CHEMICAL REVIEWS

REVIEW

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Synthesis of Heterocycles via Electrophilic Cyclization of Alkynes Containing Heteroatom

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CONTENTS

1. INTRODUCTION

The interest in synthesizing heterocycles has always been enormous. The literature contains a variety of synthetic approaches to the heterocycle ring structures, much of which has been compiled into comprehensive reviews, including a special issue of *Chemical Reviews* devoted to this field.[1] Among heterocycles, the six- and five-membered *O*- and *N*-heterocycles are probably one of the most common structural motifs spread across natural products, from simple glucose to structurally complex metabolites present in the structure of several biologically interesting compounds. Among a variety of synthetic methodologies, transition-metal-catalyzed cyclization reactions of simple acyclic precursors are one of the most attractive ways to directly construct complex heterocycles under mild conditions.[2] In this context, palladium is one of the most common transition metals used,[3] although the use of expensive transition metals together with the relatively complicated stepwise procedure employed limits the scope and general effectiveness of this method. Consequently, during the last few years an explosive increase of interest in electrophilic heteroatom cyclization has taken place, thus becoming an extremely active and original field of heterocycle synthesis. This methodology takes advantages, in most cases, of the presence of a residual halogen atom which is suitable to suffer further transformations. Electrophilic cyclizations have been demonstrated as an efficient tool in the synthesis of highly functionalized indoles, furan, thiophene, selenophene, benzo[*b*]furan, benzo[*b*]thiophene, benzo[*b*]selenophene, and pyrroles, employing electrophiles like I_2, ICl, or organochalcogen derivatives.[4]

Electrophilic cyclizations may be defined as those processes that involve addition of the electrophilic source to C(sp) or C(sp^2) bonds of alkenes, alkynes, allenes, conjugated dienes, and other carbon−carbon multiple bonds. The typical courses of this cyclization reaction involves (i) coordination of the electrophilic source to unsaturated carbon−carbon bond to generate intermediate **a**, which activates the carbon−carbon bond toward nucleophilic attack; (ii) nucleophilic anti attack of the heteroatom on the activated intermediate to produce the salt **b**; and (iii) facile removal of the group bonded to heteroatom, via S_N2 displacement by the Nu^- present in the reaction mixture, generates the heterocycle product (Scheme 1).

These heterocycle rings can be formed through endo or exo cyclization modes, depending on the chain length, the substitution pattern on the chain, and the electrophile employed (Figure 1). A series of guidelines that describe the propensity of various systems to participate in ring-forming reactions was put forth by Baldwin in the 1970s.[5] This set of guidelines, which describe the relative ease of ring formation, has become known as Baldwin's rules of ring closure and has been proved to be a useful tool in evaluating the feasibility of ring-forming reactions. Baldwin described his rules in terms of three features of the reaction: (1) the ring size being formed (indicated through a numerical prefix), (2) the hybridized state of the carbon atom undergoing the ring closing reaction (sp = digonal, sp^2 = trigonal, and sp^3 = tetrahedral), and (3) the nature of the breaking bond (exo, the breaking bond is external to the newly formed ring, and endo, the breaking bond is within newly formed ring). Examples of these formalizations are shown for the five- and six-membered ring closing reactions in Figures 2 and 3.

The relative reactivity of various functional groups toward electrophilic cyclization of alkynes bearing a nucleophile was recently defined by Larock.[6] This has been accomplished by studying competitive cyclizations of the different types of diarylalkynes bearing competing nucleophiles, using halogen or selenium as electrophilic source (Figure 4). The results showed that a number of factors affect this cyclization. These include electronic (the relative nucleophilicity of the functional groups, polarization of the carbon−carbon triple bond, and cationic nature of the intermediate) and steric effects (hindrance and geometrical alignment of the functional groups), as well as the

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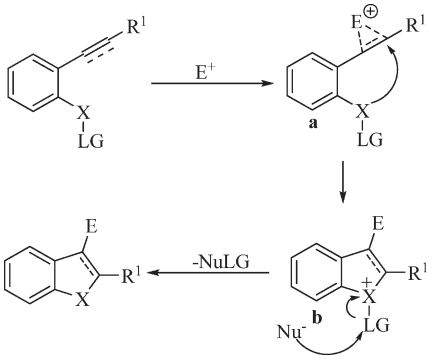
Scheme 1



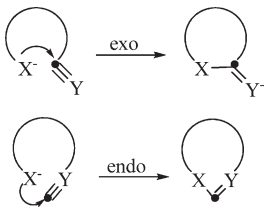


Figure 1

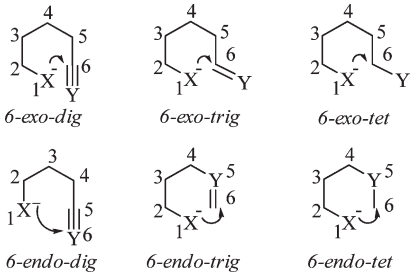


Figure 2

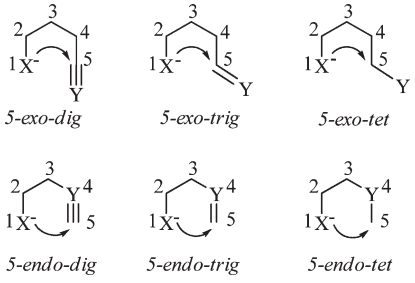
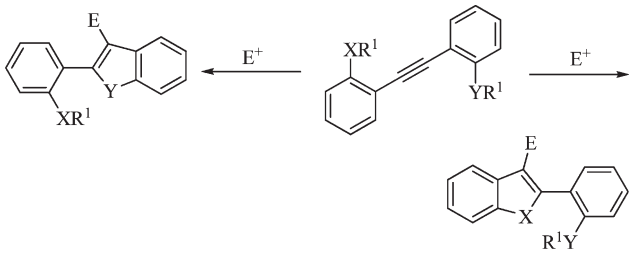


Figure 3

nature of the electrophilic source. In most cases, only one of the two possible products was obtained, however, in the cases where the mixture of both possible products was obtained, always one of them was obtained in higher amount than the other. These results indicated that there is a hierarchy of functional group reactivity toward the electrophilic cyclization. On the basis of the competitive results, Larock defined the reactivity order in the formation of cyclized products (Figure 4).

Due to the growing importance and utility of heterocycles in the field of organic synthesis and new remarkable findings and



relative reactivity of the nucleophiles toward cyclization when $XR^1 \neq YR^1$

SeMe > SMe > CO_2Me > NMe_2 > Aryl(Ph) > OMe > OBn

CH=N-t-Bu > OMe > OAc

CONHPh > CO_2Me > CHO

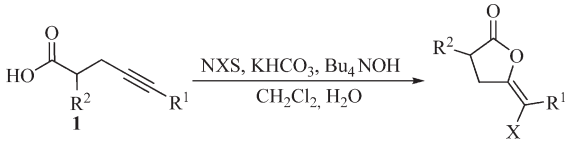
Figure 4

applications that have been published in the last years, the purpose of this review is to show the importance of the electrophilic cyclization reactions in the field of heterocycle synthesis. This survey will focus on reactions of alkynes containing heteroatom with electrophilic sources followed by an intramolecular carbo or heteroatom nucleophilic attack on the cationic intermediate via endo- or exo-dig cyclization. Furthermore, this review will also discuss the most important reactions of these cyclized compounds toward several different reaction conditions and the applicability of such transformations in organic synthesis. Since the preparation of heterocycles through endo- or exo-trig- and endo- or exo-tet cyclization[7] and those that use electrophilic transition-metal catalysts and protic reagents as electrophilic source[2b,8] has been already covered and extensively discussed, it will not be addressed here.

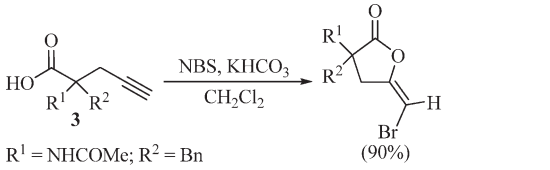
2. ELECTROPHILIC CYCLIZATION LEADING TO *O*-HETEROCYCLES VIA OXYGEN NUCLEOPHILE

The reaction of a halonium ion intermediate, resulting from an electrophilic attack of a cyclization reagent on the unsaturated bonds, with an internal nucleophile, such as CO_2H or CO_2^- group, is known as halolactonization. Since halolactonization is highly regio- and stereoselective, it has been valuably applied to synthetic organic chemistry. By means of halogen atoms of produced halolactones, halolactonization can be classified into three groups: chlorolactonization, bromolactonization, and iodolactonization. The intramolecular version of this reaction, using appropriate unsaturated compounds as the starting material and an electrophilic selenenylating agent, is usually referred to as selenolactonization. Halolactonization is an essential reaction in organic synthesis as well as in structure elucidation. The early report on the synthesis of halolactones by such a cyclization appeared in 1981, when the acetylenic acids **1** were cyclized to lactones **2** in a two-phase system, with 2 mol % tetrabutylammonium hydroxide as a phase-transfer catalyst, using potassium bicarbonate as the base and the appropriate *N*-halosuccinimide (Scheme 2). The halolactonization was completely stereoselective and resulted in exclusive formation of the *E*-olefin. This implicates a halonium ion intermediate formation, which undergoes attack by the carboxylate exclusively with inversion.[9] Subsequently, Katzenellenbogen's group studied the intramolecular halolactonization of *N*-acetylpropargylphenylalanine analogues **3** and **4** using *N*-bromosuccinimide and potassium bicarbonate in dichloromethane (Scheme 3).[10] Attempts to lactonize

