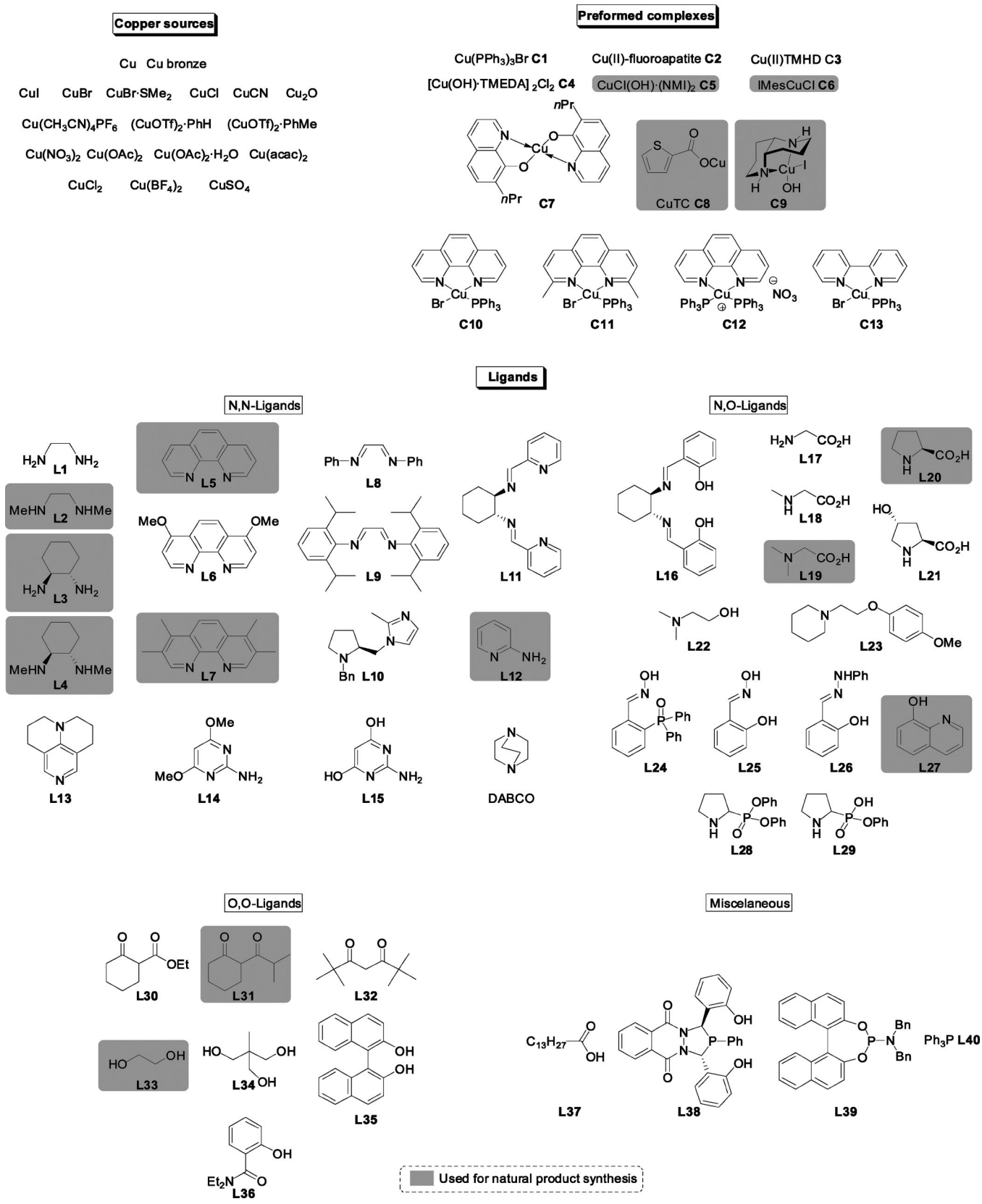
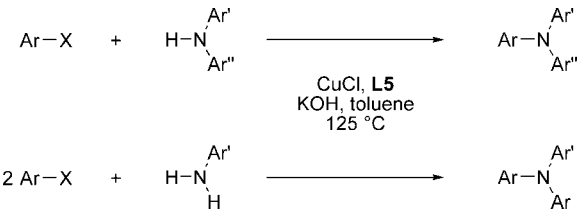


Figure 1. Copper Catalysis Toolbox: Copper Sources, Preformed Complexes, and Ligands.

not too sensitive to the choice of the copper source [copper(I) in most cases], but the choice of other parameters (ligand, base, solvent) is often crucial. Concerning the base itself, one should keep in mind a practical and important parameter: the quality and particle size of inorganic bases can have a dramatic impact on the yields and kinetics of the reactions. Copper sources, ligands, and preformed complexes that will be described in this review are shown in Figure 1; for clarity, ligands and preformed complexes used in the context of natural product synthesis are highlighted in gray.

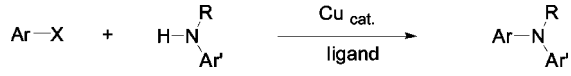
Scheme 6. Goodbrand's Synthesis of Triarylamines



2.3. C−N Bond Formation

Functionalized aromatic and heteroaromatic amines are key building blocks for the synthesis of pharmaceuticals, polymers, or materials. In recognition of their widespread importance, many synthetic methods have emerged over the years for the formation of C−N bonds, trying to overcome the shortcomings of the original Ullmann and Goldberg procedures.[12,13] The discovery of efficient palladium-catalyzed amination reactions by Buchwald and Hartwig has been a major breakthrough in this field, opening access to a huge number of aromatic amines that could hardly be obtained before and using mild and tunable reaction conditions.[14] Despite these significant improvements, limitations still exist, such as air and moisture sensitivity, functional group tolerance, or the high cost of palladium. They have forced chemists to reconsider other metal catalysts, and the Ullmann and Goldberg coupling reactions have been extensively revisited. One of the first modifications relied on the use of more reactive arylating agents involving organobismuth, -lead, -stannanes, and -siloxanes or hypervalent iodonium salts: these efficient procedures that require the preparation of the arylating agent have been extensively reviewed.[1,15] In 1998, independent publications by Chan[16] and Lam[17] revolutionized the copper-mediated arylation of *N*-nucleophiles as they reported a generally applicable protocol for the arylation of amines using stoichiometric copper(II) acetate and boronic acids at room temperature with an impressive range of nucleophiles. Over the past 10 years, the arylation of *N*-nucleophiles with arylboronic acids has become a standard and was reviewed in 2003 by Thomas and Ley.[1] Recently, the introduction of chelating ligands has led to dramatic improvements, and an impressive number of milder Ullmann-type methodologies have been reported,

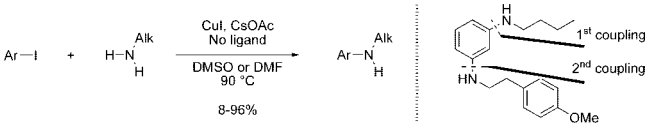
Table 1. Optimized Reaction Conditions for Copper-Mediated Arylation of Aromatic Amines



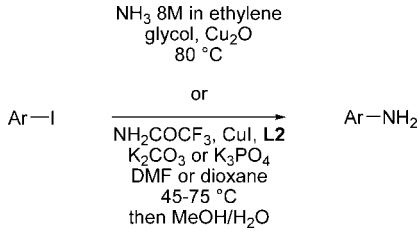
Entry	Ar	X	H−N(R)(Ar')	Copper source	Ligand	Base	Conditions	Yields	Number of examples	Ref.
1	Simple aromatics	I, Br, Cl	diphenylamine	**C11**		^{t}BuOK	Toluene, 110 °C	49-88%	6	22
2	Simple aromatics	I	primary anilines,[a] secondary aniline	CuI	**L9**	^{t}BuOK	Toluene, 120 °C	38-97%	19	23
3	Simple aromatics	I	primary anilines, cyclic secondary anilines, diarylamines	**C3**		^{t}BuOK	Toluene, 120 °C	70-95%	10	24
4	Simple aromatics	I	primary anilines,[a] secondary anilines, diarylamines	CuI	**L13**	^{t}BuONa	Toluene, 110 °C	60-96%	8	25
5	Simple aromatics	I	primary anilines	CuI	**L20**	K_2CO_3	DMSO, 90 °C	51-97%	9	26,27
6	Simple aromatics	I, Br	primary anilines, secondary aniline	CuI	**L29**	K_3PO_4	DMF, 90-110 °C	71-98%	14	28
7	Simple aromatics	I	primary anilines, diarylamines	**C1**		Cs_2CO_3	Toluene, 110-120 °C	10-88%	13	29
8	Simple aromatics	$B(OH)_2$	primary anilines, secondary anilines	$Cu(OAc)_2$	**L37**	2,6-lutidine	Toluene, air, rt	50-91%	16	30

[a] Double coupling to triarylamines.

Scheme 7. Ligand-free Arylation of Primary Alkylamines



Scheme 8. Synthesis of Primary Arylamines



allowing for the use of simpler and more accessible arylating agents such as aryl halides. They will be briefly overviewed in the following paragraphs according to the nature of the nucleophile (arylamines, alkylamines, amides, imides, carbamates, and *N*-heterocycles) and the halide (aromatic, alkenyl, alkynyl, or allenyl) with emphasis on the most general and widely applicable procedures together with a brief historical perspective.

2.3.1. Arylation of Arylamines

The copper-promoted arylation of anilines has been known for a century as the classical Ullmann coupling reaction. It necessitates the use of strongly aggressive conditions (high temperatures, extended reaction times, and strong base) and has been plagued by poor substrate scope and a capricious nature.

Following extensive mechanistic studies of the Ullmann condensation by Paine, who came to the conclusion that the active catalytic species are the soluble cuprous ions,[18] and early work by Bryant[19] and Capdevielle,[20] who reported on the use of esters as ligand for copper(I), Goodbrand and co-workers investigated the idea of a "ligated catalysis" of the Ullmann condensation and eventually found that 1,10-phenanthroline **L5** was an efficient ligand because triarylamines could be obtained at temperatures and reaction times lower than the ones usually required (Scheme 6).[21]

Following these early studies, a number of bidentate ligands were reported for the synthesis of arylamines: selected examples are collected in Table 1. They include a soluble complex with triphenylphosphine and neocuproine in combination with triphenylphosphine, which allows for the reaction to be performed in refluxing toluene and for the reaction of aryl bromides (Table 1, entry 1), azadienes (Table 1, entry 2), diketones (Table 1, entry 3), or azajulodine **L13** (Table 1, entry 4). However, these procedures still require the use of a strong base such as potassium or sodium *tert*-butoxide, but they could be replaced by weaker bases such as K_2CO_3, K_3PO_4, or Cs_2CO_3 if amino acids or aminophosphonates were used as ligands (Table 1, entries 5 and 6) or if the preformed, air-stable, and soluble $Cu(PPh_3)_3Br$ complex was employed (Table 1, entry 7).

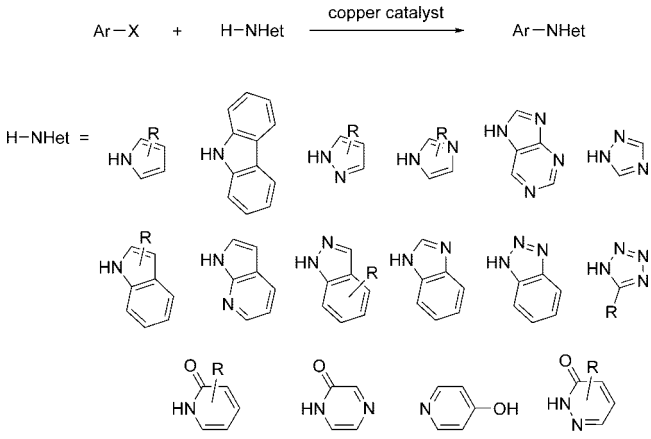


Figure 2. Arylation of *N*-heterocycles.

Because most procedures require the use of elevated temperatures for the arylation to proceed, the Chan−Lam coupling involving the reaction of an aniline with a boronic acid can therefore still be a useful method for the synthesis of di- or triarylamines: the use of myristic acid **L37** in combination with copper(II) acetate allows for a clean reaction in toluene at room temperature and is one of the most practical choices, provided that the boronic acid is readily available (Table 1, entry 8).

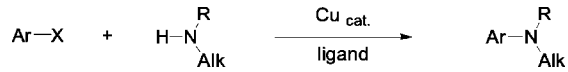
2.3.2. Arylation of Alkylamines

Extension of the Ullmann coupling reaction to the use of aliphatic amines has been a long-standing problem and first steps in this direction have only been achieved in the context of chelating substrates[31] such as α- and β-amino acids (Table 2, entry 1)[32−34] and β-amino alcohols (Table 2, entry 10).[35] An impressive improvement has, however, been reported by Fukuyama and co-workers, who were able to perform the arylation of primary aliphatic amines without using any chelating substrate or ligand: CsOAc used as a base allows for the reaction to be performed at 90 °C (except in the case of ortho-substituted aryl iodides, which do not perform well in this reaction), and synthetic applications include a protocol for the preparation of unsymmetrical *N*,*N*′-dialkylated phenylenediamines by successive aminations of 1,3-diiodobenzene (Scheme 7).[36]

For more complex substrates and also for procedures of wider scope for both nucleophiles and aryl halides, the use of chelating ligands again dramatically improves the arylation of alkylamines. The first ligand to display high activity for the arylation with aryl iodides was introduced in 2002 by Buchwald. This operationally simple protocol uses CuI as the catalyst and ethylene glycol **L3** as ligand in propan-2-ol and was efficiently used for the coupling of a variety of functionalized arylating agents with several amines (Table 2, entry 2). Amino acids possessing a secondary amine (Table 2, entry 6), bis-alkylated Goldberg's original chelating substrate (diethylsalicylamide, Table 2, entry 5), or deanol **L22** used as solvent (Table 2, entry 10) were next shown to be good chelating agents because they also allow for the use of aryl bromides. Following these early publications, an impressive number of ligands, catalytic systems, and conditions have been reported: selected examples are collected in Table 2 (entries 12−16).

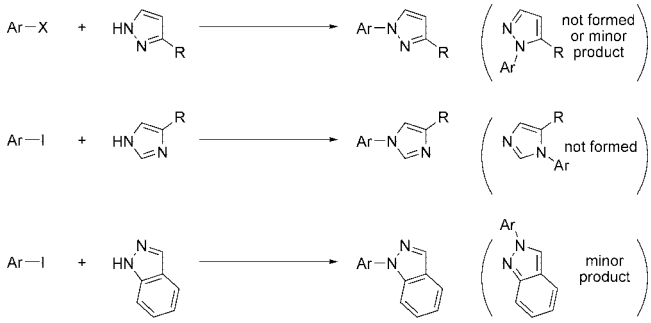
Despite this progress, long reaction times and inefficient transformation of functionalized substrates remained as limitations of the method and led to numerous studies of different ligand/catalyst/base combinations in the quest for the "holy grail" of room temperature Ullmann condensation reactions.[37] Often, the problems can be traced to catalyst deactivation through competitive arylation of the ligand. Following a report by Song[38] on the use of dipivaloylmethane in the Ullmann-type coupling of phenols, Buchwald developed a more robust catalytic system in which the delocalized

Table 2. Optimized Reaction Conditions for Copper-Mediated Arylation of Aliphatic Amines

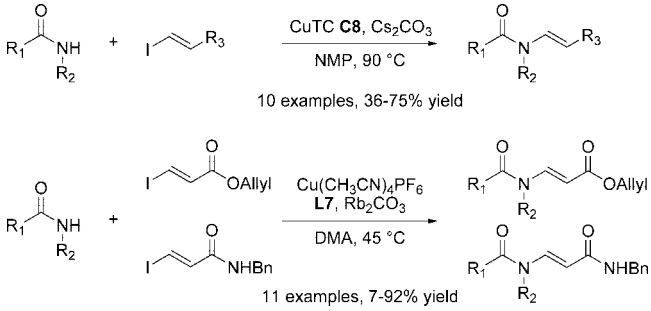


Entry	Ar	X	H–N(R)(Alk)	Copper source	Ligand	Base	Conditions	Yields	Number of examples	Ref.
1	Simple aromatics	I, Br	α–amino acids, β–amino acids, β–amino esters	CuI	-	K_2CO_3	DMA or DMF, 90-100 °C	5-92%	40	32,33
2	Simple aromatics, pyridine	I	aliphatic primary and secondary amines, cyclic secondary amines	CuI	**L33**	K_3PO_4	Isopropanol, 80 °C	58-95%	29	39
3	Simple aromatics, pyridines, thiophene, pyrazine	I	aliphatic primary amines, cyclic secondary amines, β-amino alcohols	CuI	**L31**	Cs_2CO_3	DMF, rt	79-98%	33	40,41
		Br					DMF, 90 °C			
4	Simple aromatics	Br	aliphatic primary amines, cyclic secondary amines	CuCl	**L32**	Cs_2CO_3	NMP, 120 °C	11-86%	13	42
5	Simple aromatics, pyridines, pyrimidine, benzothiophene	Br	aliphatic primary amines	CuI	**L36**	K_3PO_4	DMF or neat, 90-100 °C	71-95%	23	43
6	Simple aromatics, pyridines, uracils	I, Br	aliphatic primary amines, cyclic secondary amines	CuI	**L18** or **L20**	K_2CO_3, K_3PO_4	DMSO, 40-90 °C	59-100%	32	26,27
7	Simple aromatics	$B(OH)_2$ or BF_3K	aliphatic primary amines, cyclic secondary amines	$Cu(OAc)_2 \cdot H_2O$	-	-	CH_2Cl_2, O_2, rt-40 °C	39-98%	26	44
8	Simple aromatics	$B(OH)_2$	aliphatic primary and secondary amines, cyclic secondary amines	$Cu(OAc)_2$	**L37**	2,6-lutidine	Toluene, air, rt	50-64%	7	30
9	Simple aromatics, pyridines	I	aliphatic primary amines, cyclic secondary amines, amino acids, amino alcohol	CuBr	**L35**	K_3PO_4	DMF, 25-50 °C	55-94%	24	45
		Br		Cu + CuI		Cs_2CO_3	DMF, 110 °C	62-96%	13	46
10	Simple aromatics, thiophenes	I, Br	aliphatic primary and secondary amines, amino alcohols, cyclic secondary amines	Cu + CuI	**L22**	$K_3PO_4 \cdot H_2O$	Ligand used as solvent, 40-90 °C	15-94%	50	47,48
11	Simple aromatics	Br	β-amino alcohols	CuI	-	NaOH	DMSO/H_2O or *i*PrOH, 90 °C	63-89%	10	35
					L33	K_3PO_4	*i*PrOH, 75 °C			
12	Simple aromatics	I	aliphatic primary amines, amino alcohol	CuBr	**L38**	Cs_2CO_3	DMSO, 55-80 °C	70-92%	20	49
13	Simple aromatics	I	aliphatic primary amines, cyclic secondary amines, amino acids	CuI	**L26**	K_3PO_4	DMF, 25-35 °C	58-90%	35	50
14	Simple aromatics	I	aliphatic primary amines, cyclic secondary amines	Cu_2O	**L24**	Cs_2CO_3	CH_3CN or neat, 80 °C	60-95%	25	51
15	Simple aromatics, pyridines, pyrimidine	I, Br	aliphatic primary amines, cyclic secondary amines	CuBr	**L39**	Cs_2CO_3	DMF, 90 °C	74-99%	40	52
16	Simple aromatics	I, Br	aliphatic primary amines, cyclic secondary amines	CuI	**L29**	K_3PO_4	DMF, 90 °C	87-95%	4	28

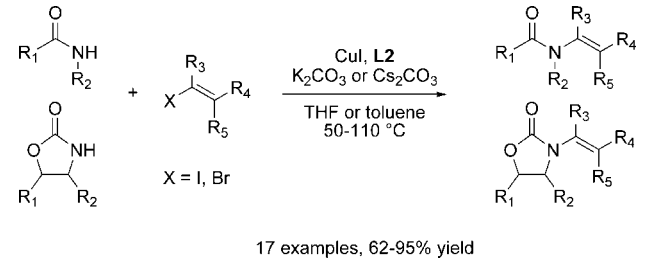
Scheme 9. Regioselectivity of the Arylation of "Unsymmetrical" *N*-Heterocycles



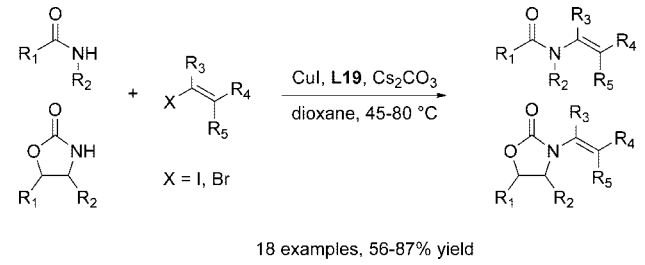
Scheme 10. CuTC-Catalyzed Coupling of Vinyl Iodides and Amides



Scheme 11. Copper Iodide/Diamine-Catalyzed Synthesis of Enamides



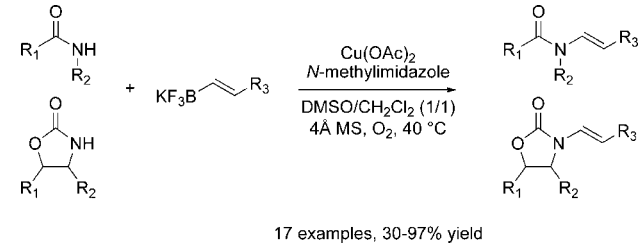
Scheme 12. Copper Iodide/*N*,*N*-Dimethylglycine-Catalyzed Synthesis of Enamides



enolate form of diketone **L31** is less prone to arylation. Combination of this ligand and copper(I) iodide allows for an especially mild coupling between aryl iodides and alkylamines in excellent yields (Table 2, entry 3). The same year, the use of Binol **L35** as ligand for copper(I) was reported by Fu and shown to be also an efficient catalytic system for the room temperature arylation of alkylamines (Table 2, entry 9). For simpler substrates, the use of boronic acids or potassium trifluoroborates remains an excellent alternative to these methods (Table 2, entries 7 and 8).

Primary arylamines, which are important intermediates for the synthesis of pharmaceutical or agrochemical compounds, can also be obtained using copper-mediated coupling reactions. They can be obtained either by direct copper(I) oxide-

Scheme 13. Synthesis of Enamides from Potassium Alkenyltrifluoroborates



catalyzed functionalization of aryl bromides or iodides in an ethylene glycol solution of ammonia under pressure[53] or by coupling with a nonvolatile ammonia surrogate, trifluoroacetamide, which can be cleaved after formation of the C−N bond by adding water and methanol to the reaction vessel (Scheme 8).[54] *N*-Aryl hydroxylamines can also be obtained in excellent yields by copper-catalyzed coupling of hydroxylamines with aryl iodides.[55]

With the development of new ligands that enable reactions to be performed even at room temperature, the copper-catalyzed arylation of aliphatic amines has clearly become an especially powerful tool for the preparation of functionalized alkylarylamines under mild conditions. Currently, the major restriction is the low reactivity of acyclic secondary amines, probably for steric reasons, and care must then be taken in the envisioning of their coupling even with reactive aromatic iodides.

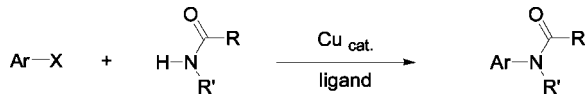
2.3.3. Arylation of Amides, Imides, and Carbamates

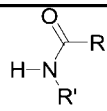
Due to its high synthetic utility, the arylation of amides has received considerable attention over the past decade: the introduction of chelating ligands resulted in major improvements and dramatic softening of the reaction conditions compared with the original Goldberg's procedure;[9] general and widely applicable reaction conditions are collected in Table 3.

Buchwald and co-workers extensively studied this reaction and developed an experimentally simple and inexpensive catalytic system based on the use of 1,2-diamine ligands **L2**, **L3**, or **L4** and K_3PO_4, Cs_2CO_3, or K_2CO_3 as base. This system, which even works with aryl chlorides and acyclic secondary amides, is highly effective, and a variety of functional groups are tolerated in the reaction, including many that are not compatible with palladium catalysis (Table 3, entry 1).[56,57] This system (or related ones) was also shown to be perfectly complementary to palladium catalysis (different chemoslectivities are observed)[58] and was later extended to the use of other coupling partners such as carbamates (Table 3, entries 1 and 2),[59,60] iodo-selenophene (Table 3, entry 8),[61] halo-furans (Table 3, entry 9),[39] and oxindoles (Table 3, entry 7).[63]

Other suitable and efficient ligands to perform this reaction include glycine **L17** (Table 3, entry 3)[64] and 1,1,1-tris(hydroxymethyl)ethane **L34** (Table 3, entry 6)[66] as well as Cristau and Taillefer's Chxn−Py−Al **L11** (Table 3, entry 4).[66] The use of β-ketoester ligand **L30** was shown to be especially efficient because the arylation of amides proceeds under especially mild conditions, even at room temperature in some cases (Table 3, entry 5).[67] Moreover, recent progress in the understanding of the reaction mechanism and the effect of the chelating ligand provides useful working guidelines for the design of *de novo* catalytic systems.[68]

Table 3. Optimized Reaction Conditions for Copper-Mediated Arylation of Amides, Imides, and Carbamates



Entry	Ar	X		Copper source	Ligand	Base	Conditions	Yields	Number of examples	Ref.
1	Simple aromatics, thiophene, pyrimidine, quinoline	I, Br, Cl	Primary amides, secondary amides, cyclic secondary amides, oxazolidinones	CuI	**L2**, **L3** or **L4**	K_3PO_4, Cs_2CO_3 or K_2CO_3	Dioxane, toluene, DMF or neat, 80-130 °C	49-99%	59	56,57,60
2	Simple aromatics, thiophene	I	Primary benzamides, secondary cyclic amides, carbamates	CuI	**L1**	K_3PO_4	Dioxane, 110 °C	41-95%	13	59
3	Simple aromatics	I	Primary amides, cyclic secondary amides, secondary aromatic amides	CuI	**L17**	K_3PO_4	Dioxane, 100 °C	66-98%	26	64
4	Simple aromatics	I	Primary benzamides, secondary cyclic amides, carbamates	Cu_2O	**L11**	Cs_2CO_3	DMF, 82 °C	81-97%	4	66
5	Simple aromatics	I, Br	Primary amides, cyclic secondary amides	CuBr	**L30**	Cs_2CO_3	DMSO, rt–75 °C	76-96%	9	67
6	Simple aromatics	I	Cyclic secondary amides, carbamates	CuI	**L34**	Cs_2CO_3 or K_3PO_4	DMF:dioxane, 110 °C	91-98%	5	65
7	Simple aromatics	I, Br	oxindoles	CuI	**L2**	K_2CO_3	CH_3CN, reflux	14-92%	20	63
8	selenophene	I	Primary amides, secondary amides, cyclic secondary amides, carbamates	CuI	**L1**	K_3PO_4	Dioxane, reflux	21-90%	11	61
9	Thiophenes, furans	I, Br	Primary amides, cyclic secondary amides, carbamates	CuI	**L2**	K_3PO_4 or K_2CO_3	Dioxane, 110 °C	11-99%	25	62
10	Simple aromatics	$B(OH)_2$	Succinimide, phthalimide	$Cu(OAc)_2 \cdot H_2O$	-	-	MeOH, air reflux	19-96%	11	69

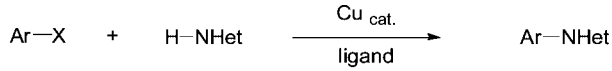
Hydrazides are also suitable substrates when reacted with copper(I) iodide, 1,10-phenanthroline, and cesium carbonate. The substitution is directed at the amide nitrogen for *para*- and *meta*-substituted aryl iodides, and a reversal in regioselectivity is observed for the arylation of benzoic hydrazide with *ortho*-substituted aryl iodides.[70]

2.3.4. Arylation of N-Heterocycles

There have been an impressive number of copper-mediated or copper-catalyzed methods published for the *N*-arylation of π-excessive heterocycles (general structures shown in Figure 2): most of them have already been reviewed,[1–3] and an overview of selected general transformations is given in Table 4.

Among all of the procedures available, the combination of copper(I) iodide and diamine **L4** developed by Buchwald for the amidation of aryl halides could be successfully applied to the arylation of an impressive number of heterocycles including pyrroles, pyrazoles, indazoles, imidazoles, benzimidazoles, triazole, benzotriazole, phthalizinones, and indoles (Table 4, entry 1);[71,72] Cristau and Taillefer's efficient catalytic system that uses structurally simple chelating ligands also provides the arylated products under especially mild and general reaction conditions (Table 4, entry 3).[66,73] Additionally, more hindered substrates such as C2-substituted imidazoles can be arylated in good yields by switching to 4,7-dimethoxyphenanthroline **L6** as ligand (Table 4, entry 2).[74] Other available catalytic systems allow for tunable reaction conditions, because the reaction can be performed with soluble bases such as TBAF (Table 4, entry 10)[75] and $(Et_4N)_2CO_3$ (Table 4, entry 6)[76] or without solvent (Table 4, entry 10).[75] Interestingly, chloro- and fluoroarenes can be used as reaction partners using copper(II) fluoroapatite **C2** with remarkable efficiency (Table 4, entry 5).[77] Finally, one should keep in mind that the Chan−Lam

Table 4. Optimized Reaction Conditions for Copper-Mediated Arylation of *N*-Heterocycles



Entry	Ar	X	H—NHet	Copper source	Ligand	Base	Conditions	Yields	Number of examples	Ref.
1	Simple aromatics, pyridines	I, Br	Substituted pyrroles, substituted pyrazoles, substituted indazoles, substituted imidazoles, substituted benzimidazoles, triazole, benzotriazole, indoles	CuI	**L4**	K_3PO_4 or Cs_2CO_3 or K_2CO_3	Toluene, dioxane or DMF, 110 °C	66-98%	70	71,72
2	Simple aromatics, pyridines, indole, furan, thiophenes	I, Br	Substituted imidazoles, benzimidazoles	Cu_2O	**L6**	Cs_2CO_3	PEG, *n*-PrCN or DMSO, 80-130 °C	60-98%	41	74
3	Simple aromatics, pyridines, thiophenes, pyrazole	I, Br	Substituted pyrazoles, imidazole, pyrrole, indole, triazole	Cu_2O	**L16** or **L25**	Cs_2CO_3	CH_3CN, 50-82 °C	50-98%	41	66,73
4	Simple aromatics, pyridines	I, Br	Imidazole, benzimidazole, indoles, pyrazole, pyrrole	CuI	**L19** or **L20**	K_2CO_3	DMSO, 75-110 °C	33-99%	26	27
5	Simple aromatics, pyridine, pyrimidine	I, Br, Cl, F	Imidazole, benzimidazole, pyrazole, pyrrole	**C2**		K_2CO_3	DMF, 120 °C	52-98%	37	77,79
6	Simple aromatics	Br	Imidazoles, benzimidazoles	CuI	**L27**	$(Et_4N)_2CO_3$	DMF/H_2O, 120-130 °C	40-90%	14	76
7	Simple aromatics	I	Imidazole, benzimidazole, indole, pyrazole	CuBr	**L38**	Cs_2CO_3	DMSO, 80 °C	71-98%	11	49
8	Simple aromatics	Br	Imidazoles, benzimidazole, pyrazole	CuI	**L5**	KF/Al_2O_3	Xylenes, 130-140 °C	71-92%	13	80
9	Simple aromatics, pyridines, pyrimidine	I, Br	Imidazole, benzimidazole, pyrazole	CuBr	**L39**	Cs_2CO_3	DMF, 90 °C	65-90%	18	52
10	Simple aromatics, pyridines, thiophene, thiazole, pyrimidines	Br, Cl	Imidazoles, benzimidazoles	CuBr	**L15**	TBAF	Neat, 145-150 °C	30-100%	20	75
11	Simple aromatics, pyridines, thiophene, thiazole, pyrimidine	I, Br, Cl	Imidazole, indole, pyrazole, triazole, pyrrole	CuI	**L10**	Cs_2CO_3	DMF, 110 °C	61-99%	28	81
12	Simple aromatics	I, Br	pyridazinones	**C7**		K_2CO_3	DMF, 100-140 °C	70-94%	7	82
13	Simple aromatics	$B(OH)_2$	Imidazole, pyrazole, indazole, benzimidazole, triazoles, tetrazoles	$Cu(OAc)_2$	-	pyridine	CH_2Cl_2, air, rt	6-88%	13	17
14	Simple aromatics	$B(OH)_2$	Imidazoles, benzimidazole	**C4**		-	CH_2Cl_2, O_2, rt	52-98%	10	78

coupling using copper(II) acetate and boronic acids remains an excellent alternative for arylation with simple substrates because the reaction typically proceeds at room temperature and requires only pyridine or triethylamine as base (Table 4, entries 13 and 14).[17,78]

Several interesting trends for the *N*-arylation of heterocycles are apparent from all of these studies and could be useful tips for the preparation of *N*-aryl-heterocycles. First, the reaction with "unsymmetrical" heterocycles proceeds with synthetically useful levels of regioselectivity: pyrazoles and imidazoles give products in which the less hindered nitrogen is selectively arylated, whereas indazoles are selectively arylated at *N*-1, provided that aryl iodides (not bromides) are used as reaction partners (Scheme 9).[71–73] Second, 2- and 4-hydroxypyridines are selectively *N*-arylated (only trace amounts of *O*-arylation are detected).[66,83] Finally, the reactivity of azoles appears to be the result of a complex balance between several parameters including nucleophilicity, catalyst complexing ability, and acidity; the following order for the reactivity of *N*-heterocycles is emerging: carbazole > imidazole > indole ~ pyrrole > triazole ≫ tetrazole.[66] The latter being a very weak nucleophile, the use of very reactive electrophiles such as diaryliodonium salts is preferable.[84]

2.3.5. Synthesis of Enamides

Enamides are key structural motifs in various classes of natural products as well as especially valuable synthetic intermediates. In addition to conventional approaches for their preparation that include condensation of amides and aldehydes,[85] addition of amides to alkynes,[86] acylation of imines,[87] Curtius rearrangement of α,β-unsaturated acyl azides,[88] amide Peterson olefination,[89] and Wittig and Horner−Wadsworth−Emmons reactions,[90] several transition-metal-catalyzed methods for the synthesis of enamides have recently emerged.[91,92] Although these protocols provide access to enamides, they often suffer from either low yield, low substrate scope, or lack of stereocontrol of the double-bond geometry.

For these reasons, the copper-catalyzed coupling of amides with vinyl halides, a modern variant of the Goldberg reaction developed by Porco, Buchwald, Ma, and others, clearly appears as the most general and widely applicable reaction for the preparation of enamides and is now widely used for the synthesis of an impressive number of molecules, including especially complex ones.

Ogawa and co-workers first reported the copper iodide-promoted coupling reaction between vinyl bromides and potassium amides using stoichiometric copper(I) in HMPA at 130 °C to afford enamides in low to moderate yields.[93] On the basis of this precedent, Porco and co-workers developed an efficient approach to the assembly of enamides using Liebeskind catalyst, copper(I) thiophene carboxylate (CuTC **C8**), cesium carbonate as base, and terminal (*E*)-vinyl iodides in NMP at 90 °C. Using this protocol, a series of (*E*)-enamides could be prepared in moderate to good yields using mild reaction conditions (Scheme 10).[94,95] As an extension of this methodology, another catalytic system based on $Cu(CH_3CN)_4PF_6$, 3,4,7,8-tetramethyl-1,10-phenanthroline **L7** and rubidium carbonate in DMA at 45 °C was developed for the preparation of vinylogous carbamic acids and ureas starting from amides and β-iodoacrylates or β-iodoacrylamides.[96]

Buchwald next reported a general and mild procedure for the synthesis of enamides that allows for the use of substituted vinyl iodides and bromides using diamine **L2** (Scheme 11). The coupling is achieved with cesium carbonate in THF at temperatures ranging from 50 to 70 °C starting from vinyl iodides, whereas vinyl bromides require the use of potassium carbonate in toluene at 110 °C. An interesting feature of these conditions is that di- or trisubstituted vinyl bromides as well as (*Z*)-vinyl iodides perform well under the reaction conditions. Lactams and oxazolidinones were shown to be equally efficient reaction partners.[97]

A year later, Ma and co-workers, in the continuation of their studies on the use of amino acids as promoters for copper-catalyzed Ullmann-type condensations, developed another efficient system for the preparation of enamides. After screening a variety of amino acids and solvents, they eventually found that vinyl iodides and bromides could be smoothly coupled with amides or oxazolidinones using copper iodide in combination with *N*,*N*-dimethylglycine **L19** and cesium carbonate in dioxane at temperatures ranging from 45 to 80 °C (Scheme 12).[98]

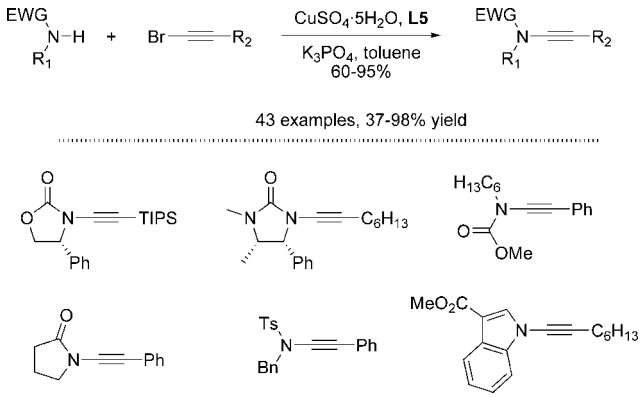
Other coupling partners include imidazoles and pyrazoles: upon treatment with catalytic copper iodide and the appropriate ligand, (*E*)-styryl azoles can be obtained in excellent yields.[99,100] Lam and co-workers have reported an alternative to vinylhalides and used (*E*)-hexenylboronic acid as room temperature vinylating agent. Unfortunately, only five examples were reported, which do not allow clear delineation of the scope of the reaction.[101] An excellent and remarkable alternative was found in the use of potassium alkenyltrifluoroborates: the tetracoordinate salts possess increased stability and can be used in copper-catalyzed cross-coupling reactions with amides and oxazolidinones under base-free conditions at 40 °C (Scheme 13): (*E*)-enamides are obtained in excellent yields.[102]

2.3.6. Synthesis of Ynamides and Allenamides

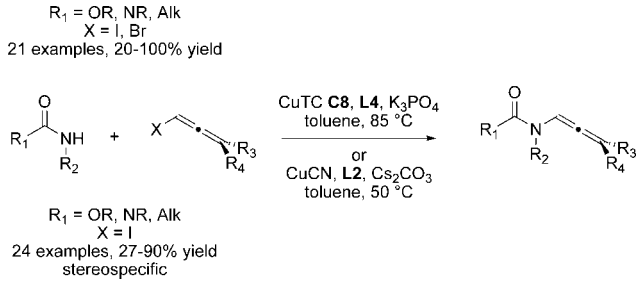
The logical continuation of the previous studies was the use of copper-mediated cross-coupling methodologies for the preparation of related compounds: ynamides and allenamides, both useful intermediates in organic synthesis. Inspired by the arylation of amides, Hsung and co-workers first developed a copper-catalyzed coupling between alkynyl bromides and amides using diamine **L2**, which provided an improved synthetic access to ynamides over existing protocols. However, severe limitations remained such as the use of high temperature and low substrate scope: although oxazolidinones were useful in the coupling, amides were mostly poor and sulfonamides were not suitable at all.[103] In addressing this limitation, Danheiser and co-workers reported a useful solution using stoichiometric amounts of copper iodide along with KHMDS: this protocol allows reactions to proceed at room temperature with carbamates and sulfonamides but still requires the use of a strong base.[104] A general and mild procedure was finally published in 2004 by Hsung, who reexamined his coupling protocol by screening a variety of copper sources and ligands. The use of copper sulfate pentahydrate in combination with 1,10-phenanthroline **L5** proved to be especially successful, allowing the reaction to occur at temperatures ranging from 60 to 95 °C with potassium phosphate as base. Representative substrates obtained using this protocol are shown in Scheme 14.[105]

The *N*-allenylation of amides, carbamates, and ureas was independently reported by Trost[106] and Hsung,[107] respec-

Scheme 14. Copper-Catalyzed Synthesis of Ynamides



Scheme 15. Copper-Catalyzed Synthesis of Allenamides



tively, using CuTC **C8** or CuCN as copper sources and diamines **L4** and **L2** as ligands (Scheme 15). Both methods allow for efficient preparations of allenamides and are complementary: whereas the first catalytic system seems to be a little bit more efficient because allenyl bromides can be used as reaction partners, the second one was shown to be stereospecific and provides an excellent entry to optically enriched allenamides. In both cases, the reaction seems to be more sluggish with amides than with carbamates.

Before we close this section and move on to the formation of C−O bonds, we ought to mentioned other procedures for the formation of C−N bonds that might be useful synthetic tools for the preparation of a variety of synthons: sulfoximines[108] and *N*-protected sulfonimidamides[109] as well as azide[110,111] and nitrite[112] anions can also be used as coupling partners in copper-mediated arylation reactions, yielding protected anilines or precursors.

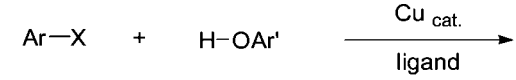
2.4. C−O Bond Formation

Diaryl ethers[113] and aryl-alkyl ethers are useful intermediates in organic synthesis and are found in an impressive number of biologically and/or natural products. The Ullmann ether synthesis[10] has been extensively used for the formation of simple diaryl ethers. However, the harsh reaction conditions, the use of a strong base, and the usual requirement for stoichiometric quantities of copper have severely limited the synthetic applications of this reaction. As for the formation of C−N bonds, the introduction of new copper sources, ligands, and aryl donors resulted in dramatic improvements for the copper-mediated C−O bond formation. Here again, one of the first modifications relied on the use of more reactive arylating agents involving organobismuth or -stannanes[114] or hypervalent iodonium salts: these efficient procedures, which require the preparation of the arylating agent, have been extensively reviewed.[1,15] A major breakthrough was simultaneously reported by Chan,[16] Lam,[17] and Evans,[115] who devised new milder conditions for the synthesis of diaryl ethers using boronic acids and stoichiometric amounts of copper(II) acetate at room temperature. The procedure has been widely used on complex substrates and is still attractive today but is, however, limited by the availability of the starting arylating agent.[1] Recently, the introduction of chelating ligands has led to dramatic improvements, and an impressive number of milder Ullmann-type methodologies have been reported, allowing for the use of simpler and more accessible arylating agents such as aryl halides. They will be briefly overviewed in the following paragraphs according to the nature of the nucleophile (phenols, aliphatic alcohols, ketones, and amides) and the halide (aryl or alkenyl). This section is not intended to be exhaustive and will focus on only selected general and widely applicable procedures. Moreover, because one of the major improvements brought about by the introduction of ligand-assisted methods is the use of relatively mild bases, at least compared to those typically used for the synthesis of aryl ethers, all procedures requiring the use of strong bases, which limit their use on complex and highly functionalized substrates, have not been taken into consideration, unless they provide access to compounds that still cannot be synthesized otherwise.

2.4.1. Arylation of Phenols

One of the major drawbacks of the classical Ullmann ether synthesis is the use of a strong base such as sodium *tert*-butoxide, which clearly limits its use to rather simple substrates. In 1997, Buchwald introduced the use of cesium carbonate, which later proved to be the base of choice in most cases and has led to considerably improved procedures for the preparation of diaryl ethers (see Table 5). Using copper triflate in combination with ethyl acetate and naphthoic acid as ligands, diaryl ethers could be obtained at 110 °C in toluene, and condensation between unactivated aryl halides and hindered phenols was possible (Table 5, entry 1).[116] This method has been successfully used in a number of syntheses, particularly in medicinal chemistry, and an interesting variation of this procedure using the less sensitive Kubas salt $Cu(CH_3CN)_4PF_6$ as source of copper(I) was reported.[117] Another improvement of the original Ullmann synthesis relying on the choice of an appropriate base was reported a year later: the use of phosphazene P_4-Bu^t base results in a "naked phenoxide anion", and its combination with copper(I) bromide allows for the coupling of most classes of aryl halides with a variety of phenols (Table 5, entry 2).[118] Another traditional drawback is the low solubility of copper(I) salts in organic solvents, which considerably slows the reaction. To overcome this problem, Venkataraman introduced the use of soluble, air-stable, copper(I) complexes **C1** and **C11**: electron-rich phenols could be coupled to aromatic bromides in good yields, except in the case of *ortho*-substituted phenols (Table 5, entries 3 and 4).[22,119] These first examples of ligand-assisted arylation of phenols[120] resulted in an impressive number of studies on the effect of various additives and ligands. Successful examples include the use of tetramethylheptadione **L32**,[38] bis-pyridineimine **L11**,[121,122] dimethylglycine **L19**,[123] an especially efficient ligand that could be used in the arylation of tyrosine derivatives without epimerization,[124] tris(hydroxymethyl)-ethane **L34**,[65] diketone **L30**,[67] or aminophosphonate **L29**,[28] which roughly display the same reactivity and selectivity profiles (Table 5). Many other ligands are available,[25,125] but they do not bring major improvements or are not readily

Table 5. Optimized Reaction Conditions for Copper-Mediated Arylation of Phenols



Entry	Ar	X	H—OAr'	Copper source	Ligand	Base	Conditions	Yields	Number of examples	Ref.
1	Simple aromatics	I, Br	Simple aromatics	$(CuOTf)_2$·PhH	AcOEt (+ $NpCO_2H$)	Cs_2CO_3	Toluene, 110 °C	20-93%	20	116
2	Simple aromatics	I, Br	Simple aromatics	CuBr (stoichiometric)	-	P_4-Bu^t	Toluene, 110 °C	56-81%	9	118
3	Simple aromatics	Br	Simple aromatics	**C1**		Cs_2CO_3	NMP or toluene, 100 °C	0-76%	12	119
4	Simple aromatics	Br	Simple aromatics	**C11**		Cs_2CO_3	toluene, 110 °C	31-99%	7	22
5	Simple aromatics	I, Br	Simple aromatics	CuCl	**L32**	Cs_2CO_3	NMP, 120 °C	51-85%	13	38
			3-hydroxy-pyridines	CuI		K_3PO_4	DMF, 80-130 °C	56-91%	7	83
6	Simple aromatics, 2-bromo-pyridine	I, Br	Simple aromatics	CuI or Cu_2O	**L11**	Cs_2CO_3 or K_3PO_4	CH_3CN, 60-110 °C	0-98%	28	121,122
7	Simple aromatics, phenyl-alanine derivatives	I, Br	Simple aromatics, tyrosine derivatives	CuI	**L19**	Cs_2CO_3	dioxane, 90-105 °C	53-97%	43	123,124
8	Simple aromatics	I	Simple aromatics	CuI	**L34**	Cs_2CO_3	dioxane, 110 °C	81-87%	8	65
9	Simple aromatics	I, Br	Simple aromatics	CuBr	**L30**	Cs_2CO_3	DMSO, 60-80 °C	72-97%	8	67
10	Simple aromatics, 2-bromo-pyridine	I, Br	Simple aromatics	CuI	**L29**	Cs_2CO_3	DMF, 110 °C	19-98%	22	28
11	Simple aromatics	Cl	Simple aromatics	CuBr	**L32**	Cs_2CO_3	DMF, 135 °C	40-99%	14	126

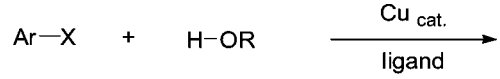
available. It can be concluded from the results collected in Table 5 that a wide range of diaryl ethers can be obtained using copper-mediated arylation of phenols: various copper salts and ligands proved to be useful catalyst precursors, and cesium carbonate is the typical base for those coupling reactions. A major drawback is the limited reactivity of aryl chlorides, which do not usually perform well under all reaction conditions, except when a combination of copper(I) bromide and diketone ligand **L32** is used (Table 5, entry 11).[126]

Other operationally simple protocols use microwave irradiation[127] and/or ligandless systems.[128] Interestingly, phenol TBS ethers can be used directly as reaction partners because they are readily deprotected *in situ* with cesium carbonate.[129] Immobilization of the catalyst has also been reported.[130]

2.4.2. Arylation of Aliphatic Alcohols

Aryl-alkyl ethers being structural motifs found in many naturally occurring and medicinal products, the quest for a mild and general method that would allow for the arylation of aliphatic alcohols has been a long-standing problem. For simple substrates stable under basic conditions, the reaction can be performed using the classical Ullmann ether synthesis starting from sodium or potassium alkoxide, aryl iodide, or bromide and catalytic amounts of copper(I) iodide, bromide, or chloride.[131] A problem commonly encountered in the methoxylation reaction of haloarenes is the reduction of the later: this side reaction can be minimized using 2-aminopyridine **L12** as ligand in ether solvents (Table 6, entry 1).[120] Since the beginning of the 21st century, milder conditions have been reported allowing the use of milder bases such as

Table 6. Optimized Reaction Conditions for Copper-Mediated Arylation of Aliphatic Alcohols



Entry	Ar	X	H—OR	Copper source	Ligand	Base	Conditions	Yields	Number of examples	Ref.
1	Simple aromatics	Br	NaOMe	CuCl	**L12**	- *(alkoxide used)*	MeOH, reflux	34-100%	20	120
2	Simple aromatics, pyridines, thiophenes	I	Primary, secondary, benzyl, allyl and propargyl alcohols	CuI	**L5** or **L7**	Cs_2CO_3	Neat or toluene, 80-110 °C	40-99%	45	133,134
3	Simple aromatics, pyridines	I	Primary, cyclic secondary, benzyl and allyl alcohols	CuI	**L19**	Cs_2CO_3	neat, 110 °C	25-91%	20	135
4	Simple aromatics	I	Primary, secondary and benzyl alcohols	CuI	**L5**	KF/Al_2O_3	neat, 100-110 °C	25-98%	14	136
5	Simple aromatics	I	Tetrahydrofurfuryl alcohol	Copper cluster $[Cu_8\{S_2P(OiPr)_2\}_6(\mu_8\text{-}Cl)]PF_6$		Cs_2CO_3	neat, 110 °C	55-93%	8	137
6	Simple aromatics, pyridines, thiophenes	I	β-amino alcohols	CuI	-	Cs_2CO_3	butyronitrile, 125 °C	47-72%	6	35
			amino alcohols		**L7**		toluene, 90 °C	79-91%	14	41
7	Simple aromatics, thiophenes	BF_3K	Primary, secondary, benzyl and allyl alcohols	$Cu(OAc)_2 \cdot H_2O$	DMAP	-	CH_2Cl_2, rt, O_2	0-100%	17	139

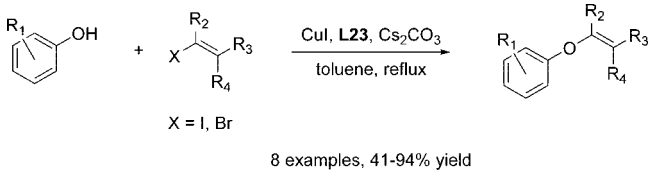
cesium carbonate. The first improvements relied on palladium catalysis: pioneering work by Hartwig and Buchwald resulted in the introduction of ligands that efficiently promote the reaction of a wide variety of alcohols with aryl halides.[132] However, a major drawback has severely limited the use of these methods: in addition to limited ligand availability, alcohols possessing β-hydrogens do not participate well in these coupling reactions due to elimination from the LnPd(II)(Ar)(alkoxide) intermediate. In these cases, copper-based catalysts provide more reliable activities because the analogous intermediates derived from these catalysts do not readily undergo β-hydride elimination reactions. The first successful application of copper-mediated arylation of aliphatic alcohols, reported in 2002 by Buchwald, resulted in a mild and general method, using phenanthroline **L5** or a tetramethylated derivative **L7**, which actually gives superior results. Arylalkyl ethers could be obtained in excellent yields starting from primary, secondary, benzyl, allyl, and propargyl alcohols (Table 6, entry 2).[133,134] A notable feature of this protocol is that only 2 equiv of the alcohol is necessary (an amount that can be further reduced for precious substrates as mentioned in section 4.2, Scheme 84) if the reaction is run in toluene, which is in sharp contrast with other methods in which the alcohol is generally used as solvent. Moreover, the method was successfully extended to the chemoselective *O*-arylation of amino alcohols (Table 6, entry 6), which is noticeable because the opposite selectivity (*N*-arylation) was obtained when another catalytic system was used (Table 2, entry 3).[41] In the case of β-amino alcohols, ligandless conditions proved to be more efficient for selective *O*-arylation (Table 6, entry 6).[35]

Following the observation that amino acids not only promoted their coupling with aryl halides but also promoted the coupling of phenols, the Ma group developed an efficient arylation procedure that complements the previous one using *N*,*N*-dimethylglycine **L19** in alcohol as solvent (Table 6, entry 3).[135] Other simple and efficient procedures include the copper-catalyzed etherification using potassium fluoride on alumina as base (Table 6, entry 4)[136] or the use of self-assembled octanuclear copper clusters (Table 6, entry 5).[137]

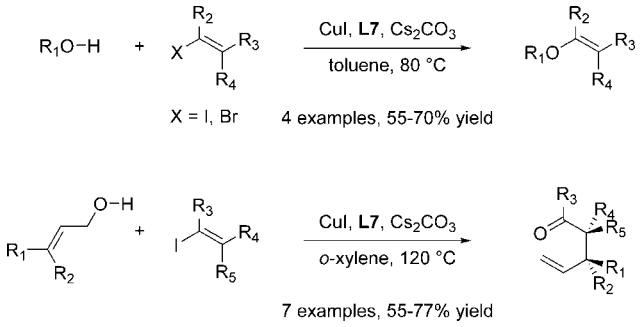
A notable feature of these procedures is the high degree of selectivity that can be achieved with both alcohol and aryl halide reaction partners. Apart from the chemoselective arylation of amino alcohols, arylating agents possessing both a bromine and an iodine are selectively arylated at the iodine position, and diols with different degrees of substitution preferentially react at the less substituted position. Properly used, these general features can be especially useful in synthesis.