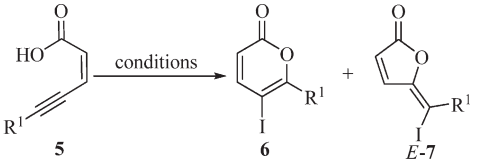
Scheme 2



Scheme 3



Scheme 4

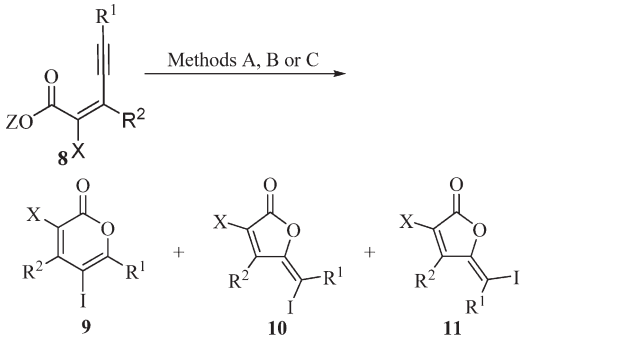


E^+	**6** / *E*-**7** molar ratio
I_2	68 / 32
ICl	72 / 28
NIS	17 / 83

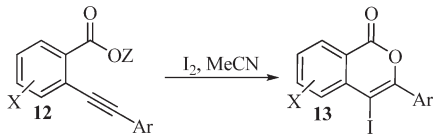
propargylphenylalanine directly proved unsuccessful; therefore, the amine was protected.

Starting from 5-substituted *Z*-enynoic acids **5**, the construction of 6-iodopyranones **6** and iodoylidenefuranones **7**, in which furanones **6** are the major products (68:32 molar ratio), was developed by employing 3 equiv of iodine and 3 equiv of $NaHCO_3$ in CH_3CN (Scheme 4).[11] Interestingly, the selectivity for the formation of either the five- or six-membered ring unsaturated lactones was governed by the choice of electrophilic source. Thus, by using 1.0 equiv of ICl as electrophilic source in CH_2Cl_2, at room temperature, the *Z*-enynoic acids **5** afforded a 72:28 ratio of lactones **6** and **7**. By contrast, compounds *E*-**7** were found to be the major products when carboxylic acids **5** were reacted with 1 equiv of NIS (*N*-iodosuccinimide) and 1 equiv of $KHCO_3$, in CH_3CN (Scheme 4). The same strategy was applied by the author to the lactonizations of esters **8**. By employing similar conditions used for acids, enynoates **8** were cyclized to iodopyranones **9** with a mixture of *E*-**10** and *Z*-**11** isomers formed by a 5-exo-dig cyclization. In this case, the selectivity of the iodolactonization depended on not only the solvents but also

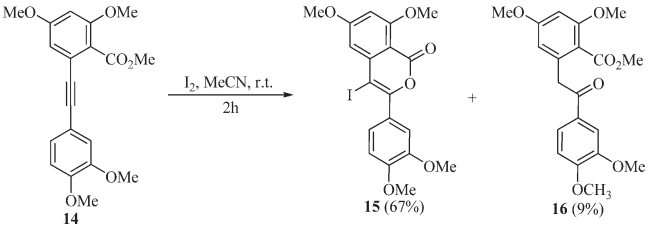
Scheme 5



Scheme 6



Scheme 7



the structures of these esters (Scheme 5). 4-Iodoisocoumarins **13** can be similarly synthesized from the corresponding arylethynylbenzoates **12** in good yields, as a single isomer, using 3 equiv of iodine, in CH_3CN and in the absence of bases. The selectivity and the yields of these cyclizations were significantly affected rather by the temperature than the electrophilic sources and nature of these benzoates (Scheme 6).[12] In a subsequent study, Rossi's group showed that the highly substituted benzoate **14** can be subjected to cyclizations using the same iodolactonization conditions to give arylisocoumarin **15** in 67% yield (Scheme 7).[13] The method was found to be highly regioselective; however, the unexpected methyl dimethoxybenzoylbenzoate **16** was detected during the chromatographic purification in 9% yield. A possible process for the formation of **16** should involve the activation of the carbon−carbon triple bond of **14** by coordination to iodine to form the iodonium **17**. Subsequent nucleophilic attack of the water on the iodonium intermediate should provide iodo ketone **18**. Protodeiodination of **18** using $Na_2S_2O_3$ as a scavenger of iodine should produce **16** (Scheme 8).

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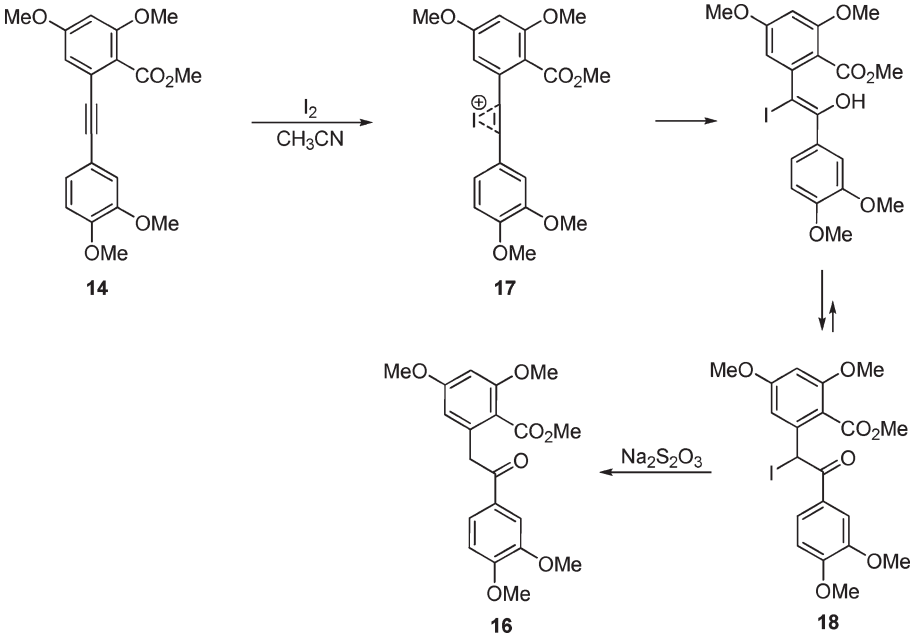
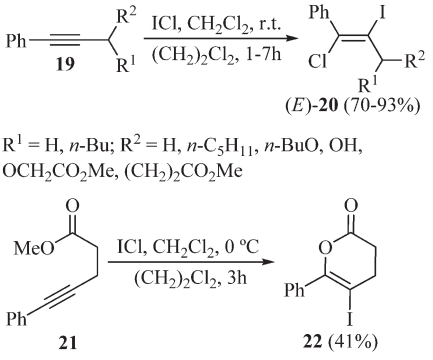
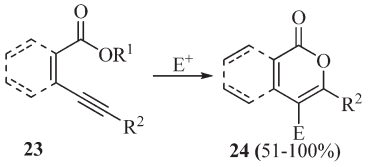
Scheme 8



Scheme 9



Scheme 10



The same group later reported an interesting comparative study between intramolecular iodolactonization promoted by iodine monochloride versus electrophilic addition reactions on phenyl-substituted alkynes **19** (Scheme 9).[14] They found that the reaction of alkynes **19** with ICl, in CH_2Cl_2 at room temperature, gave stereochemically pure *E*-chloroiodoalkenes **20** in 70−93% yields (Scheme 9). On the other hand, when the same reaction conditions were applied to the phenyl-substituted ester **21**, the six-membered product **22** was exclusively obtained (Scheme 9). These studies determined that neither exo-dig nor endo-dig electrophilic ring closure occurred when functionalized alkynes, having a nucleophilic group in the δ position from carbon−carbon triple bond, were submitted to electrophilic cyclizations, using ICl as electrophilic source.

Larock and co-workers described a highly efficient synthesis of a wide variety of substituted isocoumarins and α-pyrones **24** by the reaction of *o*-(1-alkynyl)benzoates and (*Z*)-2-alken-4-ynoates **23** via electrophilic lactonization using ICl, I_2, PhSeCl, and *p*-$O_2NC_6H_4SCl$ as the electrophilic sources (Scheme 10).[15] This methodology accommodated a variety of alkynyl esters with various functional groups and afforded the substituted isocoumarins and α-pyrones in excellent yields. In a few cases, five-membered-ring or mixtures of five- and six-membered-ring lactones were formed. They observed that the alkyl group directly bonded on ester had no effect on the reaction rate or the product yield. Even a *tert*-butyl ester cyclized in approximately the same time and yield as the corresponding methyl ester. In this way, the authors proposed that these cyclized products were obtained via a nucleophilic attack by the oxygen of the carbonyl group on the carbon−carbon triple bond activated by coordination to I^+, followed by either S_N2 attack of the chloride on the Me or perhaps S_N1 cleavage in the case of the *tert*-butyl ester (Scheme 11). This approach to iodoisocoumarins and iodopyrones provided a very useful synthesis of highly substituted heterocycles via elaboration of the resulting iodide functionality into other substituents. For instance, by using these substrates in the Sonagashira, Heck, and Suzuki reactions, the corresponding products **25**−**28** were obtained in good yields (Scheme 12).

Intramolecular electrophilic cyclization of *o*-(1-alkynyl)benzoates in the solid phase has been described by Lisowski and co-workers (Scheme 13).[16] The reaction of *o*-(1-alkynyl)benzoates

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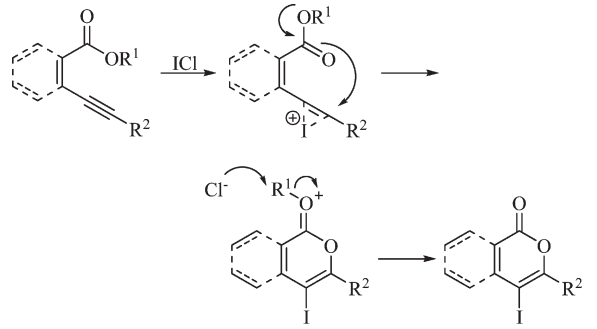
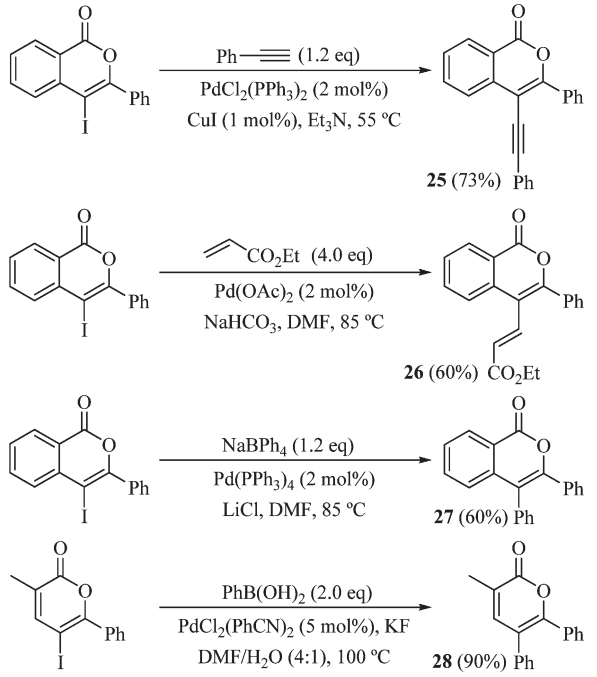
Scheme 11



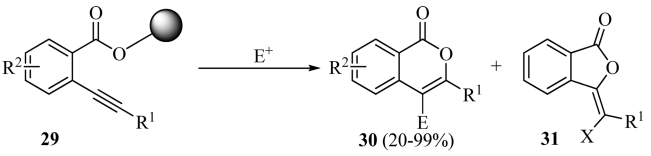
Scheme 12



29 with ICl (1.2 equiv) or I_2 (3 equiv) in CH_2Cl_2 at room temperature for 5 h produced isocoumarin products **30**, via 6-endo cyclization preferentially. When the substituent in R^1 was an aryl group, a total selectivity was observed in favor of the six-membered ring, while a mixture of six- (**30**) and five-membered rings (**31**) was detected when R^1 was an alkyl group.

The furan moiety appeared as a versatile and useful class of heterocycles due to the prevalence of this structure in a great number of biologically active compounds as well as isolated natural products, including a wide variety of therapeutic applications, such as anti-HIV, anticancer, and anti-inflammatory.[17] Recently, a series of structures containing the benzofuran nucleus, such as SKF-64346 and SKF-63058, have been identified as efficient inhibitors of β-amyloid aggregation, affording a new class of potential multifunctional drugs for Alzheimer disease (Figure 5).[18] In this context, considerable effort has been applied to the development of efficient strategies for the synthesis of furans.[19] During the last years, numerous protocols have been reported in the literature, and one of the reliable approaches for

Scheme 13



E, X = Cl, Br, I; R = *n*-Bu, Ph; R^1 = *n*-Pr, *c*-hexyl, *p*-MeO-C_6H_4, *o*-MeO-C_6H_4, 3-thienyl; R^2 = H, Me, MeO, NO_2, F, Cl

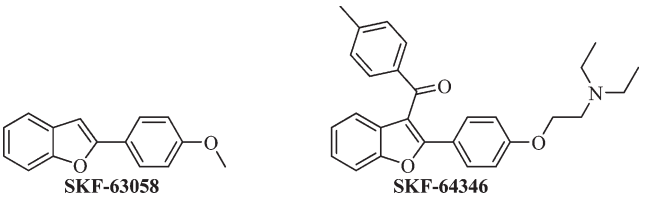
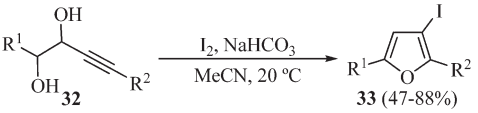


Figure 5

Scheme 14



R^1 = Me, CO_2Me, Ph; R^2 = Bu, Ph

the synthesis of this class of compounds has been based on electrophilic cyclization of unsatured compounds. In 1996, Knight and Bew described that the 5-endo-dig iodocyclization of 3-alkynyl-1,2-diols **32**, followed by in situ dehydration, led to good yields of 3-iodofurans **33** (Scheme 14),[20] which were subsequently converted into a wide range of furan derivatives **34**−**41**, using a transition-metal-catalyzed coupling reaction or halogen−metal exchange reaction (Scheme 15).

Iodoalkynol derivatives of xylose **42** also underwent the electrophilic cyclizations with iodonium-producing reagents (I_2/HTIB) to give furo[3,4]furan nucleus **43** in moderated 55−65% yields (Scheme 16).[21] The only products observed were that of 5-exo cyclization **43**; the ketopyranose **44**, resulting from a carbon nucleophilic attack on the iodonium intermediate, was not formed.

The 5-endo-dig-iodocyclization of *o*-alkynylphenols **45** with iodine in the presence of $NaHCO_3$, at room temperature, gave functionalized 2-substituted-3-iodobenzo[*b*]furans **46** (Scheme 17).[22] The cyclization took place in good yields upon exposure of *o*-alkynylphenols to 3 equiv of iodine, using acetonitrile as solvent, at room temperature for 1−12 h, in the presence of 3 equiv of $NaHCO_3$. It was found that aryl, vinyl, and alkyl groups can be used as substituent in the R^2. However, no cyclization occurred when R^2 was H or $SiMe_3$ group. In this case, only an aromatic electrophilic substitution giving 2-ethynyl-4-iodophenol **47** was observed. The authors explain this behavior as to involve the electron density on the acetylenic carbon, whereas the negative charge in the terminal alkynylphenol is higher than in the internal alkynylphenol impeding the nucleophilic attack of the oxygen on

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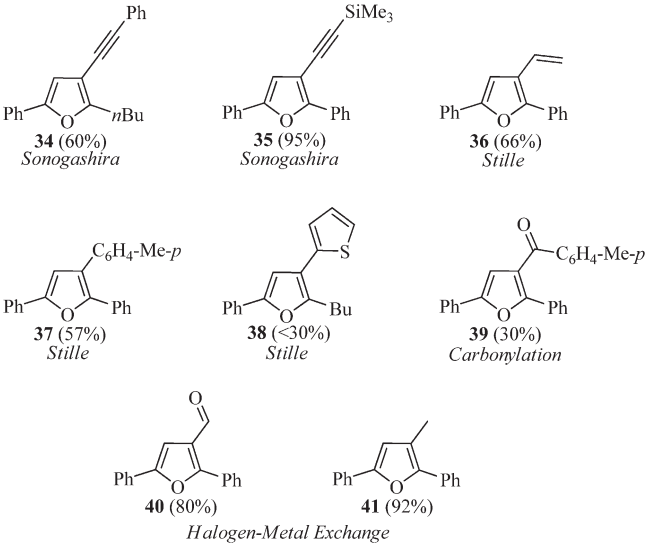
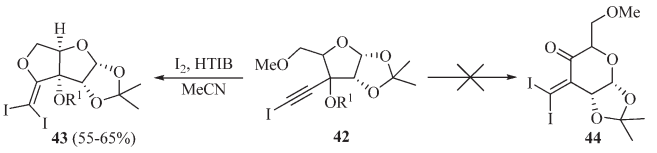
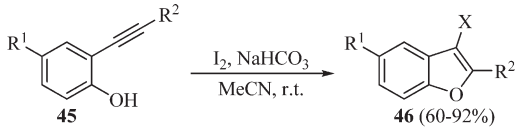
Scheme 15



Scheme 16



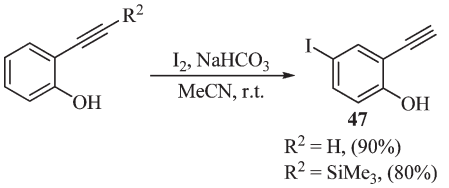
Scheme 17



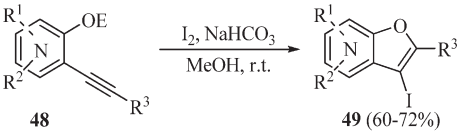
the carbon of acetylene and facilitating the aromatic substitution on the active aryl group (Scheme 18).