Finally, one should keep in mind that other arylating agents are available and that they often allow for especially mild conditions as they do not require additional base or elevated temperatures. Such organometalloid reagents include pentavalent organobismuth derivatives,[15,138] particularly con-

Scheme 16. Copper-Catalyzed Synthesis of Aryl Vinyl Ethers



Scheme 17. Copper-Catalyzed Synthesis of Enol Ethers



venient for the arylation of tertiary or hindered alcohols, and potassium organotrifluoroborates, which have recently been shown to be convenient reaction partners for the arylation of an impressive number of alcohols (Table 6, entry 7).[139]

2.4.3. Synthesis of Enol Ethers by Vinylation of Alcohols

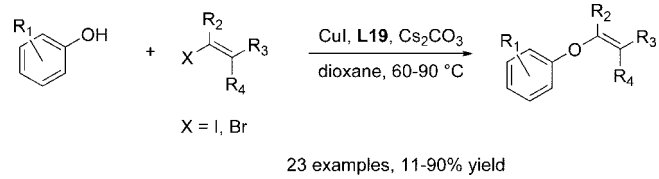
Vinyl ethers have found numerous applications as monomers in material chemistry and as key intermediates in organic synthesis. Conventional methods to elaborate these chemicals include the addition of alcohols to acetylene under high pressure and temperature,[140] Michael-type addition−elimination processes,[141] transition-metal-catalyzed vinyl transfer,[142] and allyl ether isomerization.[143] Harsh reaction conditions or substrate limitations, however, prohibit the practical application of these methods and motivated the development of mild, copper-mediated vinyl ether syntheses. Here again, the same typical development can be found: starting from anionic and harsh Ullmann-like conditions that required the use of sodium alkoxide in NMP at 110 °C,[144] the introduction of ligands allows one to dramatically soften these conditions, and the methods developed clearly are among the most efficient procedures for the preparation of enol ethers today, even in a stereospecific way.

In this context, Wan and co-workers at Eli Lilly reported on the use of amino alcohol ligand **L23** for the synthesis of aryl vinyl ethers in good to excellent yield and with full retention of configuration by direct coupling of vinyl halides and phenols (Scheme 16).[145]

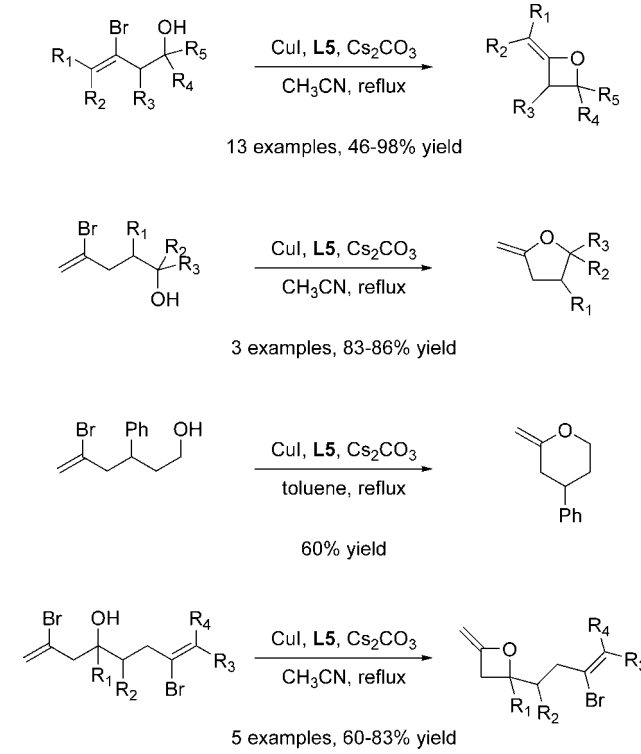
After showing that tetramethylphenanthroline **L7** was one of the best ligands to achieve the arylation of a number of aliphatic alcohols, Buchwald extended this system to the synthesis of enol ethers that could be obtained in good yields. Interestingly, with allylic alcohols and higher reaction temperatures, the alkenylation procedure could be coupled with a Claisen rearrangement in a domino process leading to γ,δ-unsaturated ketones and aldehydes (Scheme 17).[146]

The copper(I) iodide/*N*,*N*-dimethylglycine **L19** system, which had been successfully used for many copper-mediated processes, was also applied to the cross-coupling of vinyl halides with phenols. Aryl vinyl ethers were obtained in good yields, but isomerization was observed at high temperatures or when vinyl bromides were used as reaction partners (Scheme 18).[147]

Scheme 18. Copper-Catalyzed Synthesis of Aryl Vinyl Ethers



Scheme 19. Intramolecular Copper-Catalyzed Synthesis of Enol Ethers



Alternative protocols for the synthesis of enol ethers use Taillefer's bis-iminopyridine ligand **L11**,[100] vinylboronic acids,[101] or vinylpotassium trifluoroborate salts.[139]

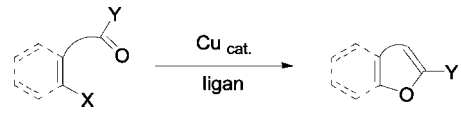
2.4.4. Synthesis of Oxygenated Heterocycles by Intramolecular Vinylation of Alcohols

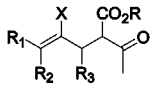
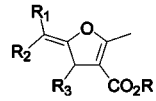
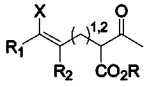
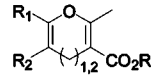
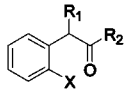
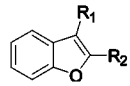
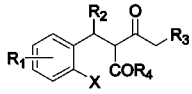
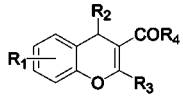
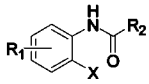
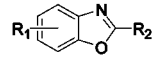
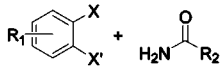
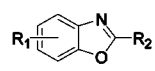
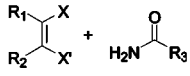
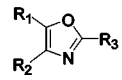
The intramolecular vinylation of alcohols has been studied in detail by Li and co-workers, who demonstrated the feasibility of the process for the formation of four-, five-, and six-membered cyclic enol ethers, respectively, in excellent, good, and fair yields. An unusual preference for 4-*exo*-ring closure in this cyclization was also observed with dibromides (Scheme 19). In this case, the differences between palladium(0) and copper(I) catalyses are truly remarkable because cyclization to four-membered ring is not a favored process with palladium: a reversal of selectivity is observed when metals are switched.[148]

2.4.5. Synthesis of Oxygenated Heterocycles by Intramolecular O-Vinylation or O-Arylation of Ketones and Amides

Ketones and amides do not systematically have the same behavior toward arylation and vinylation reactions when these reactions are performed in an intramolecular fashion. In place of reaction at the nitrogen or carbon centers and depending on the substitution pattern of the starting material,

Table 7. Oxygenated Heterocycles by Intramolecular Vinylation or Arylation of Ketones and Amides

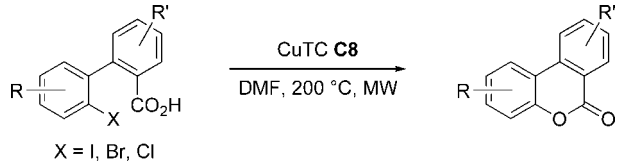


Entry	Reactant(s)	X, X'	Heterocycle obtained	Copper source	Ligand	Base	Conditions	Yields	Number of examples	Ref.
1		Br,Cl		CuI	**L2**	K_2CO_3	THF, reflux	86-99%	6	149
2		Br		CuI	**L2**	K_2CO_3	THF, reflux	83-99%	3	149
3		I, Br		CuI	-	K_3PO_4	DMF, 110 °C	76-99%	12	150
4		I, Br		CuI	**L2**	Cs_2CO_3	THF, reflux	80-99%	10	151
5		I, Br, Cl		CuI	**L5**	Cs_2CO_3	DME, reflux	62-99%	28	152
6		I, Br, Cl		CuI	**L2**	K_2CO_3	Toluene, 110 °C	59-95%	18	155
7		Br		CuI	**L2**	K_2CO_3	Toluene, 110 °C	12-70%	19	156

O-arylation or *O*-vinylation leading to heterocyclization can be a preferred pathway. The first copper-catalyzed intramolecular *O*-vinylation of carbonyl compounds was reported in 2005 by Fang and Li, who demonstrated that when reacted with copper iodide and diamine **L2** in refluxing THF, β-ketoesters possessing a 2-bromoallyl substituent furnished five-membered cyclic enol ethers without any competing *C*-arylation of the activated methylene (Table 7, entry 1). Cyclic enol ethers being useful building blocks and constituents of biologically active natural products, this reaction has a great potential and was also applied to the synthesis of six- and seven-membered ring systems (Table 7, entry 2).[149] A similar reactivity can be observed in the intramolecular arylation of 2-haloaromatic ketones, and a wide variety of benzofurans (Table 7, entry 3)[150] and benzopyrans (Table 7, entry 4)[151] were efficiently synthesized by copper-mediated cyclization reactions. An especially interesting reactivity was observed in the last case because by just moving the second carbonyl (i.e., COR_4 in Table 7, entry 4) two carbons away from the aromatic halide, *C*-arylation of the activated methylene center now becomes the exclusive reaction (see section 2.6.8, Table 17, entry 1).

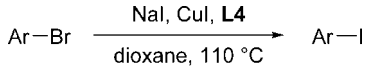
When reacted with copper iodide and 1,10-phenanthroline **L5**, *ortho*-halohanilides underwent an intramolecular C−O cross-coupling reaction, which was used by Evindar and Batey for the preparation of an impressive number of benzoxazoles in excellent yields (Table 7, entry 5).[152] This procedure was recently extended to a domino reaction starting from 2-bromoanilines and acyl chlorides[153] and found to be quite selective when another aryliodide was incorporated in the starting 2-iodoanilides (exclusive formation of benzoxazole vs azepidione).[154] These syntheses are highly competitive and compare favorably to more classical approaches to these heterocycles involving the coupling of 2-aminophenols, respectively, with carboxylic acids under strongly acidic conditions or with aldehydes via oxidative cyclization of the imine intermediate. Finally, domino copper-catalyzed C−N and C−O cross-coupling reactions of primary amides with 1,2-dihalobenzenes and 1,2-dihaloalkenes were reported by Glorius and, respectively, led to substituted benzoxazoles[155] (Table 7, entry 6) and oxazoles[156] (Table 7, entry 7) in moderate to good yields and with reasonable levels of regioselectivity. Competing *O*-alkylation of amides for the formation of five-membered rings has also been reported during the cyclization of 2-(2-bromophenyl)acetamide derivatives possessing a bulky substituent on the nitrogen atom.[157]

Scheme 20. Synthesis of Benzopyranones by Intramolecular Arylation of 2′-Halobiaryl-2-carboxylic Acids



9 examples, 63-98% yield

Scheme 21. Aromatic Finkelstein Reaction



15 examples, 93-100% yield

2.4.6. Synthesis of Benzopyranones by Intramolecular Arylation of Benzoic Acids

Although there are still no reports of the intermolecular arylation of carboxylic acids to our knowledge, a simple and highly effective $C-O_{carboxylic}$ intramolecular coupling reaction catalyzed by copper(I) has been reported in 2007 by Thasana and co-workers for the preparation of benzopyranones by cyclization of 2′-halobiaryl-2-carboxylic acids. The reaction was found to be best effected without ligand and using stoichiometric amounts of Liebeskind promoter CuTC **C8** in DMF at 200 °C under microwave irradiation for 20 min. Using these conditions, carboxylic aryl chlorides, bromides, and triflates gave the corresponding benzopyranones in excellent yields. The reaction could be extended to the preparation of indolactones and coumestans but failed to provide simpler lactones starting from nonaromatic carboxylic acids (Scheme 20).[158]

Before closing this section on the copper-mediated formation of C−O bond, we should mention that aryloxyamines and aryloximes can be obtained via cross-coupling of *N*-hydroxyphthalimide with phenylboronic acids[159] and aromatic oximes with aryl halides, respectively.[160]

2.5. C−I Bond Formation: Aromatic Finkelstein Reaction

Aryl iodides being widely used in organic synthesis, the aromatic Finkelstein reaction, that is, the transformation of readily available aryl chlorides or bromides into the iodo-derivatives, can be quite a helpful synthetic tool. Whereas traditional nickel- and copper-based methods suffer from severe limitations such as high temperatures, incomplete conversion, or formation of biaryl side-products, an efficient copper-catalyzed halogen exchange in aryl halides was reported in 2002 by Klapars and Buchwald. By heating a mixture of aryl bromide and sodium iodide (2 equiv) in dioxane at 110 °C in the presence of 5 mol % of copper(I) iodide and 10 mol % of diamine ligand **L4**, a smooth transformation of arylbromides to the corresponding iodides occurs in yields >93% (Scheme 21).[161] Two examples with vinyl bromides have been reported,[161,162] and the method has found applications for *in situ* generation of aryl iodides, which can then undergo copper-mediated transformations,[108,163] as well as for an Ullmann−Finkelstein−Ullmann multicomponent reaction yielding unsymmetrical *p*-diaminobenzenes.[164]

2.6. C−C Bond Formation

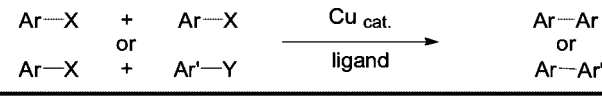
The intense attention that copper-mediated C−N and C−O bond formation has received in the past few years should not mask another exciting aspect of the renaissance of copper-mediated cross-coupling reactions, namely, the creation of carbon−carbon bonds. The development of highly efficient catalytic systems has allowed the reactions to be conducted in mild conditions (<120 °C) and with dramatically enhanced yields compared to classical procedures. The key to the success of these improved conditions was the observation that simple organic derivatives could speed the cross-couplings even though their role is not well understood.[68] In 1993, the first Sonogashira-type coupling catalytic in copper was reported by Miura, using triphenylphosphine as ligand in DMF. A significant step forward was then proposed by Liebeskind with the introduction of copper(I) thiophenecarboxylate (CuTC **C8**), a stable (stoichiometric) promoter that has found multiple applications in cross-coupling reactions as well as conjugate additions,[165] allylic substitution,[166] synthesis of conjugated materials,[167] or radical polymerization.[168] Another conceptual breaktrough by Buchwald and Taillefer in 2001 allowed the copper-catalyzed cyanation reaction of aryl halides to proceed under mild conditions and with exceptional functional group tolerance. Copper- or copper-based nanoclusters (2−5 nm range) also recently emerged as a promising new class of catalysts. The catalytic properties of these metallic (or multimetallic) clusters can be different from the well-established homogeneous or heterogeneous catalysts, therefore opening new opportunities for cross-coupling reactions. Intense research activity has also been reported on the development of ecofriendly reaction conditions, such as copper-based catalytic system immobilized in ionic liquid or in the absence of solvents. In the context of copper-mediated carbon−carbon bond formation, the excellent reviews by Beleteskaya,[3] Lemaire (formation of aryl−aryl bonds),[4] and Diederich (formation of yne−yne bonds)[5] should be noted. The following sections will give an overview of the most recent methods for the copper-mediated formation of carbon−carbon bonds from sp^3, sp^2, and sp-hybridized carbon atoms. The spectacular achievements of these new methodologies in the context of total syntheses of natural products will then be exposed. However, it should be noted that reactions requiring the formation of a discrete organometallic species before its copper-mediated cross-coupling reaction are beyond the scope of this review.

2.6.1. Synthesis of Biaryls

The metal-mediated aryl−aryl bond formation has attracted a great deal of attention since the seminal report of Ullmann.[4,7] The biaryl moieties are found in numerous naturally occurring and/or biologically active derivatives. In addition, these motifs have found multiple applications in asymmetric synthesis as privileged catalyst scaffolds or in material science due to their original physical properties. The following sections will describe recent progress in the copper-mediated cross-coupling reactions leading to this ubiquitous biaryl motif, according to the nature of the aryl partner: aryl diazonium salts, aryltin or arylboron derivatives, and aryl halides (Table 8).

2.6.1.1. Biaryls by Cross-Coupling with Diazonium Salts. Classical conditions for the homocoupling reaction of aryldiazonium salts involve an aqueous solution of a Cu(I)

Table 8. Optimized Reaction Conditions for Copper-Mediated Aryl−Aryl Bond Formation



Entry	Ar	X	Ar'	Y	Copper source	Ligand	Base/ Additive	Conditions	Yields	Number of examples	Ref.
1	Electron poor aromatics; N_2^+, BF_4^-				Cu(OTf)	-	-	MeCN, 0 °C to rt	5-96%	16	171
2	Simple aromatics; $SnBu_3$				$Cu(NO_3)_2$	-	-	THF, rt	14-67%	4	173
3	Simple aromatics	$SnBu_3$	Simple aromatic	I	CuI		NaCl	NMP, 90-120 °C	81-92%	5	174
4	2-Furyl	$SnBu_3$	Simple aromatic	ArI^+, X^-	CuI	-	-	DMF, rt	95%	1	182
5	Simple aromatics	$SnBu_3$	Simple aromatic	I, Br, Cl	Cu_2O nano-particles	P(*o*-tol)$_3$	KF	TBAB, 125-130 °C	10-92%	11	175
6	2-Furyl, 2-thienyl	$SnBu_3$	Simple aromatic	$TeCl_2$	CuI	-	Cs_2CO_3	MeCN, 70 °C	65-72%	3	176
7	Simple aromatic, thienyl; $B(OH)_2$				$Cu(OAc)_2$	-	4Å MS	DMF, 100 °C	30-95%	27	178
8	Simple aromatics	$B(OH)_2$	Simple aromatic	I, Br	CuI	DABCO	Cs_2CO_3	DMF, 125-150 °C	30-99%	14	179
9	Simple aromatics, furyl, thiophenyl, pyridyl	$B(OH)_2$	Simple aromatics, pyridyl, pyrimidinyl	I, Br	CuI	-	Cs_2CO_3, TBAB	DMSO, 135-140 °C	48-96%	24	179
10	Simple aromatic	$B(OH)_2$	Simple aromatic	I	Cu nano-clusters	-	K_2CO_3	DMF, 110 °C	62%	1	181
11	Simple aromatic	$B(OH)_2$	Simple aromatic	ArI^+, X^-	CuI	-	Na_2CO_3	DME-H_2O, 35 °C	92-99%	8	182
12	Simple aromatic; I				Cu nano-particles	-	-	Nonane, 150 °C	35-89%	5	186
13	Simple aromatics, thiophenyl, pyridinyl, indolyl; I, Br				CuTC **C8**	-	-	NMP, 0-70 °C	41-99%	16	187

reagent [prepared by reduction of an ammoniacal solution of copper(II) sulfate with hydroxylamine or sulfur dioxide].[169,170] Recently, Cepanec has developed a more practical method for the homocoupling reaction of aryldiazonium salts in very mild conditions (acetonitrile, 0 °C to room temperature) (Table 8, entry 1). Cu(OTf), prepared *in situ* from $Cu(OTf)_2$ and copper−bronze (Cu/Sn = 9:1), was an efficient promoter. The formation of azo derivatives is in competition with the biaryl formation and was found to be dependent on the nature and position of the substituents. A catalytic version of this reaction [$Cu(OTf)_2$ 20 mol %, bipy 20 mol %, copper−bronze 300 mol %] allows the coupling reaction of electron-rich aryldiazonium salts with low to good yields.[171]

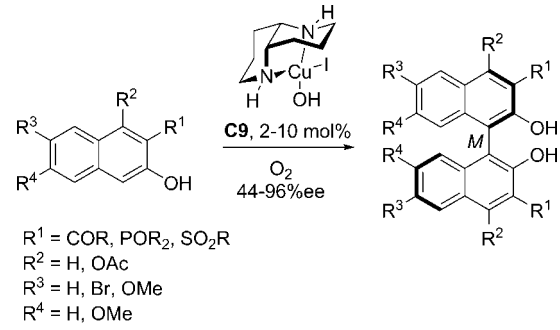
2.6.1.2. Biaryls by Stille Cross-Coupling. Stille cross-coupling reaction of organostannanes and aryl or vinyl halides/triflates is a well-established method, with a notable "copper effect".[172] The dimerization reaction of organostannanes has been studied in the intra- and intermolecular manifold for the aryl−aryl bond formation as well as for the synthesis of 1,3-dienes. Kyler reported a practical copper nitrate-mediated dimerization reaction of arylstannanes. Good yields were obtained with sterically unhindered substrates (Table 8, entry 2).[173] In a seminal study, Kang and co-workers reported that the Stille cross-coupling reaction could be catalytic in copper, although the scope was limited to highly activated electrophiles such as aryl iodides (Table 8, entry 3). The catalytic system (CuI 10 mol %, NaCl 100 mol %) was designed to enhance the transmetalation of the aryltrialkylstannanes with CuI by converting the trialkylstannyliodide formed *in situ* to the corresponding chloride. The latter was proposed to be incapable of participating again in the reversible transmetalation reaction between the organotin and copper derivatives.[174] Kang's group also reported the Stille cross-coupling reaction of 2-furyltributylstannane with phenyliodonium salts, using CuI (10 mol %) in DMF at 23 °C (Table 8, entry 4). As observed in the Suzuki−Miyaura reaction, the corresponding carbonylative coupling reaction (CuI 2.5 mol %, DME, CO 1 atm) led to the diaryl ketone in excellent yield.[182] Li and Zhang recently reported a general and reusable catalytic system for the Stille reaction of organic aryl iodides, bromides, and even activated chlorides. The use of 10% of cubic Cu_2O nanoparticles combined with 20 mol

% of P(*o*-tol)$_3$, KF·2H$_2$O in Bu$_4$NBr at 125−130 °C led to high yields of the desired biaryl products (Table 8, entry 5). In general, no loss of activity was observed after five runs with the same catalytic system. Only deactivated *p*-methoxyphenyl chloride led to poor yield (10%).[175] Diaryltellurium dichlorides are rare but efficient electrophiles in copper-mediated cross-coupling reactions of organostannanes as reported by Kang and co-workers in 1999 using 10 mol % of CuI (Table 8, entry 6). Under an atmospheric pressure of carbon monoxide, the corresponding ketones are obtained.[176]

2.6.1.3. Biaryls by Suzuki−Miyaura Cross-Coupling. The copper-catalyzed Suzuki−Miyaura cross-coupling reaction has received a lot of attention in the past few years and has already been reviewed.[177] Demir reported an aerobic dimerization reaction of arylboronic acids mediated by copper(II) acetate (50 mol %). This cross-coupling reaction could be made catalytic in copper (10 mol %) but required molecular sieves to limit the formation of side-products (Table 8, entry 7). 2-Substitution on the arylboronic acid decreases the yield, and 2,6-disubstitution totally prevents biaryl coupling.[178] In 2006, Li reported a general, effective, and inexpensive catalytic system for the coupling of arylboronic acids with aryl iodides or bromides based on a combination of CuI and DABCO (Table 8, entry 8). An increase to 100 mol % of CuI, 200 mol % of DABCO, and 200 mol % of TBAB is required with electron-rich aryl bromides, and activated aryl chlorides led only to trace amounts of the desired unsymmetrical biaryl.[179] Further improvement of this methodology was achieved a year later by a switch of solvent from DMF to DMSO (Table 8, entry 9). Aryl bromides underwent copper-catalyzed cross-coupling reaction with dramatically enhanced yields. Aryl chlorides, however, are still unreactive.[180] Copper- or copper-based nanoclusters (2−5 nm range) recently emerged as a promising new class of catalysts for the Suzuki−Miyaura cross-coupling reaction. Rothenberg reported on the Suzuki−Miyaura reaction with active and stable copper clusters in DMF at 110 °C (Table 8, entry 10). Di- or trimetallic clusters (Cu/Pd, Cu/Pd/Ru) led to enhanced reactivities, allowing the use of activated aryl bromides and even chlorides (18 examples, 25−100% conversion).[181] Highly activated electrophiles such as phenyliodonium salts were found to be suitable partners in the Suzuki−Miyaura cross-coupling reaction. Symmetrical and unsymmetrical biaryls could be prepared in high yields from arylboronic acids or arylboronates under mild aqueous conditions (CuI 2 mol %, Na_2CO_3, DME/H_2O = 4:1, 35 °C) (Table 8, entry 11). The corresponding carbonylative coupling reaction was also found to proceed in high yield (three examples, 63−78%).[182]

2.6.1.4. Biaryls by Classical Ullmann Cross-Coupling. The use of simpler and readily accessible aryl sources such as aryl halides being an attractive option, classical Ullmann conditions are still employed as a reliable method for biaryl synthesis, even for the construction of a challenging tetrasubstituted biaryl bond. An elegant example has been reported by Crudden and co-workers using the inherent directing effect of an ortho ester substituent.[183] The intramolecular diastereoselective Ullmann coupling was also shown to be an efficient synthetic route to BIPHEP derivatives.[184] In the intermolecular version, the copper-mediated Ullmann reaction of *o*-bromoaryloxazolines has been studied in detail by Meyers.[185] The chiral oxazoline proved to be a valuable auxiliary because the axial diastereomeric ratio of the biphenyl can reach 93:7 due to a thermodynamically controlled resolution. Copper nanoparticles were also reported to be efficient stoichiometric reagents for the homocoupling reaction of aryl iodides (Table 8, entry 12). The order of reactivity was shown to be dependent on the solvent used in their preparation, with the more active being Cu*/toluene.[186] Liebeskind showed that in a highly polar coordinating solvent such as *N*-methylpyrrolidone, copper(I)−thiophene carboxylate (CuTC **C8**) is able to mediate the reductive Ullmann coupling of a wide range of aromatics and heteroaromatics (Table 8, entry 13). Yields of the bi(hetero)aryls are moderate to excellent, although an *ortho*-directing group is still required in the aromatic series.[187]

Scheme 22. Enantioselective Oxidative Coupling of Naphthols with 1,5-Diaza-*cis*-decalin Copper Catalysts



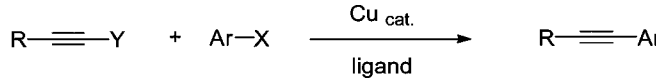
2.6.1.5. Biaryls by Enantioselective Oxidative Coupling of Naphthols. A powerful methodology for the enantioselective elaboration of chiral binaphthols was developed by Kozlowski, using 1,5-diaza-*cis*-decalin copper catalyst **C9** (Scheme 22).[188] Enantiomeric excesses up to 96% were obtained. Interestingly, substituents distal to the forming bond can have a dramatic impact on the enantioselectivity of the process. Recently, chiral polybinaphthyls were elaborated for the first time from achiral naphthols using catalytic **C9**.[189] Such polymers are of wide interest as nonlinear or liquid crystalline materials, for example. Tandem Glaser−Hay/oxidative coupling were also developed as part of these studies, thus highlighting the high chemoselectivity of Kozlowski's 1,5-diaza-*cis*-decalin copper catalysts.

2.6.2. Synthesis of Aryl−Alkynes

The copper-mediated aryl−alkyne bond formation has seen tremendous progress in recent years since the seminal report of Miura in 1993. A variety of organic ligands have been proposed, allowing a significant softening of the reaction conditions. The following sections will consider the cross-coupling reactions of alkynyltin derivatives or terminal alkynes with various aryl halides (Table 9). The inclusion of this aryl−yne bond formation in a tandem sequence leading to diversely substituted heterocycles will then be delineated (Table 10).

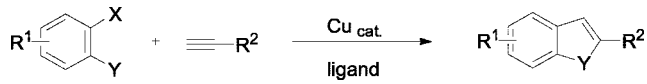
2.6.2.1. Aryl−Alkynes by Stille Cross-Coupling. Only a few studies of the Stille cross-coupling reaction between alkynyltin derivatives and aryl halides have been disclosed. An example was reported by Kang and co-workers in 1997 using catalytic CuI and stoichiometric sodium chloride in NMP at 100 °C (Table 9, entry 1).[174] The scope of the aryl halide partner was extended in 2006 by Li to aryl bromides using catalytic Cu_2O nanoparticles, although good yields were obtained only with activated aryl bromides (Table 9, entry 2).[175] Reactive electrophiles such as alkynyliodonium tetrafluoroborates are also excellent partners in copper-catalyzed Stille coupling with aryl stannanes in aqueous

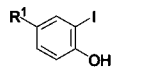
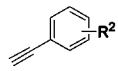
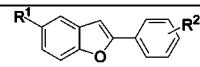
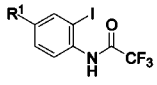
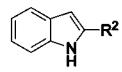
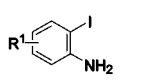
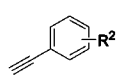
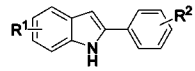
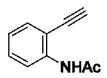
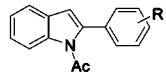
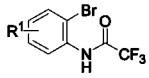
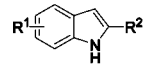
Table 9. Optimized Reaction Conditions for Copper-Mediated Aryl−Yne Bond Formation



Entry	R	Y	Ar	X	Copper source	Ligand	Base/ Additive	Conditions	Yields	Number of examples	Ref.
1	Simple aromatic	$SnBu_3$	Simple aromatic	I	CuI	-	NaCl	NMP, 100 °C	92%	1	174
2	Simple aromatic	$SnBu_3$	Simple aromatic	I, Br	Cu_2O nano-particles	P(*o*-tol)$_3$	KF	TBAB, 125-130 °C	8-93%	5	175
3	Simple aromatic, alkyl, silyl	PhI^+, BF_4^-	Simple aromatic, furyl	$SnBu_3$	CuI	-	-	DME/H_2O	66-81%	5	190
4	Simple aromatics, alkyl	H	Simple aromatic	I, Br	CuI	PPh_3	K_2CO_3	DMF or DMSO, 120 °C	5-96%	19	191
5	Simple aromatics, alkyl, alkyne	H	Simple aromatic	I, Br, Cl	CuI	DABCO	Cs_2CO_3	DMF, 135-140 °C	11-99%	21	179b
6	Simple aromatic, alkyl	H	Simple aromatic, pyridyl	I, Br	CuI	**L19**	K_2CO_3	DMF, 100-120 °C	60-98%	26	192
7	Simple aromatic, alkyl	H	Simple aromatic	I, Br	CuI	**L1**	K_2CO_3	Dioxane, 100 °C	44-96%	19	193
8	Simple aromatic, alkyl	H	Simple aromatic, allyl	I	CuI	PPh_3	K_2CO_3	DMF, 375W (MW)	80-91%	8	194
9	Simple aromatics, alkyl	H	Simple aromatic	I	CuI	PPh_3	K_2CO_3, TBAB	H_2O, 120 °C (MW)	86-99%	14	195
10	Simple aromatic	H	Simple aromatic	I	CuI	-	Cs_2CO_3	NMP, 195 °C (MW)	43-87%	15	196
11	Simple aromatic	H	Simple aromatic	I	CuI	-	K_2CO_3	PEG, 220 °C (MW)	2-100%	52	197
12	Simple aromatic, alkyl	H	Simple aromatic	I, Br	$Cu(OAc)_2$	**L14**	TBAF (TBAB)	125-130 °C	22-98%	16	198
13	Simple aromatics, alkyl	H	Simple aromatic	I	$Cu(OAc)_2 \cdot H_2O$	**L7**	TBAF (TBAB)	130-135 °C	21-98%	20	199
14	Simple aromatic	H	Simple aromatic	I, Br	Cu nano-clusters	-	TBAA	DMF, 110 °C	16-99%	13	200
15	Simple aromatic, pyridyl, alkykl	H	Simple aromatic, pyridyl, pyrimidyl, quinolyl, thiazolyl	I, Br, Cl	Cu_2O nano-particles	PPh_3	K_2CO_3, TBAB	135-140 °C	10-98%	28	201
16	Simple aromatic	H	Simple aromatic	I	Cu(Phen)(PPh_3)Br **C10**	-	K_2CO_3	Toluene, 110 °C	70-89%	9	22
17	Alkyl	TMS	Simple aromatic	I	CuCl	-	Bu_3N	DMI, 120 °C	60-88%	2	203

Table 10. Domino Sequence Aryl−Yne Bond Formation/Heterocyclization



Entry	Aromatic	Alkyne	Product	Copper source	Base/ Additive	Conditions	Yields	Number of examples	Ref.
1				[Cu(Phen)$(PPh_3)_2$]NO_3 **C12**	Cs_2CO_3	Toluene, 110 °C	62-96%	15	208
2				[Cu(Phen)$(PPh_3)_2$]NO_3 **C12**, or CuI/PPh_3	K_3PO_4	Toluene or dioxane, 110 °C	11-96%	21	208
3[a]				[Cu(Phen)$(PPh_3)_2$]NO_3 **C12**	Cs_2CO_3	Toluene, 110 °C	60-92%	6	208
4				[Cu(Phen)$(PPh_3)_2$]NO_3 **C12**	Cs_2CO_3	Toluene, 110 °C	36-83%	5	208
5				CuI	L-proline **L20**, K_2CO_3	DMF, 80 °C	25-94%	21	211

[a] Followed by Na(OtBu), 110 °C, 2 h.

DME under mild conditions (room temperature, 3 h) (Table 9, entry 3). The corresponding α,β-acetylenic ketones are also conveniently prepared using an atmospheric pressure of carbon monoxide.[190]

2.6.2.2. Aryl−Alkynes by Sonogashira Cross-Coupling. Miura reported in 1993 the first catalytic Sonogashira-type cross-coupling reaction of aryl halides and alkynes using CuI (10 mol %) and an inorganic base (K_2CO_3) in DMF (Table 9, entry 4).[191] Aryl iodides are excellent partners in this coupling reaction, whereas only one activated aryl bromide, *o*-nitrobromobenzene, led to few catalytic turnovers (23% isolated yield). Since then, the copper-catalyzed Sonogashira cross-coupling reaction has stimulated numerous studies. Li reported that CuI (10 mol %) combined with DABCO (20 mol %) was a very promising catalytic system able to promote the coupling of aryl halides including aryl chlorides, in moderate to excellent yields (Table 9, entry 5).[179b]

Ma reported that catalytic amounts of CuI and *N*,*N*-dimethylglycine hydrochloride were able to promote the coupling reaction of electron-rich and electron-poor aryl iodides and bromides (Table 9, entry 6).[192] Good to excellent yields were obtained (60−98%), and functional groups such as chloro, fluoro, nitro, carbonyl derivatives and alkyl and silyl ethers are tolerated. Thirty mole percent of the amino acid hydrochloride was found to be necessary to limit the oxidative homocoupling of the alkyne. Another useful amino-based ligand for the copper-catalyzed Sonogashira cross-coupling reaction was reported by Guo (Table 9, entry 7).[193] Ethylene diamine **L1** in combination with copper iodide is able to promote the coupling reaction of aryl iodides and bromides in dioxane at 100 °C.

Microwave-assisted copper-catalyzed Sonogashira reaction of aryl halides and alkynes has also attracted a lot of attention. The first report by Wang in 2002[194] uses Miura's catalytic system (CuI 10 mol %, Ph_3P 20 mol %, K_2CO_3 in DMF) (Table 9, entry 8). Compared to conventional heating, an increase in reaction rate was noted, from 50 to 150 times faster. An inert atmosphere was required to avoid Glaser homocoupling of the alkyne. Water could be used as a reaction medium as shown by Wan using a CuI/Ph_3P catalytic system (Table 9, entry 9), although only aryl iodides were studied.[195] Conventional heating can be used, albeit at the expense of increased reaction times (from 20−40 min under microwave conditions to 16−24 h). He reported a simplified procedure, without ligand (CuI 10 mol %, Cs_2CO_3, NMP, 195 °C −MW) (Table 9, entry 10).[196] Functional groups such as nitrile, ester, ketone, pyridine, and aniline are tolerated. Alkylalkynes were unreactive, and low conversions were obtained using aryl bromides. Lamaty reported on the use of polyethyleneglycol of various molecular weights (300 < MW < 3400) as a practical reaction medium (Table 9, entry 11).[197] The catalytic system (CuI−K_2CO_3−PEG) could be reused several times after a simple precipitation from the crude reaction mixture. 2-Aminopyrimidines are useful ligands in the aerobic and solvent-free Sonogashira coupling reaction, suppressing the oxidative homocoupling of terminal alkynes (Table 9, entry 12).[198] In combination with TBAF as a base, good yields of the coupled products were obtained, although the scope was limited to aryl iodides and bromides (in the presence of TBAB as an additive). Another aerobic and solvent-free Sonogashira-type cross-coupling reaction was reported by Li, using copper acetate (10 mol %) and 1,4-diphenyl-1,4-diazabuta-1,3-diene **L8** (20 mol %) (Table 9, entry 13).[199] The latter emerged as the most promising ligand (among 13), avoiding the Glaser homocoupling reaction of the alkyne reactant and increasing both reaction rate and yield. Higher loading of copper salt (50 mol %) and ligand (100 mol %) was required for the coupling reaction of aryl bromides.

Metal nanoclusters recently emerged as an alternative catalytic system for the C(aryl)−C bond formation. Rothenberg has shown that copper nanoclusters are efficient catalysts for the Sonogashira-type coupling reaction of aryl iodides and activated aryl bromides, whereas aryl chlorides were found to be unreactive (Table 9, entry 14).[200] Worthy of note is the fact that the clusters could be reused three times with an intact catalytic activity. Li and Zhang reported on the use of octahedral Cu_2O nanoparticles (10 mol %) in combination with Ph_3P (20 mol %) in TBAB (Table 9, entry 15).[201] This catalytic system is very efficient for the cross-coupling reaction of aryl iodides and bromides and could be extended to heteroaryl halides (including chlorides). Functional groups such as free alcohol, nitro, and methyl ketone are tolerated. In addition, the catalytic system could be reused up to three times without diminished activity.

Venkataraman developed a range of air- and moisture-stable copper(I)−phenanthroline complexes, soluble in organic solvents.[22] These complexes were the first able to mediate both aryl−carbon and aryl−heteroatom bond formation in mild conditions from aryl halides. Diversely substituted aryl iodides could be used, and good yields of the coupled products were obtained with Cu(phen)(Ph_3P)Br **C10** (10 mol %) and K_2CO_3 in refluxing toluene (Table 9, entry 16). It is interesting to note that no reaction occurred when the Cu(I) complex was replaced by CuBr (10 mol %) and phenanthroline (10 mol %). A further evaluation of six Cu(I) complexes in the cross-coupling reaction of iodobenzene with phenylacetylene showed that [Cu(phen)(Ph_3P)$_2$]NO_3 **C12** was the most active catalyst.[202]

Trimethylsilylalkynes can also be used in copper-mediated cross-coupling reactions as shown by Marshall (Table 9, entry 17). However, the coupling is efficient only with a few activated aryl iodides.[203]

In addition, the first copper-catalyzed reaction of arynes with terminal alkynes has been recently reported by Zhang and co-workers.[204]

2.6.2.3. Domino Sequence Sonogashira Cross-Coupling/Cyclization Reaction. A domino sequence copper-mediated aryl−alkyne bond formation/heterocyclization is conceivable if the aryl halide is substituted by a nucleophilic group in the *ortho*-position. This approach is known in the case of the classical Castro−Stephens reaction of aryl halides substituted by a nucleophilic carboxylic acid group in the *ortho*-position, for example. The corresponding 3-benzylidenephtalide is obtained in good yield,[205] although it has been reported recently that the isomeric product, isocoumarin, could be obtained using a highly polar aromatic substituent able to change the polarization of the alkyne.[206] *o*-Iodoaniline can also be coupled with an acetylenic copper reagent to give the corresponding indole.[207]

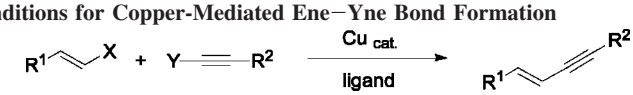
The catalytic version, however, was still a challenge. In 1993, Miura reported for the first time a set of catalytic conditions (CuI /PPh_3, DMF or DMSO, 120 °C) to promote this domino sequence, without the need of an *o*-carboxylic acid group. Isocoumarins, benzofurans, and indoles were obtained in moderate yields.[191] Venkataraman reported a more general transformation using [Cu(phen)(Ph_3P)$_2$]NO_3 **C12** (10 mol %) in refluxing toluene.[208] Good yields of 2-arylbenzo[*b*]furans were obtained from *o*-iodophenols and arylacetylenes (Table 10, entry 1). The same catalyst has been used in a domino sequence to prepare 2-arylindoles from 2-trifluoroacetamido aryl iodides and arylalkynes (Table 10, entry 2). Alkylalkynes led to poor yields of the cross-coupled product. Unprotected 2-iodoanilines could be coupled to arylalkynes and cyclized to 2-arylindoles when sodium *tert*-butoxide was added in a second step to secure complete cyclization of the intermediate 2-phenylethynylaniline (Table 10, entry 3). Alternatively, 2-ethynylacetanilide could be coupled with various aryliodides and cyclized to the corresponding indoles in moderate to good yields (Table 10, entry 4). A competitive *O*-cyclization reaction of the acetamido moiety was noted by Cacchi.[209] This side-reaction could be avoided by the use of the corresponding trifluoroacetamide. The same domino copper-catalyzed coupling/cyclization reactions was studied with a catalytic system made of an immobilized 1,10-phenanthroline (on two different polystyrene/divinylbenzene solid support) and a copper source [Cu(Ph_3P)NO_3]. Even if the cyclization step to 2-arylindole was not as efficient as in the [Cu(phen)(Ph_3P)$_2$]NO_3 **C12** case, the catalytic system could be reused at least three times without deactivation.[210] The catalytic system reported by Ma (CuI 2 mol %, L-proline **L20** 6 mol %) proved to be much more active in the synthesis of substituted indoles by domino copper-catalyzed coupling/cyclization reaction (Table 10, entry 5). Aryl bromides could be used, and good to excellent yields of the desired domino products were obtained. The functional group tolerance is very promising beause nitro, ester, pyridyl, and basic amino groups are tolerated. Even more interesting is the fact that alkylalkynes are suitable partners in this sequence.[211]

2.6.3. Synthesis of Ene−Ynes

Recent progress in the copper-mediated ene−yne bond formation is reported in Table 11. Three different approaches are presented below, namely, the reaction of vinyl halides and terminal alkynes or alkynyltin derivatives and the cross-coupling of vinylboron reagents with alkynyl electrophiles. A brief survey of copper-mediated 1,4-enyne synthesis will also be given.