In a closely related investigation, the same group reported the use of *o*-acetoxyalkynylpyridines **48** as precursors to 2-substituted 3-iodofuropyridines **49** via electrophilic cyclization using I_2/$NaHCO_3$/MeOH as cycling system (Scheme 19).[23] The reaction was performed at room temperature with acetoxyalkynylpyridines, bearing electron-donating and moderately electron-withdrawing groups in the pyridine ring. Interestingly, when the reaction was carried out under standard conditions for 4 h, in the absence of iodine, the formation of 2-(phenylethynyl)pyridin-ol **51** was obtained in 52% yield with a mixture of 2-phenylfuropyridine **50** (43% yield) (Scheme 20). This indicates that the mechanism could involve a deacetylation reaction before the formation of iodonium intermediate. An additional experiment was carried out to elucidate the mechanism of the reaction, in which the resultant 2-phenylfuropyridine **50** was treated with iodine in the standard conditions and the starting **50** was recovered in 90% yield, free of 3-iodofuropyridines **49** (Scheme 21). The

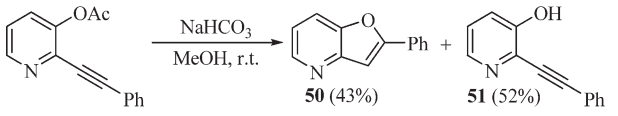
Scheme 18



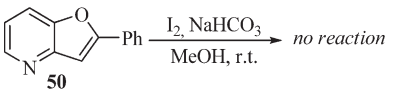
Scheme 19



Scheme 20



Scheme 21



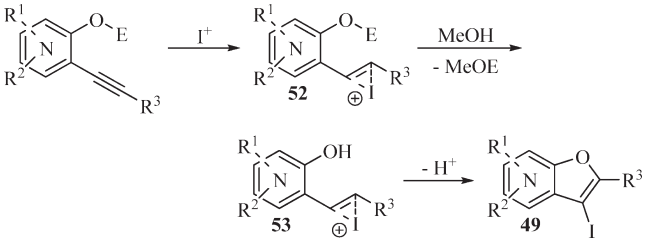
authors proposed a catalytic cycle for iodocyclization of *o*-acetoxyalkynylpyridines, where 2-alkynylpyridin-3-ol **53** is initially formed via iodonium intermediate **52**, followed by the deacetylation reaction. The oxygen-nucleophile attack on the intermediate **53** produces the 3-iodofuropyridines **49** (Scheme 22).

5-Alkynyl-2-deoxyuridines **54** were found by Dembinski and co-workers to undergo electrophilic cyclization in the presence of *N*-iodosuccinimide or *N*-bromosuccinimide, using acetone as solvent at room temperature, to afford ribofuranosyl derivatives **55** in 74−86% yields (Scheme 23).[24] Cyclopropyl and aryl directly bonded to alkyne, giving better results than the corresponding propargylic alcohols, which led to vinyl diiodides. Iodination reaction using elemental iodine was also tried, but poor yields were obtained. It is worth mentioning that although substituted furans suffer oxidative ring-opening with *N*-bromosuccinimide (NBS) in acetone, bicyclic ribofuranosyls were isolated in good yields. The authors also found that the cyclization was sensitive to the quality of the reagents, whereas the cleavage of the *N*-glycosidic bond was observed when acetone was not of high purity.

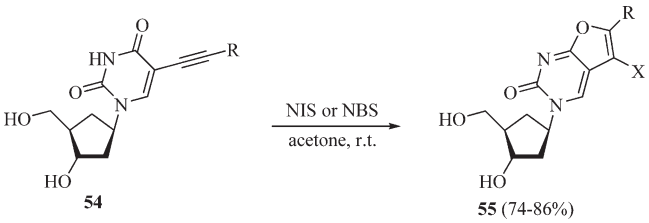
An important study on the 2,3-disubstituted benzo[*b*]furans **57** was carried out by Larock, in which *o*-alkynylanisoles **56** were transformed into 3-iodobenzo[*b*]furan derivatives **57** by

dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 22

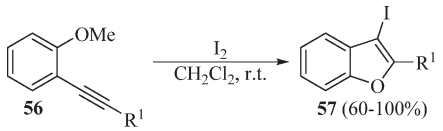


Scheme 23



X = Br, I; R = *c*-C_3H_5, *p*-MeC_6H_4, *p*-$(Me)_3CC_6H_4$;

Scheme 24



R = Ph, *p*-MeO-C_6H_4, *o*-AcO-C_6H_4, *p*-NO_2-C_6H_4, *n*-C_6H_{13}, *n*-C_8H_{17}, TMS

treatment with elemental iodine in CH_2Cl_2 at room temperature (Scheme 24).[25] The nature of the substituent attached to the alkyne had a major impact on the success of the cyclization. There was no overall yield difference when vinylic alkynes or arylalkynes were present. However, alkynes having an alkyl group failed to undergo the cyclization. In addition, both methoxy and nitro groups in the para-position to the triple bond also failed to give electrophilic cyclization, providing instead an almost quantitative yield of the simple addition of the electrophile to the alkyne triple bond, thereupon suggesting that the methoxy group increases the electron density on the triple bond (C_2), which favors electrophilic attack in that position and disfavors a five-member endo-dig cyclization (Figure 6). On the other hand, the presence of a nitro group decreases the electron density on C_1 again leading to addition, rather than the cyclization product (Figure 7). In an extension of their previous studies, Larock and co-workers demonstrated in 2008, that 3-iodobenzo[*b*]furans, prepared by electrophilic cyclization chemistry, are very useful templates for further diversification by a variety of C−C, C−N, and C−O bond-forming reactions and are thus valuable building blocks for combinatory chemistry. Performing the palladium cross-coupling reactions of 3-iodobenzo[*b*]furans with boronic acids, terminal alkynes, styrenes, and carbon monoxide plus alcohols, they were able to prepare a 121-member library of highly substituted benzo[*b*]furans.[26]

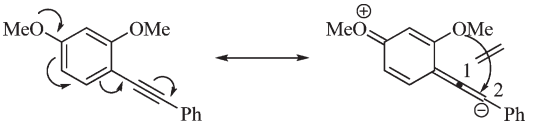


Figure 6. Methoxy electron-donating effect on the triple bond.

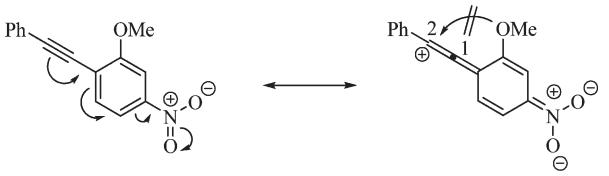


Figure 7. Nitro electron-withdrawing effect on the trile bond.

Z-Enynol derivatives **58** when treated with I_2 (3 equiv) in the presence of K_3PO_4 and THF as solvent gave exclusively *Z*-5-(1-iodoylidene)-2,5-dihydrofurans **60** in yields ranging from 66 to 86% instead the *E*-isomer **59**, atypically formed by the exo-dig iodocyclization. This rare selectivity in the electrophilic cyclization was attributed by the authors to a stereo-isomerization of *E*-**59** to give the thermodynamically more stable *Z*-**60**. The presence of K_3PO_4 was crucial for this iodocyclization to neutralize the HI formed, while the use of carbonate bases led to poor yields, due to the H_2O formation (Scheme 25).[27]

Electrophilic-promoted cycloaddition of unsaturated compounds is well-known to be a highly selective method for the overall 5-endo-dig cyclization of alkynyl ketones. This strategy was elegantly used by Larock and co-workers in the preparation of highly substituted iodofurans.[28] Thus, the reaction of 2-(1-alkynyl)-2-alken-1-ones **61** with nucleophiles induced by an electrophile provided highly substituted furans **62** in good to excellent yields, under very mild reaction conditions (Scheme 26). Various nucleophiles, including functionally substituted alcohols, H_2O, carboxylic acids, 1,3-diketones, and electron-rich arenes, readily participated in these cyclizations. Iodine, NIS, and PhSeCl have proven successful as the electrophilic sources in this process. It was found that by using 3 equiv of MeOH as nucleophile together with acetonitrile as the solvent, a mixture of desired 3-iodofuran and compound **64** was obtained. The byproduct **64** could be formed by nucleophilic attack of iodide on the carbocation intermediate **63**; in this case, the I_2 could serve as both an electrophile and a nucleophile (Scheme 27). An additional experiment was carried out by the authors to elucidate this behavior, in which 2-phenylethynyl-2-cyclohexen-1-one was reacted with 3 equiv of I_2 in CH_3CN without any MeOH, giving compound **64**, as the sole product, in a 41% yield. Thus, to obtain the desired 3-iodofuran in high yield, without any of compound **64**, an excess of MeOH was required.