2.6.3.1. 1,3-Enynes by Direct Cross-Coupling of Vinyl Halides and Terminal Alkynes. Miura was the first to report that cross-coupling reactions of vinyl halides with alkynes could be smoothly promoted by catalytic quantities of copper iodide (5 mol %) and Ph_3P (10 mol %), in the presence of K_2CO_3 (Table 11, entry 1). Without ligand, the conversion was <10%. The cross-coupling reaction was totally stereoselective, and it was noted that (*E*)-vinylhalides were more reactive than the corresponding (*Z*)-isomers. Under an atmosphere of carbon monoxide at 120 °C in DMF, the corresponding ketone was obtained, although the noncarbonylative coupling reaction could not be avoided.[191] As shown in the aryl−alkyne coupling reaction section of this review, the catalytic system reported by Ma (CuI 10 mol %, *N*,*N*-dimethylglycine hydrochloride **L19** 30 mol %) proved to be highly efficient for the cross-coupling reaction of (*E*)- and (*Z*)-vinyl iodides with alkynes (Table 11, entry 2).[211] The mild reaction conditions (dioxane, 80 °C) combined with the functional group compatibility should prove to be useful in the context of total syntheses of complex natural products. 1,3-Enynes were also prepared from vinyl halides and alkynes using the Li catalytic system (CuI 10 mol %, DABCO 20 mol %, TBAB 100 mol %) (Table 11, entry 3).[179b] Yields were moderate to good, but the scope appeared to be limited to vinyl iodides or sterically unhindered vinyl bromides. CuCl-mediated cross-coupling reaction of trimethylsilylalkynes with various vinyl iodides was studied by Marshall (Table 11, entry 4). 1,3-Enynes were obtained with

Table 11. Optimized Reaction Conditions for Copper-Mediated Ene−Yne Bond Formation



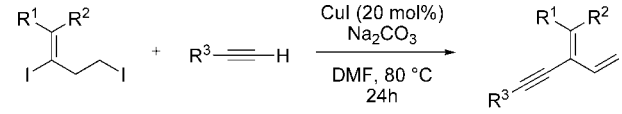
Entry	R^1	X	R^2	Y	Copper source	Ligand	Base/ Additive	Conditions	Yields	Number of examples	Ref.
1	Simple aromatic, alkyl	I, Br	Simple aromatic, alkyl	H	CuI	PPh_3	K_2CO_3	DMF or DMSO, 80-120 °C	65-93%	11	191
2	Simple aromatics, pyridyl, alkyl, ester, acid	I	Simple aromatic, alkyl	H	CuI	**L19**	Cs_2CO_3	Dioxane, 80 °C	60-91%	10	191
3	Simple aromatics	I, Br	Simple aromatic, alkyl	H	CuI	DABCO	Cs_2CO_3, TBAB	DMF, 135-140 °C	45-83%	5	179b
4	H, alkyl	I	Alkyl	TMS	CuCl	-	Bu_3N	DMI, 120 °C	64-97%	12	203
5	Ester	I	Simple aromatic, alkyl, pyridyl, thiophenyl	H	**C13**	-	K_2CO_3	Toluene, 110 °C	51-99%	17	190
6	Simple aromatic	I	Alkyl	$SnBu_3$	CuI	-	NaCl	NMP, 120 °C	74%	1	174
7	Simple aromatic, alkyl	$B(alkyl)_2$	TMS	Br	$Cu(acac)_2$	-	NaOMe or LiOH	-15 °C to rt	49-75%	14	214
8	Simple aromatic	$B(OH)_2$ or $SnBu_3$	Alkyl	I^+Ph, BF_4^-	CuI	-	-	DME-DMF-H_2O, 20 °C	71-77%	2	190

good to excellent yields, and many functional groups could be tolerated (silyl or benzyl ethers, acetates). Complex polypropionate units were thus synthesized in a straightforward manner including terminal enynes that could be easily reduced to the corresponding (*Z*)-1,3-diene, a subunit present in the natural product discodermolide.[203] Venkataraman developed a very mild Cu(I)-catalyzed cross-coupling reaction of alkyne with (*E*)- or (*Z*)-vinyliodides (Table 11, entry 5). The stereospecific reaction proceeds in refluxing toluene (compared to DMF or DMSO in Miura's coupling)[191] and tolerates many functional groups such as ethers, thioethers, basic amino groups, nitriles, nitro groups, esters, and aryl bromides. Good to excellent yields of 1,3-enynes are usually obtained, even with sterically hindered vinyl iodides. A more active catalyst, $[Cu(phen)(Ph_3P)_2]NO_3$ **C12**, could be used in challenging coupling reactions of electron-rich vinyl iodides (five examples, 78−99%).[212]

Shi reported that CuI alone was able to catalyze the cross-coupling reaction between a vinyl iodide and an alkyne at 80 °C in DMF (Scheme 23).[213] The corresponding 2-vinyl-1,3-enynes were obtained in good to excellent yields. The 2-iodobutadiene intermediate, arising from elimination of hydroiodic acid, appears to be essential to the success of this coupling reaction and limits therefore the scope of this reaction.

2.6.3.2. 1,3-Enynes by Stille-Type Cross-Coupling. Examples of copper-catalyzed Stille-type cross-coupling of acetylenic organotin derivatives are scarce, compared to the palladium- or nickel-catalyzed versions. Kang reported that this reaction proceeds efficiently with β-iodostyrene in NMP at 120 °C (Table 11, entry 6). The desired 1,3-enyne was obtained in 74% yield.[174]

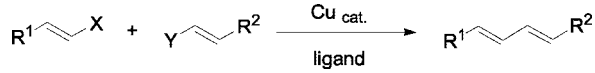
Scheme 23. Synthesis of 2-Vinyl-1,3-enynes via 2-Iodobutadiene Intermediates

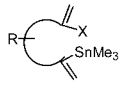


R^1 = alkyl, aryl
R^2 = Aryl
R^3 = alkyl, aryl
16 examples
41-99%

2.6.3.3. 1,3-Enynes by Suzuki−Miyaura-Type Cross-Coupling. Hoshi reported a very mild $Cu(acac)_2$-catalyzed synthesis of 1,3-enynes using (*E*)- and (*Z*)-vinyldialkylboranes and an ethynyl bromide (Table 11, entry 7). This cross-coupling reaction is stereospecific, allowing the preparation of (*E*)- and (*Z*)-1,3-enynes that were engaged in Pd-mediated Sonogashira reaction.[214] The reaction was later extended to trisubstituted vinylboranes. CuI (15 mol %) in combination with aqueous NaOH proved to be a more active catalytic system.[215] Alkynyliodonium tetrafluoroborates are also highly active partners in copper(I)-catalyzed cross-coupling reactions with vinylboronic acid or vinyl(trialkyl)tin derivatives, although the scope was not fully explored (Table 11, entry 8).[190]

Table 12. Optimized Reaction Conditions for Copper-Mediated Ene−Ene Bond Formation



Entry	R^1	X	R^2	Y	Copper source	Ligand	Base/ Additive	Conditions	Yields	Number of examples	Ref.
1	Simple aromatic, alkyl	$SnBu_3$	Simple aromatic, alkyl	$SnBu_3$	$Cu(NO_3)_2 \cdot 3H_2O$	-	-	THF, 23 °C	71-80%	4	173
2	Simple aromatics, heteroaryl, ester, alkyl	I	Simple aromatics, heteroaryl, ester, alkyl	I	CuTC **C8**	-	-	NMP, 23 °C	78-92%	7	187
3	Simple aromatic, alkyl	$SnBu_3$	Simple aromatic	I	CuTC **C8**	-	-	NMP, 0-23 °C	80-94%	4	187
4					CuCl	-	-	DMF, 23-90 °C	75-94%	9	219
5	Simple aromatics, alkyl	$SnBu_3$	Simple aromatic	I	CuI	-	NaCl	NMP, 100-120 °C	59-90%	3	174
6	Simple aromatic	Br	Ester	H	CuI	DABCO	K_2CO_3	EtOH, 80-100 °C	52-88%	1	221

2.6.3.4. 1,4-Enynes. 1,4-Enynes could be synthesized from allylic halides and terminal alkynes in DMF under copper-catalyzed conditions as shown by Jeffery in 1989.[216] Regioisomers arising from S_N2' displacement of the allylic halide are occasionally observed. Alper[217] reported that copper(I)-induced allylation reactions of terminal alkynes under phase-transfer conditions were also highly efficient and avoid the use of polar solvents such as DMF[216a] or DMSO.[216b]

2.6.4. Synthesis of 1,3-Dienes

Two recent strategies for the synthesis of symmetrical and unsymmetrical 1,3-dienes by copper-mediated cross-couplings are worthy of note in the context of this review. Table 12 compiles cross-coupling reactions of vinyltin derivatives and Heck-type reaction leading to this valuable motif.

2.6.4.1. 1,3-Dienes by Coupling of Vinyl Tin Derivatives. The copper-mediated dimerization reaction proved to be a valuable strategy for the synthesis of symmetrical 1,3-dienes. Copper nitrate was able to mediate the homocoupling reaction of diversely substituted vinylstannanes in good yields (Table 12, entry 1). These very mild conditions (THF, room temperature, 10−25 min) are worthy of note even if the scope of the reaction was not fully explored.[173] Liebeskind's promoter, copper(I)−thiophene carboxylate (CuTC **C8**) mediates the homocoupling reaction of vinyl iodides in high yields and very mild conditions (Table 12, entry 2).[218]

Unsymmetrical 1,3-dienes are also easily obtained from the CuTC-promoted Stille-type reaction of vinyltin derivatives with vinyl iodides (Table 12, entry 3). Good to excellent yields of the desired dienes were obtained.[187] Intramolecular coupling of vinylstannanes and vinyl halides mediated by copper chloride (2−3 equiv) in DMF proved to be a valuable method for the synthesis of cyclic 1,3-dienes (Table 12, entry 4) even if an excess of CuCl was required to drive the unfavorable transmetalation reaction.[219] This extremely fast cross-coupling reaction is stereospecific, and functional groups such as silyl ethers, esters, and alcohols could be tolerated. Piers later extended this methodology to the intramolecular coupling of two alkenyltrimethylstannane functions with the same success.[220] The cross-coupling reaction of vinyl- or styryltin derivatives with (*E*)- or (*Z*)-vinyl iodides could be catalyzed by CuI (10 mol %) in the presence of NaCl (100 mol%) in NMP (100−120 °C) (Table 12, entry 5).[174] However, the reaction was not totally stereospecific, thereby limiting its potential synthetic interest.

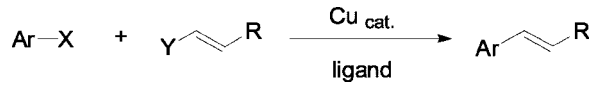
2.6.4.2. 1,3-Dienes by Heck-Type Coupling. The Heck-type coupling reaction between (*Z*)-β-bromostyrene and butylacrylate led to moderate yield of the desired 1,3-diene under catalytic conditions (Table 12, entry 6). A full equivalent of CuI is required to get excellent yield (88%).[221]

2.6.5. Synthesis of Aryl−Alkenes

Two types of copper-mediated cross-coupling reactions have been reported recently for the efficient ene−aryl bond formation and the Stille-type and Suzuki−Miyaura types of reactions. The copper-mediated Heck reaction will also be considered, although only a few examples are known.

2.6.5.1. Aryl−Alkenes by Stille-Type Cross-Coupling. In a polar solvent such as NMP, Liebeskind's promoter CuTC **C8** is able to mediate the cross-coupling reactions of aryl- and heteroarylstannanes with vinyliodides at or below room temperature within minutes (Table 13, entry 1).[187] The reaction is stereospecific and tolerant of many functional groups. The widespread acceptance of CuTC **C8** is described in the total synthesis section of this review. Hypervalent

Table 13. Optimized Reaction Conditions for Copper-Mediated Aryl−Ene Bond Formation



Entry	Ar	X	R	Y	Copper source	Ligand	Base/ Additive	Conditions	Yields	Number of examples
1	Simple aromatic, thiophenyl, pyridyl, benzofuran, uracyl, dibenzothiophenyl, 1,4-naphthoquinonyl	$SnBu_3$	Simple aromatic, alkyl, thiophenyl, ester	I	CuTC **C8**	-	-	NMP, 0-23 °C	71-97%	12
2	Simple aromatic	I^+Ph, X^-	H	$SnBu_3$	CuI	-	-	DMF, 23 °C	85-87%	2
3	Simple aromatic	$B(OH)_2$	Simple aromatic, H	I, Br	CuI	(DABCO)	Cs_2CO_3, TBAB	DMF, 125-140 °C	50-95%	11
4	Simple aromatic	I^+Ph, X^-	Simple aromatic	$B(OH)_2$	CuI	DABCO	Na_2CO_3	DME-H_2O, 35 °C	88-93%	2
5	Simple aromatic	I	Simple aromatics, ester	H	CuI, CuBr	-	K_2CO_3	NMP, 150 °C	31-85%	12
6	Simple aromatics	I, Br	Simple aromatics, ester	H	CuI	DABCO	K_2CO_3	EtOH, 80-100 °C	28-91%	10

iodonium salts could be efficiently coupled with organostannanes under CuI (2.5 mol %) catalysis, in DMF at room temperature (Table 13, entry 2). The corresponding carbonylative coupling also proceeds with high efficiency (2 examples, 83−85%).[182] A single example of copper nanoparticle-catalyzed Stille-type reaction was reported by Li in 2006 between aryl bromides and vinyltin derivatives.[175] Eventually, divinyl tellurium dichlorides are competent surrogates for vinyl halides, although the scope of the copper-catalyzed cross-coupling reaction with heteroaryltin derivatives was only briefly explored by Kang.[222]

2.6.5.2. Aryl−Alkenes by Suzuki−Miyaura-Type Cross-Coupling. In the search for an efficient copper-catalyzed cross-coupling reaction in the absence of ligand, Li reported that TBAB improved the yield of Suzuki−Miyaura-type coupling (Table 13, entry 3).[179b,180] With a full equivalent of TBAB and 20 mol % of DABCO as an additional ligand, yields could be improved from 10 to 25%. However, the reaction is sensitive to steric hindrance as 2,6-dimethylboronic acid or 1-bromo-1,2,2-triphenylethene led only to traces of the desired coupled product.[179b] Kang showed that organoboranes could be reacted with iodonium salts under very mild conditions (CuI 2 mol %, aqueous DME, 35 °C) (Table 13, entry 4).[182]

2.6.5.3. Aryl−Alkenes by Heck Cross-Coupling. Iyer reported in 1997 the first copper-catalyzed Heck reaction in NMP at 150 °C, using CuI or CuBr (10 mol %) (Table 13, entry 5).[223] Milder conditions were developed by Lee using the CuI/DABCO catalytic system in ethanol.[221] Heck-type reaction occurs at 80 °C for aryliodides and 100 °C for activated aryl bromides. Deactivated aryl bromides are unreactive (Table 13, entry 6). Calò reported on copper nanoparticle-catalyzed Heck reactions of iodobenzene and butyl acrylate in tetrabutylammonium bromide.[224] The ionic liquid solvent stabilizes this catalytic system that could be stored for months and reused without loss of activity, a very promising feature in the context of sustainable development.

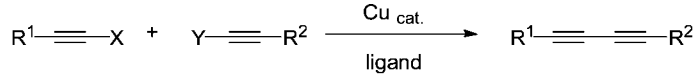
2.6.6. Synthesis of 1,n-Diynes

The copper-mediated acetylenic coupling is a venerable reaction that has found applications in numerous research fields spanning from total synthesis of polyyne natural products[6] to the straightforward elaboration of highly conjugated new materials.[5] Since the last (more general) review by Diederich,[5] a few new advances for the synthesis of symmetrical and unsymmetrical 1,3-dienes are worthy of note (Table 14.)

2.6.6.1. Symmetrical 1,3-Diynes. The classical Glaser-type coupling is a fundamental oxidative acetylenic coupling reaction that takes place in mild conditions. Owing to the high functional group tolerance of this homocoupling, the Glaser reaction has been used as a key step in the modification of complex molecules as well as for the synthesis of diacetylenic macrocycles, valuable highly conjugated molecules for electronic or photonic devices.[225] An interesting application of the oxidative acetylenic coupling reaction as a versatile postsynthetic modification of oligodeoxynucleotide was developed by Minakawa and Matsuda. At the nucleoside level, 5-ethynyl-2′-deoxyuridine could be dimerized in 68−87% using CuCl and TMEDA in various solvents under an atmosphere of oxygen.[226] This site-specific modification of oligodeoxynucleotide has been implemented on a resin-supported 12-mer. Glaser coupling with a fluorescein derivative gave the desired unsymmetrical diyne in 83% yield (Scheme 24).

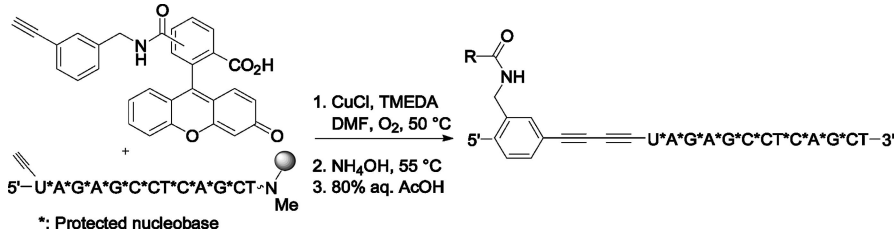
Mori developed an efficient aerobic synthesis of symmetrical 1,3-diynes from (trimethyl)silyl alkynes with a stoichiometric amount of CuCl in DMF at 60 °C (Table 14, entry 1).[227] Good to excellent yields of the desired coupled products were obtained. A polar solvent (DMF) is required

Table 14. Copper-Mediated Yne−Yne Bond Formation



Entry	R^1	X	R^2	Y	Copper source	Ligand	Base/ Additive	Conditions	Yields	Number of examples	Ref.
1	Simple aromatic, thienyl, alkyl	TMS	Simple aromatic, thienyl, alkyl	TMS	CuCl	-	-	DMF, 60 °C	70-99%	5	227
2	NTs(alkyl) or NTs(aryl)	H	NTs(alkyl) or NTs(aryl)	H	CuI	TMEDA	-	acetone, 23 °C	84-100%	5	228
3	Simple aromatic, alkyl	H	Simple aromatic, alkyl	H	$CuCl_2$	-	NaOAc	MeOH-$scCO_2$, 40 °C	71-100%	13	229
4	Simple aromatic, alkyl	$SnBu_3$	Simple aromatic, alkyl	$SnBu_3$	$Cu(NO_3)_2 \cdot 3H_2O$	-	-	THF, 23 °C	50-85%	3	173
5	Simple aromatic, thienyl, alkyl	$B(OR)_2$	Simple aromatic, thienyl, alkyl	$B(OR)_2$	$Cu(OAc)_2$	-	-	DMI, 60 °C	71-85%	11	230
6	Simple aromatic, alkyl, alkenyl	BF_3K	Simple aromatic, alkyl, alkenyl	BF_3K	$Cu(OAc)_2$	-	-	DMSO, 60 °C	28-97%	12	69
7	Trialkylsilyl	H	Simple aromatic, alkyl	Br	CuCl	-	$NH_2OH \cdot HCl$	$BuNH_2$-H_2O, 23 °C	75-95%	13	232
8	Simple aromatics	TMS	Simple aromatics	Cl	CuCl	-	-	DMF, 80 °C	43-97%	11	227
9	Pyran-2-one	TMS	Vinyl, alkyl	Br, I, Cl	CuCl	-	-	DMF or DMI, 80 °C	8-54%	9	234
10	Simple aromatics, alkyl, ester	H	Alkyl	Br	CuCl	-	NaOAc	MeOH-$scCO_2$, 40 °C	42-93%	21	235

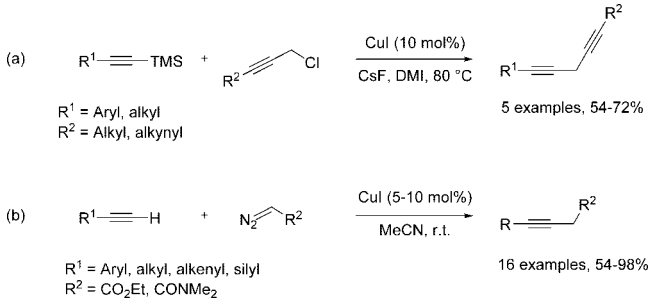
Scheme 24. Glaser-Type Site-Specific Modification of Oligodeoxynucleotide



and supposed to coordinate to the alkynylsilane to form a pentacoordinate species, prone to transmetalate to the corresponding copper derivative. Ynamides were also shown to be suitable partners for dimerization reaction using CuI (10 mol %), TMEDA (20 mol %) in acetone under an oxygen atmosphere (Table 14, entry 2).[228] Recently, the development of supercritical CO_2 as an environmentally benign reaction medium has attracted considerable attention. Copper-mediated oxidative homocoupling reactions of alkynes could be conducted in such a medium provided that methanol was used as a cosolvent, allowing an increase in solubility of cupric chloride (Table 14, entry 3).[229] Above the critical point pressure of CO_2 (4.5 MPa), no homocoupling reaction occurred. Kyler reported the copper-mediated dimerization of alkynylstannanes in very mild reaction conditions (THF, 23 °C, 10 min) (Table 14, entry 4). Good yields of the 1,3-diynes were obtained, and functional groups such as acetals are tolerated.[173] Homocoupling of alkynylboronates was studied by Nishihara. In the presence of copper(II) acetate in DMI at 60 °C, the corresponding 1,3-butadiynes were obtained in good yields (Table 14, entry 5). Polar solvents are required, and other sources of Cu(I) (CuI, CuTC **C8**) could be used with almost the same success.[230] The convenient dimerization reaction of alkynyltrifluoroborates was recently reported using catalytic $Cu(OAc)_2$ (10 mol %) in DMSO and open air. The reaction is general, and the very mild conditions should prove useful in the context of straightforward preparation of 1,3-diynes (Table 14, entry 6).[231]

2.6.6.2. Unsymmetrical 1,3-Diynes. Standard Cadiot−Chodkiewicz reactions are often incompatible with base-sensitive trimethylsilylacetylene, even in 30% aqueous butylamine (a less basic solvent system compared to the usual 70% ethylamine in water). Marino showed that more robust

Scheme 25. Copper-Catalyzed Synthesis of 1,4-Diynes and 3-Alkynoates



bulky trialkylsilyl groups such as triethylsilyl or triisopropylsilyl were advantageous in the Cadiot−Chodkiewicz reaction in terms of both yields and ease of handling (Table 14, entry 7).[232] Höger's (3-cyanopropyl)dimethylsilyl (CPDMS) protecting group was also adopted in the context of this coupling reaction by López (see section 6.4). The CPDMS group combines the mild conditions required to remove a trimethylsilyl moiety together with a hydroxyl-group polarity, thereby facilitating chromatographic purification.[233]

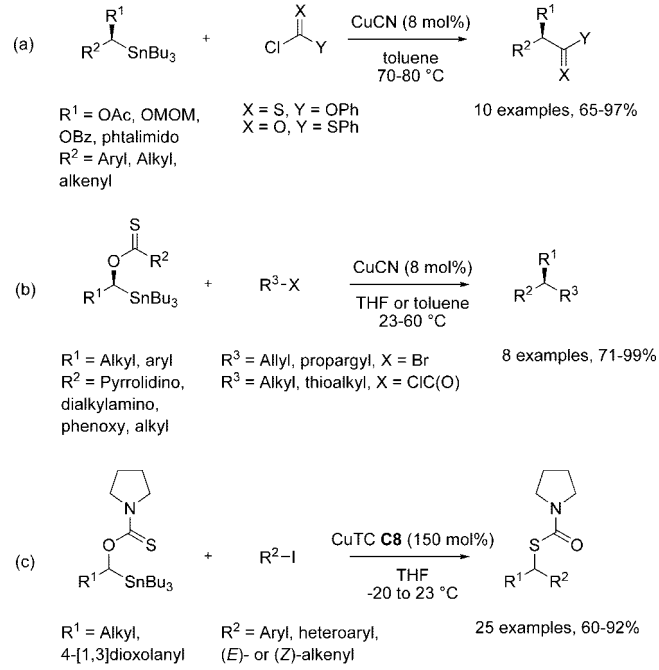
The CuCl-promoted homocoupling reaction conditions of trimethylsilylalkynes developed by Mori[227] (Table 14, entry 1) could also be applied to the Cadiot−Chodkiewicz reaction of a silylated alkyne with a chloroalkyne (Table 14, entry 8). Moderate to good yields were obtained in DMF at 80 °C. Alkynylbromides and iodides were also competent partners in the reaction promoted by 50 mol % of CuCl in DMF or DMI (Table 14, entries 9 and 10).[234] Provided that methanol was used as cosolvent, supercritical CO_2 proved to be highly efficient in the Cadiot−Chodkiewicz reaction of bromoalkynols with terminal alkynes using catalytic CuCl and sodium acetate as a base.[235]

2.6.6.3. 1,4-Diynes and 3-Alkynoates. Jung and coworkers reported an original and efficient access to 1,4-skipped diynes by a Cu(I)-catalyzed cross-coupling reaction of a silylated alkyne with a propargylic chloride (Scheme 25a). A fluoride source such as CsF decreased the reaction time and reduced the formation of byproduct. Worthy of note is the fact that germanium or tin acetylides were competent nucleophiles in this reaction.[236] A straightforward access to 3-alkynoates was reported by Fu from simple alkynes and a diazoester or diazoamide (Scheme 25b). The copper-catalyzed coupling occurs in mild conditions (acetonitrile, room temperature), and a variety of functional groups are tolerated.[237]

2.6.7. Coupling Reactions of α-Hydroxystannanes

In 1995, Falck reported that simple α-(acyloxy)alkyl stannanes were poor partners in the copper-catalyzed reaction with highly reactive electrophiles.[238] However, when paired with an electrophile able to coordinate the copper intermediate such as thiono- or thiolchloroformates, excellent results were obtained (Scheme 26a). Switching from an α-acyloxy to an α-carbamoyloxy group enhanced their reaction rates and increased the yields while significantly decreasing the temperature. Cross-coupling reaction could even be conducted at room temperature in THF (Scheme 26b). This method has been extended with great success to chiral α,β-dialkoxy- and α-alkoxy-β-aminostannanes.[239] In 2007, Falck reported an efficient copper-mediated cross-coupling reaction of pyrrolidinylthiocarbamoyl (PTC)-protected stannanes with alkenyl and aryl electrophiles, historically sluggish organic

Scheme 26. Falck's Copper-Mediated Reactions of α-Hydroxystannanes with Organic Electrophiles



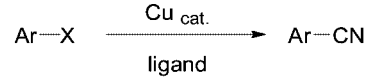
halides in this reaction (Scheme 26c).[240] Cross-coupling occurred in neutral conditions with retention of configuration and unexpectedly led to the products of *O*- to *S*-rearrangement with good to excellent yields. The synergic effect of copper and fluoride observed by Baldwin[241] was not operant in this study.

2.6.8. Cyanation of Aromatic, Rosenmund−von Braun Reaction

The Rosenmund−von Braun reaction is a classical transformation that allows the cyanation of aryl halides.[242] A major drawback is that a stoichiometric amount of copper(I) cyanide and high temperature are required to get useful yields of the desired benzonitriles. Other methods to prepare benzonitriles have also been developed such as diazotization of anilines and subsequent (catalytic) Sandmeyer cyanation reaction (Table 15, entry 1)[243] or ammoxidation reaction of toluene derivatives.[244] Metal-catalyzed cyanation reaction of aryl bromides and chlorides has also been intensively studied but suffers from poor reliability, potential catalyst poisoning,[245] and the high cost of the palladium and nickel catalytic systems.[246,247] Harsh reaction conditions and/or limited functional group compatibility have spurred the chemical community to greater efforts.

A recent modification of the classical Rosenmund−von Braun reaction consists in the addition of L-proline **L20** (100 mol %) as a ligand of CuCN (200 mol %) in a highly polar solvent (DMF) (Table 15, entry 2). A dramatic increase in the yields of the desired arylnitriles was observed.[248] A catalytic Rosenmund−von Braun reaction in a reusable ionic liquid media was developed by Ren in 2002 (Table 15, entry 3). This immobilized copper catalyst concept was a step forward to a more general and practical procedure.[249] In 2001, two independent reports brought conceptual breakthrough in this field. Buchwald reported on a Cu(I)-catalyzed domino halide exchange/cyanation reaction of aryl- and heteroarylbromide.[250] The use of a full equivalent (relative to the aryl bromide) of *N*,*N*-dimethylethylenediamine **L2** was

Table 15. Optimized Reaction Conditions for Copper-Mediated Cyanation of Aryl Halides



Entry	Ar	X	Copper source	Ligand	Cyanide source/ Additive	Conditions	Yields	Number of examples	Ref.
1	Simple aromatic	N_2^+, BF_4^-	CuCN/phen/ $Cu(BF_4)_2$	Dibenzo-18C6	KCN	MeCN, 23 °C	52-93%	7	243
2	Simple aromatic, pyridyl	I, Br	CuCN	**L20**	-	DMF, 80-120 °C	56-98%	18	248
3	Simple aromatic	I, Br	CuX	-	NaCN	BMIX[a], 120 °C	50-100%	10	249
4	Simple aromatic, indolyl, quinolinyl, pyrazolyl, benzothiophenyl, pyridyl	Br	CuI	**L2**	NaCN, KI	Toluene, 110-130 °C	70-98%	15	251
5	Simple aromatic, pyridyl	I, Br	CuI	**L5**	$(CH_3)_2C(OH)CN$/ Bu_3N, KI	DMF, 110 °C	40-98%	12	251
6	Hindered aromatics, pyridyl, furyl, thiophenyl, indolyl, isoquinolinyl, thiazolyl, pyrimidinyl	Br	CuI	-	$K_4[Fe(CN)_6]$, 1-Butylimidazole	Toluene, 140 °C	58-99%	31	253

[a] BMI, 1-*n*-Butyl-3-methylimidazolium.

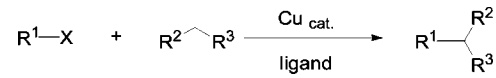
beneficial to the cyanation reaction (Table 15, entry 4). In a very detailed study, Taillefer proposed a Cu(I)-catalyzed cyanation reaction of aryl bromides and iodides using a catalytic amount of ligand and a practical source of cyanide: acetone cyanhydrin/tributylamine (Table 15, entry 5).[251] The arylnitriles were obtained in good yields, and excellent functional group tolerance was observed. As in Buchwald's report, the copper-catalyzed *in situ* production of aryl iodide was key to the success of the reaction. In 2005, Beller described catalytic cyanation reaction with potassium hexacyanoferrate(II) $K_4[Fe(CN)_6]$, one of the least toxic cyanide sources available.[252] Inspired by the binding site of most metalloenzymes (containing from one to three histidine units per metal atom), Beller evaluated several alkylimidazoles as additives in the Cu(I)-catalyzed cyanation of aryl- and heteroaryl bromides. Excellent results were obtained using 1-butylimidazole in toluene, even for sterically hindered arylbromides or highly functionalized heteroaryl bromides (Table 15, entry 6).[253]

2.6.9. C-Arylation Reactions of CH-Acid Derivatives: Hurtley Reaction

In 1929, Hurtley described the *C*-arylation reaction of CH-acid derivatives such as malonic esters with 2-bromobenzoic acid using a catalytic amount of copper−bronze or copper acetate.[254] Strong bases (NaH,[255] MeONa[256]) and the necessity of an *ortho*-directing group[257] were serious limitations. In the absence of such a substituent able to coordinate the intermediate copper species, harsh reaction conditions were required [high temperature,[191] (over)stoichiometric amount of copper,[258] toxic solvents],[258,259] leading to poor yields of the desired *C*-arylated products.[260] Extensive efforts to broaden the scope of the Hurtley reaction in the development of a more efficient copper-based catalytic system have been reported and reviewed up to 2004.[243] An ever-increasing number of reports on copper-catalyzed Hurtley reactions have been disclosed in the literature, allowing the reaction to be conducted in practical and mild conditions (economical catalytic system, very low reaction temperature). The enantioselectivity of the process as well as its inclusion as part of domino sequences have also been reported.[261]

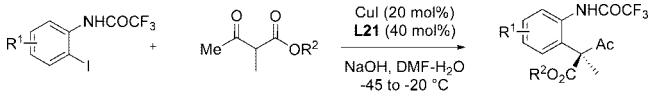
Taillefer reported on the efficient coupling of iodobenzene with diethylmalonate, ethylcyanoacetate, and malononitrile using CuI (10 mol %) and chelating Schiff base **L11** (20 mol %) (Table 16, entry 2).[66] Good to excellent yields were obtained. Side reactions that were reported by Buchwald (Table 16, entry 1)[262] such as arylation of the 2-phenylphenol ligand or decarboxylation of the products were avoided. In 2005, Ma extended the scope of the Hurtley reaction to arylbromide (whether electron-rich or -deficient), lacking an *ortho*-directing group using the CuI/L-proline **L20** catalytic system (Table 16, entry 3).[263] Ma's catalytic system was also successful for the coupling reaction of acetylacetone or ethylcyanoacetate with aryliodides and of vinylbromides with diketones, β-ketoesters, and dialkylmalonates (Table 16, entries 4 and 5).[264] Interestingly, it was observed that 2-alkyl-substituted β-ketoesters were poor substrates in the Cu(I)-catalyzed Hurtley reaction. The introduction of a trifluoroacetamido moiety in the *ortho* position of the arylhalide solved this problem and allowed Ma to perform enantioselective arylation reactions of 2-methylacetoacetate (Scheme 27). The very low temperature (−45 °C) and excellent enantiomeric excess (up to 93%) are especially noteworthy in the context of Ullmann-type coupling reactions.[261,265]

Table 16. Optimized Reaction Conditions for Copper-Mediated Alkylation of CH-Acids Derivatives



Entry	R^1	X	R^2	R^3	Copper source	Ligand	Base/ Additive	Conditions	Yields	Number of examples	Ref.
1	Simple aromatics	I	CO_2Et	CO_2Et	CuI	2-phenylphenol	Cs_2CO_3	THF, 70 °C	61-98%	16	262
2	Simple aromatics	I	CO_2Et, CN	CO_2Et, CN	CuI	**L11**	MS 3Å	THF or MeCN, 50-70 °C	69-98%	6	66
3	Simple aromatics	I, Br	Ketone, ester	CO_2Et	CuI	**L20**	Cs_2CO_3	DMSO, 40-50 °C	71-94%	35	263
4	Simple aromatics	I	Ketone	Ketone, nitrile	CuI	**L20**	K_2CO_3	DMSO, 90 °C	20-92%	26	264
5	Alkenyl	Br	Ketone, ester	Ketone, ester	CuI	**L20**	Cs_2CO_3	DMSO, 90 °C	50-84%	11	264
6	Simple aromatics, pyridyl, thiophenyl	I, Br	CO_2Et	CO_2Et	CuI	2-picolinic acid	Cs_2CO_3	Dioxane, 23-100 °C	68-96%	20	266

Scheme 27. Enantioselective Arylation Reactions of 2-Methylacetoacetates



R^1 = H, alkyl, ether, halo, ester
R^2 = Alkyl

11 examples, 29-82%
60-93% *ee*

The first room temperature Hurtley reaction of simple aromatics was reported by Kwong in 2007 using catalytic CuI and 2-picolinic acid as a bidentate ligand (Table 16, entry 6).[266] The catalyst loading can be reduced to 1 mol % (at 70 °C), and aryl bromides were found to undergo cross-coupling in refluxing dioxane. Eventually, it is interesting to note that prolonged heating of a Cu(I)-catalyzed cross-coupling reaction of aryl iodides (without additional ligand) results in the deacylation of the arylated acetoacetate esters, thus constituting a straightforward access to 2-aryl-acetic esters.[267]

The Hurtley reaction can also constitute the first step of a domino sequence leading to synthetically valuable heterocyles as shown by Miura in his seminal reports on copper-catalyzed alkylation of aryl halides with activated methylenes.[191] More recently, intramolecular *C*-arylation reactions of aryl halides were observed using catalytic CuI/TMEDA in dioxane or CuI/L-proline **L20** in DMSO. The corresponding heterocycles, 3,4-dihydronaphthalen-2(1*H*)-ones (Table 17, entry 1),[151] 3-acyloxyindoles (Table 17, entry 2),[268] or carbazolones,[269] were obtained in good yields. An especially interesting reactivity was observed in the first case; by just moving the second carbonyl (i.e., COR_4) two carbons closer to the aromatic halide, *O*-arylation of the ketone became the exclusive reaction (see section 2.4.4, Table 7, entry 4).

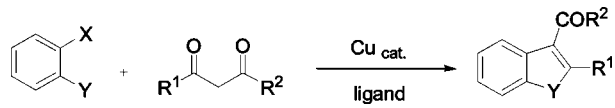
In the intermolecular version of this domino sequence, the CuI-catalyzed coupling of 1-bromo-2-iodoaryls with β-ketoesters affords the corresponding benzofurans via the intramolecular C−O bond formation (Table 17, entry 3).[270] Moderate to excellent yields were obtained in mild conditions (THF, 100 °C). Polysubstituted indoles are also accessible from 2-halotrifluoroacetanilides in wet DMSO using the CuI/L-proline **L20** catalytic system developed by Ma (Table 17, entry 4). β-Ketoesters and amides are suitable CH-acidic derivatives in this cascade reaction. Without a strong electron-withdrawing substituent in the 4-position of the aryl halide, an acidic hydrolysis step is required to produce indoles from the Hurtley products.[271] In anhydrous DMSO, an interesting deacylation reaction occurs, leading to functionalized 2-(trifluoromethyl)indoles, pharmaceutically valuable scaffolds (Table 17, entry 5).[272] Tanimori reported the use of free 2-iodoanilines in the Cu(I)-catalyzed Hurtley reaction/C−N bond formation. 2,3-Disubstituted indoles were obtained in moderate to excellent yields. BINOL **L35** as a ligand proved to be superior to L-proline **L20**, *N*-methylglycine **L18**, or 2-thienyl carboxylic acid (Table 17, entry 6).[273]

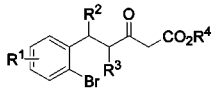
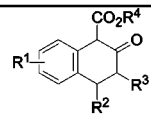
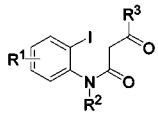
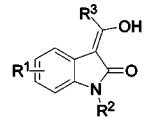
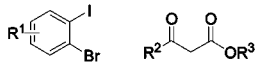
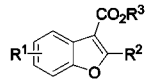
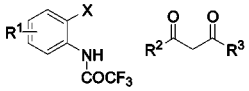
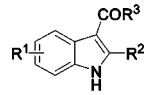
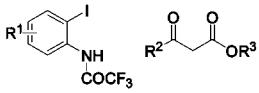
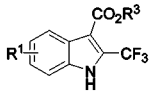
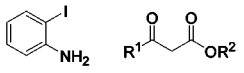
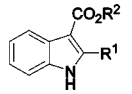
2.6.10. Methylenation Reaction

Copper-catalyzed methylenation reactions of aldehydes (Scheme 28a) and ketones (Scheme 28b) have been disclosed by Lebel. Copper(I or II) halide or NHC−Cu (NHC = *N*-heterocyclic carbene) complexes[274] were found to be extremely effective methylenation catalysts in the presence of Ph_3P, *i*PrOH, and trimethylsilyldiazomethane. The high functional group tolerance associated with a broad scope of the reactive carbonyl derivatives is of great interest in the context of complex synthetic applications, as exposed in the total synthesis section (section 6.7) of this review.[275]

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity. Straightforward and reliable methods for C−N, C−O, and C−C bond formation being an ongoing challenge in synthetic organic chemistry, the recent developments in copper-mediated coupling reactions have found an

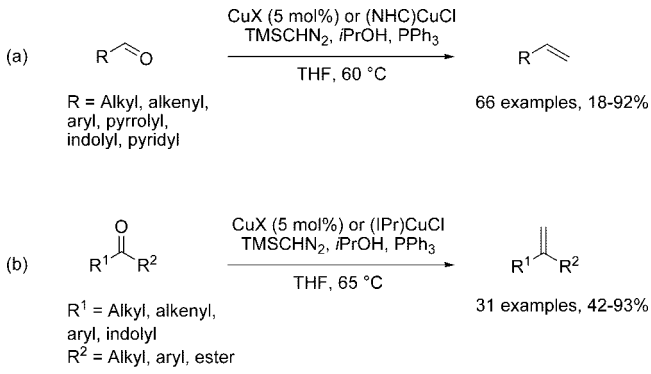
Table 17. Copper-Catalyzed Heterocyclization Reactions



Entry	Reactant(s)	Product	Copper source	Base/ ligand	Conditions	Yields	Number of examples	Ref.
1			CuI	Cs_2CO_3, **L2**	Dioxane, 100 °C	57-94%	7	151
2			CuI	Cs_2CO_3, **L20**	DMSO, 23 °C	66-83%	16	268
3[a]			CuI	K_2CO_3	THF, 100 °C	48-88%	16	270
4			CuI	Cs_2CO_3, **L20**	DMSO-H_2O, 23-50 °C	44-99%	29	271
5			CuI	Cs_2CO_3, **L20**	DMSO, 40-80 °C	27-93%	14	272
6			CuI	Cs_2CO_3, **L35**	DMSO, 50 °C	46-95%	11	273

[a] Followed by Na(OtBu), 110°C, 2 h.

Scheme 28. Copper-Catalyzed Methylenation Reactions of Aldehydes and Ketones



impressive number of applications for the synthesis of complex natural products with exceptional efficiencies, as will appear in the next sections of this review. From a "copper perspective", new bond disconnections are clearly emerging.

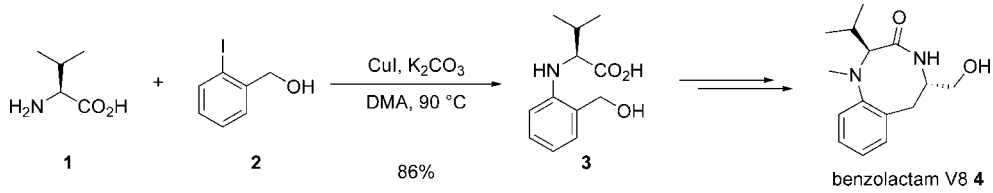
3. Natural Product Total Synthesis: Formation of C−N Bonds

3.1. Arylation of Alkylamines

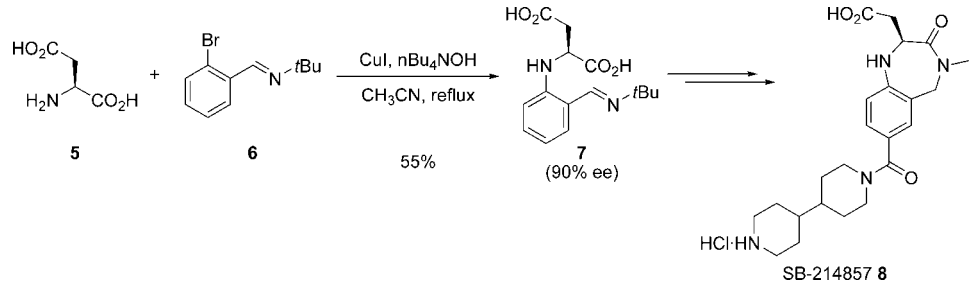
On a time frame, the first uses of copper-mediated coupling reactions closely followed the development of mild methods. Whereas the introduction of organobismuth reagents for the arylation of amines found only a couple of applications in the field of natural product synthesis, mainly for the phenylation of compounds such as morphine alkaloids[276] or abietic acid,[277] the discovery of the accelerating effect induced by α- or β-amino acids had clearly a deep impact on the development of copper-mediated coupling reactions. Applications of these powerful synthetic tools for the formation of C−N bond have flourished recently. One of the first applications was reported by Ma and co-workers for the preparation of the protein kinase C inhibitor benzolactam V8 **4**, featuring a copper-catalyzed coupling between valine **1** and aromatic iodide **2** that allowed for the synthesis of enantiopure benzolactam V8 precursor **3** (Scheme 29).[32] Interestingly, the reaction was less efficient when the nitrogen was methylated or when the free alcohol was protected as its benzyl ether. Compared to previous syntheses that used non-diastereoselective reductive amination with methyl 2-oxoisovalerate[279] or S_N2 displacement of chiral valine derived triflate,[280] the efficiency of the copper-mediated amination route is simply astounding.

A similar strategy was used by Hayes and co-workers at GSK for the synthesis of lotrafiban (SB-214857) **8**, a potent glycoprotein IIb/IIIa receptor antagonist. The use of tetrabutylammonium hydroxide allowed the low solubility of amino acids bearing polar substituents, such as aspartic acid **5**, to be overcome and gave coupled product **7** with slight erosion of the enantiomeric purity, a decrease that was shown to

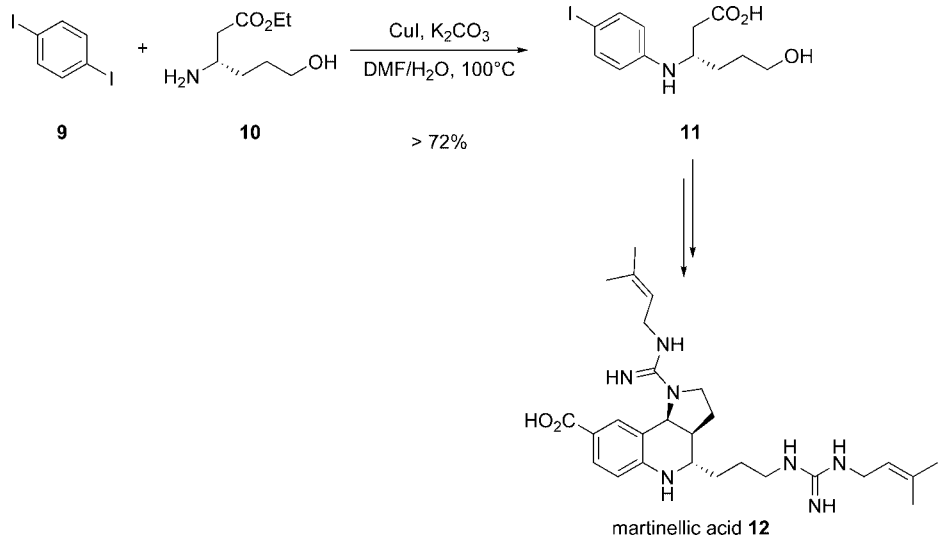
Scheme 29. Synthesis of Benzolactam V8



Scheme 30. Synthesis of SB-214857



Scheme 31. Synthesis of Martinellic Acid



increase with reaction time (Scheme 30).[34] In parallel, an intramolecular version of this reaction evolved and was used for the synthesis of **8** by Ma and co-workers (Scheme 64).

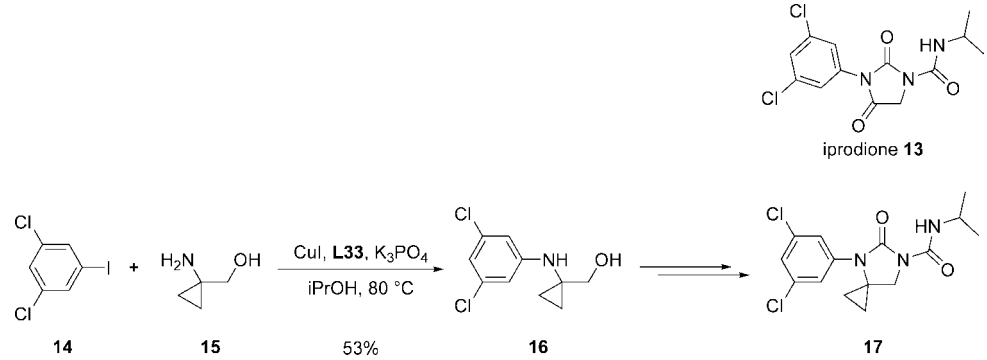
β-Amino acids and β-aminoesters being also excellent substrates for the copper-mediated coupling reaction with aryl halides, they were successfully used as starting materials for the synthesis of tetrahydroquinoline alkaloids such as angustureine[280] or martinellic acid **12**.[281] Coupling of **9** and **10** with copper(I) iodide, K_2CO_3 in DMF at 100 °C for 24 h provided monoaminated amino acid **11** in 72% yield (Scheme 31). Consecutive elaboration of the two nitrogen heterocycles from this substrate and installation of the side chains allowed for the completion of an especially elegant synthesis of martinellic acid **12**. For comparison, all previous syntheses started from anilines already possessing the C−N bond.

The recently reported mild ligand-assisted copper-catalyzed arylation reactions of aliphatic amines are especially convenient for diversity-oriented synthesis because they are highly tolerant to other functional groups. Examples of natural product analogues synthesized using such reactions in a key step include cyclopropanated analogues of iprodione **17** and hydrophilic analogues of the ABCB1 transporter inhibitors tariquidar **20** and **21**. In the first case, a selective *N*-arylation of bulky cyclopropylamino alcohol **15** was achieved in reasonable yield using ethylene glycol as ligand. The yield went down upon scaling up of the reaction (65% on 2 mmol scale, 53% on 15−25 mmol scale) and, as is often the case with hindered amines, arylation of the ligand was observed as a side reaction (Scheme 32).[282] The second case is quite typical of the relative reactivity of amines toward arylation: whereas the arylation of primary or cyclic secondary amines, respectively, afforded anilines **20** and **21** in moderate to good yields (the reaction conditions used for the synthesis of tariquidar analogues are quite standard ones),[283] acyclic secondary amines usually do not perform well under all reaction conditions (Scheme 33). Even with this limitation, the use of copper catalysis still provides a more efficient access to arylated amines compared to palladium catalysis because these conditions give less than 10% of the desired products.