In addition to this work, the electrophilic cyclization of 2-(1-alkynyl)-2-alken-1-ones **65**, promoted by iodine as electrophilic source and K_3PO_4 as base, was described by Liu and Zhou.[29] The authors suggested that the reaction proceeds via the formation of cyclic iodonium ion **66** through coordination of the triple bond of iodine, followed by the anti attack of oxygen on iodonium ion to give the intermediate **67**, which after a Michael-type addition of a nucleophile to the double bond delivers the highly substituted iodofurans **68** in good yields. The reaction was

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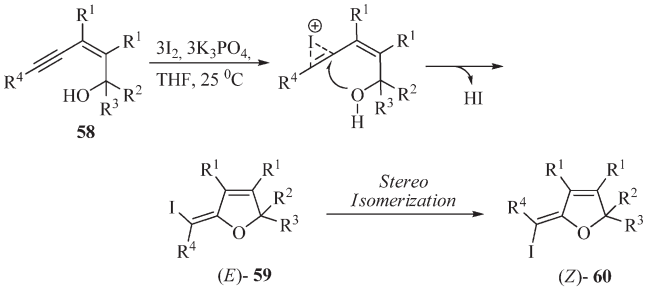
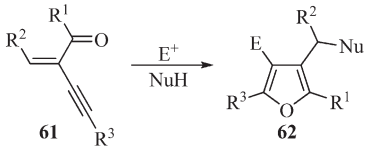
Scheme 25



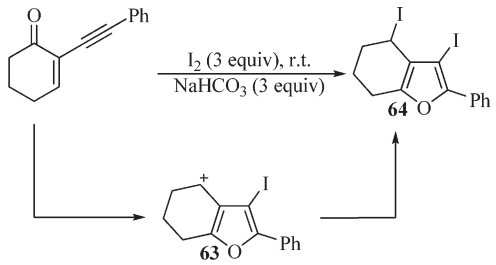
R^1 = Ph, *n*-C_3H_7; R^2 = Me, Et; R^3 = Ph, *p*-FC_6H_4, *o*-BrC_6H_4, *o*-ClC_6H_4, 2-thienyl; R^4 = *n*-Bu, Ph;

Scheme 26

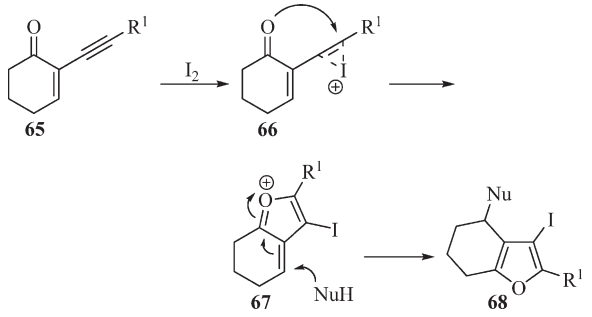


E = I, PhSe; NuH = ROH, RCO_2H, H_2O

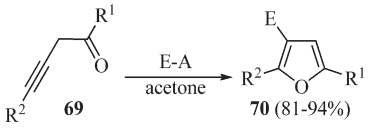
Scheme 27



Scheme 28

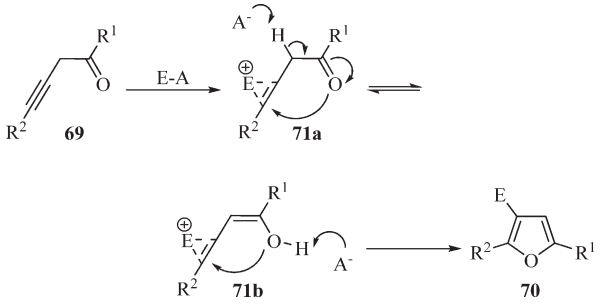


Scheme 29



E-A = NBS, NIS, ICl/CH_2Cl_2; R^1 = Ph, *p*-Cl-C_6H_4, *p*-Br-C_6H_4; R^2 = *p*-Me-C_6H_4, *p*-*t*-Bu-C_6H_4

Scheme 30



performed at room temperature, and alcohols, amines, terminal alkynes, phenols, and alkenes were used as the nucleophilic source (Scheme 28).

A convenient method for the preparation of 2,5-unsymmetrical substituted 3-halofurans **70** by the direct electrophilic cyclization of 1,4-diaryl-but-3-yn-1-ones **69** with *N*-bromosuccinimide or *N*-iodosuccinimide/acetone and iodine monochloride/CH_2Cl_2, at room temperature, in the absence of base was described (Scheme 29).[30] The reaction is believed to proceed by an initial formation of the bridged-ion intermediate, followed by the α-hydrogen abstraction or deprotonation to give the equilibrium structures **71a** and **71b**. The intramolecular nucleophilic attack of oxygen across the activated carbon−carbon triple bond delivers the desired 3-halofurans **70** (Scheme 30).

Alkynylpyridin-2(1*H*)-ones **72** were also competent nucleophiles and their electrophilic cyclization generated 3-iodofuropyridinium triiodide salts **73**, via iodine-promoted 5-endo-heteroannulation (Scheme 31).[31] The reaction proceeded cleanly at room temperature in CH_2Cl_2 in the presence of 2 equiv of I_2 to afford within 5 h the corresponding pyridinium triiodide salt **73** exclusively, in good yields. The dealkylation in situ of pyridinium triiodide salt by reaction with iodide provided the corresponding 3-iodofuro[2,3-*b*]pyridin-4(1*H*)-ones **74**. It is important to point out that the electrophilic cyclization and dealkylation were carried out in the same reaction vessel using a sequential step without isolation of the triiodide salts. A plausible mechanism is shown in Scheme 32: the activation of the carbon−carbon triple bond by coordination to I^+ and subsequent intramolecular attack of the carbonyl oxygen to give the pyridinium-fused furan **75** and the displacement of the protective methyl group via S_N2 with iodide to give the 3-iodofuran derivatives.

The preparation of 4-iodo-3-furanones **77** can be achieved through a sequence consisting of cyclization/rearrangement of 2-alkynyl-2-silyloxy carbonyl compounds **76** (Scheme 33).[32] The best condition used for this transformation was 1.5 equiv of NIS and CH_2Cl_2 (0.1 M) at room temperature. When the reaction was carried out in the presence of I_2 and $NaHCO_3$ in CH_3CN at room temperature, instead of NIS, the major product was the enedione **78**. However, the formation of **78** was significantly lowered without $NaHCO_3$. The reaction tolerated substitution

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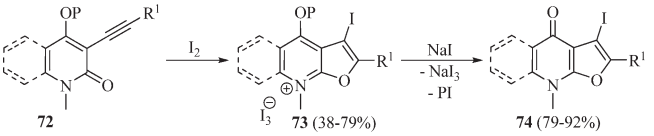
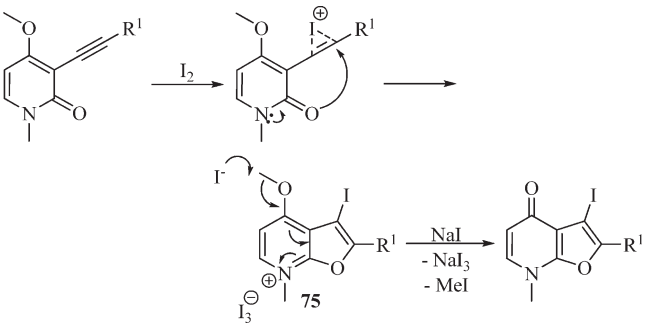
Scheme 31

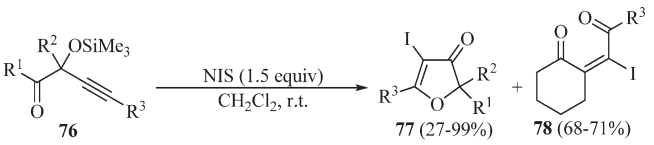


P = Me, Bn; R^1 = Ph, *p*-CO_2Me-C_6H_4, *n*-Bu

Scheme 32



Scheme 33

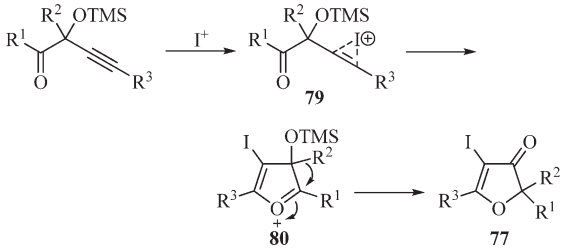


R^1, R^2 = -$(CH_2)_4$-, Et, Ph; R^3 = Ph, 2-thienyl, 1-*c*-hexenyl, *n*-Pent

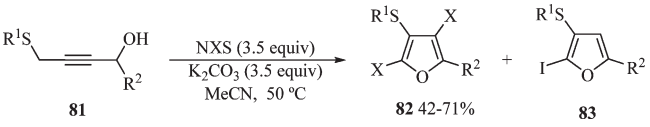
on the alkyne with R^3 being aryl, alkenyl, and alkyl groups. When acyclic substrates were present in R^1/R^2, the desired 4-iodo-3-furanones were obtained in poor yields. The following reaction pathway has been proposed: the process is initiated by coordination of iodine with the alkynyl π-system to give the iodonium intermediate **79**, which after nucleophilic attack of the carbonyl oxygen generates oxonium ion **80**. Subsequent ketol rearrangement gives the 4-iodo-3-furanone **77** (Scheme 34).