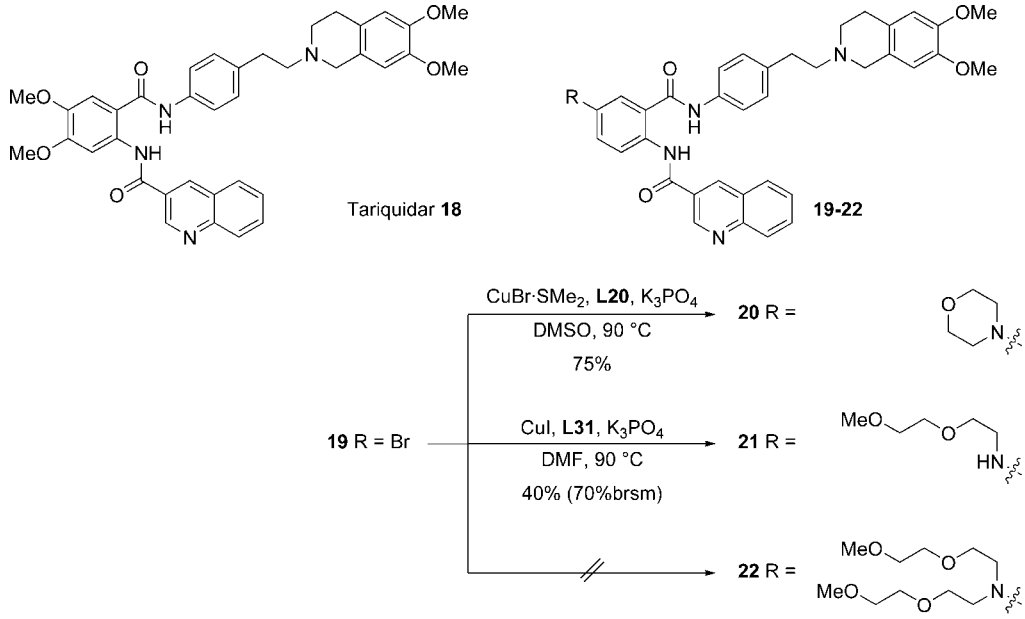
3.2. Arylation of Amides and Carbamates

Due to their quite impressive substrate scope and relatively mild reaction conditions, ligand-assisted protocols for the arylation of amides and carbamate have found numerous applications in natural and/or biologically active product synthesis and now clearly allow for new synthetic discon-

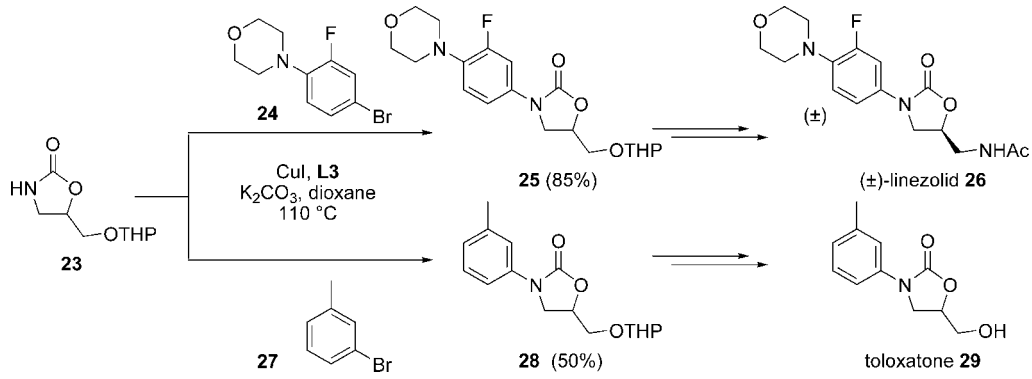
Scheme 32. Synthesis of Cyclopropanated Analogues of Iprodione



Scheme 33. Synthesis of Analogues of Tariquidar



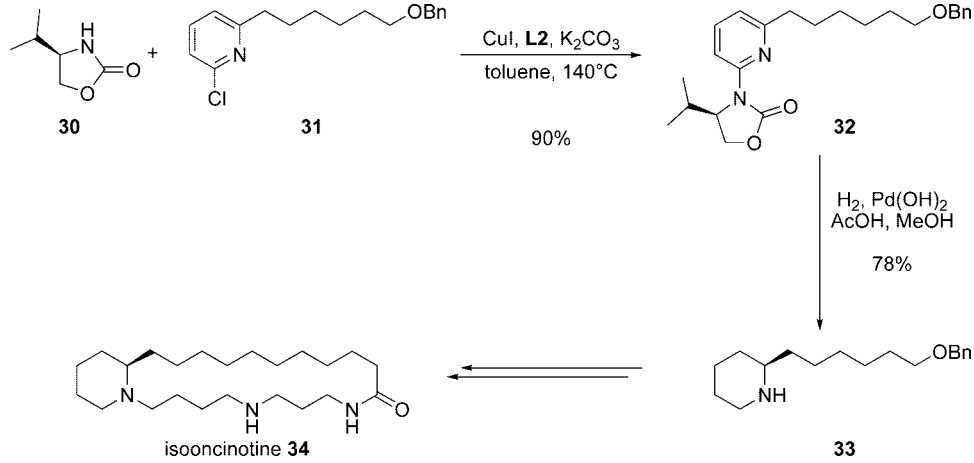
Scheme 34. Synthesis of Linezolid and Toloxatone



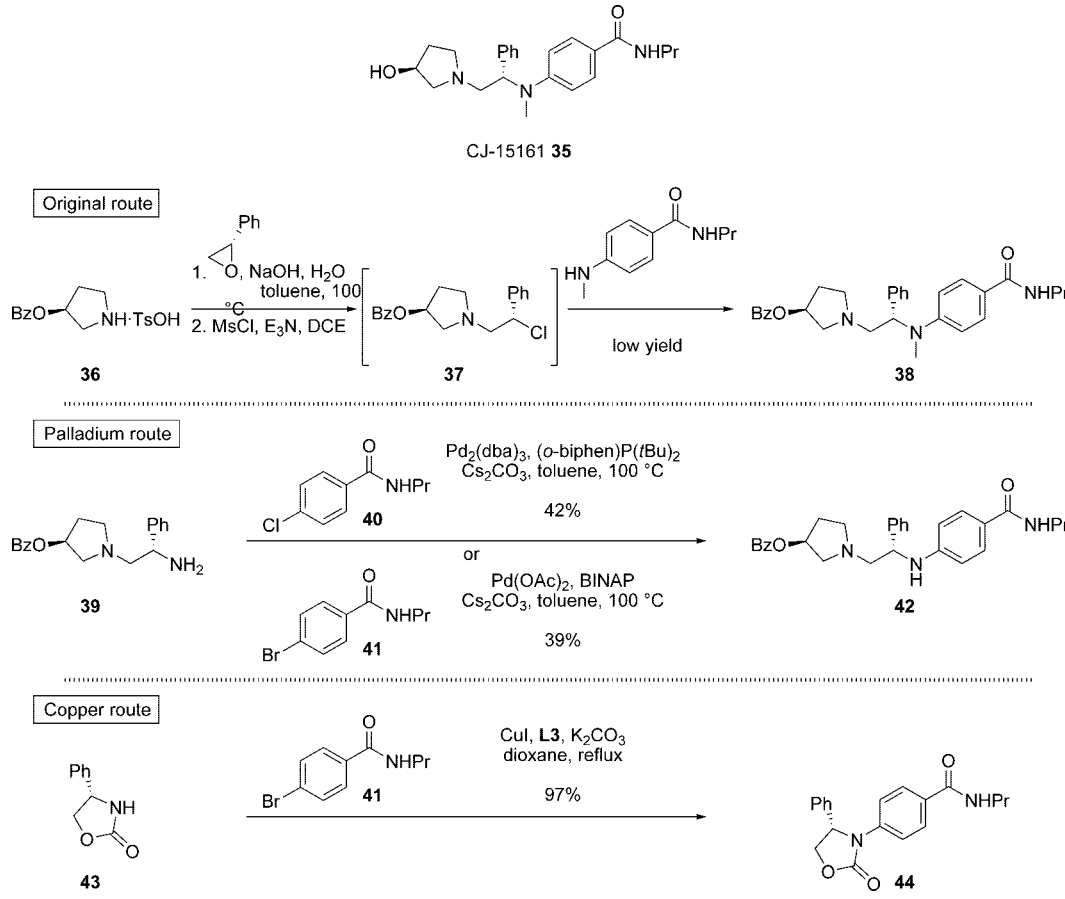
nections. Whereas the preparation of aryl amides and carbamates used to be envisioned from acylation of anilines, they can now efficiently be disconnected to aryl halides and amides or carbamates. Striking examples include the preparation of two oxazolidinone antibiotics: linezolid and toloxatone. Whereas the elaboration of the oxazolidinone ring used to be the key step for the preparation of such compounds, and although efficient palladium-catalyzed coupling reactions of oxazolidinones with aryl bromides have been developed, they can now easily and efficiently be obtained using copper-mediated cross-coupling technologies. The procedure, in addition to being cost-effective, can also tolerate some functional groups that are otherwise problematic with palladium catalysis and has been extended to the use of carbamates. This was nicely exemplified with efficient preparations of linezolid **26** and toloxatone **29** starting from oxazolidinone **23** and aryl bromides **24** and **27**. Using copper iodide, *trans*-cyclohexanediamine **L3**, and potassium carbonate in dioxane at 110 °C, arylated products **25** and **28** could be obtained in good to excellent yields and further elaborated to the target molecules (Scheme 34).[60]

Fürstner and co-workers used a copper-mediated heteroarylation reaction for the preparation of chiral oxazolidinopyridine **32**, a substrate that was used as starting material for the total synthesis of the macrocyclic spermidine alkaloid isooncinotine **34**. Chiral oxazolidinone **30**, serving as the

Scheme 35. Synthesis of Isooncinotine



Scheme 36. Synthesis of CJ-15161



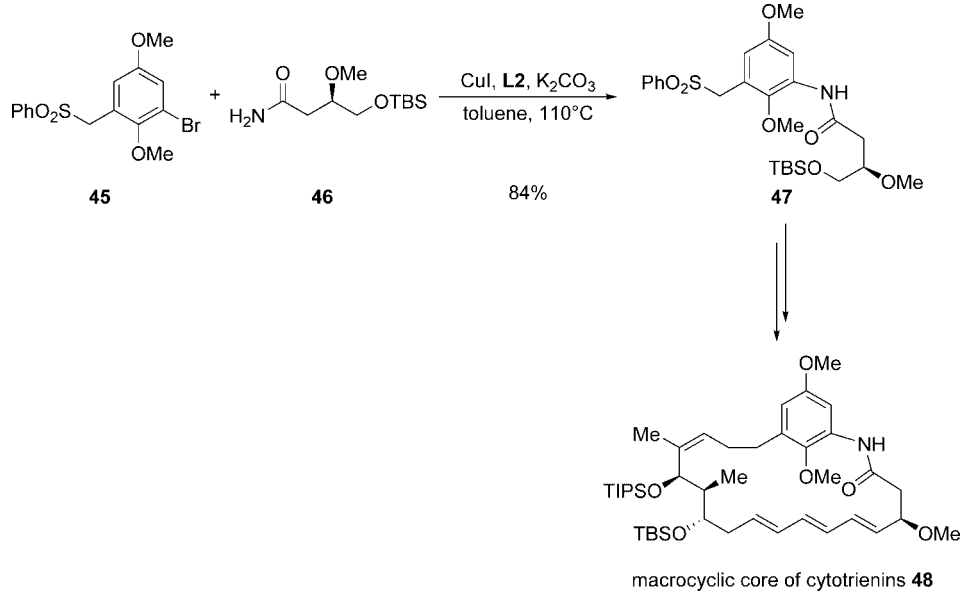
stereochemical control element in the following hydrogenation step, was conveniently introduced using copper iodide and *N*,*N*′-dimethylethylenediamine **L2**. This reaction gave the desired product **32** in 90% yield and can be conveniently performed on a gram scale (Scheme 35).[284]

On the same perspective, researchers at Pfizer developed an efficient and straightforward synthesis of the κ-opiod receptor agonist CJ-15161. Due to limitations of the original synthetic route (Scheme 36), which included poor regioselectivity during the epoxide ring opening and low overall yield, they decided to change strategy for the synthesis of intermediate **38** and envisioned an alternative disconnection using metal-mediated C−N bond formation. Considering that the palladium-catalyzed amination of aromatic chloride **40** or bromide **41** with **39** gave the desired intermediate **42** only in modest yield,[257] a major improvement was found in the use of a mild, cost-effective, and scalable copper-mediated arylation of oxazolidinone **43** with aryl bromide **41**. The process was found to be quite general because other aryloxazolidinones could be obtained in high yields.[286]

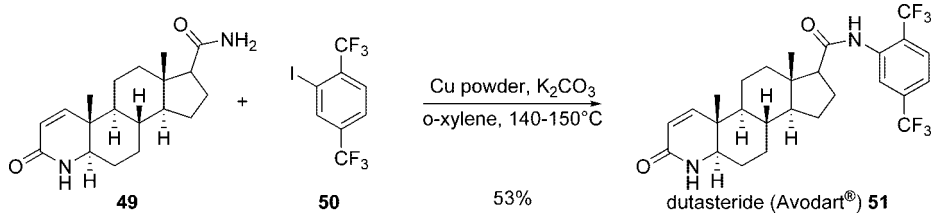
Whereas the arylation of oxazolidinones is typically used for the introduction of chiral auxiliairies or amino alcohol surrogates, the arylation of amides certainly has a broader scope in natural product synthesis because anilides are found in an impressive number of targets that can now, from a retrosynthetic point of view, be disconnected at the C−N bond.

One of the first natural product syntheses featuring such a disconnection was reported in 2004 by Panek and coworkers, who revisited the synthesis they devised earlier for

Scheme 37. Synthesis of the Macrocyclic Core of Cytotrienins



Scheme 38. Scalable Synthesis of Dusteride (Avodart)



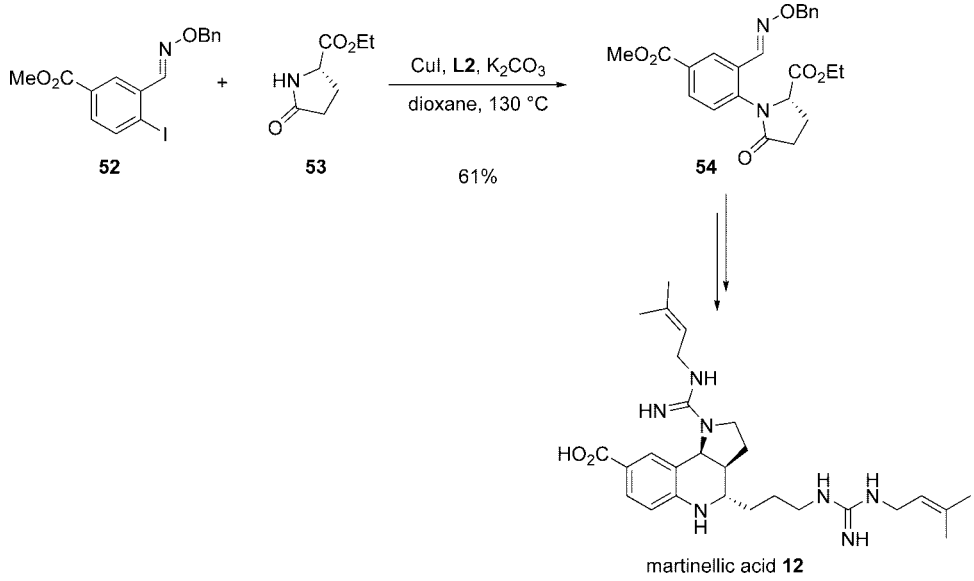
ansamycins. One of the major improvements was the formation of the aromatic amide, which used to be installed using a rather sluggish aniline acylation[287] and which was finally envisioned by a copper-mediated amidation reaction. Therefore, and to undertake the assembly of the aromatic fragment **47**, a copper-mediated amidation between aryl bromide **45** and amide **46** was investigated. After several reaction conditions had been screened, it was determined that this coupling was best effected using 20 mol % of CuI, 40 mol % of *N*,*N*′-dimethylethylenediamine **L2**, potassium carbonate as a base in toluene at 110 °C, and a slight excess (1.2 equiv) of the amide **46**. Under these conditions, amidation product **47** was obtained in 84% yield. Moreover, a 1:1 ratio of bromide **45** and amide **46** did not significantly decrease the yield of this reaction because the right-hand fragment for the preparation of the macrocyclic core **48** of cytotrienins could be obtained in 82% yield and in multigram quantities (Scheme 37).[288]

One impressive example of amide arylation was reported in 2007 for the preparation of dutasteride, a selective 5α-reductase inhibitor currently available as a drug for the treatment of various prostate diseases under the brand name Avodart **51**. In the first reported synthetic route, the aromatic amide was elaborated on large scale by acylation of a tetracyclic carboxylic acid with 2,5-bis(trifluoromethyl)-aniline and thionyl chloride. A more convenient route was found in the use of an Ullmann−Goldberg-type condensation starting from amide **49** and 2-iodo-1,4-bis(trifluoromethyl)-benzene **50**. Their coupling in the presence of potassium carbonate, sodium carbonate, sodium methoxide, sodium hydroxide, or potassium hydroxide as a base, in DMF, toluene, DMA, DMSO, or dimethyl imidazole as solvent, at high temperatures was unsuccessful. When the reaction was conducted using copper powder and potassium carbonate without any solvent (neat reaction), the reaction proceeded but with the formation of unacceptable amounts of impurities. However, when the reaction was conducted using copper powder and potassium carbonate in *o*-xylene at a temperature of 140−150 °C, **51** was obtained in 63% crude yield, on a 22 g scale, a yield that could certainly be further increased by using a ligand-assisted procedure and copper(I) (Scheme 38).[289] Worthy of note is the complete regioselectivity of the reaction for the primary amide because the secondary cyclic conjugated amide is not arylated during the reaction.

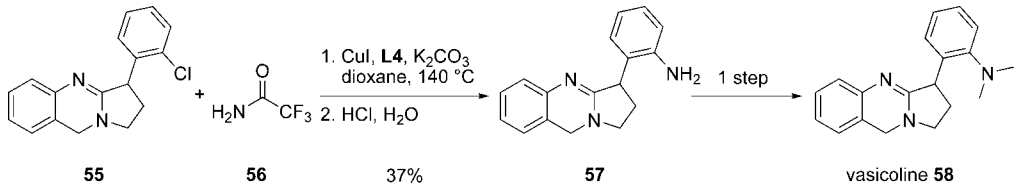
Martinellic acid **12** has attracted considerable interest from the synthetic community because of both its challenging structure and biological activities. A recent and quite straightforward approach to this molecule was reported in 2006 by Naito and co-workers. The strategy used for the formation of the aniline bond mirrors the one used by Ma and co-workers (Scheme 31) and features and arylation of pyroglutamate ester **53** with aryl iodide **52** (Scheme 39). The product **54** was isolated in 61% yield,[290] but the use of palladium catalysis was a lot more efficient in this case because the yield could be improved to 98% by using a mixture of $Pd_2(dba)_3$, xanthphos, and cesium carbonate in refluxing dioxane. Although the reason for the limited success met by copper catalysis in this case is rather unclear, this example nicely shows the interesting complementarities that exist between catalytic systems based on palladium and copper(I).[291]

Amides, and more specifically trifluoroacetamides, can also serve as ammonia surrogates as nicely exemplified by Ellman, Bergman, and co-workers in their synthesis of vasicoline. At the end of their synthesis and after elaboration of the whole carbon framework of vasicoline, the authors

Scheme 39. Synthesis of Martinellic Acid



Scheme 40. Synthesis of Vasicoline



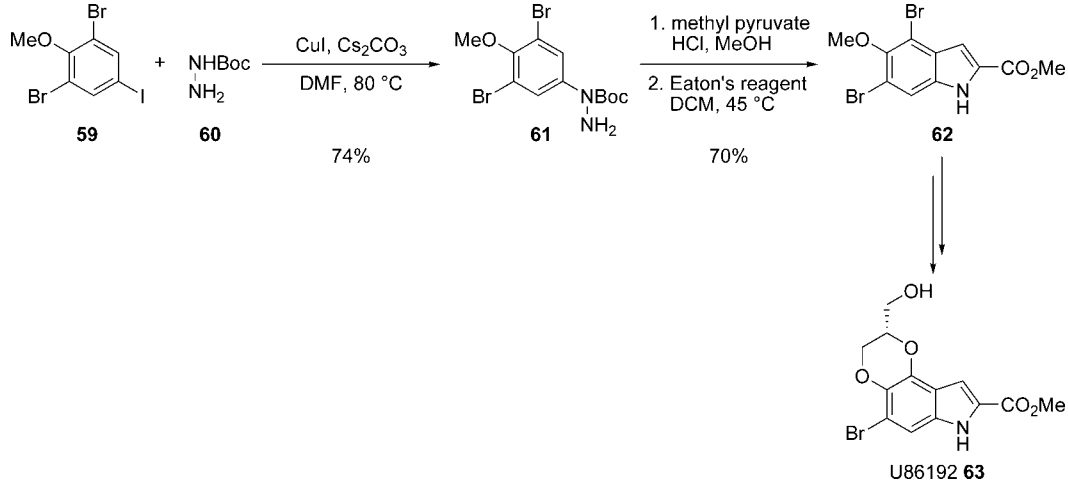
were confronted with the challenging amination of **55**. Because the metal-catalyzed substitution of an aryl chloride by dimethylamine had not been previously disclosed, nor did this reaction proceed in the presence of various catalysts, and because the metal-catalyzed substitution of aryl chlorides with ammonia surrogates has been extensively studied, the substitution of **55** with an ammonia equivalent to give didesmethylvasicoline **57** was especially attractive. A number of arylhalide amination methods, employing a variety of ammonia equivalents, were therefore evaluated on **55**. It should be noted that this compound is a relatively unreactive intermediate (bad leaving group and steric hindrance at the ortho position), possessing an acidic position α to the amidine that renders this amination particularly challenging. Having quickly eliminated Pd-catalyzed carbamate couplings because they exhibit low reactivity toward aryl chlorides, and catalytic amination methods relying on M[HMDS] for similar reasons, benzophenone imine emerged as the most appropriate ammonia synthon for the amination because it is not sterically demanding, its N−H bond is quite reactive, and it has been shown to operate in conjunction with mild heterogeneous bases. Despite this, slow hydrodechlorination was observed as the only reaction between **55** and benzophenone imine in the presence of $Pd_2(dba)_3$ and Buchwald's biaryl ligand, 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl.

These disappointing results led the authors to broaden their search of amination methods to include less conventional approaches, and they next considered amide couplings for the preparation of **57**. If Pd-catalyzed amide-coupling conditions proved to be unreactive with **55**, successful C−N bond formation was finally achieved with Buchwald's copper-mediated amidation method. At elevated temperatures, various aryl and alkyl primary amides were coupled to **55** in fair yield and trifluoroacetamide **56** was found to give the highest yield of aminated product **57** after hydrolytic workup (Scheme 40). Changes to catalyst loading, reaction temperature, and other conditions did not improve conversion without leading to increased substrate decomposition as well.[292]

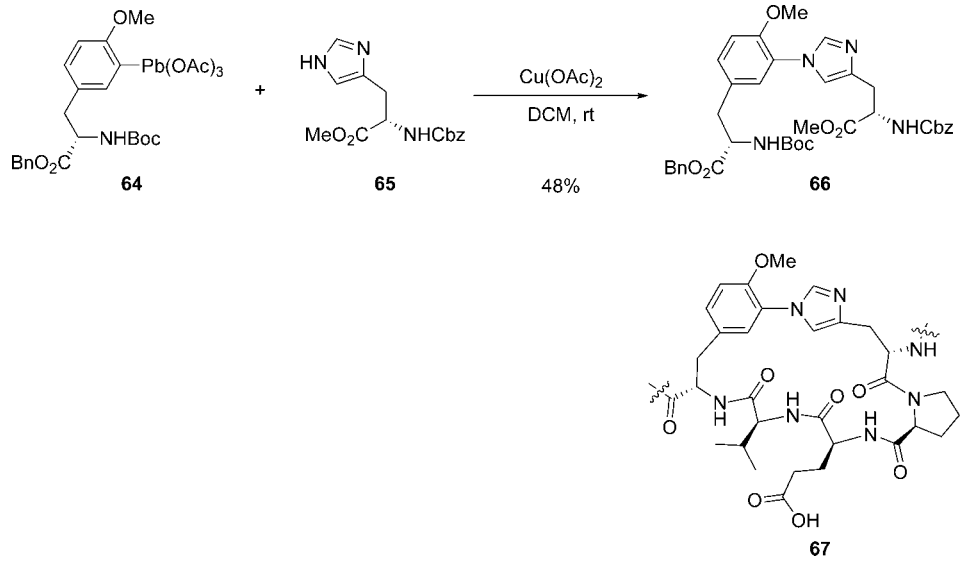
One last example, the enantioselective synthesis of indolodioxane U86192A **63**, ought to be mentioned in this section since it nicely illustrates the use of hydrazines as reaction partners for C−N bond formation. This tricyclic molecule is a potent antihypertensive agent among the derivatives of the nonnatural hybrid of three 5-HT_{1A} receptor binding molecules: 5-hydroxytryptamine, spiroxatrine, and pindolol. The indole core could be obtained using a three-step sequence starting from aryl iodide **59**. The copper-catalyzed formation of the *N*-aryl *N*-Boc hydrazide **60** proceeded smoothly to give **61** in 74% yield (Scheme 41); this substrate was then used in Fischer's indole synthesis to yield the fully elaborated, conveniently substituted indole derivative **62**.[293]

In addition to application in natural product synthesis, a number of sequential or cascade processes starting with amide arylation have been developed. They include synthesis of 7−10-membered ring nitrogen heterocycles using an arylation with β-lactam−ring expansion process,[294] two-step synthesis of 2-aryl-4-quinolones from *o*-halophenones using a sequential copper-catalyzed amidation−base-mediated Camps cyclization,[295] synthesis of benzimidazolones by a cascade coupling−cyclization process,[296] synthesis of 1*H*-indazoles from copper-mediated condensation of *o*-halophenones with hydrazines,[297] and synthesis of benzimidazoles by a copper-catalyzed cascade arylamination/condensation process.[298]

Scheme 41. Synthesis of U86192



Scheme 42. Synthesis of the Histidine−Tyrosine Side Chain Coupled Dipeptide of Cytochrome *c* Oxidase



3.3. Arylation of *N*-Heterocycles

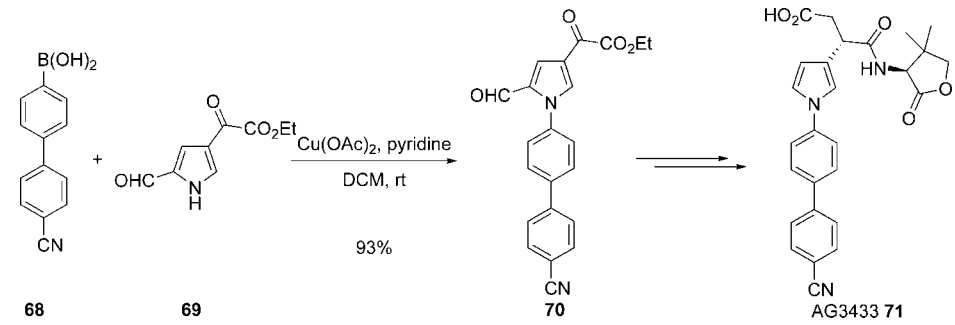
Arylation of heterocycles has been rarely used in the total synthesis of natural and/or biologically active products. One of the first examples was reported by Elliott and Konopelski for the synthesis of side chain coupled histidine−tyrosine dipeptide **66** found in the active site of cytochrome c oxidase **67** (Scheme 42). Under catalysis by copper(II) acetate, complete regiocontrol (*N*-1 versus *N*-3) was obtained in the arylation of substituted imidazoles with aryllead reagents. The mildness of the reaction conditions (room temperature, no base, equimolar ratio) allowed for the first synthesis of **66**.[299]

Even though not readily available, arylboronates are still one of the best arylating agents for the reaction with amines. As seen in section 2.3, they usually readily react at room temperature under mild reaction conditions, and the procedure is especially practical. The synthesis of aryl pyrrole **70**, an intermediate in the synthesis of the potent inhibitor of matrix metalloproteases AG3433 **71**, from pyrrole **69** and arylboronate **68** (obtained in two steps via borylation of the corresponding bromide), is a nice illustration of the synthetic utility of this protocol. By just stirring a mixture of **69** with **68** (2 equiv), copper acetate (1.5 equiv), and pyridine in dichloromethane at room temperature open to air for 2 days, the desired arylated pyrrole **70** was obtained in 93% yield (Scheme 43).[300]

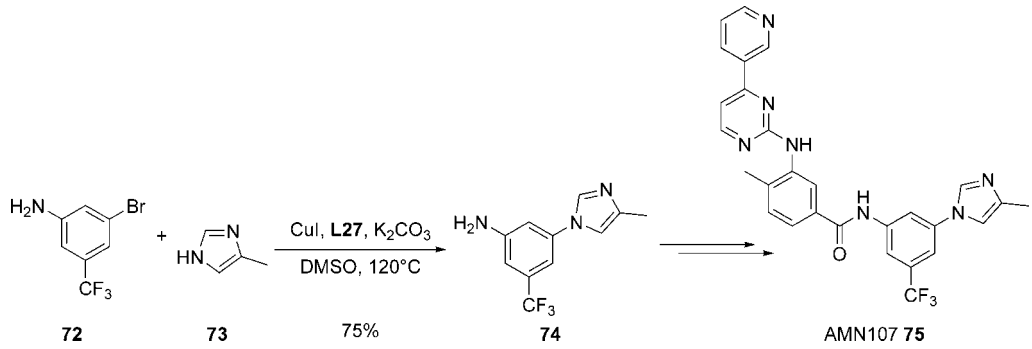
Due to recent developments and the introduction of ligand-assisted methods, arylation of heterocycles with aryl halides is now also a powerful synthetic tool, even if the conditions required are in most cases a bit harsher than the one required for Chan−Lam coupling reactions. An interesting example was reported for the synthesis of AMN107 **75** (Nilotinib), a compound currently undergoing phase II/III clinical trials for chronic myelogenous leukemia. In this synthesis, the aromatic imidazole **74** is regioselectively synthesized from arylation of 4-methylimidazole **73** with aryl bromide **72** in 75% yield and without any competing self-arylation of bromoaniline **72** (Scheme 44).

In 2007, an especially impressive example of *N*-heterocycle arylation was reported by researchers at Abbott, who reported an expedient, multikilogram scale synthesis of the naphthalenoid H_3 antagonist **79**. To have a facile and scalable synthesis, they decided that the aryl pyridazinone would be installed at the end of the synthesis by arylation of pyridazinone **77** with substituted naphthalenyl iodide **76**. The authors first focused on palladium-catalyzed cross-coupling technologies for this step, and many reaction parameters were screened, including ligand (dppf, Xantphos, X-phos, BINAP), palladium source [$PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$],

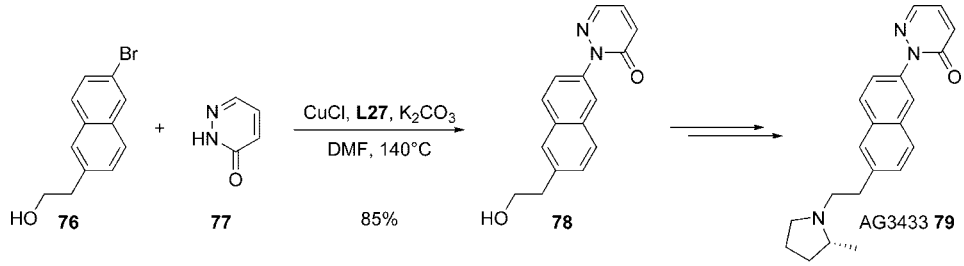
Scheme 43. Synthesis of AG3433



Scheme 44. Synthesis of AMN107



Scheme 45. Gram-Scale Synthesis of a Naphthalenoid H3 Antagonist



appropriate base (K_2CO_3, Cs_2CO_3, K_3PO_4, *t*BuONa, *t*BuOK), and solvent (THF, DME, dioxane, toluene). Unfortunately, these efforts were unsuccessful: no desired product was detected, and the starting materials were mostly recovered. The low reactivity of pyridazinone in the Pd-catalyzed cross-coupling reaction might be rationalized by the fact that the decreased nucleophilicity of the pyridazinone anion reduces coordination to the catalyst or, more likely, diminishes the tendency of the intermediate aryl−Pd−pyridazone complex to undergo reductive elimination.

The above disappointing results prompted the authors to consider the copper-mediated cross-coupling reaction as a viable method, and they began the optimization of this step by varying copper and ligand sources. From these studies, copper(I) chloride was found to be the best copper catalyst and 8-hydroxyquinoline **L27**, the best ligand. Other reaction conditions were also examined, including base, solvent, and reaction temperature. Eventually, the coupling of **76** with **77** proceeded remarkably well at 130−140 °C, using catalytic amounts of CuCl and 8-hydroxyquinoline **L27** in DMF with K_2CO_3 as a base. These conditions were ultimately used to prepare **78** in 85% assayed yield...on a 13.2 kg scale and without competing *O*-arylation! It is worthwhile to point out that most of the copper catalyst used in this step was efficiently removed by washing the organic phase with aqueous ammonia solution and Na_2EDTA solution, respectively, during the workup (Scheme 45).[301]

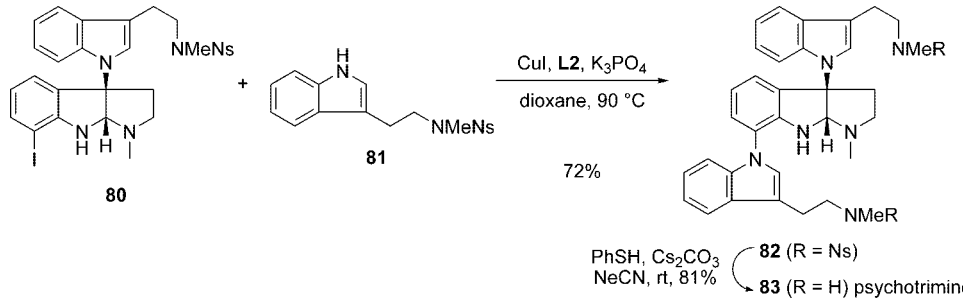
Finally, the total synthesis of the trimeric indole alkaloid psychotrimine **83** features a quite spectacular, especially efficient, late-stage copper-mediated indole arylation. After several experiments, it was revealed that the ligand−base combination was, as it is in a lot of cases, an important factor for the success of this coupling reaction. When the reaction was carried out using *N*,*N*′-dimethylethylenediamine **L2** as ligand and K_3PO_4 as base, the desired coupling product **82** was obtained in 72% yield. Side chain deprotection then allowed for the completion of the first total synthesis of psychotrimine **83** (Scheme 46).[302]

3.4. Enamides

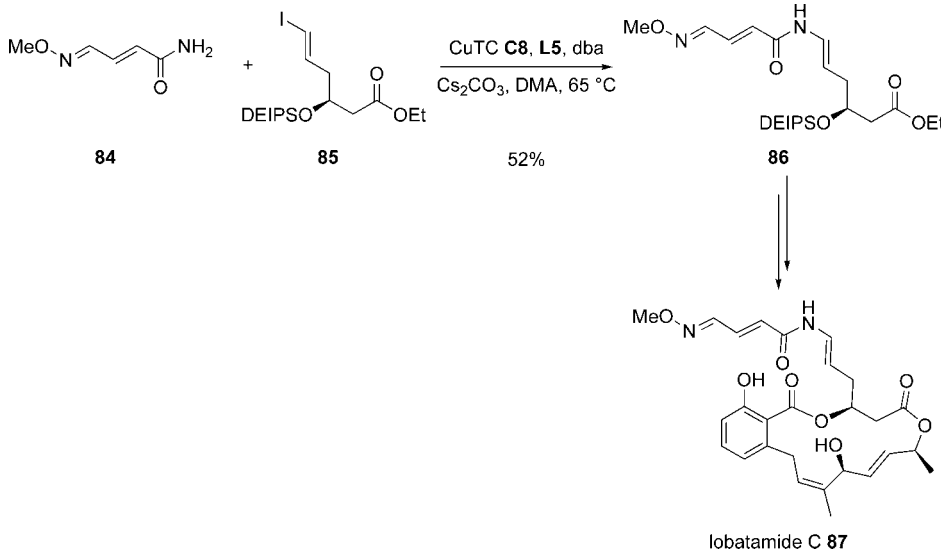
Enamides are unique functional groups present in many natural products discovered during the past decades, which include protease inhibitors TMC-95-A-D, sedative, antibacterial and antiplasmodic cyclopeptide alkaloids, cytotoxic agents aspergillamides, chondriamides, antitumor macrolides lobatamides, salicylihalamides, and related compounds. In addition, enamides are clearly emerging as most useful synthons and have found applications for the preparation of heterocycles and in asymmetric synthesis of amides and amino acids.

It is then not surprising that synthetic interest in this target has been considerable, even if up to 2000 no general and efficient method existed for their stereoselective synthesis.

Scheme 46. Synthesis of Psychotrimine



Scheme 47. Synthesis of Lobatamide C



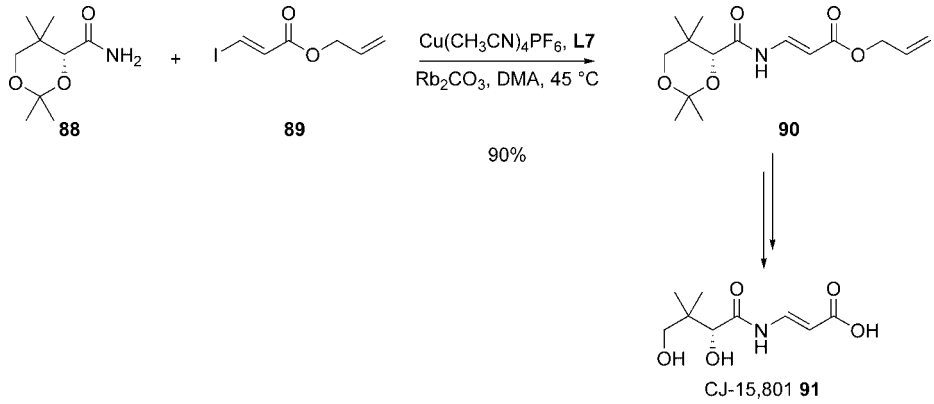
Among the emerging methods, and as seen in section 2.3.5, copper-catalyzed coupling reaction of amides with vinyl halides has received increasing attention and found applications in the total synthesis of natural products. The development of mild procedures that allow for the preparation of both (*E*)- and (*Z*)-enamides on complex substrates clearly allowed for the resolution of a long-standing synthetic problem as will appear with selected examples described in this section. Anyone considering the synthesis of an enamide-containing molecule should really think about using copper-mediated cross-coupling technologies.

Pioneering work by the Porco group in this area paved the way for the use of copper-mediated amide vinylation in natural product synthesis. After developing a new approach to the assembly of enamides using copper(I) thiophenecarboxylate mediated substitution of vinyl iodides with amides, modified conditions were optimized to synthesize the *O*-methyloxime enamide side chains related to the salicylate antitumor macrolides.[94] The synthetic utility of this strategy was next further demonstrated in a total synthesis of lobatamide C **87**. The key step featured a Cu(I)-mediated vinylic substitution of **85** with butenamide **84** and led to a 52% yield of the C1−C10 enamide fragment **86**, which was used for the preparation of lobatamide C **87**. Critical to the success and reproducibility of this reaction were the use of a moderate reaction temperature (65 °C) to suppress elimination of the sensitive β-silyloxy ester coupling substrate, together with 1,10-phenanthroline **L5** and dibenzylideneacetone as supporting ligands for CuTC **C8** and high-purity cesium carbonate as base (Scheme 47).[95,303] A similar strategy was next used for the preparation of simpler, acyclic photoactivable analogues of the natural product.[304]

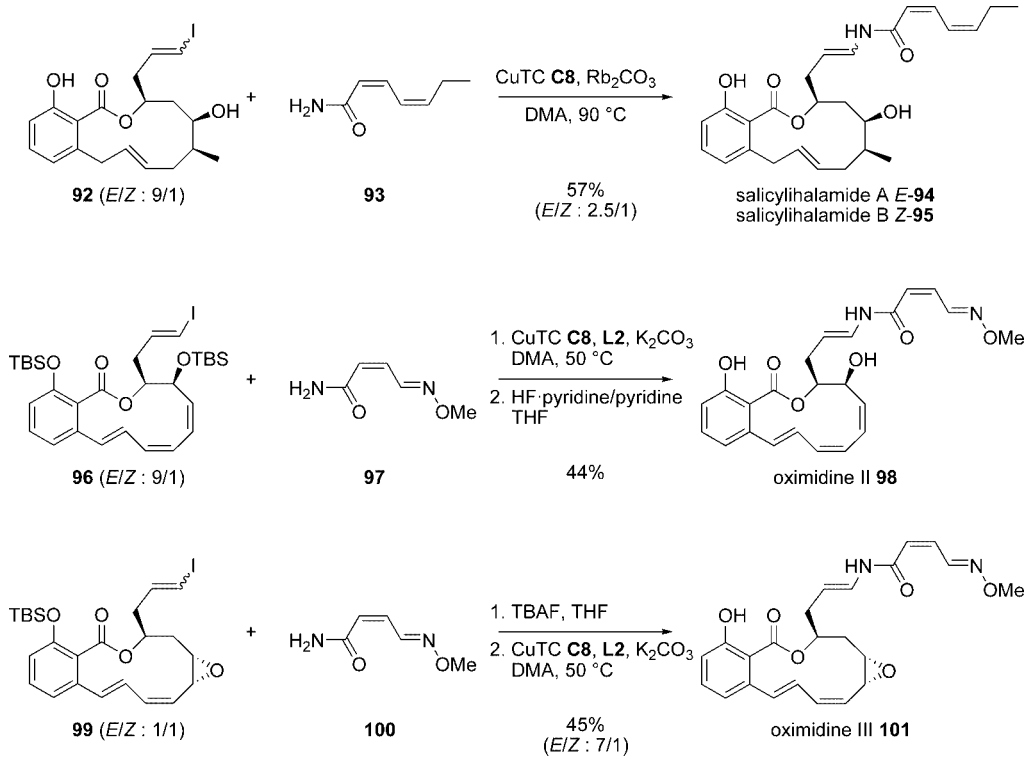
The amidation protocol was next extended to the preparation of vinylogous carbamic acids and ureas, uncommon moieties present in a number of bioactive products, including palytoxin, enamidonin, and cyclic lipopeptides K97-0239A and B as well as antibiotic CJ-15,801 **91** and for which various approaches had been previously devised (acylation of vinylogous carbamates, palladium-catalyzed coupling of lactams and alkenes, and elimination of thioacetals and phenylselenides). After extensive model studies for the coupling of benzamide with allyl β-iodoacrylate, Porco and co-workers eventually found that a combination of Kubas salt, 3,4,7,8-tetramethyl-1,10-phenanthroline **L7**, and rubidium carbonate in DMA was the most efficient catalytic system. This system was next used for the preparation of CJ-15,801 starting from amide **88** and iodoacrylate **89**. A two-step deprotection sequence from the vinylogous carbamic acid **90** obtained in 90% yield then furnished the target molecule **91** (Scheme 48).[96]

These results generated considerable interest, and salicylate macrolides salicylihalamides and oximidines were the next complex targets to be envisioned from a "copper-perspective". In 2001, Fürstner and co-workers reported a total synthesis of salicylihalamides A **94** and B **95** featuring a late-stage amide vinylation reaction for the installation of the enamide side chain based on Porco's amidation procedure. On the basis of preliminary results obtained from model studies demonstrating that the cross-coupling of substrates containing an unprotected phenol group proceeded well and that, in some cases, isomerization of the double bond of vinyl iodide could not be avoided, the amidation of vinyl iodide **92** with 3 equiv of amide **93** was envisioned. Gratifyingly, the coupling proceeded relatively well in the presence of 50%

Scheme 48. Synthesis of CJ-15,801



Scheme 49. Synthesis of Salicylate Natural Macrolides

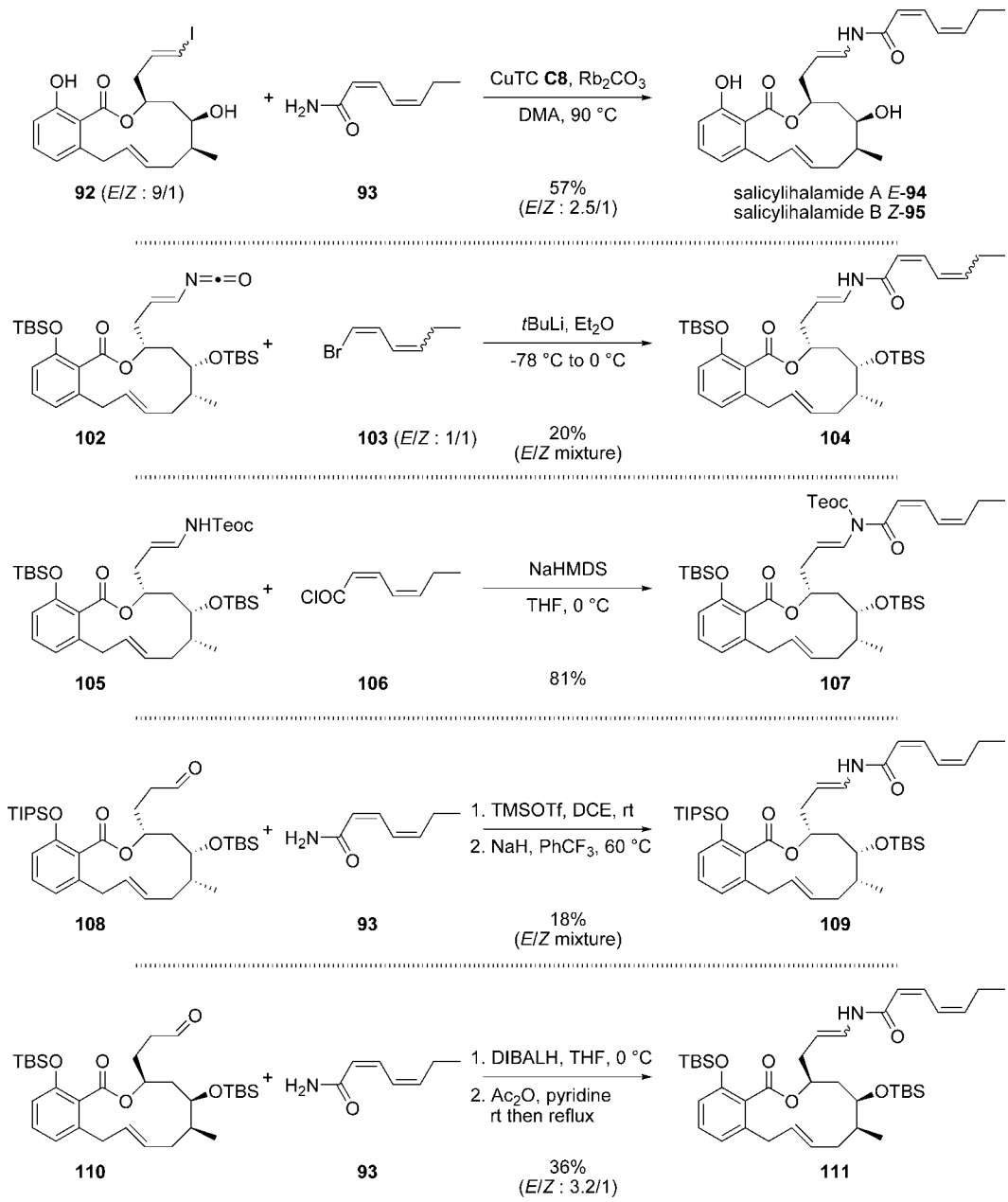


CuTC **C8** and 3 equiv of rubidium carbonate, allowing for the introduction of the rather labile side chains of salicylihalamides A **94** and B **95** in 57% yield. In this particular case, the use of cesium carbonate failed to afford the desired target molecules under otherwise identical conditions (Scheme 49).[305] In a series of publications in 2003 and 2004, Porco and co-workers next reported the use of a modified, ligand-assisted system for the installation of the side chain of oximidines II **98** and III **101**. Whereas amidation of **96** with oxime amide **97** using standard conditions gave low yield due to competitive elimination under basic conditions, the use of an additional diamine ligand **L2** allowed for a smooth coupling reaction because oximidine II **98** could be obtained, after desilylation of the phenol, in 44% yield and with high stereospecificity.[306] Similar conditions were used in the synthesis of oximidine III **101**: using stoichiometric CuTC **C8**, a 7/1 mixture of *Z* and *E* isomers was obtained in 45% yield, starting from a 1/1 mixture of vinyl iodide isomers. In this particular case, extended reaction times resulted in the decomposition of the target molecule and a higher ratio of (*Z*)-enamide (Scheme 49).[307] A unified strategy for the divergent and stereocontrolled introduction of the (*E*)- and (*Z*)-enamide side chains of oximidines I−III and salicylihalamides A and B as well as lobatamides A and D was reported by Coleman and Liu the same year. This procedure uses a three-step sequence starting with a copper-promoted C−N coupling of (*E*)- and (*Z*)-vinyl iodides with a protected maleimide hemiaminal followed by deprotection and reaction of the resulting (*E*)- or (*Z*)-enelactam hemiaminals with *O*-methylhydroxylamine or propylidenetriphenylphosphorane.[308]

The challenging structural features of these natural products combined with their novel mode of action have stimulated a number of synthesis programs and culminated in various total syntheses of salicylihalamides.[309] In all cases, these synthetic routes have required the installation of the highly sensitive enamide side chain at a late stage, which clearly provides an interesting opportunity to compare different approaches used to put this side chain on (Scheme 50).

In the first total synthesis of (+)-salicylihalamide **94**, completed by the De Brabander group in 2000, the dienyl enamide was incorporated through the addition of hexadienyllithium (prepared *in situ* by metal−halogen exchange

Scheme 50. Other Approaches to the Enamide Side Chain of Salicylihalamide A

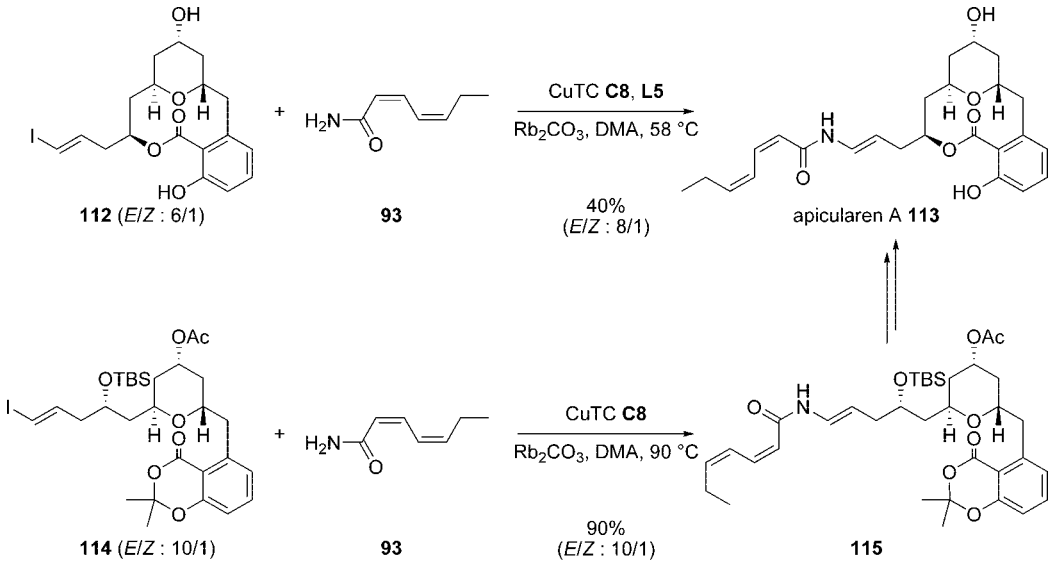


from **103**) to a solution of isocyanate **102** [derived from the corresponding (*E*)-α,β-unsaturated carboxylic acid by acyl azide formation followed by Curtius rearrangement]. The desired compound **104** was obtained as an inseparable mixture of *E* and *Z* isomers in 20% yield together with a dimer resulting from the addition of the intermediate lithium amide to the starting isocyanate.[310] In a similar perspective, Snider and co-workers showed that the yield of the desired *all-Z* isomer could be raised to 43% by preparing the hexadienylcuprate *in situ* from ethyllithium, copper bromide dimethyl sulfide complex, and acetylene.[311] The next year, Smith reported a high-yielding, stepwise elaboration of the side chain using an acylation of sodium salt of **105** (obtained by Curtius rearrangement and trapping of the intermediate isocyanate with trimethylsilylethanol) with dienyl acyl chloride **106**. Using this sequence, protected salicylihalamide A **107** could be obtained in 81% yield and as a single isomer.[312]

In two other syntheses, the enamide side chain was envisioned from the condensation of aldehyde **108** (or its enantiomer **110**) and dienylamide **93**, a reaction that typically gives mixture of isomers and is relatively hard to control. Labrecque and co-workers, however, managed to use this condensation for the installation of salicylihalamide side chain. Condensation of excess amide **93** with aldehyde **108** provided an intermediate *N*,*N*′-bis-acylated aminal (incorporating two side chain residues), which underwent elimination upon treatment with sodium hydride in trifluorotoluene at 60 °C to give a mixture of enamides in 18% yield.[313] Starting with the same precursors but using different reaction conditions, the enamide side chain could be attached by treating aldehyde **110** with the aluminum carboximidoate derived from **93** followed by formal elimination of water. These conditions resulted in a mixture of (*E*)- and (*Z*)-enamides in a 3.2/1 ratio (Scheme 50).[314,315]

When all of the different approaches designed for the installation of the salicylihalamide side chain are put together, it clearly appears that it is quite a tricky and delicate task and that controlling the enamide geometry is a real challenge. Although in this particular case the acylation of an enecar-

Scheme 51. Synthesis of Apicularen A



bamate proved to be especially efficient, in terms of both yield and stereocontrol, the use of a copper-mediated amidation holds great potential and is a highly competitive process.

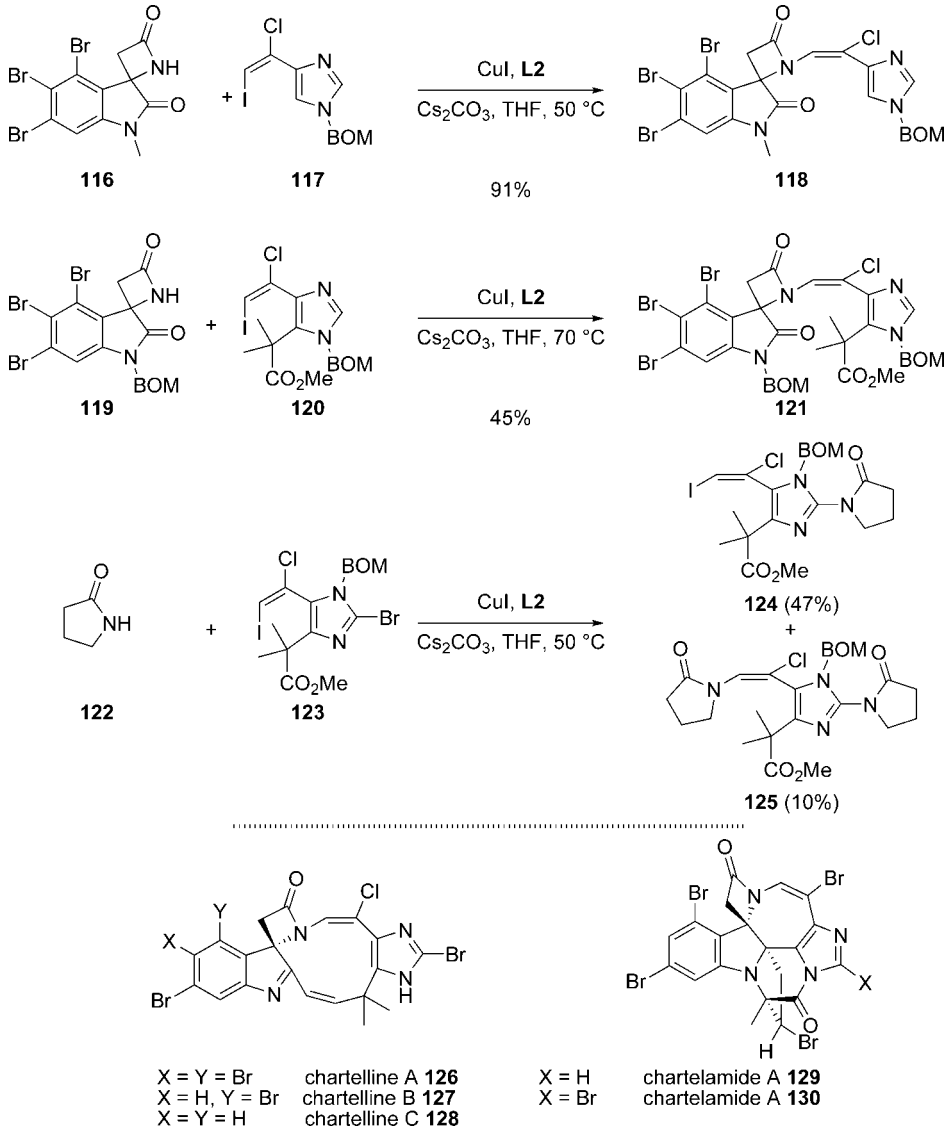
The Nicolaou and Panek groups have reported the use of a copper-mediated amide vinylation for the installation of a similar side chain as a pivotal reaction en route to apicularen A. In the final stage of their synthesis, Su and Panek used Porco's protocol for the CuTC **C8**-catalyzed formal substitution of vinyl iodide **112** with amide **93**, which proceeded in 40% yield at 58 °C. In this case, the diamine ligand and reaction temperature were crucial to the success of the reaction because no diamine resulted in decomposition of **112** and higher temperatures (80 °C) resulted in olefin isomerization (Scheme 51).[316] A similar system without diamine ligand was used in Nicolaou's synthesis and stereospecifically furnished the desired apicularen precursor **115** with 90% yield at 50% conversion.[317] Other strategies have been evaluated for the stereospecific elaboration of the dienamide side chain but met only moderate success. The addition of a dienyl lithium to an isocyanate gave the desired apicularen precursor but in low yield and as a mixture of stereoisomers,[318] the condensation of an aldehyde with the dienyl amide gave a bis-amide derivative that could not be converted to apicularen,[317] and the same condensation using the aluminum amide gave an aminal which, after formal elimination of water, gave the desired (*E*)-enamide in 39% yield along with 13% of its *Z* isomer.[319]

The chartellines **126**−**128** and chartelamides **129** and **130** are a small family of marine-derived, architecturally unique alkaloids possessing puzzling structures that have been a real synthetic challenge because they incorporate an array of unusual functional groups, including a β-halogenated enamide moiety. Besides one total synthesis of chartelline C by the Baran group,[320] little work has focused on the formation of the β-halogenated enamide moiety, which can be envisioned through a copper-mediated regioselective coupling reaction between a 1,2-dihaloalkene and a lactam. This was indeed confirmed by model studies aimed at both developing the chemistry required to construct the required haloenamide and determining the functional group compatibility of this methodology: results from these studies, which use Buchwald's conditions, are shown in Scheme 52. First, the coupling of dihalovinylimidazole **117** with tribromospiro-β-lactam **116** resulted in the smooth, regioselective, formation of haloenamide **118** in high yield. 5-Substituted imidazole **120** also reacted with BOM-protected lactam **119** to produce, although in a lower yield (45%, 67% based on recovered **120**), coupled product **121**, a potentially useful intermediate for the synthesis of chartelline A. Because the chartellines and chartellamides contain a 2-bromoimidazole moiety, the compability of this group with the copper-mediated vinylation was finally assessed. However, a reverse regioselectivity was observed in the reaction of **122** with **123** because the undesired lactam **124** was obtained together with a small amount of bis-lactam **125**.[321,322]

Cyclopeptide alkaloids are a group of closely related polyamide bases of plant origin. They are distinguished by their structural similarity and possess a 13-, 14-, or 15-membered cycle containing an aromatic ring. The remainder of the macrocycle consists of a peptide unit that is connected to the aromatic ring in either a 1,4- or a 1,3-orientation by enamide and alkyl−aryl ether linkages. To date, over 200 structures have been described, and these natural products, which have been used historically for the treatment of a variety of ailments, have also been shown to have numerous biological activities including sedative, antibacterial, antifungal, and antiplasmodial activities.

Their biological properties together with their intriguing structures have caused a steady stream of studies directed toward the synthesis of these natural products during the past decades. A common feature of the previous synthetic efforts was the use of a four-step sequence to install the enamide (starting from the corresponding amino-alcohol via thermal elimination of an intermediate selenoxide) after the crucial macrocyclization step, which somehow reduced the overall efficiency of the syntheses. In 2007, Ma and we reported the use of a copper-mediated amidation reaction to form this enamide, which proceed under mild conditions and offered an efficient solution to the problematic installation of the macrocyclic enamide. Indeed, coupling of vinyl iodide **131** with protected prolinamide **132** proceeded remarkably well because acyclic enamide **133** was obtained in 75% yield and without epimerization using copper(I) iodide as the source of copper(I), *N*,*N*-dimethylglycine **L19** as ligand, and cesium carbonate as base in dioxane at 80 °C (Scheme 53).[323] This

Scheme 52. Model Studies for the Synthesis of Chartellines

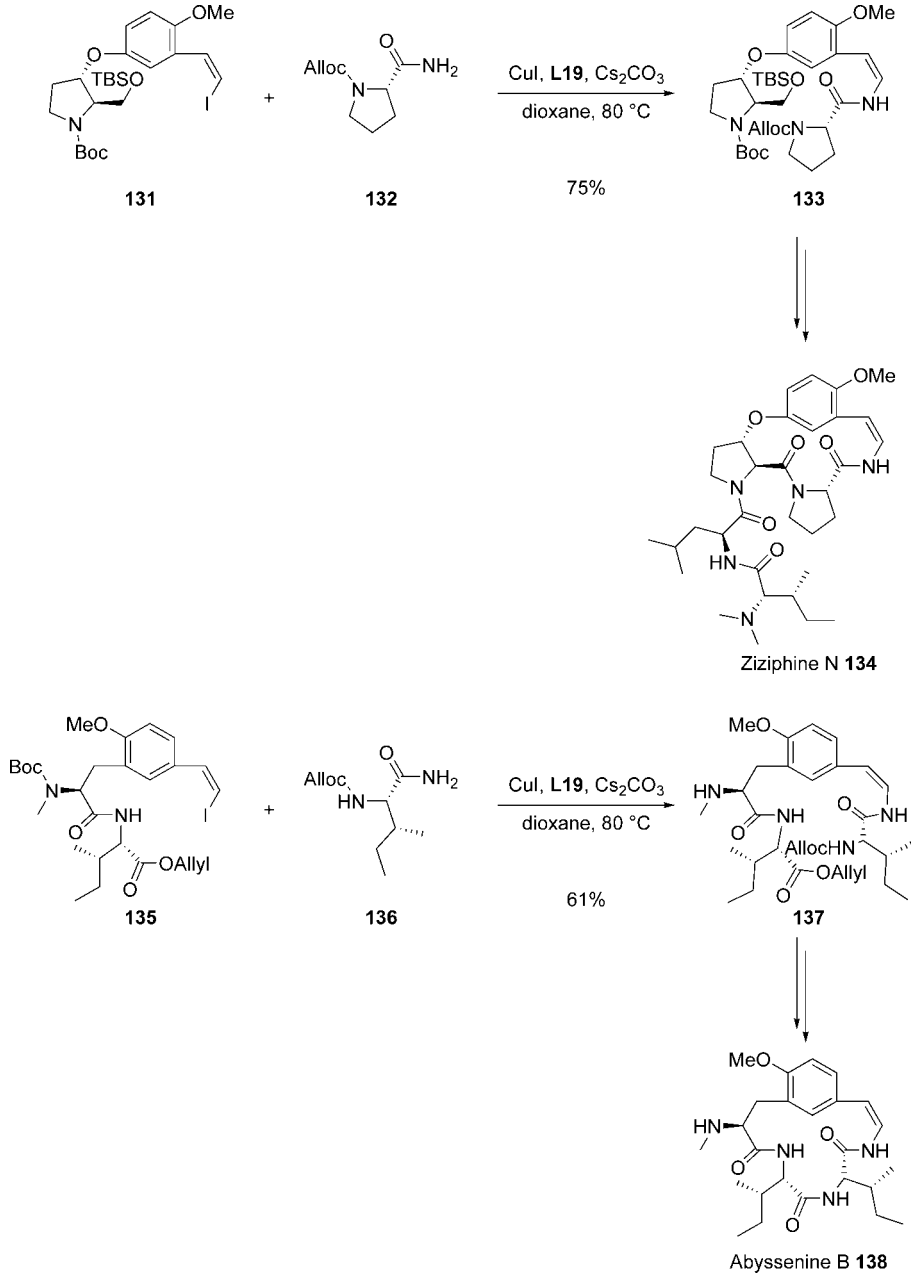


acyclic precursor was then used for the completion of the total synthesis of ziziphine N **134**, and a similar procedure was applied to the synthesis of the 15-membered ring cyclopeptide alkaloids abyssenine B **138** and mucronine E.[324] It should be noted that in these last two syntheses, the vinylation reaction proceeded with complete regioselectivity for the amide (versus the carbamate, Scheme 53). An intramolecular version of this reaction was used for the concomitant installation of the enamide and formation of the macrocycle (see section 3.6.1, Scheme 75).[325]

Enamide being a structural component of many natural products, the copper-mediated amidation has been used in a number of total syntheses: examples from Scheme 54 show the high potential of this reaction on complex substrates and its high tolerance for other functionalities. Its has been used in an end-game strategy for the installation of the terminal *N*-methyl-*N*-vinyl formamide moiety of scytophycin C **139**, a potent anticancer agent isolated from the blue-green alga *Scytonema pseudohofmanni*. Whereas the assembly of this terminal enamide using various Wittig- or Horner−Emmons-type reagents from the corresponding β-methoxyaldehyde merely resulted in elimination of methanol, the use of the Buchwald's amidation protocol afforded the long-awaited enamide by coupling of *N*-methylformamide with a terminal, fully protected vinyl iodide in 85% yield without epimerization of the relatively sensitive α-chiral ketone.[326] In 2005, Dias and co-workers reported the total synthesis of crocacin D **140**: the (*Z*)-enamide was here again installed by treatment of the terminal (*Z*)-vinyl iodide with the primary amide using a combination of 5% copper(I) iodide, 20% *N*,*N*′-dimethylethylenediamine **L2**, and cesium carbonate in THF at 70 °C.[327] The use of *N*,*N*-dimethylglycine **L19** in dioxane as solvent led to similar results. In comparison, installation of the (*Z*)-enamide by condensation of the appropriate aldehyde and amide gave small amounts of what appeared to be a mixture of crocacin D with the corresponding (*E*)-enamide isomer,[327] and acylation of an ene-carbamate with a dienyl acyl chloride under basic conditions provided a precursor of crocacin D in 30% yield.[328] TBAF-mediated Peterson elimination of an α-trimethylsilyl-β-hydroxy-amide proved to be a quite efficient strategy in this case because the (*Z*)-enamide was produced in 78% yield.[329]

The synthesis of palmerolide A **141**, a polyketide secondary metabolite with an impressive structure and biological profile, was also completed by installing the enamide side chain at the last step of the synthesis of a fully deprotected, highly sensitive, vinyl iodide precursor in 50% yield, a relatively modest yield that can be attributed to competitive

Scheme 53. Synthesis of the Cyclopeptide Alkaloids Ziziphine N and Abyssenine B

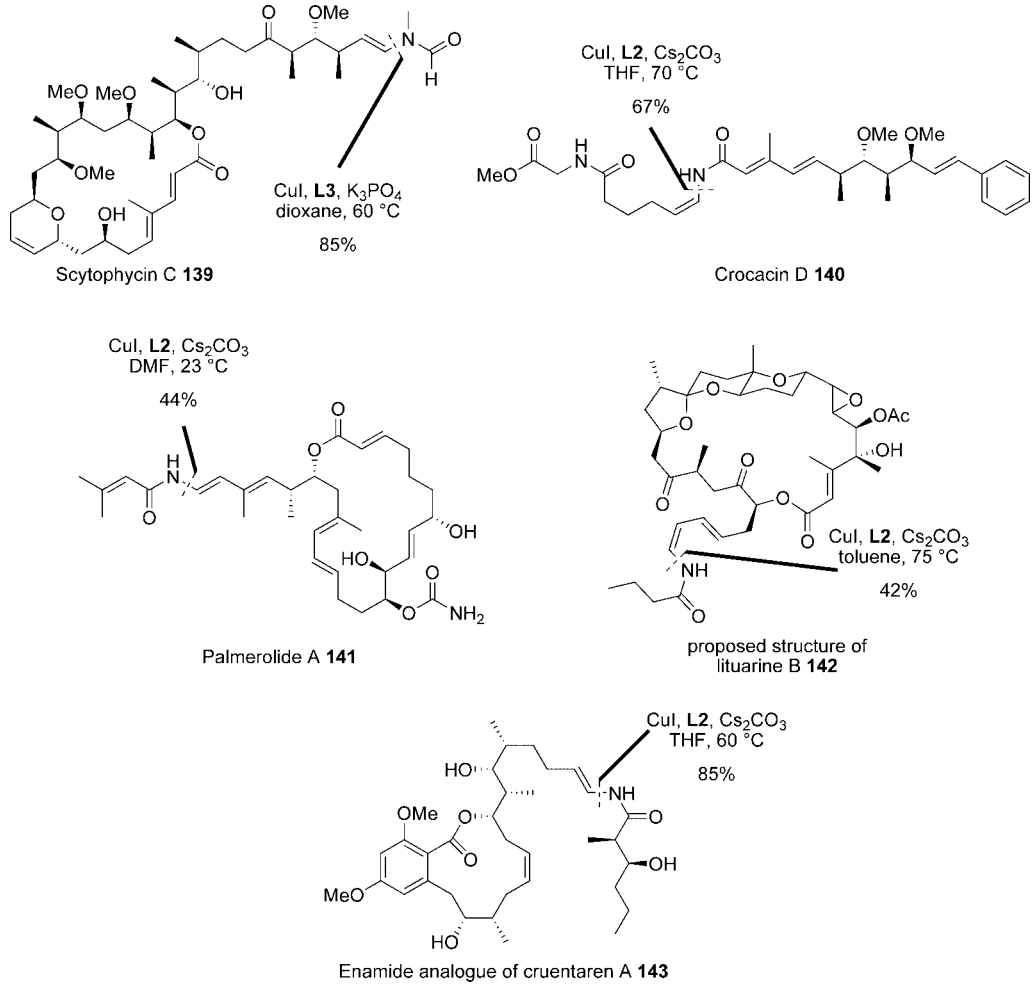


decarbamatation under the reaction conditions.[330] The proposed structure of lituarine B **142** was synthesized by Smith and co-workers and features a copper-mediated union of butyramide with *cis*-iodomethylacrylate to yield, after saponification and iodo-decarboxylation, a *cis*-iodoenamide that was used as an intermediate for the elaboration of the dienylenamide side chain by a Stille coupling (Scheme 54).[331] Finally, an enamide analogue **143** of cruentaren A, a highly selective potent inhibitor of F-ATPase bearing an allylamide side chain, was obtained by coupling of the corresponding primary amide with a fully protected macrocyclic precursor possessing a terminal (*E*)-vinyl iodide.[332]

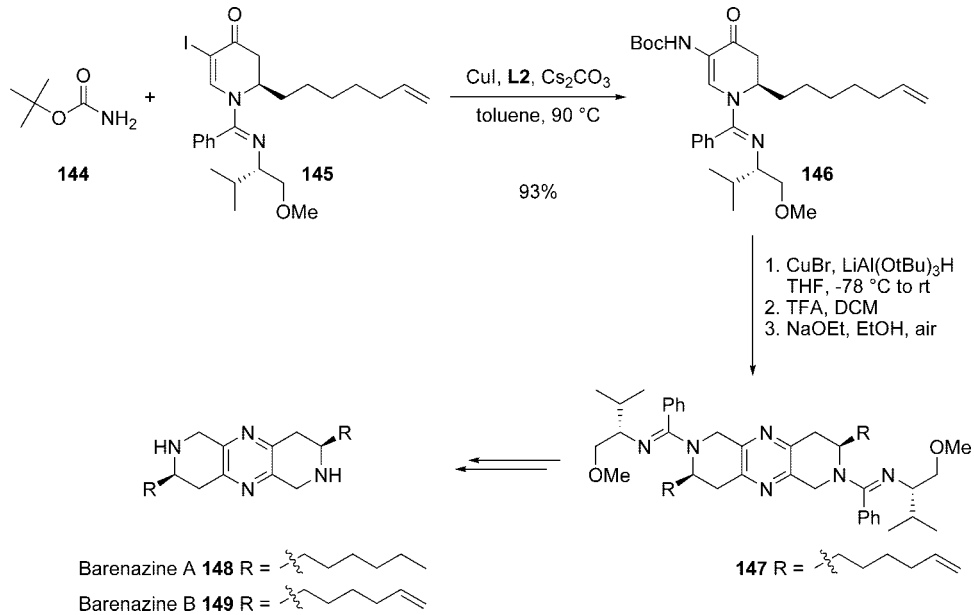
Enamides being important intermediates, the copper-catalyzed vinylation of amides also served for the preparation of important intermediates in the synthesis of natural products that do not necessarily incorporate an enamide moiety in their skeleton, as exemplified by the total synthesis of barenazines A **148** and B **149** by Focken and Charette. One of the key steps of the preparation of these naturally occurring hexahydropyridinopyrazines relies on the diastereoselective reduction of 5-amino-2,3-dihydro-1*H*-pyridin-4-one **146**, which is then dimerized to the core structure **147** of the barenazines. This intermediate **146** was itself conveniently prepared using a cross-coupling between cyclic iodo-aminoenone **145** and *tert*-butylcarbamate **144** in excellent yield (Scheme 55).[333] This approach is especially interesting and straightforward because although iodo-aminoenones are readily accessible by iodination of the corresponding aminoenones, the preparation of their amino derivatives, such as **146**, is usually a lengthy process.

If the functional group tolerance of one chemical transformation is highly challenged when applied in an end-game strategy on a very complex and sensitive substrate, its synthetic utility and practical use also becomes quite evident when it can be used for the preparation of starting material, which typically requires efficient and high-yielding processes. To build the first two rings of the galbulimina alkaloid 13 **155** using a Diels−Alder reaction from triene **153** at the early

Scheme 54. Enamide Natural Products and Analogues Synthesized via a Copper-Mediated Amidation



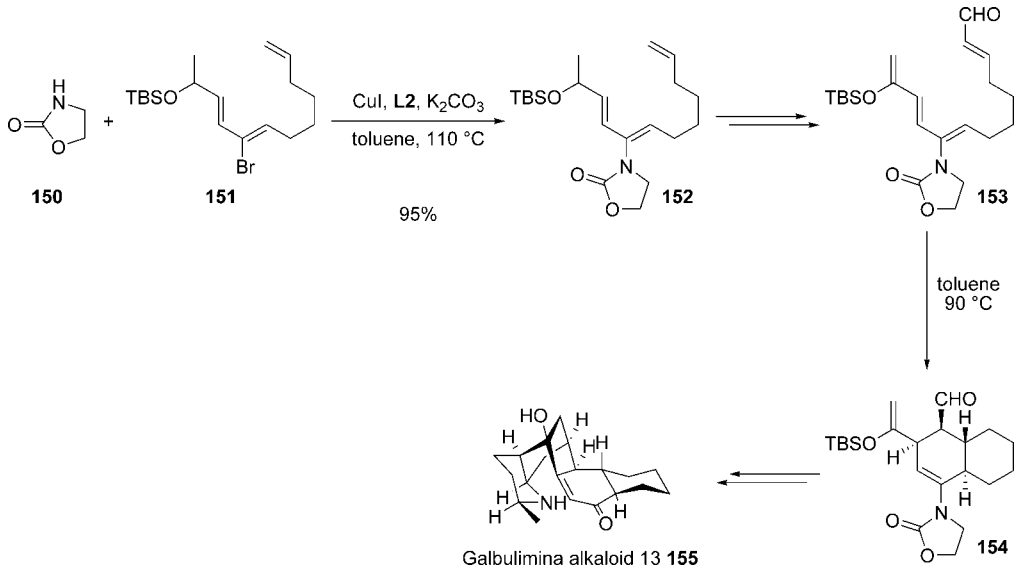
Scheme 55. Synthesis of Barenazines



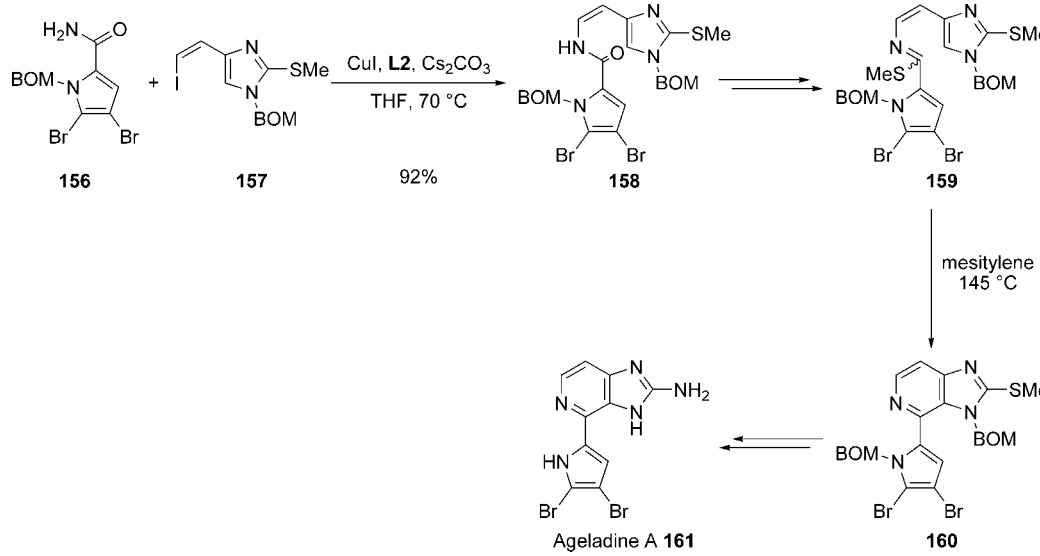
stage of their synthesis, Movassaghi and co-workers devised an efficient preparation of triene precursor **152** based on a copper-catalyzed coupling of bromotriene **151** with oxazolidinone **150**. The desired triene **152** was obtained in excellent yield, and this proved to be a remarkably efficient strategy for masking the carbonyl of the target polycyclic alkaloid (Scheme 56).[334]

In 2007, a highly convergent synthesis of the zinc matrix metalloproteinase inhibitor ageladine A **161** was reported by Meketa and Weinreb. One of the key steps of this synthesis involved the coupling of fragments **156** and **157**, which were smoothly combined using Buchwald's protocol in a remarkable 92% yield, despite the presence of two aromatic bromides, which could have interfered in the reaction. The

Scheme 56. Synthesis of Galbulimina Alkaloid 13



Scheme 57. Synthesis of Ageladine A



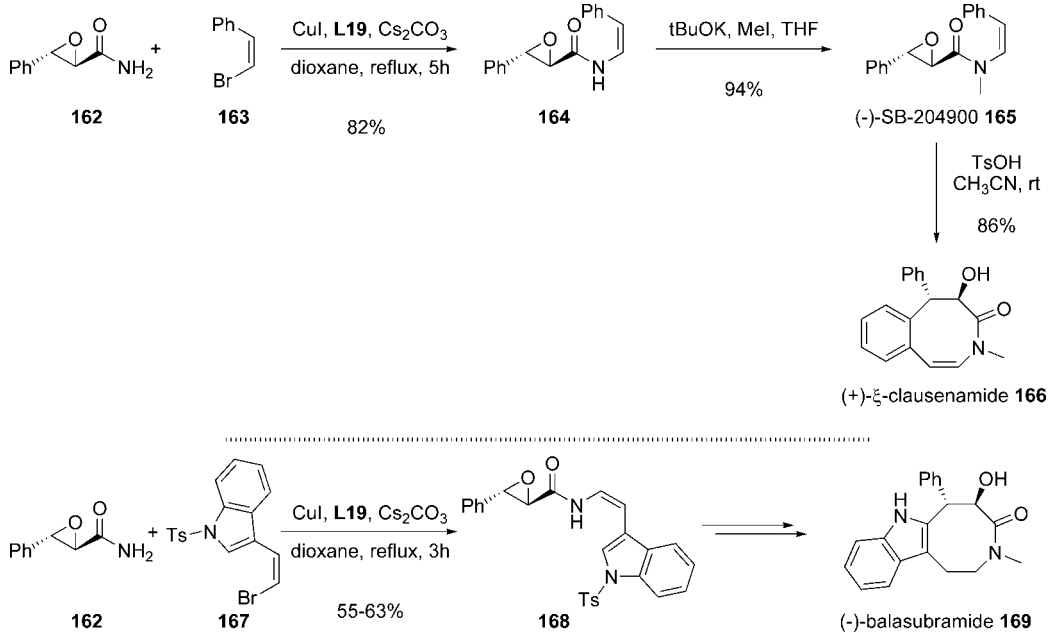
enamide in **158** served as a precursor for the preparation of azadiene **159** which, upon heating at 145 °C in mesitylene, underwent a highly efficient, biomimetically inspired, electrocyclization to give the tricyclic core **160** of ageladine A **161** (Scheme 57).[335]

The syntheses of (−)-SB-204900 **165**, (+)-ξ-clausenamide **166**, and (−)-balasubramide **169** by Wang and co-workers represent an especially interesting use of copper-mediated amidation reaction for the preparation of enamide that can either be incorporated in the target molecules or serve as synthetic intermediates for the preparation of complex, polycyclic natural products. The syntheses of (−)-SB-204900 **165** and (+)-clausenamide **166** commenced with a copper-mediated amidation of oxiranecarboxamide **162** with bromostyrene **163**. As expected, this coupling appeared to be quite challenging because of the low reactivity of the amide and the lability of the epoxide ring. After extensive experimentations, the authors eventually found that the coupling was best effected using *N*,*N*-dimethylglycine **L19** as ligand in refluxing dioxane for 3 h: the desired enamide **164** could be obtained in 82% yield with only little isomerization of the double bond. Methylation of the enamide then gave (−)-SB-204900 **165**, which underwent an acid-promoted 8-*endo*-aryl-epoxide cyclization, yielding (+)-ξ-clausenamide **166**. In a similar way, vinylation of amide **162** with (*Z*)-bromovinylindole **167** allowed for the preparation of enamide **168**, which served for the preparation of (−)-balasubramide **169** (Scheme 58).[336]

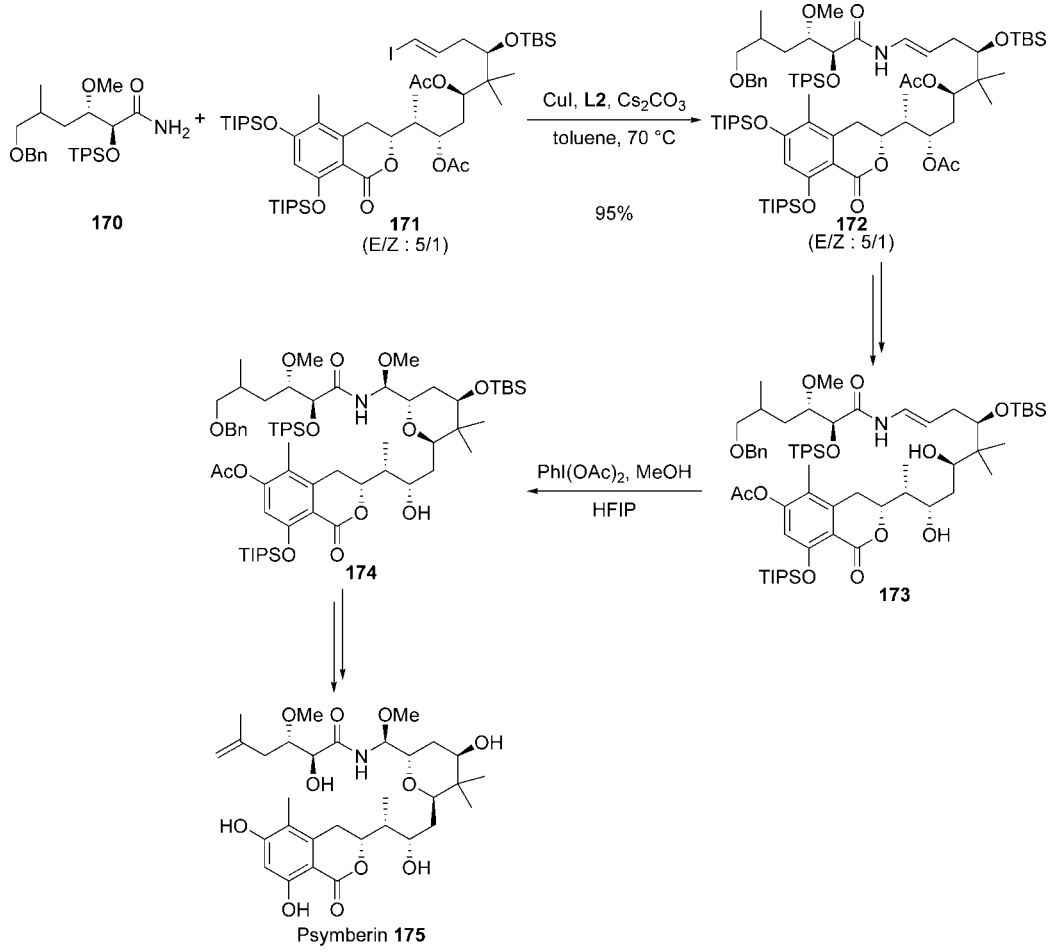
Psymberin **175** is a new member of the pederin family of natural products displaying extremely potent and selective cytotoxic properties. In 2007, Huang and co-workers at the Schering-Plough Research Institute reported an extremely efficient and convergent synthesis using their $PhI(OAc)_2$-mediated oxidative entry to 2-(*N*-acylaminal)-substituted tetrahydropyrans as the key step of the synthesis.[337] The enamide **172** required for this cyclization was obtained in 95% yield using a copper-catalyzed amidation of vinyl iodide **171** (obtained as a 5/1 mixture of *E*/*Z* isomers through Takai olefination of the corresponding aldehyde) with amide **170**. After protecting group manipulations, enamide **173** was cyclized by oxidative addition of the alcohol to the enamide to yield tetrahydropyran **174**, which served for the completion of the synthesis of psymberin **175** (Scheme 59).[338]

Finally, other synthetic applications of the copper-mediated vinylation of amides include the synthesis of substituted pyrroles by two sequential vinylation of bis-Boc-hydrazine

Scheme 58. Synthesis of (−)-SB-204900, (+)-Clausenamide and (−)-Balasubramide



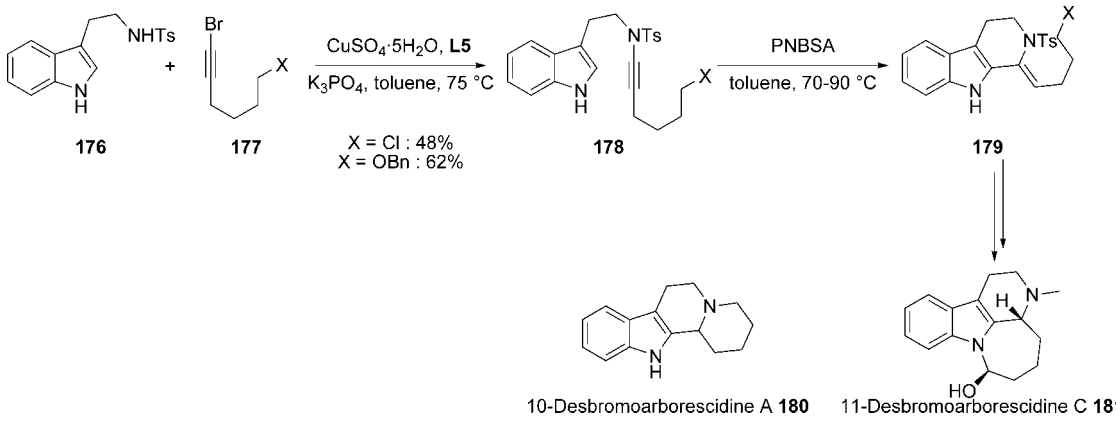
Scheme 59. Synthesis of Psymberin



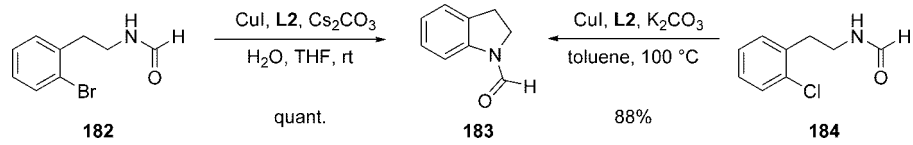
followed by thermal rearrangement/cyclization,[339] the preparation of pyrroles and pyrazoles by domino amidation/hydroamidation,[340] and an efficient synthesis of functionalized oxazoles by sequential copper-catalyzed vinylation/cyclization promoted by iodine.[341]

Taking advantage of the exceptional efficiency and mild conditions of the copper-mediated enamide synthesis, over 20 total syntheses featuring this reaction as one of the key steps or central strategy have been reported. It is noteworthy that all of these syntheses have been published after 2000 and that the number of copper-mediated amides/carbamates vinylation in total synthesis has grown steadily year by year. The potential of this reaction continues to grow, and it is likely that research in this area will continue to develop and

Scheme 60. Synthesis of 10-Desbromoarborescidine A and 11-Desbromoarborescidine C



Scheme 61. Intramolecular Aryl Amidation



will result in new efficencies in total synthesis, provided that the required (*E*)- or (*Z*)-vinyl halide can be obtained with sufficient levels of stereoselectivity.

3.5. Ynamides and Allenamides

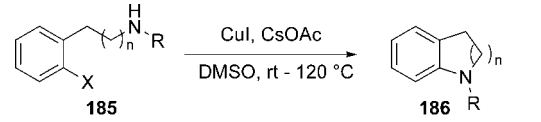
Copper-mediated alkynylation or allenylation of amides and carbamates provides an exceptionally mild and efficient entry to ynamides and allenamides, most useful intermediates in organic synthesis.[342–344] However, these developments were only reported starting from 2005, and they have been used only once in the context of natural product synthesis, for the preparation of 10-desbromoarborescidine A **180** and 11-desbromoarborescidine C **181** starting from arene-ynamides **178**. The synthesis started with mild alkynylation of *N*-tosyltryptamine **176** with bromoalkynes **177**, yielding the required ynamides **178** in moderate to good yields. These arene-ynamides **178** then served as keteniminium precursors, generated upon activation with *p*-nitrobenzenesulfonic acid, which underwent a keteniminium Pictet−Spengler cyclization, leading to heterocycles **179** (Scheme 60). This highly stereoselective cyclization of areneynamides was used to complete the total syntheses of desbromoarborescidines A **180** and C **181** and represents the first application of ynamides in natural product synthesis.[345] Other uses of copper-mediated coupling of halo-alkynes with amines or derivatives include the synthesis of oxazolones[346] and tetrahydropyrazines,[347] respectively, by gold- and copper-mediated cyclization of ynamides.

3.6. Intramolecular Reactions

3.6.1. Formation of Small- to Medium-Sized Nitrogen Heterocycles

Intramolecular copper-mediated, ligand-assisted, C−N bond formation reactions can be used for the formation of heterocycles. For example, 5-membered ring formation via intramolecular amidation of an aryl bromide **182** in the presence of ligand **L2** could be performed at room temperature in quantitative yield (Scheme 61). In contrast, only a trace of the desired product was observed even at 80 °C if no ligand was added to the reaction mixture.[57] Even aryl

Scheme 62. Intramolecular Aryl Amination

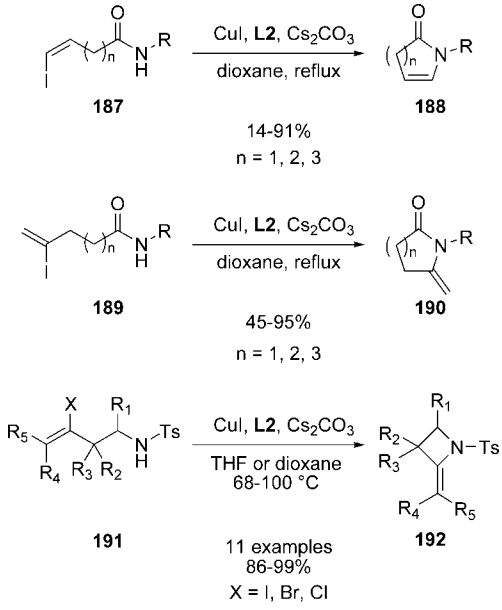


chloride **184** provided an 88% yield of the cyclized product **183** with ligand **L2**, although heating at 100 °C for 23 h was necessary. This reaction was also shown to proceed smoothly with unprotected primary amines using diethylsalicylamide **L36**,[43] proline **L20**,[27] or diketone **L30**[40] as ligands for copper iodide. These results indicate that intramolecular amidation reactions are more facile than the corresponding intermolecular versions, which have been observed for the analogous Pd-catalyzed amidation reactions as well. These intramolecular arylation reactions of amines, amides, or carbamates have found many synthetic applications such as indazole synthesis,[348] preparation of 2-aminobenzimidazoles,[349] 1,4-benzodiazepine-2,5-diones,[350] or carbolin-1-ones.[351] One limitation has been found in the intramolecular arylation of acyclic secondary amides possessing a *N*-bulky substituent: in this case, coordination with the amide at the nitrogen is much more difficult and renders *O*-arylation of amides competitive.[157]

Ligandless conditions have also been reported by Fukuyama and co-workers, who showed that a unique combination of copper iodide and cesium acetate could efficiently promote the intramolecular amination of aryl halides **185** under relatively mild conditions (Scheme 62). The reaction proceeds at room temperature with primary or *N*-benzyl amines and at moderately elevated temperatures with other amine derivatives and has been applied to the formation of 5-, 6-, and 7-membered rings **186**. Remarkably, halogens at the *meta*-position were retained, providing a definitive advantage over palladium-catalyzed systems.[352]

The intramolecular vinylation of iodovinyl-amides has also been investigated. With copper iodide as the catalyst, *N*,*N*′-dimethylethylenediamine **L2** as ligand, and cesium carbonate as base in refluxing dioxane, 5−7-membered ring lactams

Scheme 63. Intramolecular Vinyl Amidation



188 and **190** could be obtained in moderate to excellent yield (Scheme 63).[353] The reaction is remarkably efficient and even relatively strained heterocycles such as azetidines **192** can be obtained in excellent yields by intramolecular amidation of vinyl chlorides.[354] This last result is especially interesting in that it demonstrates the high efficiency of the ring closure to 4-membered ring, which was rationalized by the intermediacy of a sterically and thermodynamically favorable 5-membered ring metallacycle. Similar reactions have also been used for the preparation of indoles and pyrrolopyridines,[355] 2,3-dihydropyrroles,[356] pyrazoloindoles,[357] and pyrroles.[358] In the last case, double *N*-alkenylation procedures have also recently been published.[359]

As seen in section 3.1, the discovery of the accelerating effect of α-amino acids by Ma and co-workers boosted the development of copper-mediated amination technologies and was used as a key step in the total syntheses of benzolactam V8, SB-214857, and martinellic acid. The intramolecular version of this reaction proved to be equally efficient and was used in an efficient synthesis of SB-214857 **8** (Scheme 64),[33] a synthesis that mirrors the one reported by Hayes and that used an intermolecular arylation of glutamic acid derivative **193** (Scheme 30). Interestingly, the benzadiazepinone core of **194** was initially synthesized using an intramolecular displacement of an activated fluoride as the key step. However, this reaction needed to be carried out at 130 °C to give the desired cyclized product in 30−40% yield and with unacceptable levels of racemization.[360]

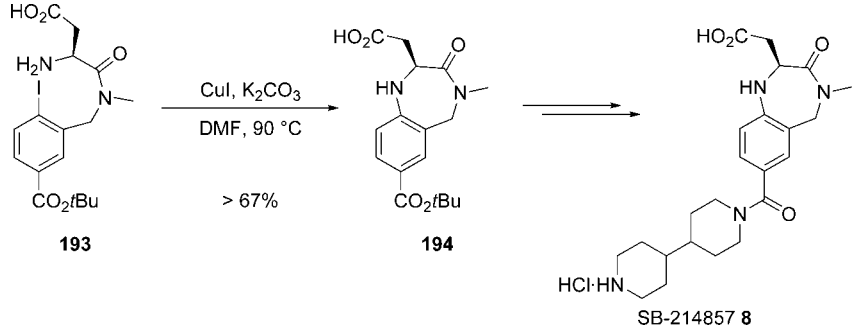
Fürstner and co-workers also employed an intramolecular amination reaction for the total synthesis of two aporphine alkaloids, *O*-methyl-dehydroisopiline **196** and 7,7′-bisdehydro-*O*-methylisopiline **197**, using Fukuyama's ligandless procedure.[352] Simply heating a mixture of amino-arylbromide **195** with copper iodide and cesium acetate in DMSO resulted in a smooth and high-yielding intramolecular amination that allowed the completion of the first total synthesis of *O*-methyl-dehydroisopiline **196** and 7,7′-bisdehydro-*O*-methylisopiline **197**, the latter being obtained by copper-mediated oxidative dimerization of the former (Scheme 65).[361]

The utility of this methodology was later highlighted by Fukuyama and co-workers in their efficient synthesis of the natural antitumor agents duocarmycins and yatakemycin. The first key transformation in their synthesis of duocarmycin A **202** was the intramolecular amination of aryldibromide **198**, a challenging reaction due to the presence of an additional bromide, the retention of which was required for ensuing transformations. Whereas palladium-catalyzed amination conditions failed to give the desired cyclized product in decent yields, presumably due to the complications arising from the unwanted oxidative addition to the remaining bromide by the palladium catalyst, the use of catalytic copper iodide without ligand and with cesium acetate as base cleanly gave the desired indoline **199**. This indoline was then used for the preparation of aryl bromide **200**: here again, the application of an intramolecular aryl amidation, using stoichiometric amounts of copper iodide in this case, quantitatively provided tricyclic compound **201**, which was finally transformed to duocarmycin A **202** (Scheme 66). It is noteworthy that preparation of the indolecarboxylic acid moiety involved once again a successful implementation of the copper-mediated aryl amination. When treated with excess copper iodide and cesium acetate at room temperature, the heterocyclization from **203** proceeded smoothly to give the desired indole **204**, a precursor of fragment **205**, in nearly quantitative yield.[362]

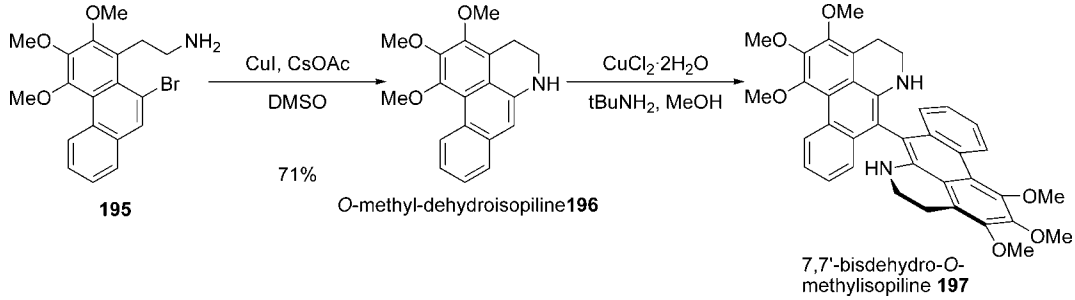
For the synthesis of duocarmycin SA **208**, the common indoline intermediate **199** was first converted to acyclic dehydroamino acid **206**, which was cyclized to **207** using the aforementioned arylation protocol (Scheme 67).