Functionalized 2,4-dihalothiofurans **82** were efficiently prepared using a two-step sequence: electrophilic cyclization and 1,2-migration of the thiol group from 4-thiobut-2-ynols **81** (Scheme 35).[33] The electrophilic cyclization was carried out at 50 °C, using NIS as nucleophilic agent, in the presence of K_2CO_3 in acetonitrile. The lack of base gave a mixture of the 2,4-dihalothiofurans **82** and monoiodo-substituted compound **83**. The methodology was extended to a series of 4-thiobut-2-ynols, using NIS, NBS, or NCS as the halogenating reagent, and the 2,4-dihalo-3-thiofurans were obtained in moderate to good yields. A plausible mechanism to explain the exclusive formation of the 2,4-dihalothiofurans **82** was based on the key intermediate **86**, which is formed by initial coordination of iodine electrophile to the triple bond to produce iodonium **84**, and nucleophilic attack of the sulfur atom gives the structure **85**. In the presence of base, the hydrogen is transferred to form **86**. The oxygen-nucleophilic attack on the **86** produces the dihydrofuran **87**, which after elimination and dihalogenation affords the product (Scheme 36).

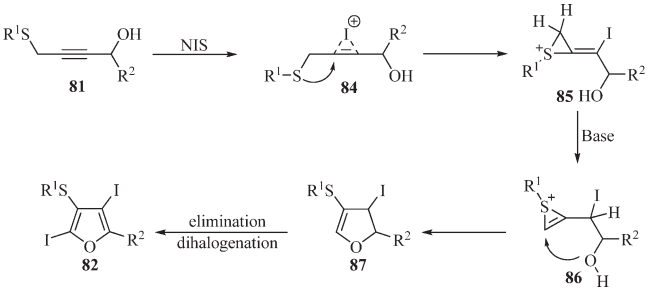
Scheme 34



Scheme 35



Scheme 36

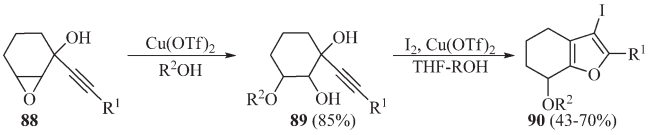


Alkynyl-2,3-epoxy alcohols **88** were suitable substrates for the preparation of polysubstituted 3-iodofurans **90** via tandem ring-opening/iodine-cyclization sequence. First, the epoxy alcohols **88** were subjected to copper(II) triflate in methanol at room temperature. The reaction afforded the epoxide ring-opening product **89** in good yields. When the reaction was carried out using the same conditions in the presence of iodine for 24 h at 20 °C, the 3-iodofurans **90** were obtained in moderated to good yields (Scheme 37).[34] A range of cyclic and acyclic epoxy alcohols was investigated as substrates, and the results showed similar trends. The presence of alcohols was crucial for the reaction, since they converted regioselectively the epoxide to the corresponding opened product. The authors observed that the steric hindrance of the alcohol greatly affected the yields, whereas ethanol and propan-2-ol gave lower yields than methanol. A mechanistic rationale was proposed by the authors, who explained the 3-iodofuran obtained as a result of a coordination of the electrophile to the triple bond, nucleophilic attack of oxygen on iodonium ion to give the intermediate **91**, and anti elimination of water to produce the iodofuran **90** (Scheme 38).

In an extension of their previous studies, Liang and co-workers disclosed, in 2008, a new approach for substituted 3-iodofurans **93** via electrophilic cyclization of propargyl oxirane derivatives **92**.[35] This approach consists of the reaction of propargyl oxiranes **92** instead of alkynyl-2,3-epoxy alcohols. The advantages of this

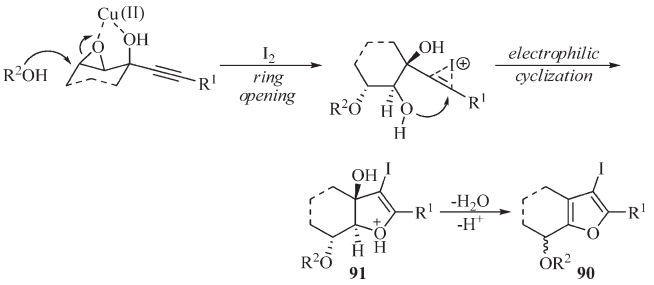
dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 37

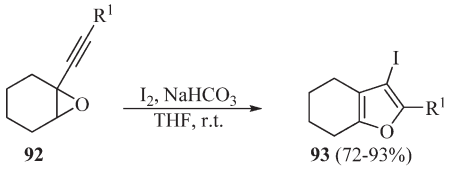


R^1 = Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4; R^2 = Me, Et, *i*-Pr

Scheme 38



Scheme 39



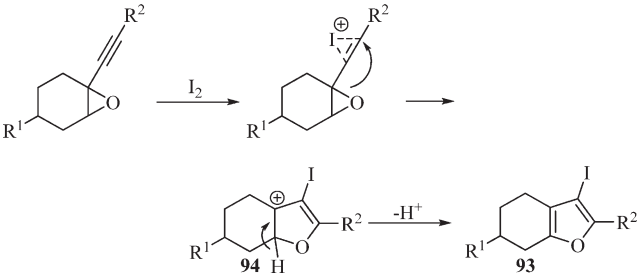
R^1 = Ph, *p*-Me-C_6H_4, *p*-Cl-C_6H_4, *o*-Br-C_6H_4, *m*-Br-C_6H_4, *p*-Br-C_6H_4

method are the easy availability of propargyl oxiranes and the cyclization conditions that were carried out using only I_2 in the presence of $NaHCO_3$ and THF without the previous ring-opened conditions (Scheme 39). The reaction is believed to proceed via the intermediate **94**, which by elimination of hydrogen led to the formation of 3-iodofuran **93** (Scheme 40).

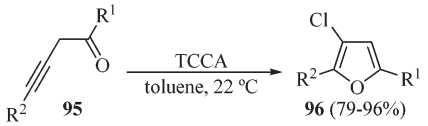
The use of trichloroisocyanuric acid (TCCA) **97**, as chlorination agent, in the electrophilic cyclization reaction to prepare furan derivatives was reported by Dembinski and co-workers. They described that propargylic ketones **95** underwent an electrophilic cyclization reaction when treated with TCCA in toluene, giving 2,5-disubstituted 3-chlorofurans **96** in almost quantitative yields (Scheme 41).[36] A synthetic application of this methodology was carried out for the preparation of the potent antiviral furopyrimidine nucleoside analogues **99** from 5-alkynyl-2-deoxyuridines **98** (Scheme 42).

Another alternative to anisoles or phenols, as starting materials in the electrophilic cyclization, is the use of the corresponding ethoxyethyl ether **100**. Although several different conditions, including I_2, ICl, and NIS, were examined, the $I(coll)_2PF_6$/$BF_3 \cdot OEt_2$ system has still proven to be the most effective as electrophilic source to give the 3-iodobenzo[*b*]furans **101** in high yields (Scheme 43).[37] The use of I_2 gave the products in poor yields, and ICl afforded **101** in acceptable yields; however, in each case, the simple addition of the electrophile to the alkyne triple bond occurred as a side product. The authors have suggested that

Scheme 40

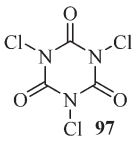


Scheme 41

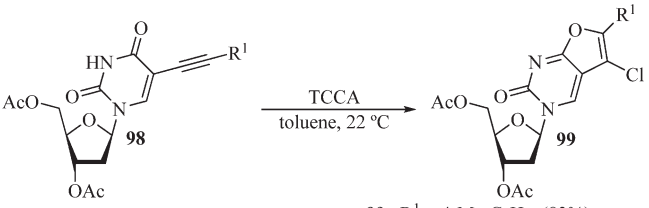


R^1 = Ph, *p*-Cl-C_6H_4, *p*-Br-C_6H_4; R^2 = *c*-C_3H_6, *p*-Me-C_6H_4, *p*-*t*-Bu-C_6H_4;

TCCA =

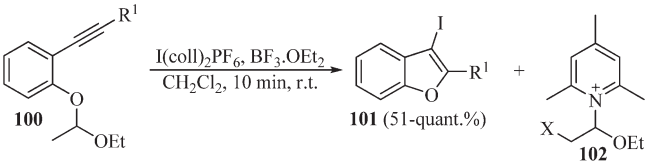


Scheme 42



99a R^1 = 4-Me-C_6H_4; (83%)
99b R^1 = 4-Me$(CH_2)_4C_6H_4$; (76%)

Scheme 43



X = H, I; R^1 = Ph, *n*-Bu, *t*-Bu, Bn, thienyl

the reaction of $I(coll)_2PF_6$ and $BF_3 \cdot OEt_2$ gives the iodonium species **103**, which by coordination with the triple bond generates the iodonium ion **104**. The anti attack of the oxygen of the ethoxyethyl ether on the alkyne gives the intermediate **105**. The ethyl ether is eliminated to afford the 3-iodobenzo[*b*]furans **101**, delivering oxonium ions **106** and **107**, which are trapped by 2,4,6-collidine to afford the salts **102a** and **102b** (Scheme 44).