Finally, a similar and quite spectacular strategy was used for the total synthesis of yatakemycin **210**, a remarkably potent antitumor antibiotic through a sequence-selective DNA alkylation at the activated cyclopropane. The second total synthesis of this natural product was achieved by the Fukuyama group in 2006 and is probably one of the most impressive examples of the efficiency of copper-catalyzed C−N bond formation reactions in natural product synthesis. In their approach, all five aromatic C−N bonds were formed

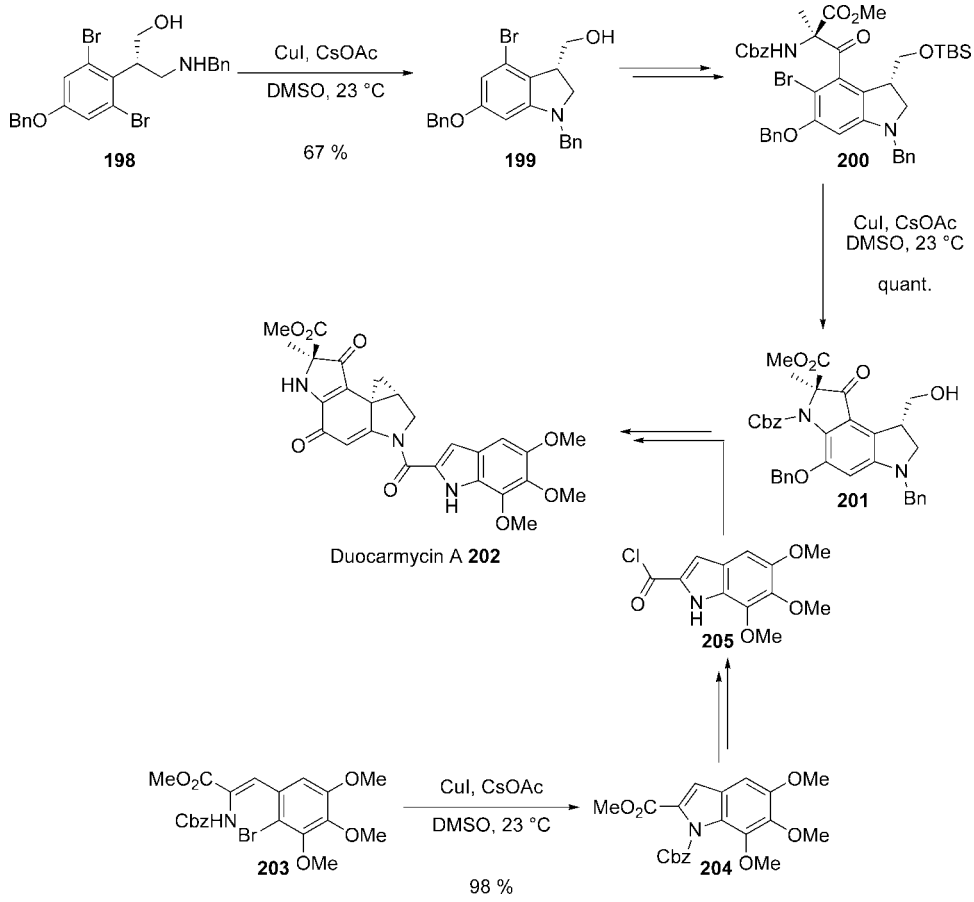
Scheme 64. Synthesis of SB-214857 by Intramolecular Amidation



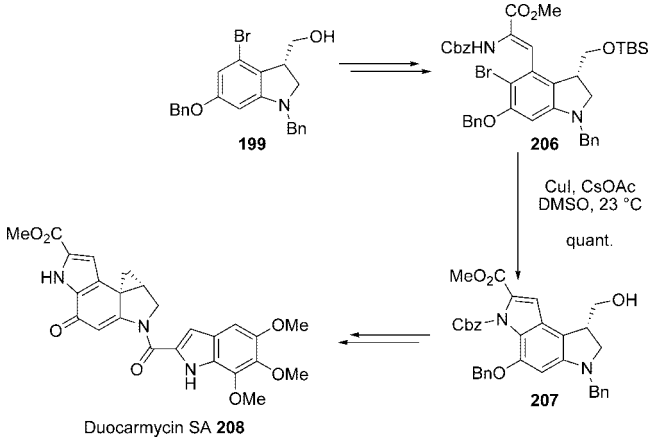
Scheme 65. Synthesis of *O*-Methyl-dehydroisopiline and 7,7′-Bisdehydro-*O*-methylisopiline



Scheme 66. Synthesis of Duocarmycin A



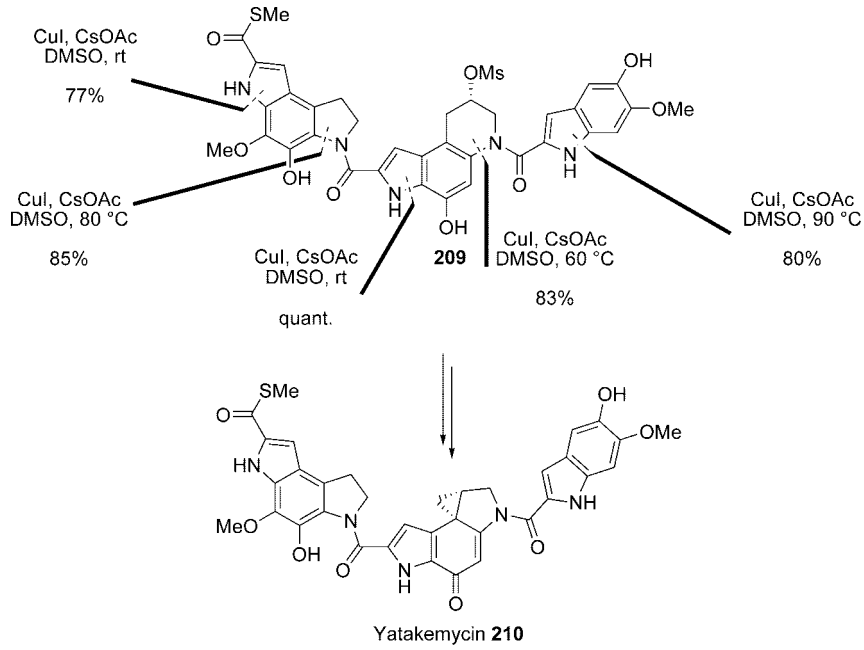
Scheme 67. Synthesis of Duocarmycin SA



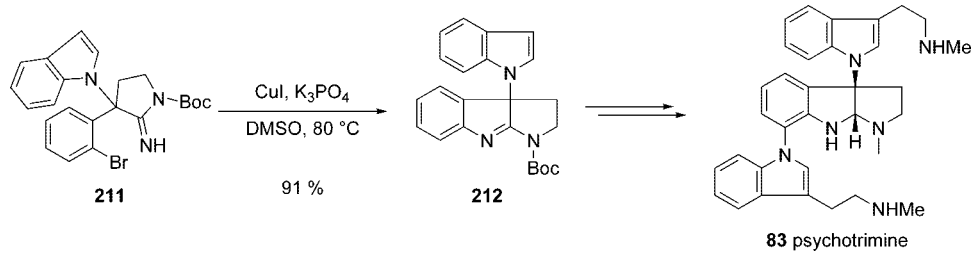
using ligandless intramolecular aryl amination reaction with excellent yields (Scheme 68). The efficiency of this strategy was highlighted by the remarkable overall yield (13%) that allowed the authors to conduct a half-gram preparation of the complex target **210**.[363]

It is quite interesting to note that ligand-assisted and ligandless protocols are somehow complementary, as shown by Takayama and co-workers in their synthesis of the trimeric indole alkaloid psychotrimine **83**, where the formation of the fully saturated pyrroloindole core **212** was envisioned through the use of an intramolecular challenging amidine arylation reaction from **211**. Copper iodide being selected as the source of copper(I), the authors undertook optimization of the other parameters (ligand, solvent, and base). In this particular case, diamine ligands **L2**, **L3**, and **L5** proved to be completely inefficient because the desired cyclization product was obtained in very low yield, which was attributed to the very low reactivity of the amidine nitrogen. Switching to stoichiometric amounts of copper(I) iodide, ligand-free conditions, and potassium phosphate as base in DMSO led to a dramatic improvement as the desired product **212** could then be obtained in an excellent 91% yield (Scheme 69). As

Scheme 68. Synthesis of Yatakemycin



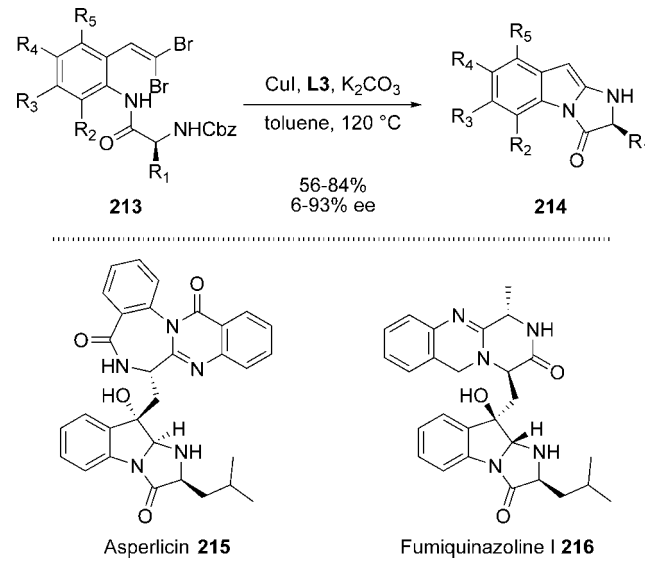
Scheme 69. Synthesis of Psychotrimine



in most cases, the choice of the base was crucial (cesium and potassium carbonate gave inferior results).[302]

If Fukuyama's ligandless stoichiometric or catalytic intramolecular arylation protocols have found many applications in complex natural product synthesis, ligand-assisted intramolecular amination or amidation reactions also allowed for the formation of nitrogen heterocyclic cores of various targets. In this context, Lautens and co-workers developed a selective tandem coupling of readily accessible gem-dibromovinyl systems **213** to give imidazoindolones **214**, a key structural motif found in natural products such as the potent cholecystokinin antagonist asperlicin **215** or the antifungal fumiquinazoline **216** (Scheme 70). Initial studies focused on the selection of a diamine ligand. Screening a range of diamine ligands revealed that racemic *trans*-1,2-cyclohexyldiamine **L3** was found to be slightly superior followed closely by *N*,*N*-dimethylethylenediamine **L2**, whereas the use of chiral *trans*-1,2-cyclohexyldiamine did not significantly change the yield or ee. Toluene was found to be the best solvent for this reaction; dioxane gave a much lower yield, and DMF failed to give any product. Screening of a range of bases (K_2CO_3, K_3PO_4, Cs_2CO_3, and DABCO) revealed that K_2CO_3 gave the highest yield, whereas the weaker organic base, DABCO, failed to promote the reaction. The greatest effect on yield and ee was observed by simply changing the ratio and quantity of ligand, CuI, and base. Finally, the best ratios of copper/ligand/base were found to be 5 mol %/10 mol %/2 equival or 2.5 mol %/5 mol %/2 equiv. In some cases, however, the ee of the product considerably decreased, which was attributed to epimerization

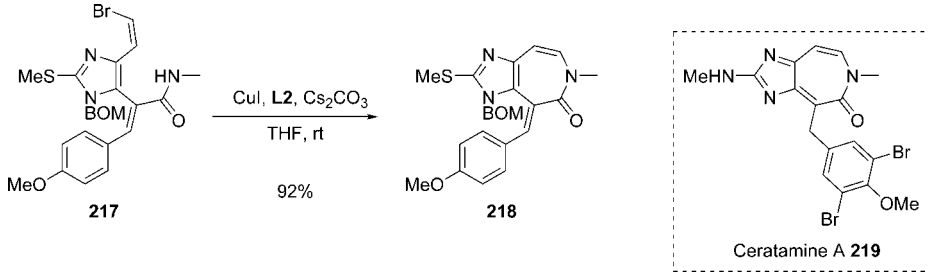
Scheme 70. Synthesis of the Imidazoindolone Core of Asperlicin and Fumiquinazolines



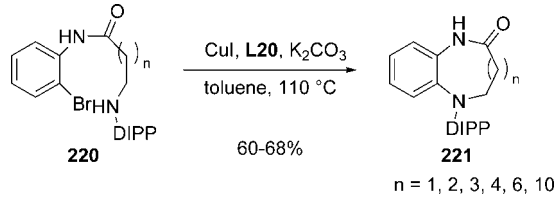
of the 2-bromoindole intermediate. This epimerization is related to its lifetime, which depends on the rate of the second amidation step. Thus, more electron-rich intermediates experience more epimerization, which explains the poor ee values with such compounds.[364]

The use of palladium catalysis was unsuccessful in producing the desired products **214** but gave the corresponding bromoindoles in moderate yields.

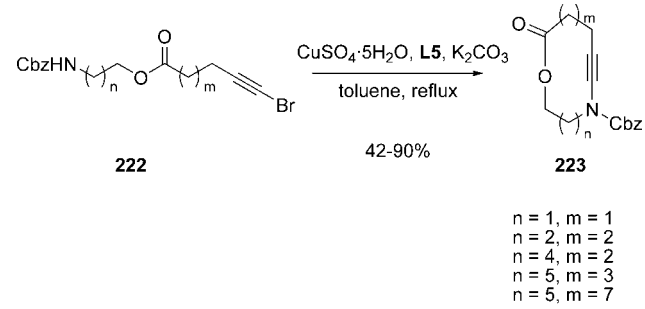
Scheme 71. Synthesis of Antimitotic Analogs of Ceratamine A



Scheme 72. Macrocyclization by Intramolecular Aryl Amination



Scheme 73. Macrocyclization by Intramolecular Bromoalkyne Amination



An intramolecular amide vinylation reaction was also used in the synthesis of antimitotic analogues of the microtubule-stabilizing sponge alkaloid ceratamine A **219**. The key step of this synthesis is the formation of the azepine ring via an intramolecular cross-coupling reaction between a vinyl bromide and a *N*-methylamide from **217** using Buchwald's conditions, which represents the first successful synthesis of a fully unsaturated imidazoazepine (Scheme 71). Compound **218** was then used for the preparation of a series of analogues of the natural product.[365]

3.6.2. Intramolecular C−N Cross-Coupling Reactions as Macrocyclization Procedures

Recently, these intramolecular copper-catalyzed coupling reactions have been used as challenging but efficient macrocyclization procedures for the synthesis of macrocyclic lactams or enamides, which will be referred to as "macroamidation" and "macroenamidation" reactions in the following paragraphs. One of the first detailed papers in this field was published in 2005 by the Fu group, who systematically studied the macrocyclization of acyclic bromo-phosphoramidates **220**. Results from these studies clearly demonstrated that these compounds can be efficiently cyclized to medium- and large-sized nitrogen heterocycles **221** via copper-catalyzed intramolecular *N*-arylation (Scheme 72). In this case, the presence of a phosphoryl or carbamate is strictly required for the macrocyclization to proceed.[366]

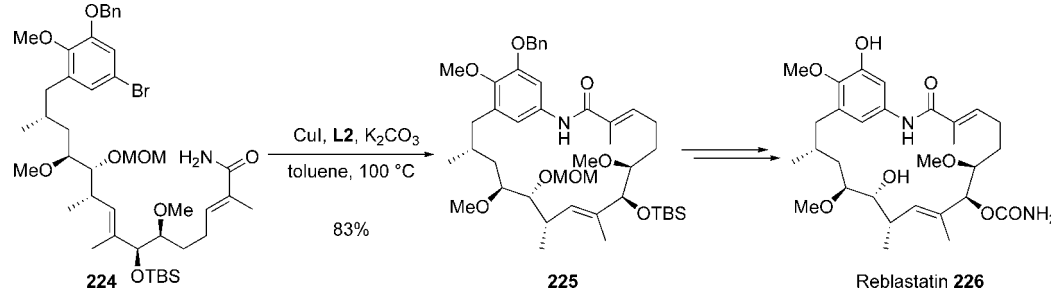
Macrocyclization by intramolecular amidation of bromoalkynes was also studied in details. Carbamates **222** tethered to the alkynyl bromide cyclized smoothly to give 9−19-membered macrocyclic compounds **223**, although yields began to diminish with increasing size (Scheme 73). The macrocyclic ynamides could then be transformed to the corresponding (*Z*)-enamides by controlled hydrogenation using Lindlar catalyst.[367]

Intramolecular cross-coupling reactions are efficient macrocyclization protocols that allow for original and straightforward disconnections in natural product synthesis. This was quite spectacularly exploited by the Panek group in their synthesis of reblastatin **226**, an ansamycin shown to exhibit promising antitumor activity. Whereas the synthesis of related ansamycin such as herbimycin A,[368] macbecin I,[369] or geldanamycin[370] relied on the use of macrolactamization procedures for the formation of the macrocyclic core, a challenging intramolecular amidation reaction was envisioned to form the macrocycle (Scheme 74). This reaction proved to be especially efficient because when treated with copper iodide and diamine ligand **L2**, acyclic precursor **224** smoothly cyclized to macrocyclic amide **225** in 83% yield, a yield that compares well to the ones obtained by standard macrolactamization procedures.[371] A similar strategy was later used for the preparation of a related ansamycin, the Hsp90 inhibitor geldanamycin.[372]

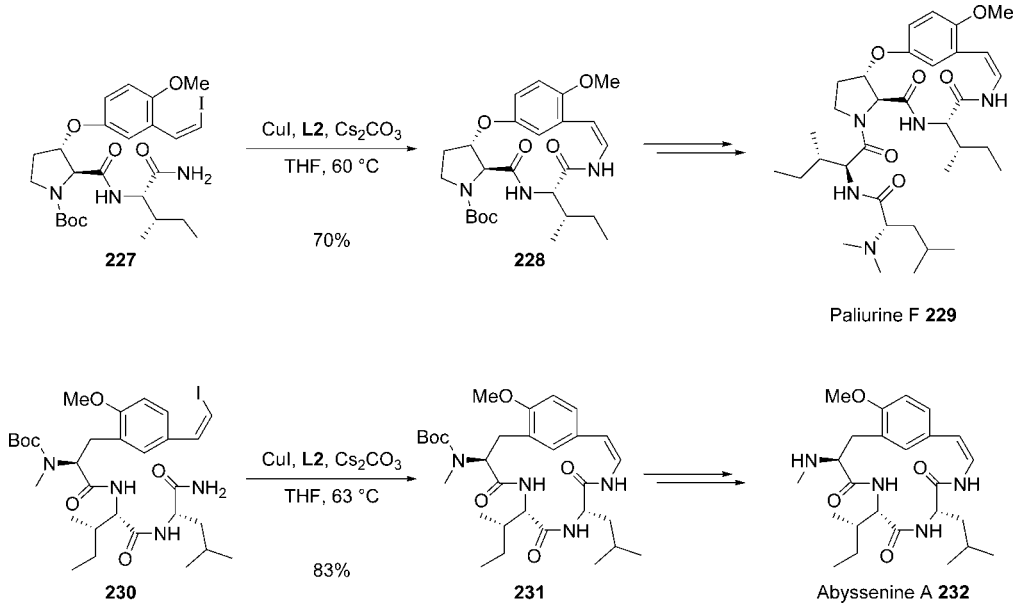
We reported in 2007 a total synthesis of the cyclopeptide alkaloid paliurine F **229** featuring an efficient late-stage intramolecular amide vinylation to form the macrocycle and the enamide in a single operation. The cyclization of acyclic precursor **227** was envisioned, and different catalytic systems proved to have dramatically different reactivities. Whereas initial investigation of intramolecular amidation using combinations of copper iodide and triphenylphosphine or *N*,*N*-dimethylglycine, a system used by Ma in a related intermolecular process (Scheme 53),[323] failed to give any cyclized product, $Cu(CH_3CN)_4PF_6$, which was also examined as copper(I) source using 3,4,7,8-tetramethyl-1,10-phenanthroline as ligand, afforded the desired product but in trace amounts only. However, subjection of the acyclic skeleton **227** to copper(I) thiophene-2-carboxylate (CuTC **C8**) in NMP at 90 °C provided the desired macrocyclic enamide **228** in 60% yield. Finally, switching to a last catalytic system (CuI/*N*,*N*′-dimethylethylenediamine) improved the yield slightly, providing **228** in 70% yield, all along with 20% of unreacted starting material, which cleanly allowed for a straightforward installation of the cyclic enamide group of the target molecule (Scheme 75).[325] A similar strategy could also be successfully applied to efficient preparations of the cyclopeptide alkaloids abyssenine A **232**[345] and mucronine E.[374]

One of the best ways to test the efficiency of a reaction is probably its comparison with other techniques used for a similar purpose. Therefore, other synthetic efforts en route to various cyclopeptide alkaloids provide an excel-

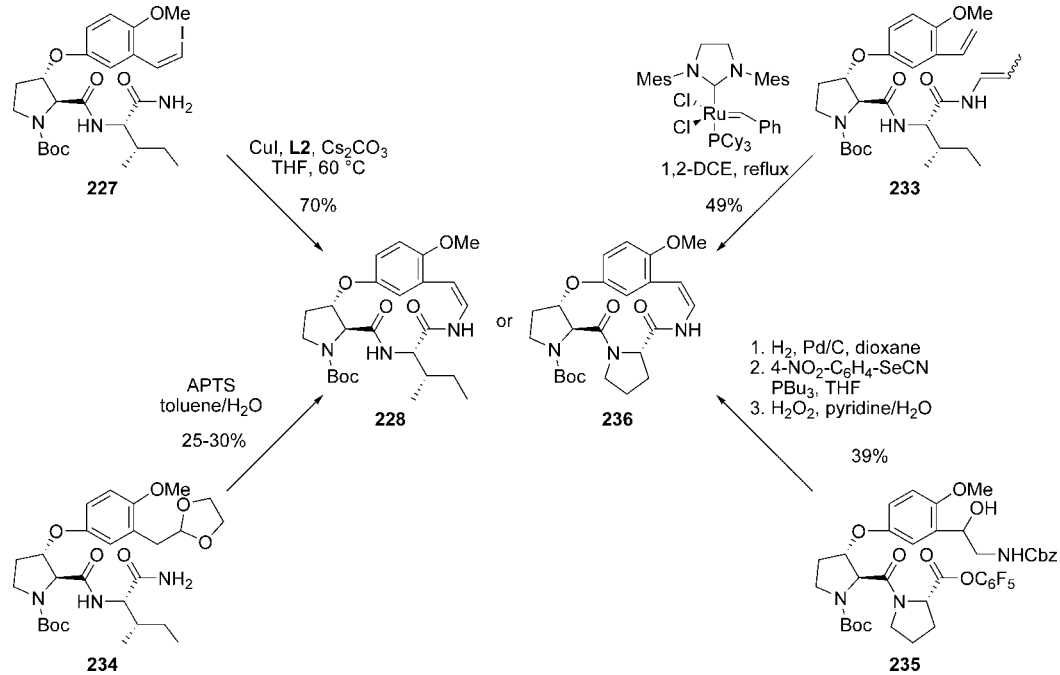
Scheme 74. Synthesis of Reblastatin by Intramolecular Macroamidation



Scheme 75. Synthesis of the Cyclopeptide Alkaloids Paliurine F and Abyssenine A by Intramolecular Macroenamidation

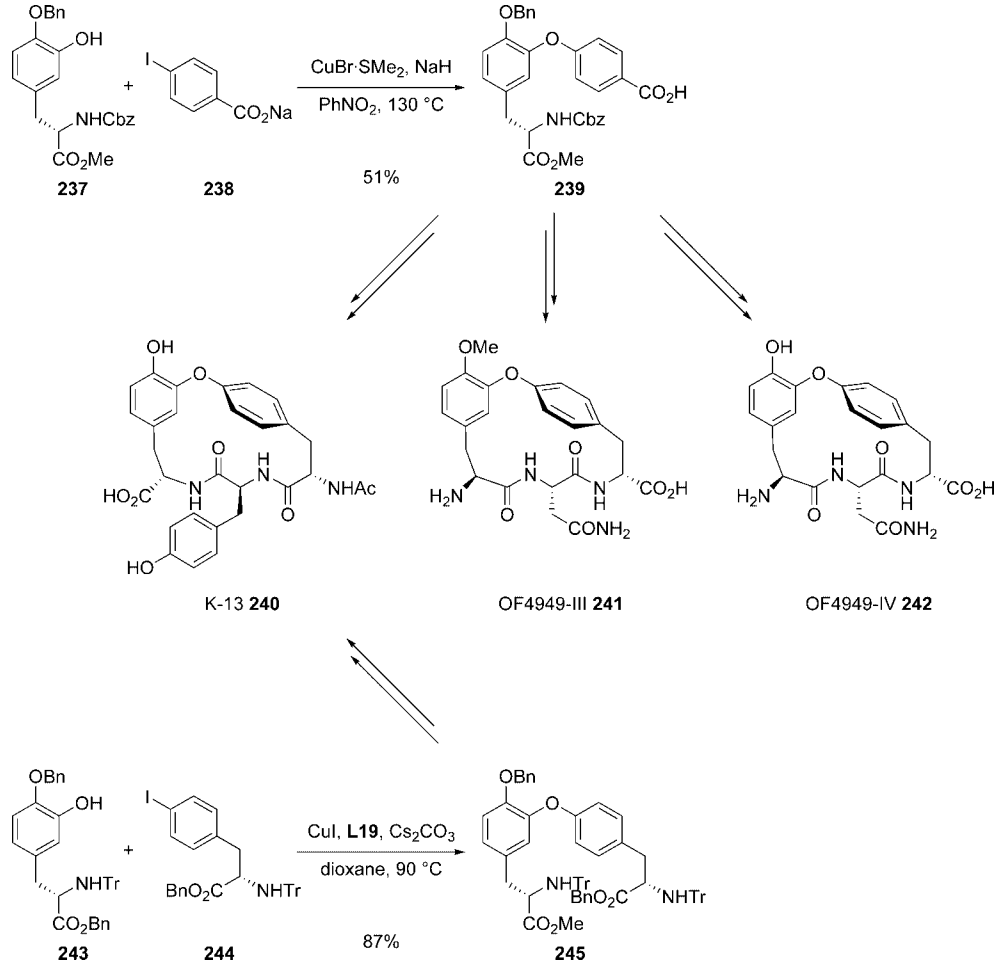


Scheme 76. Other Approaches to the Macrocyclic Enamide Core of Cyclopeptide Alkaloids



lent opportunity to evaluate the efficiency of the intramolecular macroenamidation procedure. The first total syntheses of cyclopeptide alkaloids used a stepwise sequence to install the macrocycle and the enamide, the latter being installed after the crucial macrolactamization step starting from acyclic precursor **235** by transformation of the alcohol to the corresponding selenide and further elimination via an intermediate selenoxide (Scheme 76).[375] The major drawback of this sequence, which was successfully applied to the total synthesis of various cyclopeptide alkaloids, is that the number of steps involved decreases the overall efficiency of the process. Other approaches were

Scheme 77. Synthesis of K-13, OF4949-III, and OF4949-IV



devised and involve concomitant formation of both the macrocycle and the enamide using an ene-enamide ring closing metathesis[376] or a cyclodehydration reaction,[377] respectively, starting from acyclic compounds **233** and **234**. In both cases, the macrocyclic enamide **228** is formed, but in rather low yields, which do not favorably compare with the one obtained using the copper-mediated macroenamidation procedure.

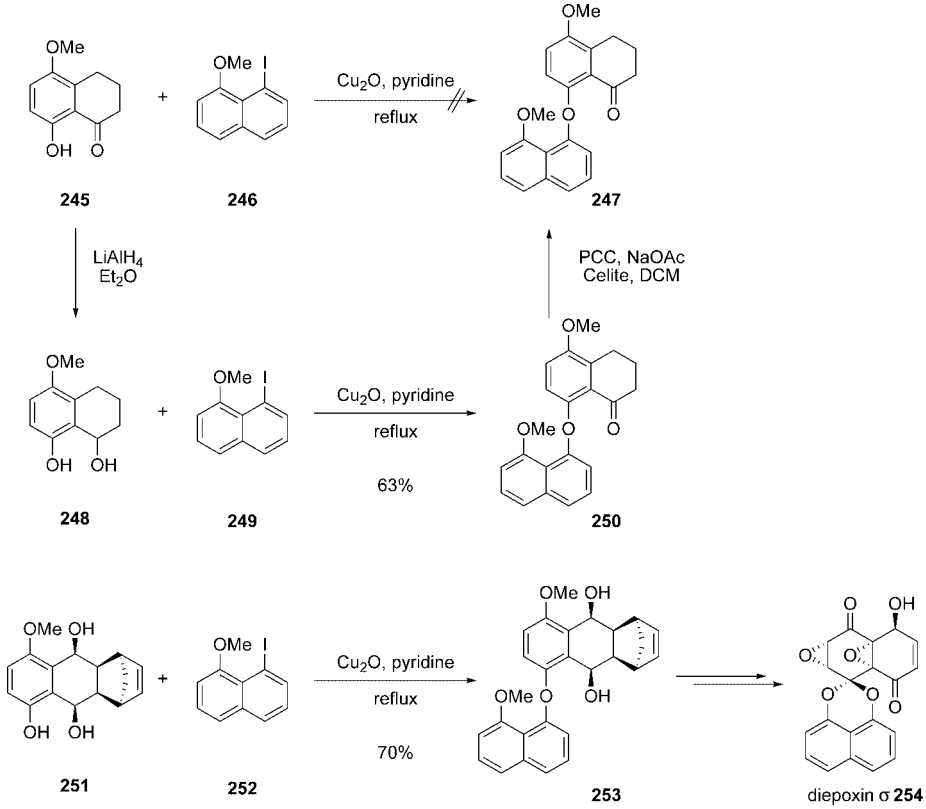
4. Natural Product Total Synthesis: Formation of C−O Bonds

4.1. Arylation of Phenols

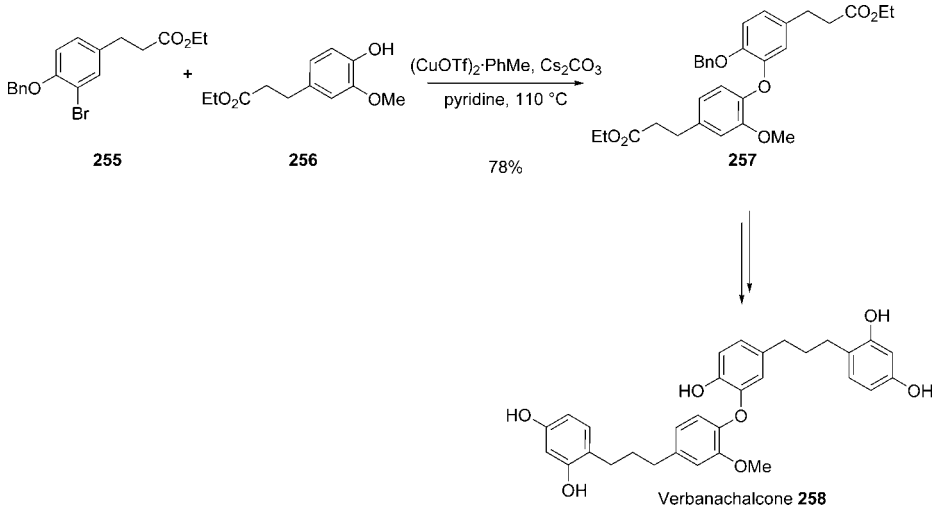
A number of natural products possess a diaryl ether core, and the copper-mediated arylation of phenols has been widely used in total synthesis, especially for intramolecular reactions (see section 4.4.2). Due to the highly capricious nature of the classical Ullmann diaryl ether synthesis, which proved over the years to be highly dependent on the substitution pattern of both aryl rings, its application started to considerably increase only after the introduction of aryl boronic acids as arylating agents by Chan, Lam, and Evans (see section 2.4). However, implementation of the classical reaction conditions allowed for the intermolecular preparation of diaryl ethers starting from base-sensitive substrates and was used by the Boger group in the total synthesis of three cycloisodityrosine-derived agents, K-13 **240**, OF4949-III **241**, and OF4949-IV **242**, starting from common intermediate **239**. This latter derived from Ullmann condensation of L-DOPA derivative **237** with sodium *p*-iodobenzoate **238** upon treatment with sodium hydride and copper bromide dimethyl sulfide complex at 130 °C in nitrobenzene. These conditions allowed the coupling to proceed without amino acid racemization (Scheme 77). In contrast, the use of standard reaction conditions (pyridine, 130 °C) resulted in considerable epimerization.[378] The scope of this reaction, which proved to be especially successful and efficient in its intramolecular version (see section 4.4.2), however, strongly depends on the nature of both reaction partners. In fact, this Ullmann condensation of electron-rich aryl iodides with unactivated phenols has proven to be successful for simple substrates, modestly successful for simple electron-rich aryl iodides bearing an *o*-alkoxy substituent and for reactions of a single functionalized tyrosine derivative, but failed when applied to the coupling of two functionalized tyrosine or phenylalanine derivatives. Another synthesis of K-13 **240** published some 16 years later by Ma and co-workers clearly shows the great progresses made in the area of copper-mediated C−O bond formation because by using a *N*,*N*-dimethylglycine **L19**-promoted reaction, L-DOPA derivative **243** could be successfully coupled with suitably protected iodo-phenylalanine **244** in an excellent 87% yield (Scheme 77).[124]

The dependence of the classical Ullmann procedure on the substitution pattern of the reaction partners also clearly appeared in Wipf's synthesis of diepoxin-σ **254**, a highly oxygenated antifungal anticancer natural product. Although attempts to couple tetralone **245** and 1-iodo-8-methoxynaph-

Scheme 78. Synthesis of Diepoxin-σ



Scheme 79. Synthesis of Verbanachalcone

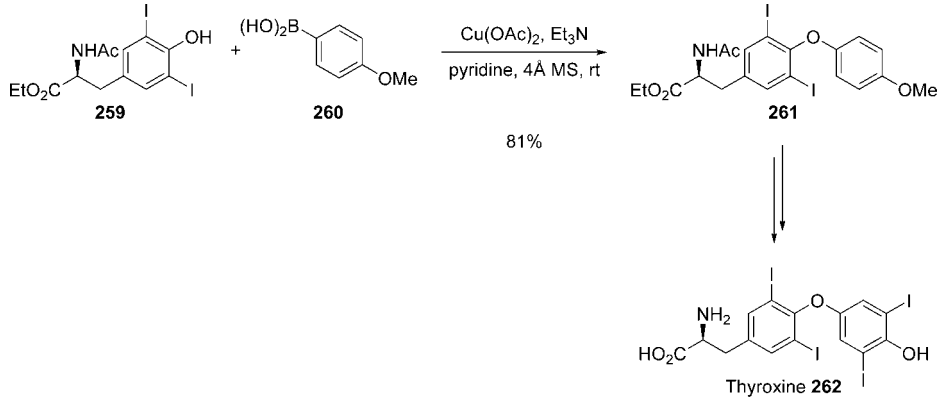


thalene **246** proved to be unsuccessful, possibly due to the lack of reactivity of the deactivated phenol under standard copper-mediated coupling conditions, the corresponding reduced compound **248** was nicely coupled under similar conditions. These preliminary results set the stage for completion of the total synthesis of diepoxin-σ **254** starting from diaryl ether **253** (Scheme 78).[379] Similar procedures were successively used by Fürstner[380] and Ramana[381] to prepare the diaryl ether core of aspercyclide C at early stages of the syntheses as well as by Kametler and co-workers for the preparation of plagiochins A and B.[382]

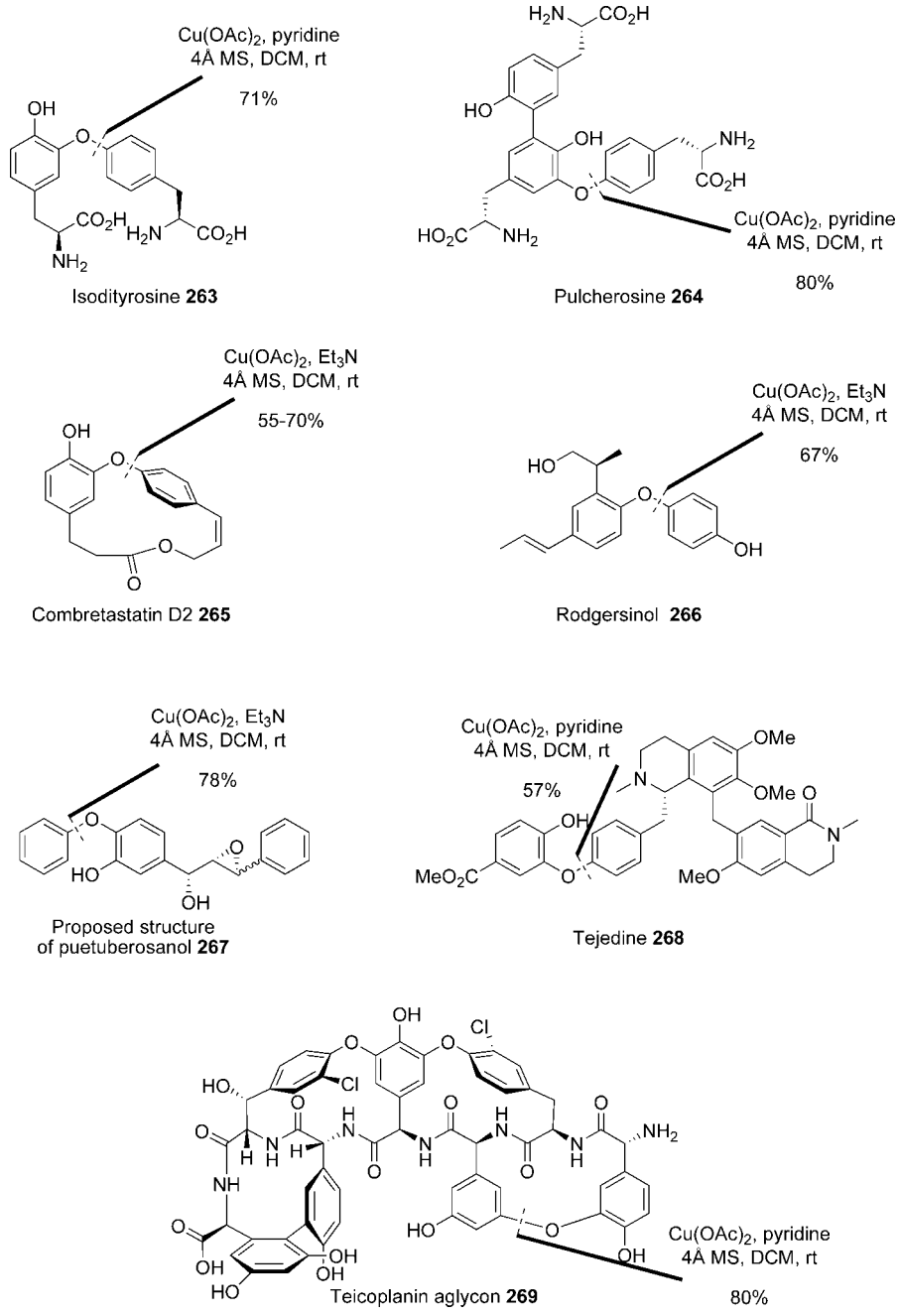
As seen in section 2.4, the introduction of cesium carbonate by Buchwald as base for the copper-catalyzed synthesis of diaryl ethers has led to much improved procedures with broader reaction scopes, even if it does not really compete anymore with ligand-assisted methods. This procedure was, however, used as the pivotal reaction in the total synthesis of verbanachalcone **258** by the Cuny group, who assembled the central diaryl ether core **257** by coupling of aryl bromide **255** and phenol **256** in the presence of cesium carbonate in pyridine (Scheme 79).[383] Model studies on simpler substrates, however, revealed that small changes in functional groups close to reacting centers could still have a dramatic impact on the reaction outcome using this catalytic system. Other published syntheses of diaryl ethers using this catalytic system include analogues of the antibacterial agent triclosan[384] and antimitotic analogues of combretastatin A-4.[385]

More than just a significant conceptual breakthrough, the introduction of boronic acids as arylating agents in combination with the use of copper(II) acetate simultaneously by Chan,[16] Lam,[17] and Evans[115] (see section 2.4) has been

Scheme 80. Synthesis of Thyroxine

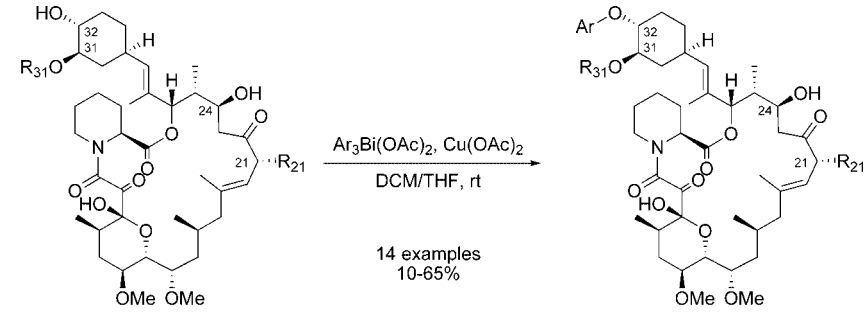


Scheme 81. Chan, Lam, and Evans Synthesis of Diaryl Ether in Natural Product Synthesis



widely used in the synthesis of natural products, most likely due to the high efficiency of the method, which proceeds at room temperature, as well as its high functional group tolerance. In this context, and following initial success with

Scheme 82. Arylation of FK-506 and Affiliated Macrolides



FK 506 **270** R_{21} = allyl R_{31} = methyl
Asconomycin **271** R_{21} = ethyl R_{31} = methyl
L-638,742 **272** R_{21} = ethyl R_{31} = H

273

the arylation of structurally complex phenols and base-sensitive substrates, Evans and co-workers evaluated the impact of steric hindrance in the context of a short formal synthesis of thyroxine **262**: reacting 1 equiv of phenol **259**, phenyl boronic acid **260**, and copper acetate together with pyridine and triethylamine at room temperature in dichloromethane nicely provided the desired diaryl ether **261** in 81% yield (Scheme 80).[115] Although evidence is still currently lacking, triethlyamine and pyridine could have a dual role in this reaction as both base and ligand for one of the organocopper intermediates.

The mildness and efficiency of the reaction conditions together with the publication of efficient and general methods for the preparation of boronic acids clearly solved a long-standing problem and attracted quite a number of synthetic and medicinal chemists. Examples of application for the synthesis of medicinal and/or natural compounds are shown in Scheme 81 and highlight the great potential of the procedure. They include isodityrosine **263**,[386] pulcherosine **264**,[387] combretastatin D2 **265**,[388] rodgersinol **266**,[389] the proposed structure of puetuberosanol **267**,[390] tejedine **268**,[391] starting material for the synthesis of teicoplanin aglycon **269**, which features an interesting epimerization-free arylation with a substituted arylglycine derivative,[392] and trace amine-associated receptor agonists[393] or ultrapotent HIV protease inhibitors.[394]

4.2. Arylation of Alcohols

In contrast to the Ullmann-type synthesis of diaryl ethers, the synthesis of aryl alkyl ethers by means of metal-catalyzed arylation of alcohols clearly remained a difficult task until the development of efficient ligand-assisted, copper-mediated arylation procedures. Planning to use such bond disconnection in the synthesis of a complex natural product bore considerable risk and probably even seemed somewhat counterintuitive due to the low reactivity of alcohols toward arylation and the relatively harsh conditions needed. This probably accounts for the use of more classical strategies and different bond disconnections involving Mitsunobu reactions or S_N2 displacements in most cases, even if they sometimes required longer reaction sequences or additional steps. The copper-mediated synthesis of aryl alkyl ethers has, however, been recently used for the preparation of relatively complex substrates, and some examples that will be overviewed in the following paragraphs show the great potential of these procedures.

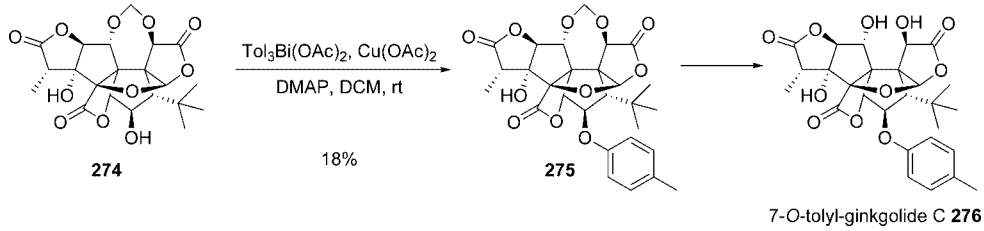
In the late 1990s, copper-mediated intermolecular synthesis of structurally complex aryl alkyl ethers was used for the first time for chemical modifications of some natural products and pharmaceuticals. Because the classical Ullmann procedure was easily ruled out,[395] less common arylating agents such as organobismuth were used in most cases.

In this context, and in an effort to reduce undesired side effects associated with the clinical use of the immunosuppressant macrolide FK-506 **270**, researchers at Merck envisioned the arylation of FK-506 and the affiliated macrolide asconomycin **271** using pentavalent organobismuth reagents. These reagents were prepared by *in situ* oxidation of the triarylbismuthine to the pentavalent diacetate and then reacted with the macrolide and copper(II) acetate in a mixture of DCM and THF at room temperature. The aryl group was selectively transferred at C32 (except in the case of L-638,742 **272**), thus making the protection of the 24-hydroxyl unnecessary (Scheme 82).[396] In addition, the preparation of pentavalent organobismuth reagents and subsequent arylation of the macrolides were shown to be compatible with a variety of substituted aromatic groups, even if it does sometimes require extensive optimization.[397]

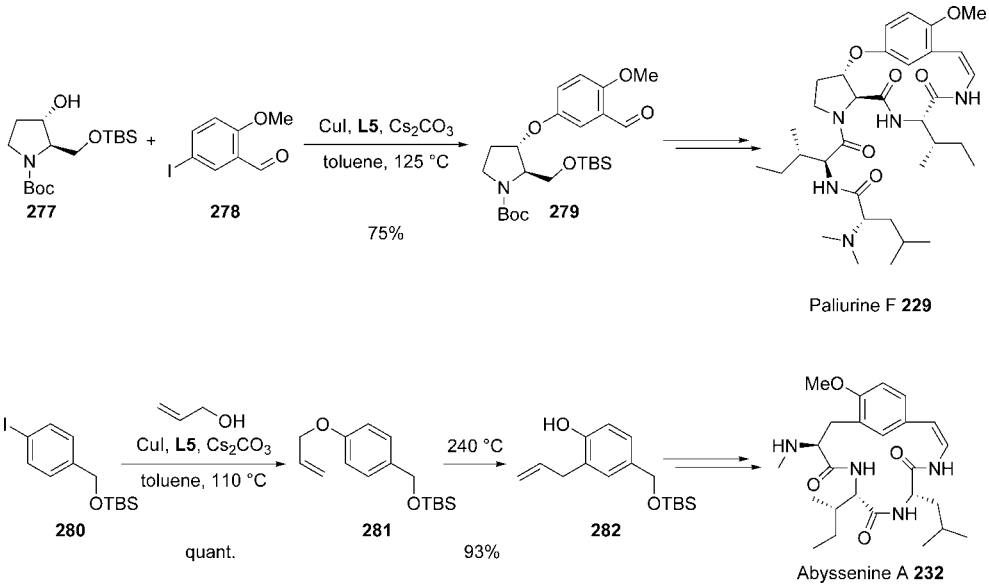
Similarly, Pietri and co-workers prepared a 7-*O*-tolyl derivative of ginkgolide C **276** to demonstrate that its cardioprotective effect is unrelated to platelet-activating factor. The aryl group could be introduced starting from protected ginkgolide C **274** and using the appropriate triorganobismuth diacetate in the presence of catalytic amounts (10%) of copper diacetate, although in only 18% yield (Scheme 83).[398]

We reported in 2007 the first application of copper-mediated, ligand-assisted arylation of alcohols for the preparation of two cyclopeptide alkaloids, paliurine F **229** and abyssenine A **232**. To undertake the assembly of the acyclic fragment **279** and to install the aryl alkyl ether bond of paliurine F, the highly functionalized hydroxyprolinol **277** and aryl iodide **278** were coupled using a slight modification of Buchwald's procedure: 10 mol % CuI, 20 mol % 1,10-phenanthroline **L5**, cesium carbonate as a base in toluene at 125 °C, and a moderate excess (1.4 equiv) of the iodide **278**. Under these conditions, pyrrolidinyl-aryl ether **279**, which could not be obtained using a palladium-catalyzed coupling reaction, was obtained in 75% yield (Scheme 84).[325] In comparison, other strategies used for the formation of this key structural element include nucleophilic substitution, inter- or intramolecular aromatic nucleophilic substitution, and Mitsunobu reaction.[399] This strategy was next extended to an efficient preparation of the trisubstituted aromatic core of abyssenine A **232**. Exposure of a mixture of aromatic iodide **280** and allyl alcohol to catalytic amounts of copper

Scheme 83. Arylation of Protected Ginkgolide C



Scheme 84. Synthesis of the Cyclopeptide Alkaloids Paliurine F and Abyssenine A



iodide and 1,10-phenanthroline followed by simply heating the intermediate allyl ether **281** to 240 °C allowed for a clean and efficient intermolecular Ullmann coupling−Claisen rearrangement sequence giving the trisubstituted aromatic core **282** of abyssenine A in excellent yield.[373]

4.3. Enol Ethers

The recently reported copper-mediated coupling of vinyl halides with alcohols represents an experimentally attractive means for the preparation of enol ethers and has been elegantly applied in natural product synthesis in combination with Claisen rearrangement, one of the most powerful methods for the construction of carbon−carbon bonds. The lack of a general process for the stereoselective synthesis of simple allyl vinyl ethers for the classical aliphatic Claisen rearrangement has been, however, quite frustrating for synthetic chemists. Recent progress in this area based on copper-catalyzed methods allowed for this problem to be efficiently solved, and the synthesis of the tricyclic core of vinigrol **289** by the Barriault group nicely illustrates this point. This synthesis began by copper(I)-catalyzed coupling between iodide **283** and alcohol **284** in the presence of tetramethylphenanthroline **L7** and cesium carbonate at 90 °C in *o*-xylenes to give enol ether **285** in 83% yield along with aldehyde **286** as a mixture of epimers. This reaction proved to be quite sensitive to thermal conditions as a slight increase in temperature above 90 °C led to a significant amount of the Claisen rearrangement product **286**, which epimerizes readily under the reaction conditions. Upon treatment with triisobutylaluminium, acting both as a catalyst for the Claisen rearrangement and as a reducing agent, enol ether **285** could then be smoothly transformed to alcohol **287**, which was then carried on to the rest of the synthesis of the tricyclic core **288** of vinigrol **289** (Scheme 85).[400] A one-pot intramolecular version of this coupling/rearrangement sequence was also used for a remarkably efficient synthesis of three hexahydropyrrolo[2,3-*b*]indole alkaloids: debromoflustramines B and E and debromoflustramide B (see section 4.4.1, Scheme 88).[401,402]

Before closing this section and moving on to intramolecular processes, we ought to mention that the copper-mediated cross-coupling of phenylboronic acids and *N*-hydroxyphthalimide leading to *O*-arylhydroxylamines after deprotection[159] was used for an efficient, large-scale, preparation of starting materials in Naito's synthesis of stemofuran A and eupomatenoid.[403]

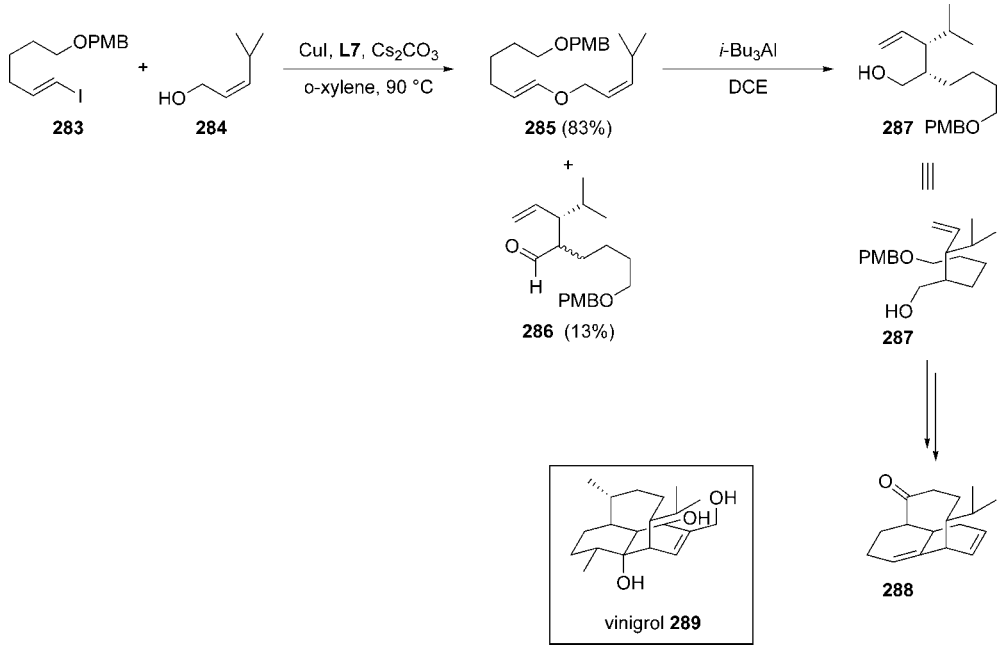
4.4. Intramolecular Reactions

4.4.1. Formation of Small- to Medium-Sized Oxygenated Heterocycles

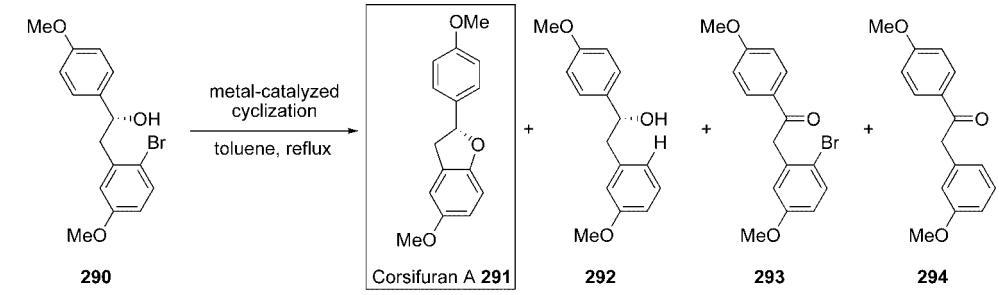
Intramolecular copper-mediated arylation of alcohols and carboxylic acids has also found interesting application in natural product synthesis, even if, which is in deep contrast with the cyclization to nitrogen heterocycles, most cases deal with the formation of macrocycles. Despite the "youth" of the methodologies involved, examples that will be overviewed in the following paragraphs, however, show that the use of intramolecular C−O bond formation reactions allows for high levels of efficiency as well as original and efficient bond disconnections.

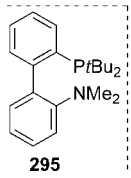
The key step in Jones' asymmetric synthesis of corsifuran A **291** relied on the use of a metal-catalyzed cycloetherification reaction to form the furan system starting from enantiopure acyclic precursor **290**. Using palladium catalysts, the desired corsifuran A **291** was produced in only two

Scheme 85. Synthesis of the Tricyclic Core of Vinigrol



Scheme 86. Synthesis of Corsifuran A by Intramolecular Arylation



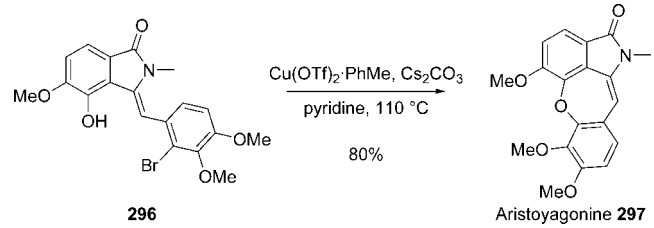


metal source	ligand	base	% **290** (ee)	% **291** (ee)	% **292** (ee)	% **293**	% **294**
$Pd(OAc)_2$	**BINAP**	NaO*t*Bu	0	5 (100)	5 (40)	3	87
$Pd(OAc)_2$	**BINAP**	Cs_2CO_3	97 (100)	0	0	0	3
$Pd(OAc)_2$	**BINAP**	KO*t*Bu	0	0	0	0	100
$Pd_2(dba)_3$	**295**	NaO*t*Bu	0	100 (45)	0	0	0
$Pd_2(dba)_3$	**295**	Cs_2CO_3	100 (100)	0	0	0	0
$Pd_2(dba)_3$	**295**	KO*t*Bu	0	0	0	5	95
CuCl	-	NaH	-	76 (100)	-	-	-

assays, neither of which gave satisfactory results because the product was obtained with either low yield or racemization. Using other catalytic systems produced in some instances varying quantities of unreacted starting material **290**, debrominated starting material **292**, and ketones **293** and **294**. In deep contrast, the use of a copper-mediated cycloetherification system developed by Zhu and co-workers[404] resulted in the isolation of corsifuran A **291** in 76% yield and with complete preservation of the stereochemical integrity (Scheme 86).[405] A similar cycloetherification reaction was also reported to yield dihydrobenzofuran and chroman in excellent yield using 2-aminopyridine as ligand for copper(I).[120]

A total synthesis of the aristocularine alkaloid aristoyagonine **297** was reported using an intramolecular diaryl ether formation to form the key dibenzoxepine skeleton starting from acyclic precursor **296**, which cyclized smoothly using Buchwald's first-generation catalytic system to give the target natural product in 80% yield. A notable and remarkable feature of this cyclization is that the configuration of the double bond in the starting material is not crucial for the

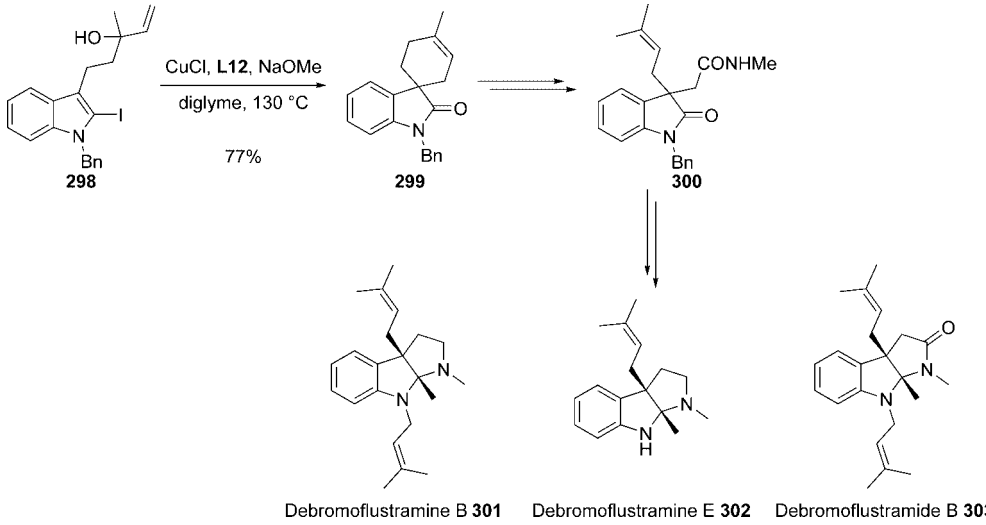
Scheme 87. Synthesis of Aristoyagonine by Intramolecular Arylation



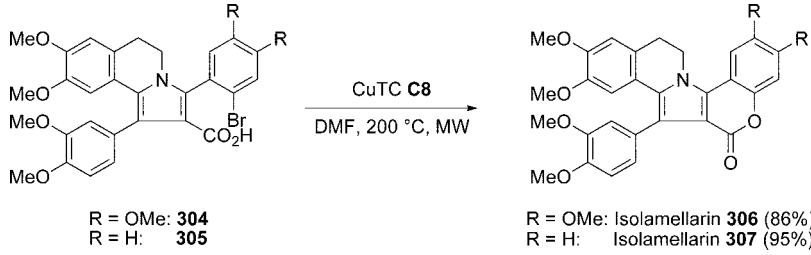
creation of the diaryl ether linkage, ensuring the construction of the benzoxepine system (Scheme 87).[406] Another cyclization to a related dibenzo[*b*,*f*]oxepine framework has also been reported by intramolecular arylation of a phenol. The use of both copper and palladium catalyses in this case offers an interesting comparison with regard to the scope of each procedure, the first one being more tolerant in terms of substitution of the cyclization precursors.[407]

As already illustrated with Barriault's synthesis of the tricyclic core of vinigrol (Scheme 85), the combination of

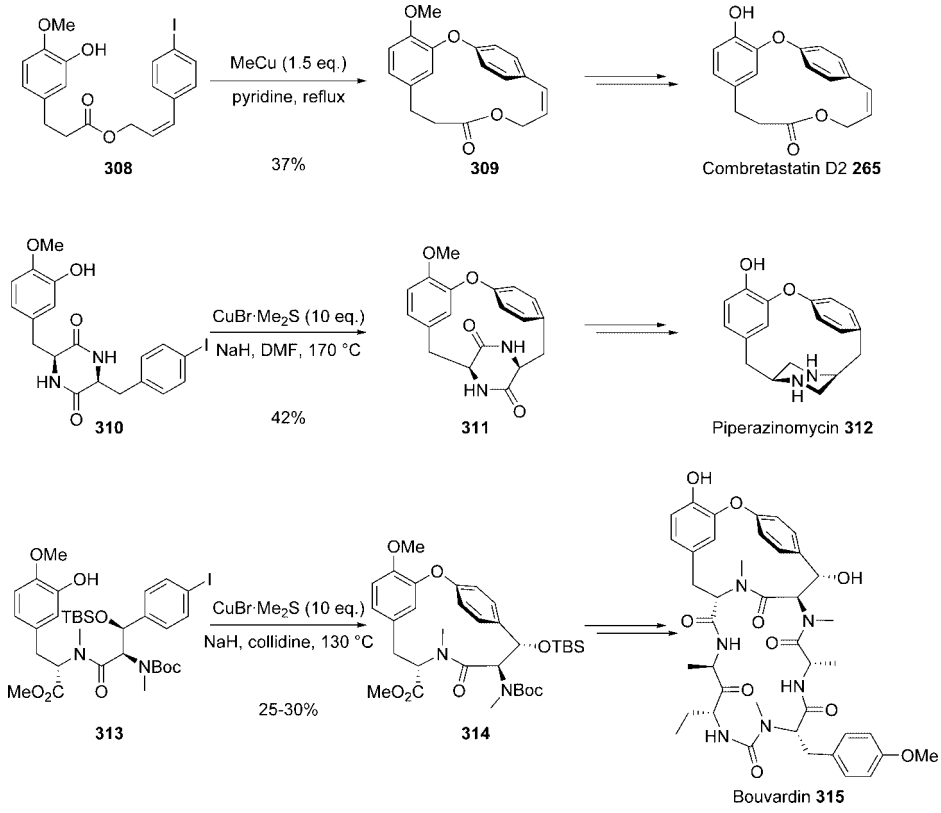
Scheme 88. Synthesis of Debromoflustramines B and E and Debromoflustramide B by Intramolecular Ullmann Coupling/ Claisen Rearrangement



Scheme 89. Synthesis of Isolamellarins by Intramolecular Carbocylic Acid Arylation

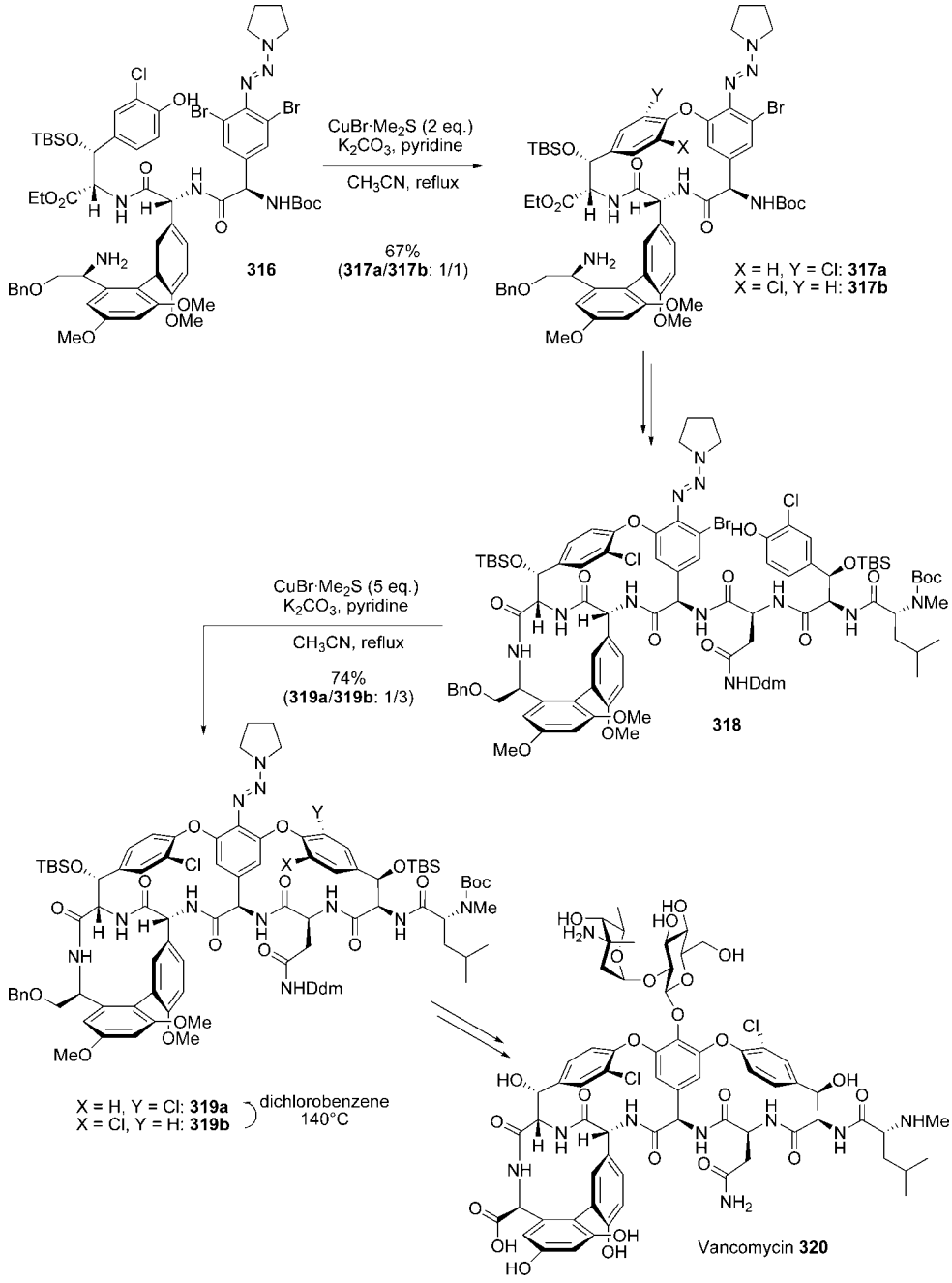


Scheme 90. Synthesis of Naturally Occuring Macrocyclic Ethers by Intramolecular Phenol by the Boger Group



Ullmann coupling and Claisen rearrangement provides an especially efficient tool that allows for the synthesis of complex molecules starting from readily available starting materials. The intramolecular version of this reaction is even more spectacular and was used by Kobayashi and co-workers in efficient syntheses of debromoflustramines B **301** and E **302** and debromoflustramide B **303** (Scheme 88).[402] The common intermediate in these syntheses, oxindole **300**, was

Scheme 91. Synthesis of Vancomycin by Successive Intramolecular Phenol Arylation Reactions



obtained using a previously reported expedient preparation of spirocyclic oxindoles such as **299** using a one-pot intramolecular Ullmann coupling/Claisen rearrangement sequence[401] starting from acyclic precursor **298**. Conversion of **298** to **299** was efficiently carried out on multigram quantities using sodium methoxide as base, copper(I) chloride as catalyst, and 2-aminopyridine **L12** as ligand. Substrates possessing a 1,2-disubstituted double bond provided spirocyclic oxindoles with high diastereoselectivities.

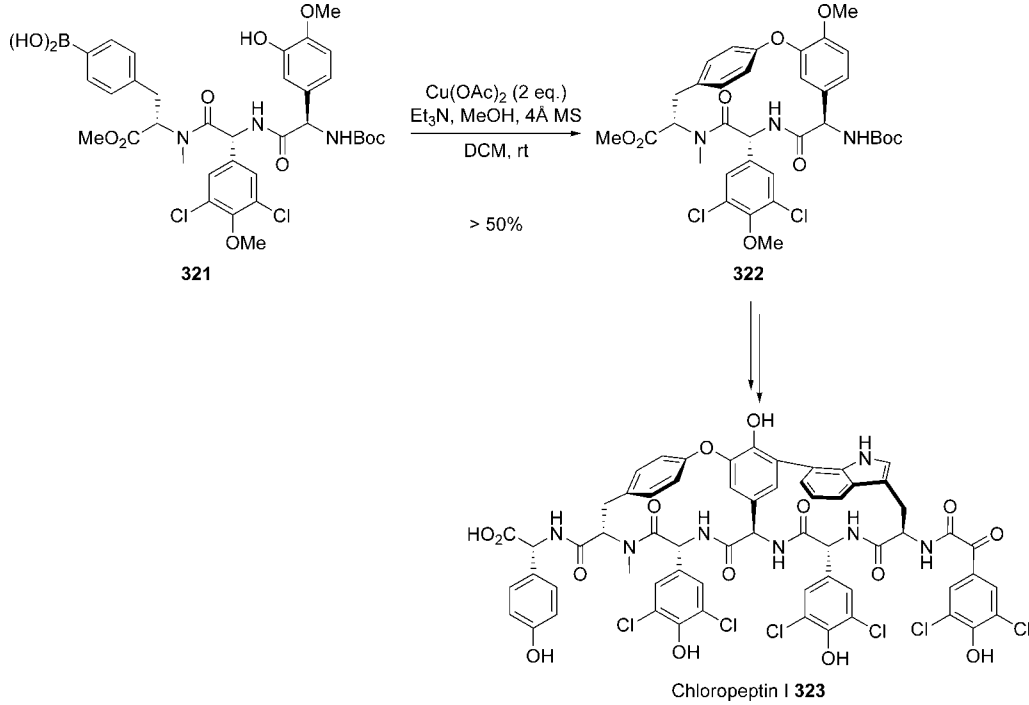
Finally, the efficiency of the intramolecular arylation of carboxylic acids developed by Thasana was demonstrated with the synthesis of isolamellarins **306** and **307**. Upon treatment with 2 equiv of Liebeskind catalyst CuTC **C8** in DMF at 200 °C under microwave irradiation, bromoaryl benzoic acids **304** and **305**, respectively, cyclized to the desired polycyclic targets in 86 and 95% yield (Scheme 89).[158] An alternative protocol for the formation of the lactone ring starting from a debrominated analogue of **304** and using lead(IV) acetate provided the desired lactone **306** but in a disappointing yield (7%).

4.4.2. Intramolecular C−O Cross-Coupling Reactions as Macrocyclization Procedures

The macrocyclic diaryl ether motif is abundant in a number of naturally occurring compounds, including important medicinal molecules, the most famous one probably being vancomycin.[408] Copper-mediated syntheses of such natural products have been, in part, previously reviewed[1,113] but the latest impressive developments and comparisons with previous approaches show the amazing progress resulting from intense research aiming at the development of efficient catalytic sytems, going from classical Ullmann conditions to room temperature, catalytic processes.

Up to 2001, the copper-mediated cyclization to naturally occurring macrocyclic diaryl ethers relied on adaptation of

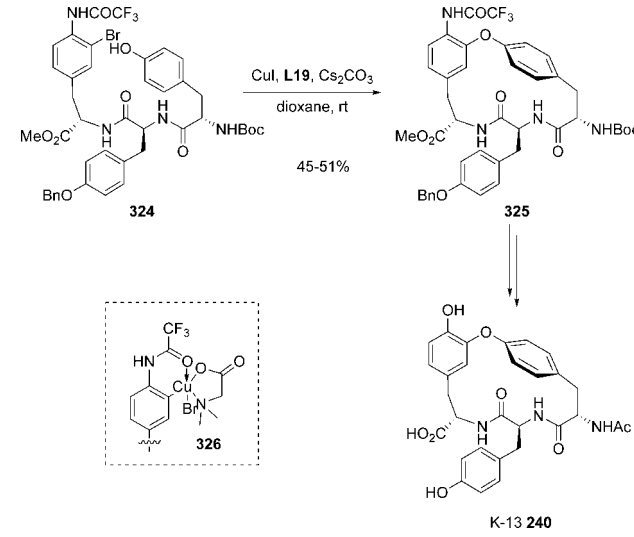
Scheme 92. Synthesis of Chloropeptin I by Intramolecular Phenol Arylation



the classical Ullmann condensation between aryl halides and phenols, and extensive research in this area has been reported by the Boger group. They first reported in 1991 suitable reaction conditions for the intramolecular Ullmann reaction using stoichiometric sodium hydride as base and excess of $CuBr \cdot Me_2S$ or methylcopper as copper(I) source in collidine or pyridine under high dilution conditions.[409] These conditions allowed for the preparation of a wide range of macrocyclic diaryl ethers in modest to moderate yields (depending on the substitution pattern of the starting material) and clearly reinstated the intramolecular Ullmann reaction as a useful synthetic tool that could, at least in some cases, compete with other approaches including nucleophilic aromatic substitution, oxidative phenolic coupling, or bromoquinone substitution. On the basis of these results, the conditions developed were used as key macrocyclization step for the synthesis of various macrocyclic natural products including combretastatin D2 **265**[410] and piperazinomycin **312**,[411] as well as bouvardin **315** and related compounds (Scheme 90).[412] Just as a note, another classical procedure relying on the use of copper(II) oxide and potassium carbonate in refluxing pyridine has been used for the preparation of the naturally occurring macrocyclic ethers acerogenins C and L, galleon, and pterocarine with 49−76% yield for the macrocyclization.[413]

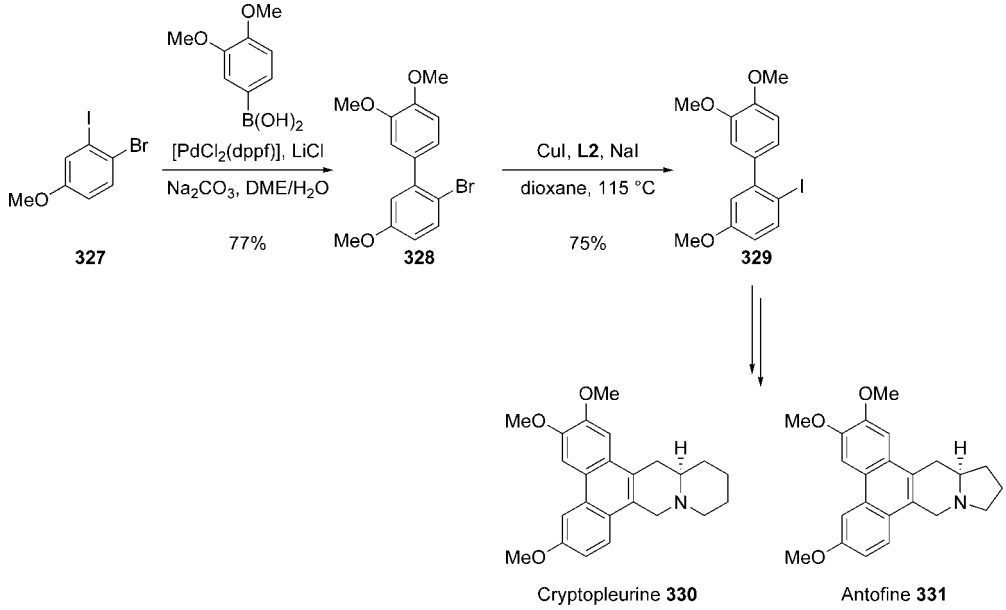
A seminal contribution came from the Nicolaou group, who devised an efficient total synthesis of vancomycin **320** based on copper-mediated intramolecular arylation of phenols to build the AB-COD and DOE ring systems of the complex polycyclic target. For this synthesis, a mild copper arylation reaction was designed on the basis of the ingenious incorporation of a triazene unit in the starting material strategically placed *ortho* to the bromine:[414] this internal helper auxiliary would serve both as a potential "electron sink" and to coordinate the intermediate copper species, this last effect being well documented with carboxylic acids, amides, or sulfone groups. The triazene indeed considerably helped the reaction because both cyclizations (i.e., **316** → **317** and **318** → **319**, Scheme 91) gave cyclized products in rather high yield for such a transformation and did not require the presence of strong bases or too high temperatures, which allowed for the completion of a remarkably efficient total synthesis of vancomycin **320**.[415] In some cases, high atroposelectivity can even be achieved.[416] As triazenes are easily prepared and converted to a variety of functional groups such as halides, amines, and phenols, the utility of this protocol is rather wide.

Scheme 93. Synthesis of K-13 by Intramolecular Room Temperature Phenol Arylation



In an effort to complement the intermolecular copper(II)-mediated Chan−Lam−Evans coupling, Decicco, Song, and Evans reported in 2001 the intramolecular *O*-arylation of a phenol with a boronic acid. This macrocyclization was found to be mild and tolerant of common chemical functionalities and is still one of the mildest procedures described to date, even if it can be limited by the availability of the starting material.[417] This procedure was central to Snapper and Hoveyda's strategy for the total synthesis of the anti-HIV agent chloropeptin I **323** (Scheme 92).[418] In this case, the presence

Scheme 94. Synthesis of Cryptopleurine and Antofine Featuring an Aromatic Finkelstein Reaction



of 10 equiv of methanol is crucial for the cyclization of **321**, which was attributed to a possible increased solubility of the copper salt or to *in situ* formation of the boron dimethyl ester. Moreover, the use of triethylamine (in place of pyridine) as base led to notably more facile transformation. This strong base effect (typically triethylamine vs pyridine) that is often observed in the Chan−Lam−Evans coupling was also noted by Takeya and co-workers during the preparation of cycloisodityrosine: in their case, the macrocyclization using 5 equiv of DMAP led to improved yields and considerably reduced the amounts of deborylated side products.[419]

Finally, the combination of *ortho*-substituent and ligand effects was used by the Ma group for the development of room temperature Ullmann-type diaryl ether formation and exemplified in one of the most efficient total synthesis of the macrocyclic diaryl ether K-13 **240** to date. Therefore, introduction of a trifluoroacetamido group in the cyclization substrate **324** allowed for the *N*,*N*-dimethylglycine **L19**-catalyzed reaction to proceed smoothly at room temperature to give macrocyclic diaryl ether **325** in 45−51% yield (Scheme 93).[420] For comparison, other syntheses of K-13 **240** relying on an intermolecular copper-mediated arylation to form the diaryl ethers required temperatures ranging from 90 to 130 °C (Scheme 77). An explanation for the high reactivity observed in this case would involve the intermediacy of a complex such as **326** resulting from oxidative addition. In this complex, additional stabilization by the trifluoroacetamido group would account for the accelerating effect.

5. Natural Product Total Synthesis: Aromatic Finkelstein Reaction

To date, the aromatic Finkelstein reaction has been used only once in the context of natural product synthesis by Fürstner and Kennedy for the preparation of the cytotoxic tylophora alkaloids cryptopleurine **330** and antofine **331**. After selective Suzuki coupling starting from 1-bromo-2-iodo-4-methoxybenzene **327** to give **328**, a bromide−iodide exchange was performed using either a standard lithiation−iodination sequence or Buchwald's procedure using excess sodium iodide together with copper(I) iodide and diamine **L2** to give the more reactive iodide **329** that was used for the preparation of **330** and **331** (Scheme 94).[421] Although the yields were comparable for both procedures, the standard lithiation was, however, preferred due to long reaction times required in the second case. A vinylic Finkelstein reaction was also used to prepare 1-iodo-2-methylpropene from the corresponding bromide during synthetic studies toward the total synthesis of kaitocephalin.[162]

6. Natural Product Total Synthesis: Formation of C−C Bonds

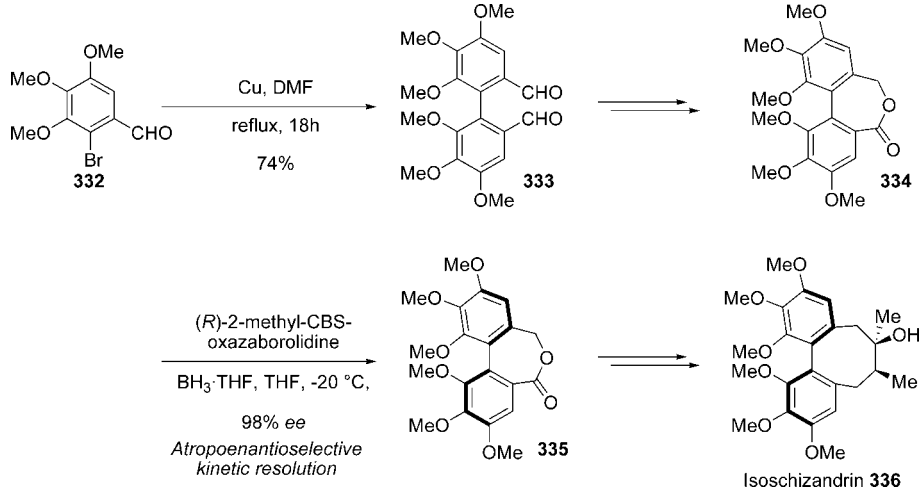
The impressive achievements of the copper-mediated C−C bond-forming reactions in the past few years had a profound impact on the field of total synthesis of biologically relevant natural products. The mild conditions (below room temperature) now available for the Cu-mediated cross-coupling reactions combined with the exceptional functional group tolerance have confirmed that copper is highly complementary to palladium-catalyzed reactions.[422] A copper mediator will be frequently encountered in the following sections, namely, copper(I) thiophenecarboxylate (CuTC **C8**). Since its introduction by Liebeskind in the late 1990s, the exceptional activity of this stable and economical promoter has been highlighted in numerous total syntheses of complex natural products. The more recent methodologies presented in the previous sections will certainly contribute to ever-more efficient retrosynthetic disconnections in the near future.

6.1. Biaryls

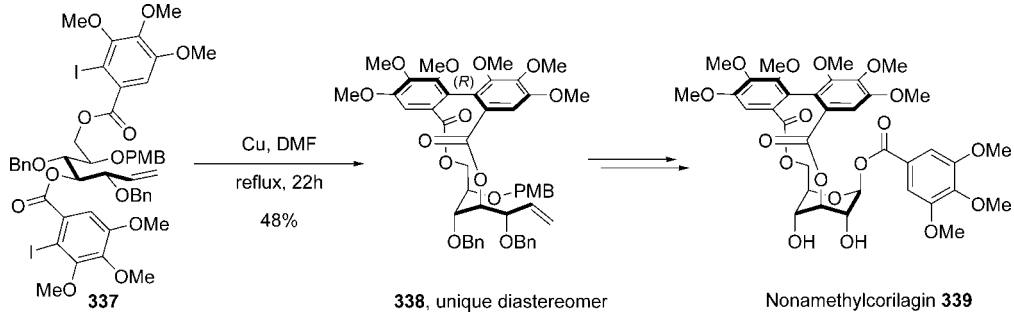
6.1.1. Biaryls by Classical Ullmann Cross-Coupling

In the context of natural product synthesis, fascinating Ullmann cross-coupling strategies have been reported and have been extensively and thoroughly reviewed.[4] One of the variants of this venerable coupling reaction, the Ziegler−Ullmann coupling of aryl halides,[423] is a general and mild method that has been used as a key step in the total synthesis of numerous naturally occurring derivatives.[4,424] Because this reaction required the preformation of an arylcopper reagent,

Scheme 95. Synthesis of (+)-Isoschizandrin



Scheme 96. Synthesis of 3,6-Bridged Ellagitannins

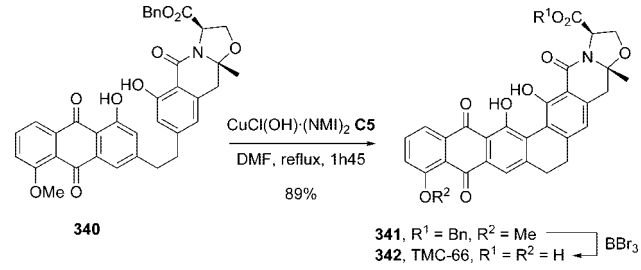


it is beyond the scope of the present review. Similarly, Baran recently reported on the mild, copper-mediated oxidative coupling of carbonyls and heterocycles such as indoles or pyrroles. These impressive methodological achievements have been exploited in new straightforward total syntheses of complex natural products.[425] As in the Ziegler−Ullmann reaction, the formation of an organometallic reagent (carbonyl enolate) prior to the coupling step is imperative.

Classical Ullmann type coupling of **332** has been reported recently by Molander in the total synthesis of (+)-isoschizandrin **336**, a dibenzocyclooctadiene lignin isolated from the fruits of *Schizandra chinesis* (Scheme 95).[426] Bisaldehyde **333**, obtained in 74% yield, could then be transformed into racemic lactone **334**, which then underwent kinetic resolution using an atropoenantioselective reduction according to Bringmann's method.[427] (+)-Isoschizandrin **336** was further elaborated in an elegant seven-step sequence featuring a samarium(II) iodide-promoted 8-endo ketyl-olefin cyclization.

A highly diastereoselective Ullmann-type coupling was used in the total synthesis of nonamethylcorilagin **339**, closely related to corilagin, one of the simplest 3,6-bridged ellagitannins (Scheme 96).[428] This 3,6-bridged structure presents a real challenge in terms of synthesis because it imposes a $^1C_4$ or skew boat conformation to the D-glucose core of the molecule. Yamada reported that intramolecular Ullmann coupling of **337** led in 48% yield to the desired biaryl **338** as a single diastereosiomer that was transformed in four additional steps into nonamethylcorilagin. The preopening of the pyranose ring was key to the success of this sequence.

Scheme 97. Synthesis of TMC-66

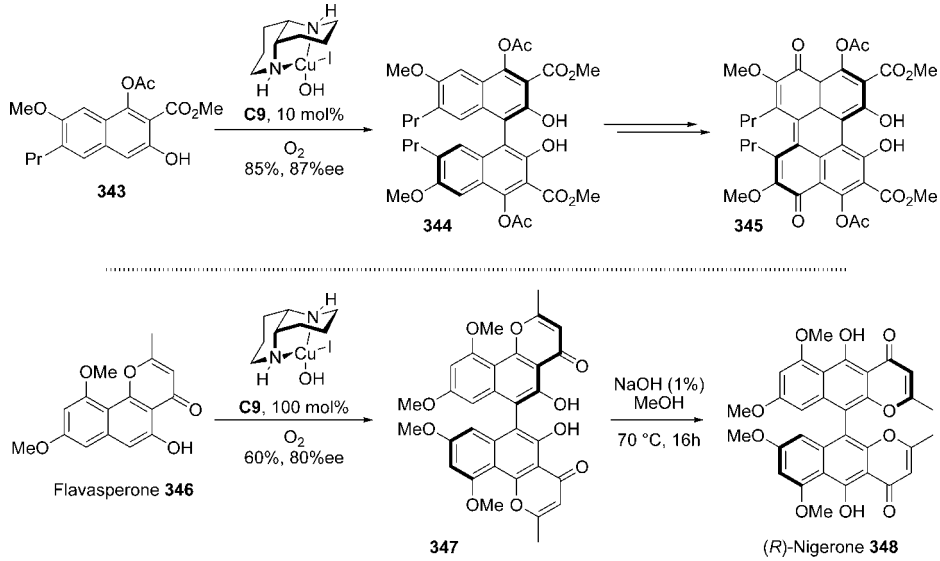


6.1.2. Biaryls by Oxidative Coupling of Phenols

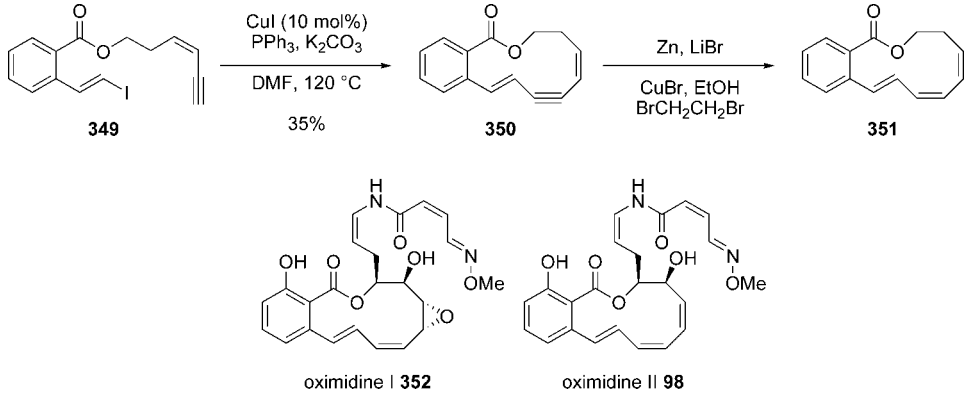
Oxidative coupling reactions of strongly deactivated phenols is quite challenging from both the reactivity and regioselectivity points of view. Hosokawa and Tatsuta reported an efficient access to biphenol **341** from **340** using a new copper(II) reagent CuCl(OH)·(NMI)$_2$ in DMF (89%) (Scheme 97).[429] Compound **341**, obtained in 89% yield, was then elaborated into TMC-66 **342**, an endothelin converting enzyme inhibitor. For comparison, Koga's reagent [CuCl(OH)·(TMEDA)] led only to 20% of the desired **341**.

Capitalizing on the powerful asymmetric oxidative coupling of naphthols using 1,5-diaza-*cis*-decalin copper catalysts, Kozlowski and co-workers engaged in the total syntheses of various challenging natural products (Scheme 98). The naturally occurring perylenequinone of general structure **345** has attracted a great deal of attention due to its potent protein kinase C inhibitory activity: Kozlowski reported the first asymmetric synthesis of a perylenequinone containing only an axial chirality element.[430] After fine-tuning of the electronic character of the substituents to avoid the racemization of the product, the catalytic asymmetric enantioselective coupling of 2-naphthol **343** was found to

Scheme 98. Synthesis of Perylenequinone and Bisnaphthopyrone Natural Products



Scheme 99. Synthesis of the Macrocyclic Core of Oximidines



proceed in good yields and enantioselectivity (85%, 87% ee). Kozlowki's catalytic system has also been used with success in the oxidative biaryl coupling of flavasperone **346** (Scheme 98),[431] which possesses ideal geometric (bidentate keto-phenolic structure) and electronic (electron-withdrawing substituent at C4) requirements for a successful coupling with the 1,5-diaza-*cis*-decalin copper catalyst **C9**. With 100 mol % of **C9**, (*R*)-**347** was obtained in good yield and enantiomeric excess. Further isomerization reaction in basic media led to (*R*)-nigerone **348**, a bisnaphthopyrone natural product isolated from *Aspergillus niger*.

6.2. Ene−Ynes

Decisive progress has been reported in the past few years on copper-mediated cross-coupling between vinyl halides and terminal alkynes. As discussed in the background section of this review, a catalytic amount of copper can be used, the functional group tolerance is broad, and the reaction conditions are very mild. Therefore, the impact of these new methodologies on the field of total synthesis of biologically relevant targets should increase significantly in the near future.

Coleman[432] showed that the polyene macrocyclic fragment of oximidines I **352** and II **98** (Scheme 99), cytotoxic macrolactones isolated from *Pseudomonas*, could be obtained by reduction of the corresponding enyne **350**, the latter being obtained via an intramolecular coupling of **349** using Miura's conditions (catalytic CuI, PPh_3, K_2CO_3, DMF, 120 °C).[191a] The strained 12-membered lactone was obtained in a modest 35% yield together with 10−15% of the corresponding dimer. Worthy of note is the fact that Pd(0)-catalyzed Sonogashira couplings did not afford the desired coupling product.[432]

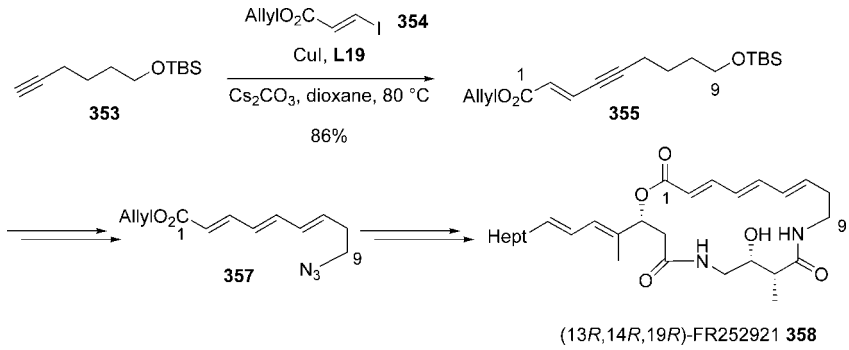
The powerful catalytic system proposed by Ma (CuI, *N*,*N*-dimethylglycine **L19**)[192] was used in a flexible and straightforward synthesis of one of the possible stereoisomers of FR252921 (Scheme 100), a novel immunosuppressive agent isolated from *Pseudomonas fluorescence* no. 408813.[433] The intermolecular cross-coupling of (*E*)-β-iodoacrylate **354** with terminal alkyne **353** afforded the desired enyne **355** (86% yield) in very mild conditions (dioxane, 80 °C) and further transformations led to (13*R*,14*R*,19*R*)-FR252921 **358**, which proved to be different from the natural product.