A method involving the microwave-assisted electrophilic cyclization of *gem*-difluorohomopropargyl alcohols **108** was also

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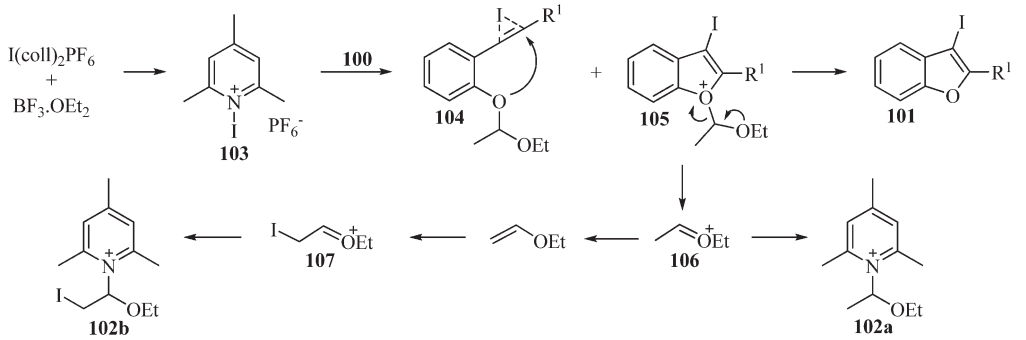
Scheme 44



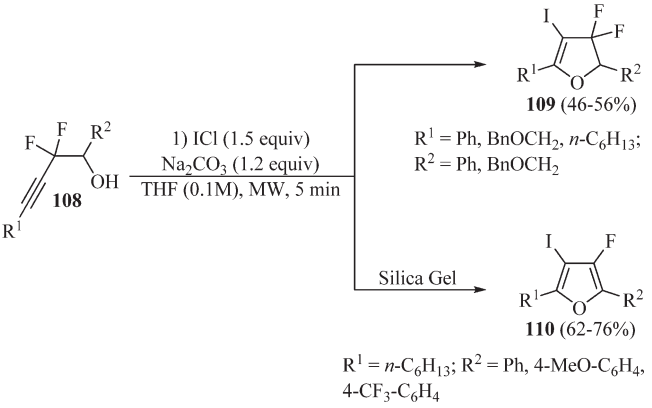
developed, leading to the formation of trisubstituted 3-fluorofurans **110**.[38] The reaction was performed under 5 min of microwave irradiation using ICl as electrophilic source and Na_2CO_3 as base in THF to produce 2,3-dihydrofuran derivatives **109**, which after aromatization using silica gel gave the 4-iodofuran **110** (Scheme 45).

Similar to the illustration in Scheme 26, furan derivatives **112** were achieved by the electrophilic cyclization of alkynyl cyclopropyl ketones **111** using I_2, ICl, or PhSeBr as the electrophilic sources (Scheme 46).[39] The most promising results were obtained when the substrate was allowed to react with 1.1 equiv of electrophile, in CH_2Cl_2 at room temperature, using 3 equiv of $NaHCO_3$ as base in the presence of an alcohol as the nucleophile. The best results were obtained with MeOH and *i*-PrOH as nucleophile. Tertiary alcohols were not suitable nucleophiles for this cyclization. According to mechanistic studies, it proceeds through the formation of a bridged intermediate ion **114**, following the intramolecular anti attack of oxygen from carbonyl group onto the cation **114** to give the intermediate **115**, which could be attacked by the nucleophile in a Michael-type addition to yield furan derivatives **112** or **113** (Scheme 47). When the reaction was carried out in the absence of alcohols, the furan diodide product **113** was obtained exclusively.

Larock and co-workers subjected a series of acetylenic esters and acids **116** as substrates to the electrophilic cyclization conditions in the preparation of 2(3*H*)-furanones **117** (Scheme 48).[40] These reactions were run under mild conditions, tolerated a number of functional groups, and generally provided the highly substituted 2(3*H*)-furanones **117** in good to excellent yields. They found that the electrophiles I_2, ICl, and PhSeCl can be used in this chemistry. In most cases the I_2 cyclization gave 4-iodo-2(3*H*)-furanones **117** as pure product in high yields. For some substrates, the use of ICl as an electrophile afforded mixtures of 4-iodo- and 4-chloro-2(3*H*)-furanones **117** and **118**, respectively. The ratio of these two products depends on the amount of ICl employed. According to a plausible mechanistic pathway, the cyclizations of the 3-alkynoate esters proceeds by the formation of iodonium ion **119**, followed by anti attack of oxygen on iodonium ion to give the intermediate **120**, and removal of the alkyl group via S_N2 displacement by the nucleophile present in the reaction mixture affords 2(3*H*)-furanones **117** (Scheme 49). In the case of acetylenic acids, the anionic oxygen, formed under the basic reaction conditions, attacks the iodonium ion intermediate **121**, giving the 4-iodo-2(3*H*)-furanone **117** directly (Scheme 50).

We have recently reported our results on the electrophilic cyclization reaction of 2-chalcogenoalkynylanisoles **122** with different electrophilic sources, such as I_2, ICl, Br_2, and PhSeBr.[41]

Scheme 45



Optimal condition for this cyclization was the combination of 1.0 equiv of 2-chalcogenoalkynylanisoles, 1.1 equiv of electrophilic source, and CH_2Cl_2 as solvent, at room temperature. The cyclization reaction proceeded cleanly under mild conditions, and 2-chalcogen-3-substituted-benzo[*b*]furans **123** were obtained in good to excellent yields (Scheme 51). We observed that the reaction was sensitive to the nature of the substituent in the aromatic ring of anisole and to the chalcogen atom directly bonded to the triple bond. In this study, we found some limitation in our methodology, since considerable difficulties were found when we attempted to react 2-chalcogenoalkynylanisoles having an electron-donating group in the para-position in the aromatic ring of anisole. In this case, we observed only the triple bond reduction product and byproduct with no formation of benzofuran product. These suggest that the presence of an electron-donating group, in the para-position regarding the triple bond, increased the electronic density in C-2 at the triple bond, which was stabilized by the selenium atom,[42] making this center susceptive to nucleophilic attack on iodine instead of the cyclization process, providing exclusively the iodine addition product **124** (Scheme 52). Conversely, the cyclization of 2-telluroalkynylanisoles **125** containing the tellurium atom did not react in the same way as the substrates containing the selenium or sulfur atoms. Our experiments showed that the addition of the electrophilic source consumed the starting material; however, the product formation was not detected. After 10 min, we observed the formation of a red precipitate, and the analysis of TLC showed a very polar spot, a common characteristic of tellurium-(IV) species **126**, which were further confirmed and identified by GC/MS. In addition, treatment of these red precipitates with an

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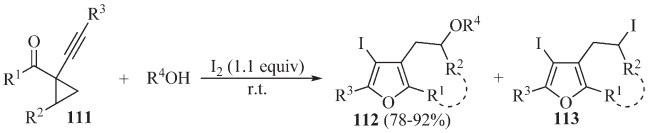
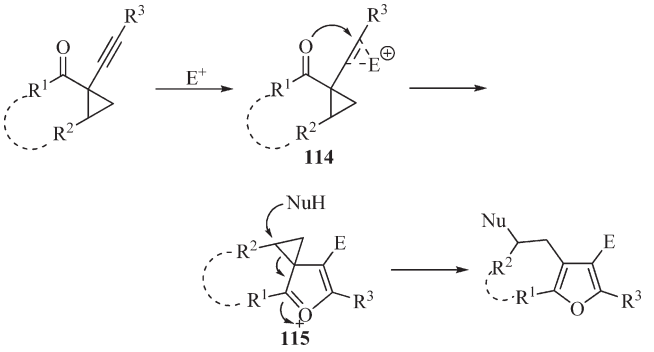
Scheme 46

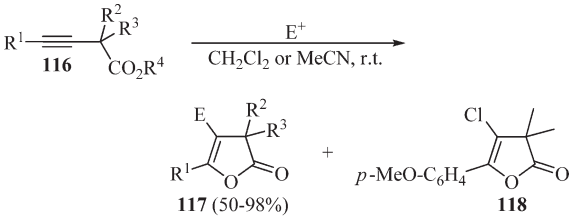


R^1, R^2 = -$(CH_2)_3$-; R^3 = Ph, *n*-C_4H_9, R^4 = Me, *i*-Pr

Scheme 47



Scheme 48

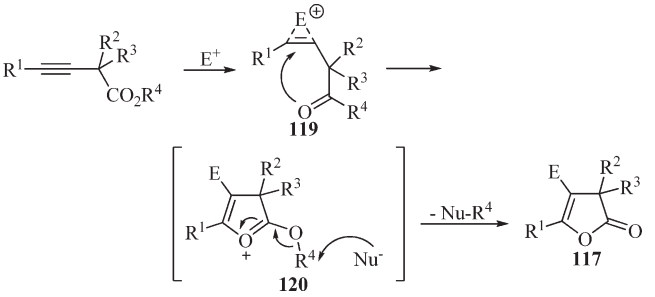


E^+ = I_2, ICl, PhSeCl; R^1 = Et, Ph, *p*-MeO-C_6H_4; R^2 = R^3 = H, Me, allyl; R^4 = Me, Et, *n*-Bu

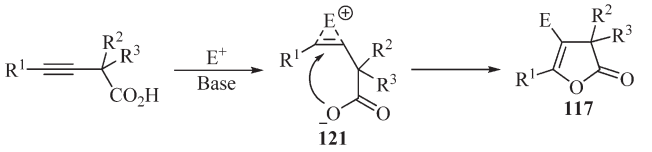
excess of sodium bisulfide regenerated the starting telluride,[43] confirming that the reaction of this telluride with iodide did not allow the cyclized product, even when using an excess of iodide, reflux, and long reaction time (Scheme 53). The benzo[*b*]furans obtained in the current protocol appear to be highly promising and attractive intermediates for the synthesis of more highly substituted benzo[*b*]furans. In fact, using the palladium- or copper-catalyzed cross-coupling reactions with thiols, diphenyl diselenides and zincates we were able to convert 3-iodo-2-chalcogenbenzo[*b*]furan to Ullmann- or Negishi-type products in good yields (Scheme 54).