6.3. 1,3-Dienes

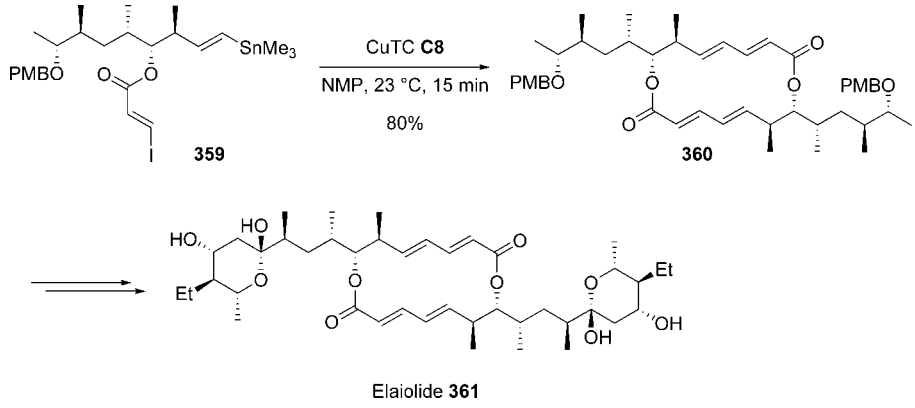
6.3.1. 1,3-Dienes by CuTC-Promoted Stille-Type Cross-Coupling

Copper-mediated coupling reactions of monosubstituted vinyltin derivatives have enjoyed a lot of success in total syntheses of complex natural products. Natural products possessing a C_2 symmetric structure could be efficiently prepared by copper-mediated cyclodimerization as shown by Paterson as early as 1997, in the first report on the use of CuTC **C8** in the context of total synthesis (Scheme 101).[434] Elaiolide **361** is the aglycon of elaiophylin, a 16-membered macrolide with

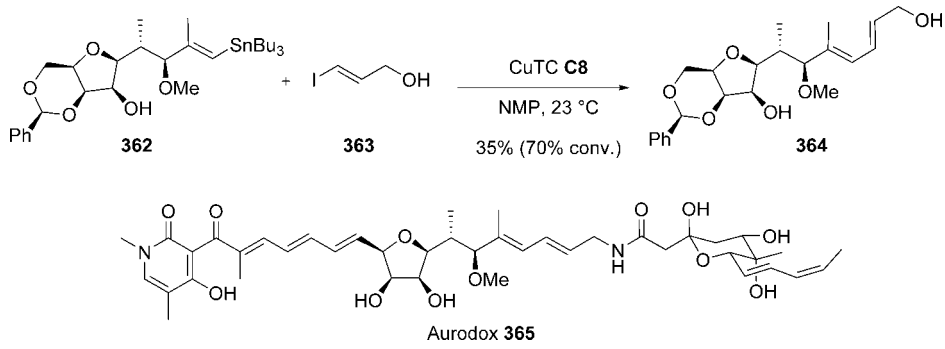
Scheme 100. Synthesis of FR252921



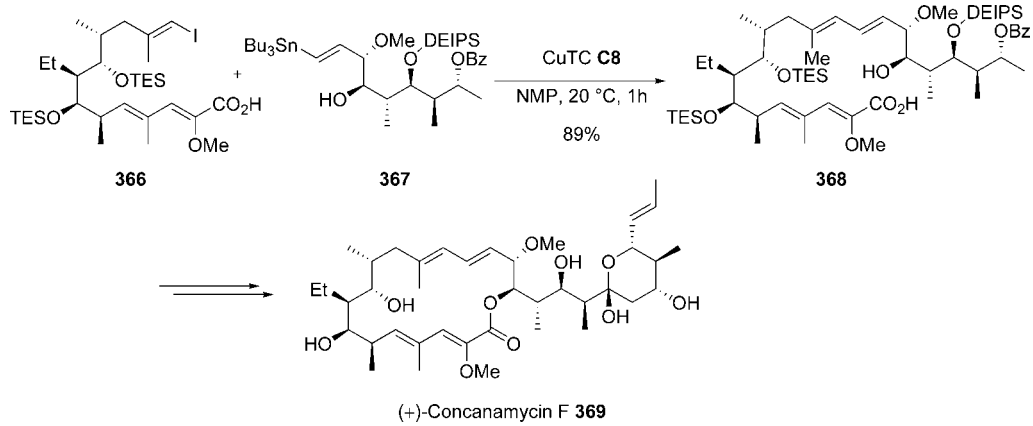
Scheme 101. Synthesis of Elaiolide



Scheme 102. Synthesis of the Dienyl Side Chain of Aurodox



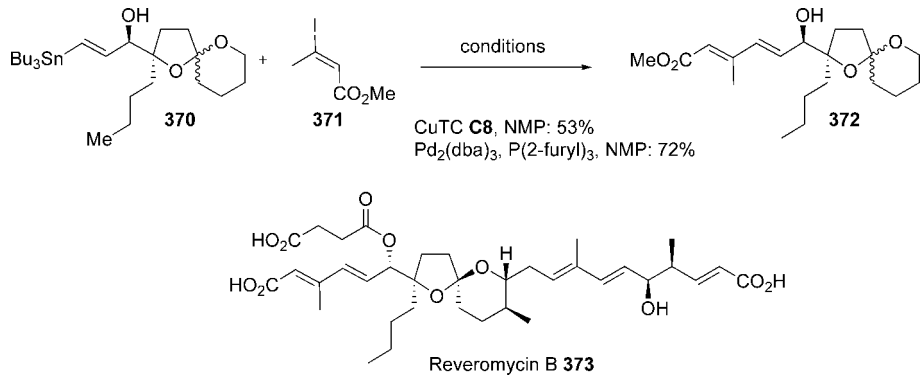
Scheme 103. Synthesis of Concanamycin F



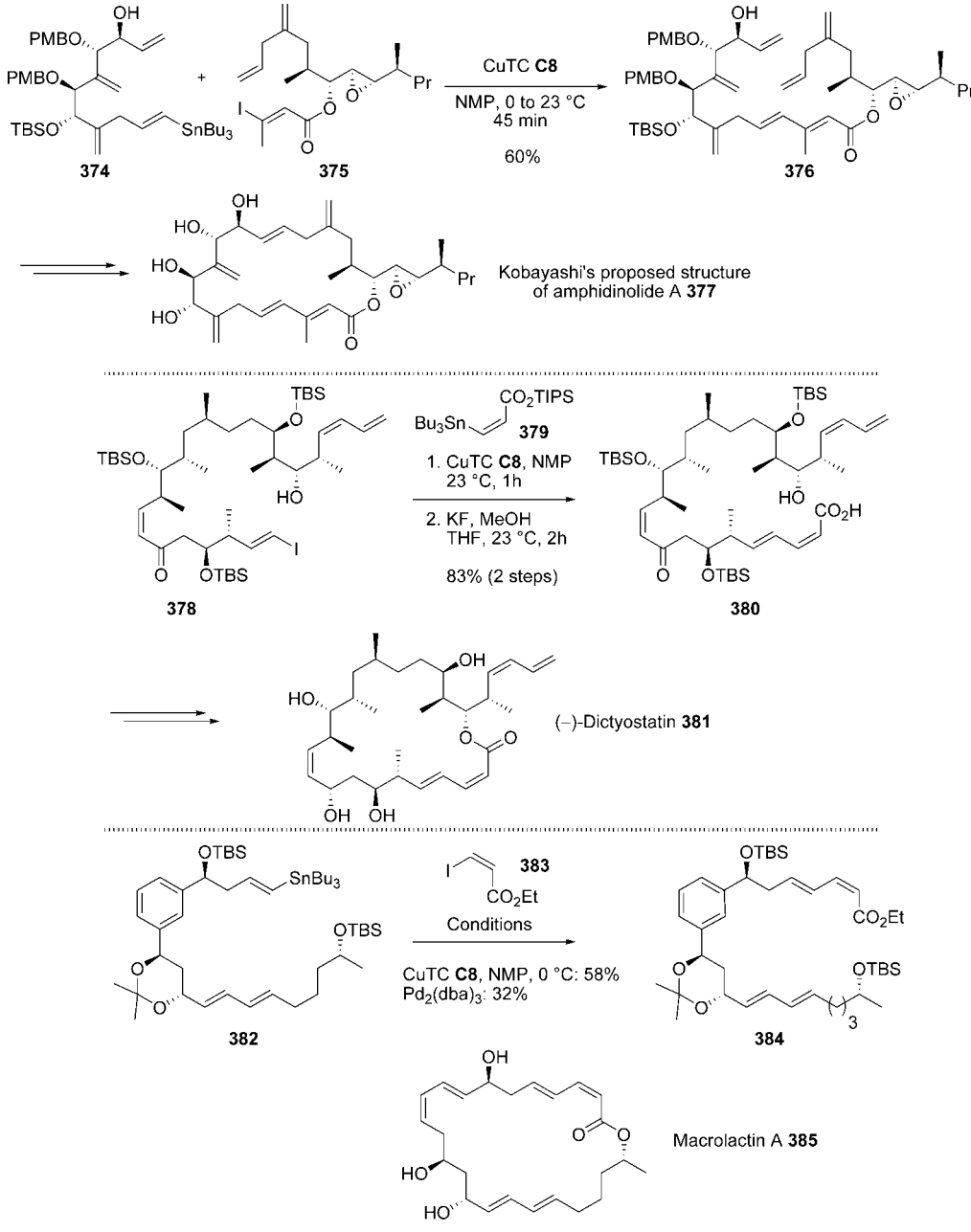
antimicrobial and antihelminthic activities isolated from cultures of *Streptomyces melanosporus*. The macrocyclic C_2 symmetric core of elaiolide **360** could be obtained by CuTC-mediated cyclodimerization of vinylstannane **359**, which simultaneously created C3C4 and C3′C4′ bonds in high yield at room temperature for 15 min. The influence of the concentration was observed as more dilute conditions (0.01 M) led to higher selectivity in favor of the cyclodimer.

One of the first applications of Liebeskind promoter in the context of total synthesis was disclosed by Craig in 1998

Scheme 104. Synthesis of the Dienoic Acid Fragment of Reveromycin



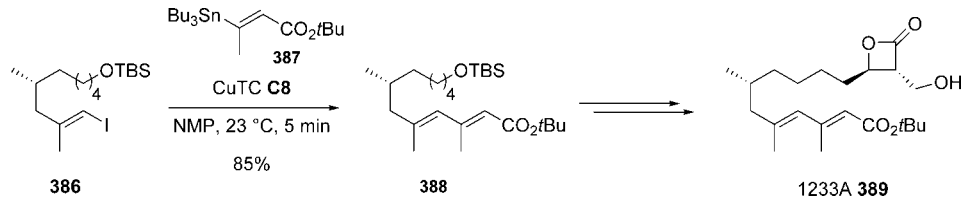
Scheme 105. Synthesis of Proposed Amphidinolide A, Dictyostatin, and Macrolactin A Analogues



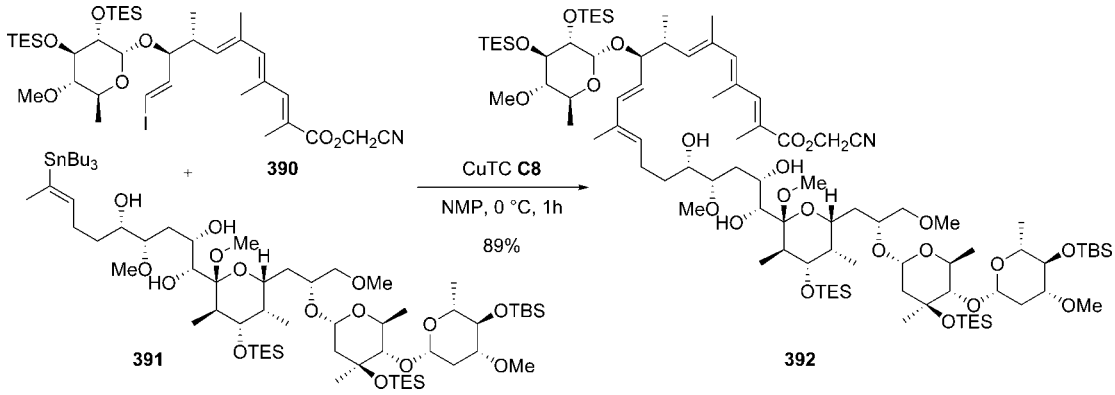
(Scheme 102).[435] The dienyl side chain of the elfamycin antibiotic aurodox **365** was constructed by a CuTC-mediated coupling of **362** with (*E*)-3-iodo-2-propen-1-ol **363**; based on a 70% conversion, the yield was, however, only 35%.

In the 2000 total synthesis of concanamycin F **369**, Paterson reported on the remarkably efficient CuTC-promoted intermolecular coupling of **367** with complex vinyl iodide **366** (Scheme 103).[452] The desired 1,3-diene **368** was

Scheme 106. Synthesis of 1233A



Scheme 107. Synthesis of Apoptolidin



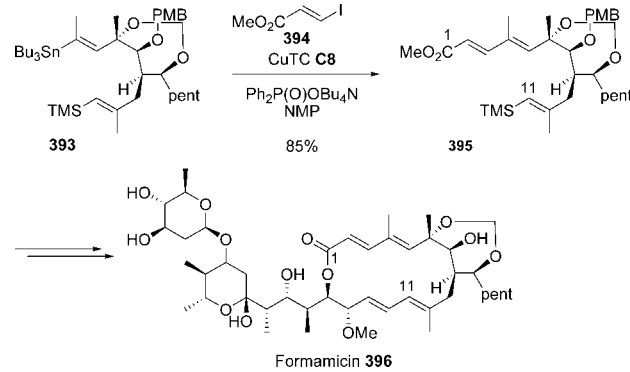
obtained in an excellent 89% yield under mild reaction conditions, in contrast to Pd(0)-catalyzed conditions (20%).

A monosubstituted alkenylstannane was also used by Rizzacasa in the total synthesis of the epidermal growth factor inhibitor (−)-reveromycin **373** (Scheme 104).[436] In model studies for installation of the dienoic side chain, a CuTC-mediated cross-coupling reaction between alkenylstannane **370** and iodoacrylate **371** led to the desired C21C22 double-bond derivative **372** in 53% yield. Palladium-catalyzed conditions were, however, more efficient in this case [$Pd_2(dba)_3$, P(2-furyl)$_3$, NMP, 72%].

Apart from more practical reaction conditions, CuTC-promoted couplings also display an important rate acceleration compared to Pd-catalyzed unions, as seen in the total synthesis of amphidinolide A **377** (proposed structure) by Maleczka (Scheme 105).[437] Only 45 min was required to obtain **376** under CuTC **C8** conditions compared to 18 h with Pd(0) catalysis.[438] Cross-coupling reactions with (*Z*)-monosubstituted vinyltin derivatives also occurred with high efficiency as shown by Paterson in the total synthesis of (−)-dictyostatin **381**, a microtubule-stabilizing macrolide isolated from a marine sponge: the desired (2*Z*,4*E*)-dienoate **380** was obtained in an impressive 83% yield (two steps) in 1 h at room temperature.[439] The same type of (2*Z*,4*E*)-dienoate **384** has been obtained by Takemoto in the synthesis of macrolactin analogues, using the alternative combination of (*E*)-vinyltin derivative and (*Z*)-vinyl halide (Scheme 105).[440] The moderate yield (58%) is almost twice the yield obtained in Pd-catalyzed conditions (32%).

The 2-substituted-1,3-diene unit is commonly found in natural products such as the amphidinolides, the reveromycins, the iejmalides, and numerous plecomacrolides (hygrolidin, concanamycin, etc.). The CuTC-promoted coupling of disubstituted alkenylstannanes provides an efficient entry into this synthetically valuable motif, often surpassing the palladium-catalyzed cross-coupling in terms of functional group compatibility and simplicity of reaction conditions. As early as 1998, Kocienski reported on the high-yielding cross-coupling of disubstituted vinyltin derivatives **387** with vinyl iodide **386** (Scheme 106): the desired dienoate **388** was

Scheme 108. Synthesis of Formamicin

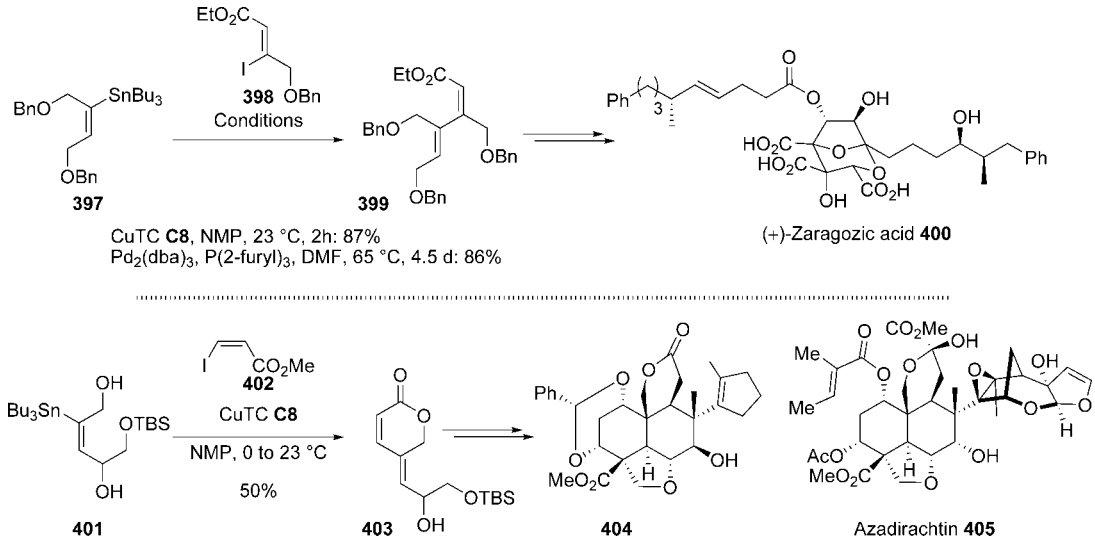


obtained stereoselectively in 5 min.[441] Further functional group transformations finally afforded 1233A**389**, a metabolite from *Scopulariopsis* and from *Fusarium*.

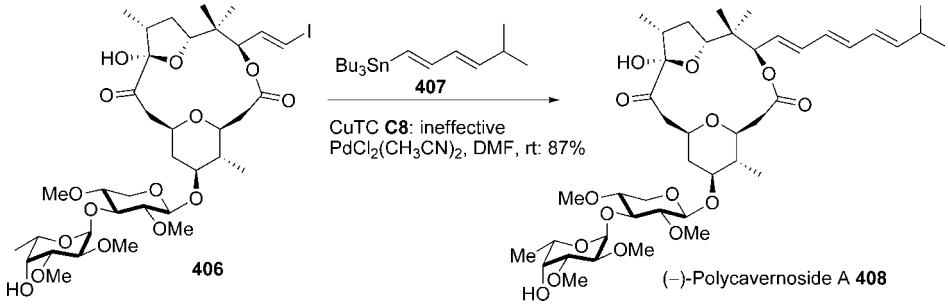
Fascinating CuTC-mediated couplings have been reported by Koert during the total synthesis of apoptolidin A[442] and its aglycon (Scheme 107).[443] In very mild conditions (0 °C, 1 h), the disubstituted vinyltin derivative **391** could be coupled with vinyl iodide **390** in 89% yield. Worthy of note is the exceptional functional group compatibility as sensitive disaccharide units and highly conjugated cyanomethyl ester survived. To compare, Pd(0)-catalyzed Stille coupling led to low yields in the apoptolidin A aglycon studies (yields < 30%, 60 °C, prolonged reaction time).[443]

Another challenging CuTC-promoted Stille cross-coupling reaction was reported by Roush in 2004 in the total synthesis of formamicin **396**, a plecomacrolide exhibiting vacuolar H^+-ATPases inhibitory activity (Scheme 108).[444] The sterically hindered vinyl stannane **393** was coupled with methyl (*E*)-3-iodopropenoate **394** in 83% yield. The addition of a stoichiometric quantity of the tin scavenger tetrabutylammonium diphenylphosphinate[445] was necessary to reach a useful yield of the C1C11 fragment **395** of formamicin. It is worth noting that the sensitive 7-membered ketal and the C10C11-vinylsilane moiety were absolutely stable under these very mild conditions. In contrast, Pd(0)-catalyzed cross-couplings were unsuccessful.

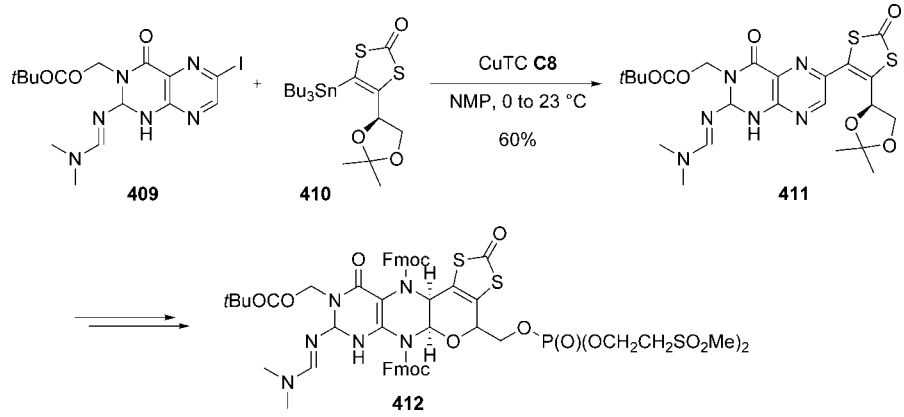
Scheme 109. Synthesis of Zaragozic Acid and AB Ring System of Azadirachtin



Scheme 110. Synthesis of (−)-Polycavernoside A



Scheme 111. Synthesis of the Organic Ligand of Oxomolybdoenzymes Cofactor

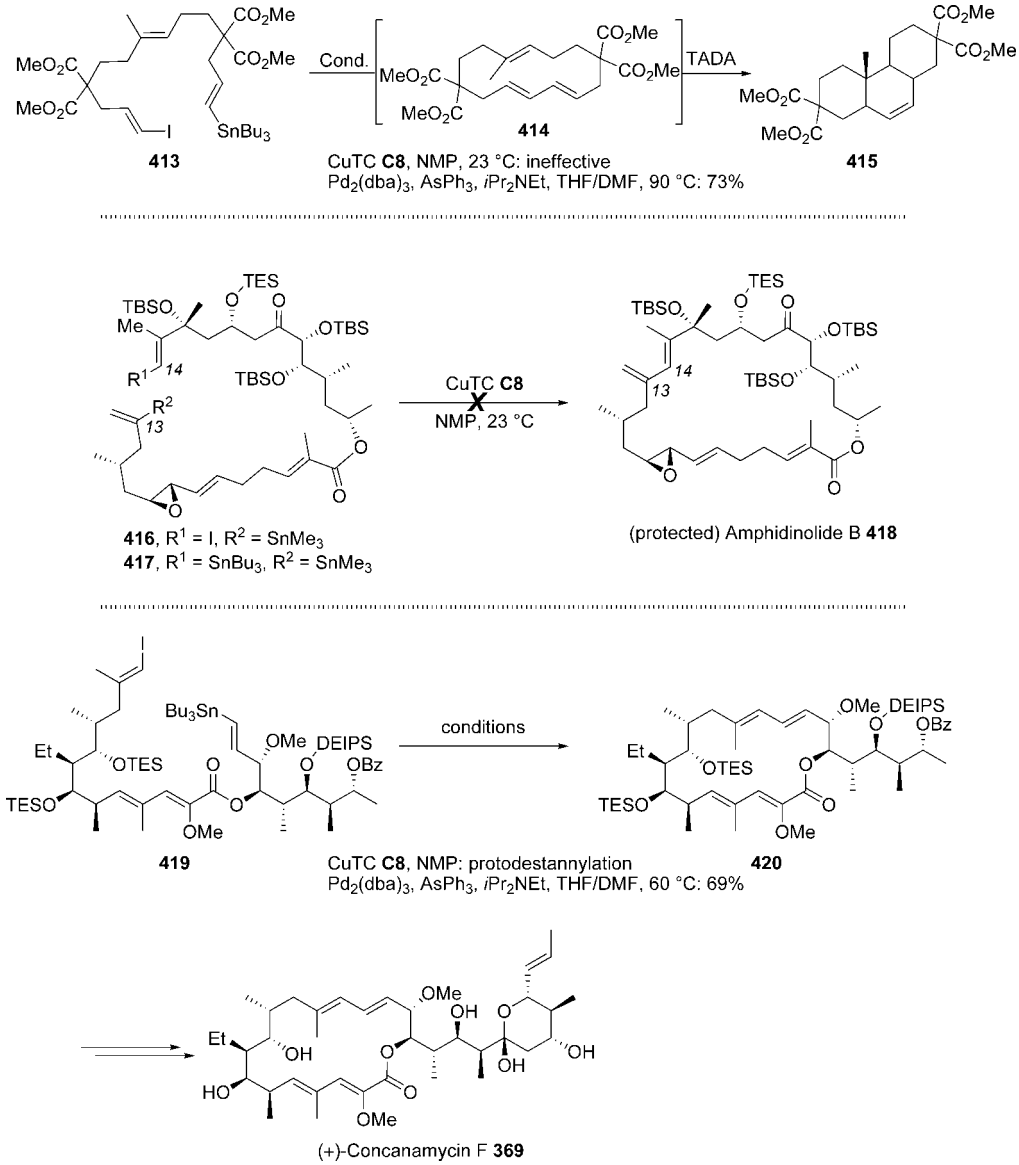


As mentioned earlier in the CuTC-mediated coupling of monosubstituted vinyltin derivatives, a dramatic rate enhancement is generally observed compared to Pd(0)-catalyzed conditions. Armstrong reported the same phenomenon with disubstituted vinyltin **397** in the cross-coupling with (*Z*)-vinyliodide **398** (Scheme 109). Palladium(0) conditions [$Pd_2(dba)_3$ (2 mol %), P(2-furyl)$_3$ (4 mol %), DMF, 65 °C] required 4.5 days for completion in contrast to 2 h for CuTC-mediated conditions (NMP, 23 °C).[446] 1,3-Diene **399** was then further transformed into (+)-zaragozic acid C **400**, a potent squalene synthase inhibitor. Compound **401**, a deprotected version of vinyltin **397**, is an efficient building block for the rapid elaboration of multifunctional lactone **403**. CuTC-mediated cross-coupling of **401** with **402** led to **403**, a dienophile for intramolecular Diels−Alder cycloaddition in an approach to the fully elaborated AB ring system **404** of azadirachtin **405** by Watanabe.[419]

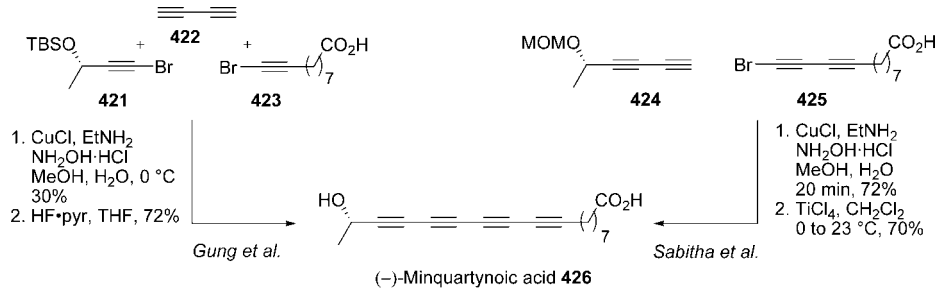
Copper-mediated coupling of a dienylstannane with a vinyl halide remains a challenging area. In their total synthesis of (−)-polycavernoside **408**, a human toxin extracted from the red alga *Polycavernosa tsudai*, Paquette and co-workers observed that CuTC **C8** was not able to promote the cross-coupling reaction of derivatives **406** and **407** (Scheme 110).[448] Only bis(acetonitrile)dichloropalladium(II) in DMF was efficient, affording the desired target compound **408** in 87% yield.

Eventually, it is important to note that the vinyltin motif can be substituted by a heteroatom, such as sulfur. Joule reported that the vinyltin derivative **410** could be cross-coupled to 6-iodopteridin-4-one **409** with CuTC **C8** as a promoter to give **411** in moderate yield (Scheme 111).[449]

Scheme 112. Ineffective Intramolecular CuTC-Mediated Stille-Type Couplings



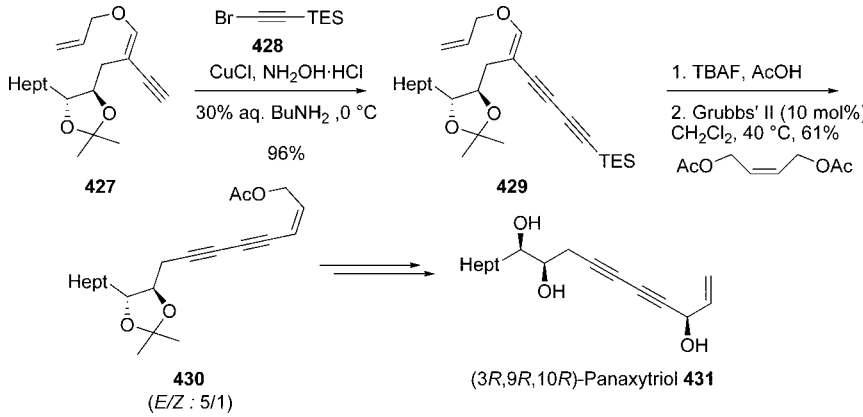
Scheme 113. Synthesis of Minquartynoic Acid



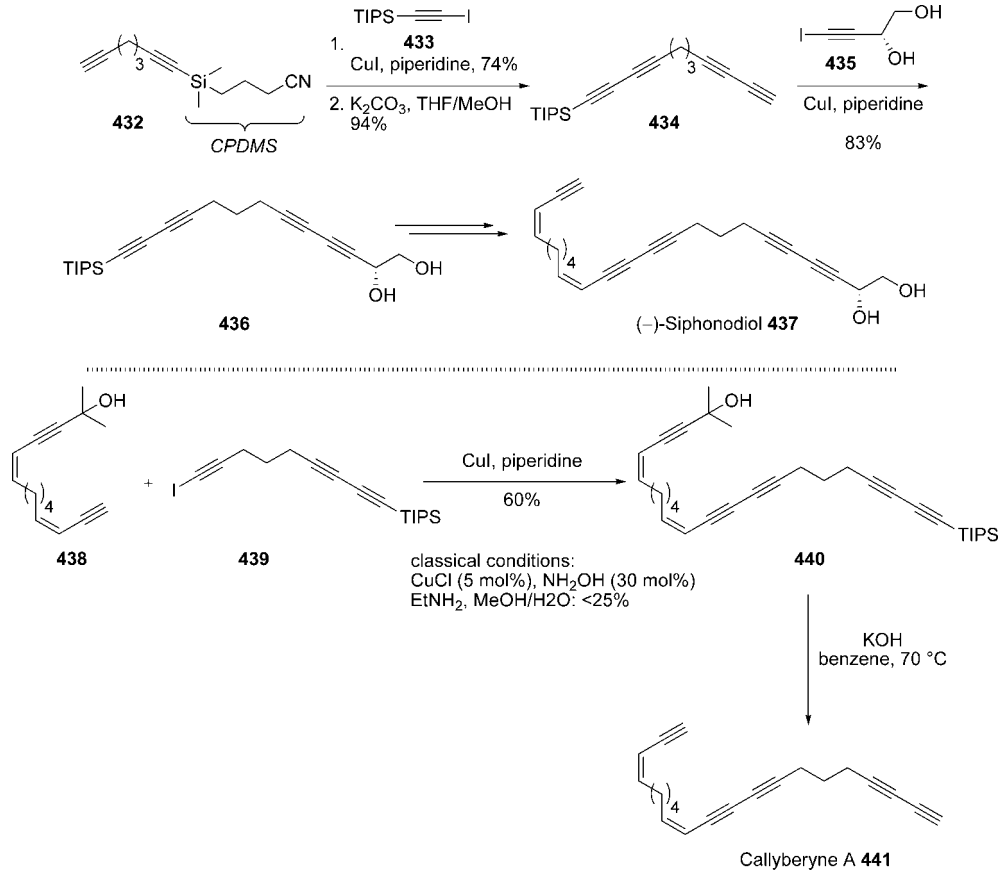
The latter could be further elaborated into **412**, the (protected and masked) organic ligand of oxomolybdoenzymes cofactor.

In sharp contrast to Piers' studies, intramolecular Stille cross-coupling reactions promoted by CuTC **C8** alone are quite inefficient in the context of natural products. Investigations on transannular Diels−Alder cycloadditions by Deslongchamps revealed that macrocylic trienes **414** could be obtained only through Pd-mediated Stille protocols (Scheme 112).[450] Decomposition of **413** was observed with CuTC **C8** in DMF or NMP. Actually, the Piers-type vinylstannane dimerization reaction seems to be often preferred compared to the vinyltin−vinyl halide coupling. In studies related to amphidinolide B, a polyol-based macrolide isolated from *Amphidinium*, Pattenden reported that CuTC-promoted Stille coupling of **416** or Piers-type coupling of **417** did not yield the desired 26-membered macrolide but the C13−C13 dimer (Scheme 112).[451] Instead of intramolecular CuTC-promoted coupling, protodestannylation reaction of vinyltin derivatives can also occur. In Paterson's total synthesis of (+)-concanamycin F **369**, compound **419** led only to the loss of the tin moiety when treated with copper(I) thiophenecarboxylate **C8**

Scheme 114. Synthesis of (3*R*,9*R*,10*R*)-Panaxytriol



Scheme 115. Synthesis of Siphonodiol and Callyberyne A



(Scheme 112).[452] In contrast, smooth cyclization to **420** occurred with $Pd_2(dba)_3$, $AsPh_3$, and Hünig's base in DMF/THF at 60 °C.

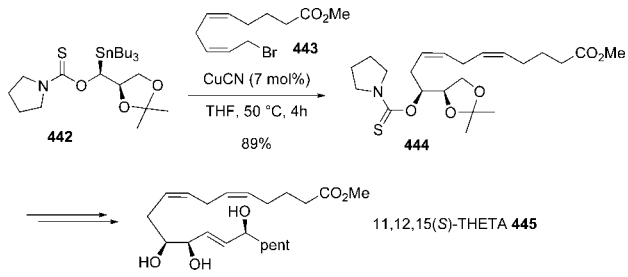
6.3.2. 1,3-Dienes by Stille-Type Cross-Coupling: Use of CuTC as an Additive

More recently, CuTC **C8** proved to be a valuable additive in Pd(0)-catalyzed cross-coupling reactions of vinyltin derivatives with vinyl halides, often surpassing the classical CuI in terms of yield.[453,454] In the context of total synthesis, Sasaki was the first to report a CuTC-cocatalyzed Stille coupling in model studies directed toward the elaboration of gambierol, a polycyclic ether isolated from the ciguatera causative dinoflagellate, *Gambierdiscus toxicus*.[455] A similar increase in yield from CuI to CuTC cocatalysis of the Pd(0)−Stille reaction was observed in Sasaki's total synthesis of (−)-brevenal (from 54% to 84% on a model system).[456] Sasaki's procedure was also adopted by Fürstner[457] in the total synthesis of iejmalides A−D in conjunction with $Ph_2PO_2Bu_4N$ and by Trauner[458] in his straightforward synthesis of (−)-archazolid B.

6.4. Polyynes

Hundreds of naturally occurring polyynes have been isolated since 1826.[6] Fascinating structures combined with a broad range of biological activities have stimulated synthetic chemists for decades. A 2006 review by Tykwinski[6] compiled the more recent total syntheses of these challenging derivatives, including the copper-mediated yne−yne bond formation strategies. Thus, only a few relevant reports are of interest in the context of this review.

Scheme 116. Synthesis of THETA



Minquartynoic acid **426** (a potent anthelmintic) and (−)-(*S*)-18-hydroxyminquartynoic acid (a cytotoxic agent) are two tetraynes isolated from the stem bark of *Minquartia guianensis* and from the twigs of *Ochanostachys amentacea* (Scheme 113). A closely related ene−triyne compound, (*S*)-(−)-(*E*)-15-dihydrominquartynoic, possesses a promising activity against several cancer cell lines. A conceptually new approach to the synthesis of these three polyynes was reported in 2002 by Gung using a highly efficient one-pot multicomponent Cadiot−Chodkiewicz reaction. The use of CuCl, diethylamine, and hydroxylamine hydrochloride [which reduces Cu(II) back to Cu(I)] allows the cross-coupling of **421**, **422**, and **423** in 30% of 59% of three tetraacetylenic products.[6,459] Such an approach avoids the isolation of reactive terminal di- and triynes. A more classical retrosynthesis was envisaged by Sabitha where the cross-coupling reaction of terminal diyne **424** and bromodiyne **425** was efficiently performed in 70−78% yield (Scheme 113).[460]

Actually, classical conditions still enjoyed a great deal of popularity, generally leading to high yields of the coupled products as can be seen in the recent total syntheses of (3*R*,9*R*,10*R*)-panaxytriol **431** (Scheme 114),[461] bidensyneoside A1,[462] and montiporyne F.[463]

López introduced the use of Höger's polar (3-cyanopropyl)dimethylsilyl group[233] in the Cadiot−Chodkiewicz cross-coupling reaction, in the total synthesis of (−)-siphonodiol **437**, a C_{23} hydrocarbon isolated from sponges of the family Callyspongiidae (Scheme 115).[464] Under Alami's conditions,[465] the first coupling reaction occurred in 74% yield. Slightly basic conditions then allowed the deprotection of the CPDMS group, unmasking a terminal alkyne **434** that is readily coupled with the iodoalkynyldiol **435** (83%). Two more steps were necessary to complete the first synthesis of (−)-siphonodiol **437**. The family Callyspongiidae also includes C_{21} hydrocarbons, the callyberynes A−C. López reported their synthesis in 2006, using Alami's conditions in the key cross-coupling reaction of **438** and **439**. Worthy of note is the fact that classical conditions led to a very low yield (<25%).[466]

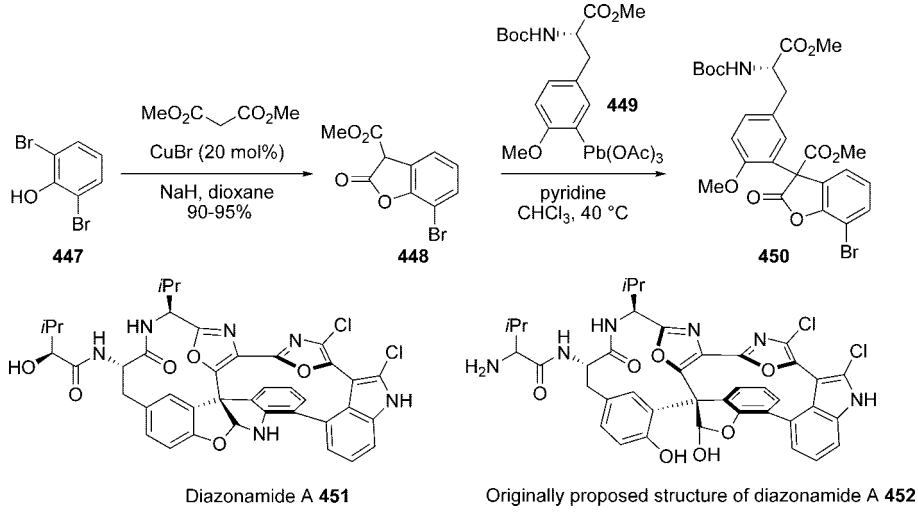
6.5. Using α-Hydroxy Stannanes

As discussed in the background section of this review (see section 2.6.7), Falck developed a powerful and general methodology allowing the coupling reaction of chiral sp^3 tin derivatives with organic electrophiles. Retention of configuration was observed in this reaction. On the basis of these precedents, Falck reported the total synthesis of four stereoisomers of the endothelial-derived vasorelaxant 11,12,15(*S*)-trihydroxyeicosatrienoic acid [11,12,15(*S*)-THETA **445**] (Scheme 116).[467] The cross-coupling of tin derivative **442** with the allylic bromide **443** under CuCN catalysis (7 mol %) led to ester **444** with retention of configuration at the C(11) stereocenter, in excellent yield. Functional group transformations, including cleavage of the orthogonal thionocarbamate protecting group (H_2O_2, NaOH, MeOH, 23 °C) yielded the target product **445**.

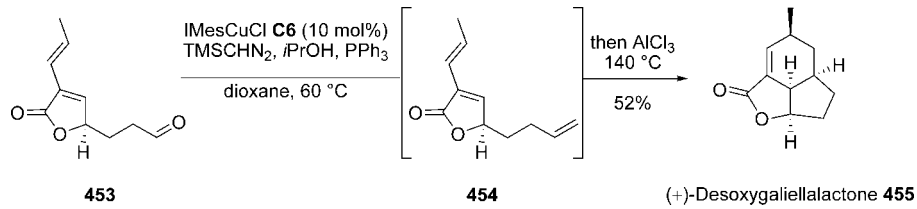
6.6. Using the Hurtley Reaction

Examples of Hurtley reactions in the context of total synthesis of natural products are scarce. In model studies directed toward the synthesis of the originally reported structure of diazonamide

Scheme 117. Approach to the First Structure of Diazonamide A



Scheme 118. Synthesis of (+)-Desoxygaliellalactone



A **452**, Konopelsky used a catalytic amount of CuBr in the cross-coupling of dimethyl malonate with dibromophenol **447** (Scheme 117).[468] The coupled product **448**was then further elaborated into the advanced synthetic intermediate **450** via reaction with the aryllead compound **449**.

6.7. Using a Methylenation Reaction

The mild copper-catalyzed methylenation reaction developed by Lebel was key to the success of the total synthesis of (+)-desoxygaliellalactone **455**, the enantiomer of a naturally occurring tricyclic lactone isolated from ascomycetes *Galliela rufa* (Scheme 118).[469] Using 10 mol % of a (NHC)−copper complex **C6**, aldehyde **453** was efficiently transformed into the terminal alkene **454**, the substrate of a [4 + 2] cycloaddition reaction. A one-pot procedure was developed, allowing straightforward access to (+)-desoxygaliellalactone **455** in an impressive 52% yield for two steps.

7. Conclusions and Future Prospects

Since the first realization that small organic molecules could considerably improve copper-mediated C−N, C−O, and C−C bond formation reactions, the use of these processes has become a vibrant area of study, and they have found application as central strategic steps in total syntheses of a wide variety of natural products. Impressive and elegant bond formations have been documented and showcased in this review. These precedents, which demonstrate nicely that new and efficient bond disconnections can be made, should continue to stimulate the interest of synthetic chemists.[261] Three major factors contribute to the broad utility of copper-mediated chemistry: its high functional group tolerance, which has been recently implemented in the development of orthogonal catalytic systems for selective C−N or C−O bond formation,[41] the relatively mild reaction conditions newly developed, and the low cost of both copper sources and ligands.

Many substrates, however, failed to react, which in most cases render palladium and copper catalysis remarkably complementary, and the choice of proper reaction conditions is still open to trial and optimization. Improvements in scope, mildness of the procedures, and catalyst loading are still necessary: if room temperature couplings have been successfully achieved in some cases, they often require an *ortho*-directing group in the substrate, and the coupling of aryl chlorides remains a challenging task. These improvements will no doubt require a better understanding of the catalytic cycles: to date, these have been only speculated or touched upon.[68,172] A clear understanding of the exact role of ligands as well as the copper species involved will be an exciting task in the near future for the development of more efficient copper-catalyzed processes.

Two other future trends are easy to predict: the development of enantioselective copper-catalyzed reactions and functionalization of C−H bonds. Impressive progress in these areas has been recently reported,[265,442] and these developments will be among the most exciting challenges in the near future.

8. Uncommon Abbreviations

BMI	1-*n*-butyl-3-methylimidazolium
BOM	benzyloxymethyl
Ddm	4,4-dimethoxydiphenylmethyl
DEIPS	diethylisopropylsilyl
DIPP	diisopropylphospho
DMI	1,3-dimethylimidazolidin-2-one
Ns	2-nitrobenzenesulfonyl
PNBSA	*p*-nitrobenzensulfonic acid
TADA	transannular Diels−Alder
Teoc	2-trimethylsilylethyloxycarbonyl

9. Acknowledgments

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10. Note Added in Proof

The area of copper catalysis is ever expanding with various groups across the world actively participating in the research. Since the submission of this review, the following major developments have appeared.

Recent advances have been made in the copper-catalyzed formation of C–N bonds. Pyrrole-2-carboxylic acid was found to be an effective ligand for the copper iodide-catalyzed monoarylation of anilines with aryl iodides and bromides (Altman, R. A.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5167). *N*-Substituted 1,3-dihydrobenzimidazole-2-ones could be obtained by copper-catalyzed cyclization of *N*-(2-halophenyl-ureas under microwave heating (Li, Z.; Sun, H.; Jiang, H.; Liu, H. *Org. Lett.* **2008**, DOI: 10.1021/ol8011106). New routes to pyrrole[1,2-*a*]quinoxalines and carbapenems were reported, respectively, by a one-pot coupling/hydrolysis/condensation process from pyrrole-2-carboxylate esters and 2-halo-trifluoroacetanilides (Yuan, Q.; Ma, D. *J. Org. Chem.* **2008**, *73*, 5159) and by successive copper-catalyzed C–N and C–S cross-couplings (Jiang, B.; Tian, H.; Huang, Z.-G.; Xu, M. *Org. Lett.* **2008**, *10*, 2737). Syntheses of iodolines, respectively, by intramolecular arylation of hydrazines (Hasegawa, K.; Kimura, N.; Arai, S.; Nishida, A. *J. Org. Chem.* **2008**, DOI: 10.1021/jo8010864) and by a domino copper-catalyzed amidation/cyclization reaction (Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721) have been reported. Copper-diphosphine (Daly, S.; Haddow, M. F.; Orpen, A. G.; Rolls, G. T. A.; Wass, D. F.; Wingad, R. L. *Organometallics* **2008**, *13*, 3196) and trinuclear copper(I) complex with a chelating tricarbene ligand (Tubaro, C.; Biffis, A.; Scattolin, E.; Basato, M. *Tetrahedron* **2008**, *64*, 4187) have been shown to be efficient catalysts for C–N bond formation, and oxazolidin-2-one was found to be an efficient ligand for the copper-promoted amidation of aryl halides and cyclization of *o*-halobenzanilides (Ma, H. C.; Jiang, X. Z. *Synlett* **2008**, 1335).

Recent progresses have been made in the copper-catalyzed Sonogashira reaction. Under 20 atm of CO and 5 mol % of $Cu(TMHD)_2$ aliphatic/aromatic alkynes and aryl iodides led to the corresponding alkynylketones in good yields (Tambade, P. J.; Patil, Y. P.; Nandurkar, N. S.; Bhanage, B. M. *Synlett* **2008**, 886). A novel silica-anchored proline–copper(I) catalyst was reported by Wang. Aryl bromides and iodides could be cross-coupled with aliphatic and aromatic alkynes in good yields. Recovery of the catalyst is possible, and no loss of activity was observed after up to six consecutive cycles (Wang, Z.; Wang, L.; Li, P. *Synthesis* **2008**, 1367). Mao reported that 8-hydroxyquinoline was an efficient ligand for CuI. This bifunctional copper catalyst allows the cross-

coupling of aryl and heteroaryl halides with terminal alkynes in good yield (Wu, M.; Mao, J.; Guo, J.; Ji, S. *Eur. J. Org. Chem.* DOI: 10.1002/ejoc.200800394). Aryl and alkenyl boronic esters can be transformed to the corresponding carboxylic acids by a copper(I)-catalyzed carboxylation reaction (Takaya, J.; Tadami, S.; Ukai, K.; Iwasawa, N. *Org. Lett.* **2008**, *10*, 2697). The Hurtley reaction can be included in domino sequences leading to valuable heterocycles (see section 2.6.9). Ma recently reported that 2-halobenzylamines and β-keto esters or 1,3-diketones could lead to isoquinolines under CuI catalysis (Wang, B.; Lu, B.; Jiang, Y.; Zhang, Y.; Ma, D. *Org. Lett.* **2008**, *10*, 2761). Kozlowski's catalytic enantioselective coupling of naphthols was elegantly applied to the first total synthesis of hypocrellin A (O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Angew. Chem. Int. Ed.* DOI: 10.1002/anie.200800734). The mechanism of the oxidative coupling of naphthols catalyzed by Cu(OH)Cl·TMEDA was investigated in the gas phase (Roithová, J.; Schröder, D. *Chem. Eur. J.* **2008**, *14*, 2180). Starting from aryl halides, aryl–aryl bond formation using a copper(II) catalyst immobilized on silica gel has been reported by Wang. Good to excellent yields of the homocoupled product were obtained (Wu, Q.; Wang, L. *Synthesis* **2008**, 2007). Copper powder dispersed in PEG-400 is an attractive catalyst for the Suzuki coupling reaction of aryl halides (including chlorides) with aryl boronic acids (Mao, J.; Guo, J.; Fang, F.; Ji, S.-J. *Tetrahedron* **2008**, *64*, 3905).

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