The electrophilic cyclization reactions of alkynes are a powerful approach to the preparation of functionalized isochromenes, which are key structural units of a variety of biologically important compounds, many of which are pharmaceutically significant. Starting from alkynylbenzaldehydes **127**, the construction of highly substituted isochromenes **128** was developed by employing IPy_2BF_4 as iodinating reagent and alcohols as nucleophile (Scheme 55).[44] Alternatively, isochromenes **129** were obtained, in the absence of alcohols, by using the reaction of **127** with IPy_2BF_4 in the presence of $B(OMe)_3$, which acts both as a Lewis acid and as the electrophilic source (Scheme 56).

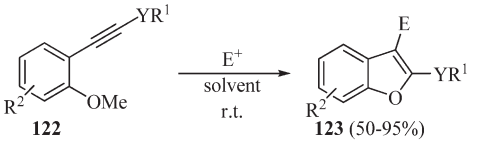
Scheme 49



Scheme 50



Scheme 51



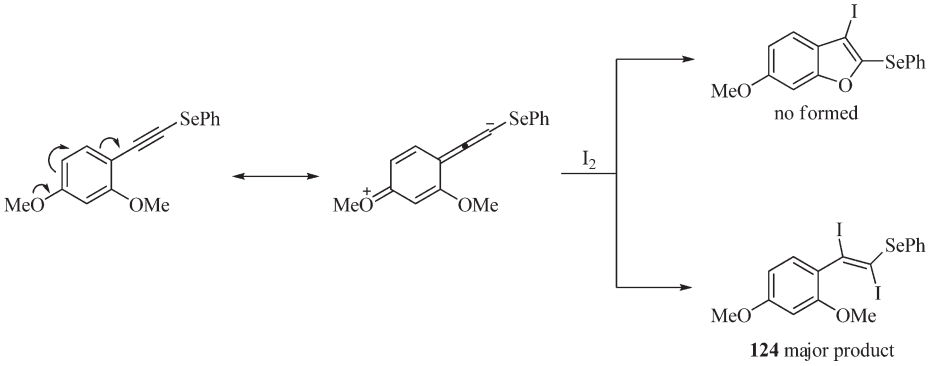
E^+ = I_2, Br_2, ICl, PhSeBr; E = I, Br, PhSe; YR^1 = SePh, SeBu, SMe, SPh; R^2 = H, Me, OMe, F

Alkynylaryl ketones **130** were also employed as suitable substrates for iodine cyclization with IPy_2BF_4. In this case, different from alkynylbenzaldehydes **127**, a 5-exo-dig cyclization worked to give the five-membered heterocycles **131** as product (Scheme 57). Finally, it must be mentioned that by this methodology carbon-based nucleophiles, such as silyl-masked or electron-rich arenes, were also used as nucleophilic source, giving highly substituted isochromenes **132** in moderate to good yields (Scheme 58).

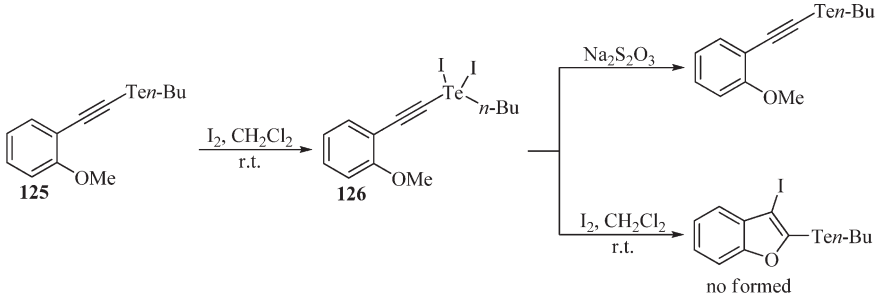
In addition to IPy_2BF_4, electrophiles such as I_2, ICl, NIS, Br_2, NBS, *p*-$O_2NC_6H_4SCl$, and PhSeBr were a suitable electrophilic source in the intramolecular electrophilic cyclization of *o*-alkynyl carboxaldehydes **133** to prepare haloisochromenes **134** (Scheme 59).[45] The reaction was carried out under mild conditions and the haloisochromene derivatives were obtained upon treatment of the starting material (0.25 mmol) with 0.30 mmol of the electrophilic source, 0.25 mmol of K_2CO_3, and 0.30 mmol of electrophile in 2.5 mL of CH_2Cl_2 at room temperature. The authors also examined the cyclization of ketone-containing alkyne. This reaction proceeded smoothly to provide the 5-exo-dig cyclization product **135** rather than the six-membered ring ether formed by the electrophilic cyclization of analogous benzaldehyde derivatives (Scheme 59).

Very recently, Larock and co-workers also reported the preparation of a variety of iodo-substituted isochromenes **137** in good to excellent yields under mild conditions via iodocyclization of 2-(1-alkynyl)benzylic alcohols **136** (Scheme 60).[46] The reactions were carried out in MeCN at 25 °C with 3 equiv of I_2 as

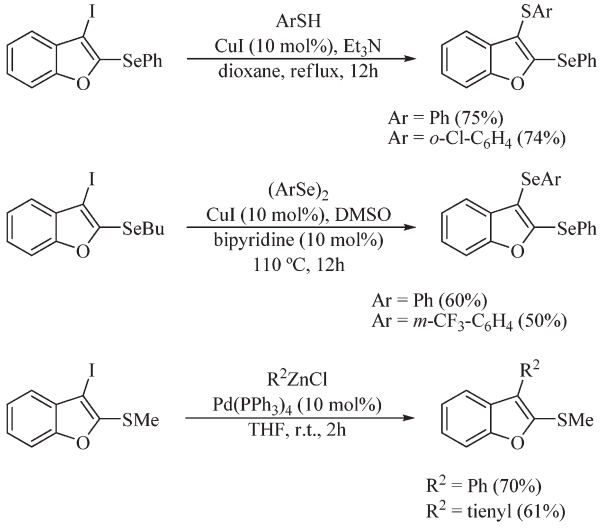
Scheme 52



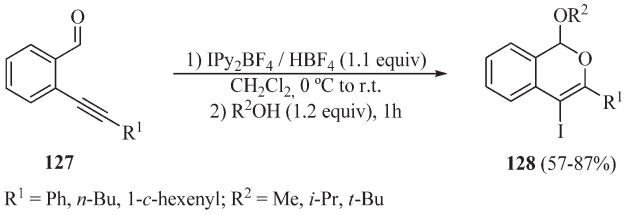
Scheme 53



Scheme 54



Scheme 55



the electrophilic source and $NaHCO_3$ (3 equiv) as the base. They obtained both 6-*endo*-*dig*-**137** and 5-*exo*-*dig*-**138** products, and the regiochemical effect of the reaction was strongly dependent on the substitution pattern of the starting material. In particular, the 5-exo-dig cyclization mode, leading to dihydroisobenzofurans, was observed in the case of substrates bearing a tertiary alcoholic group, while the 6-endo-dig cyclization mode, leading to isochromene, was the usually preferred pathway in the case of substrates bearing a primary or secondary alcoholic group. The mechanism shown in Scheme 61 was proposed for this process. It consists of the following key steps: (1) initial formation of iodonium intermediate **139** via coordination of iodine with the carbon−carbon triple bond of alkyne; (2) nucleophilic attack by the hydroxyl group via both anti-6-endo-dig and anti-5-exo-dig to afford the intermediates **140** or **141**, respectively; and (3) deprotonation of intermediate **140** to give the isochromene product **137**, while deprotonation of **141** gives, after isomerization, the most stable *Z*-5-membered-ring product **138**.

2-Methoxyaryl-containing alkynones **142** were also utilized as starting materials in 6-endo-dig cyclizations, involving ICl as electrophilic source, in a highly efficient approach to 3-iodochromones **143** (Scheme 62).[47] This process was run under mild conditions, tolerated various functional groups, and generally provided chromones in good to excellent yields; however, it failed to promote the cyclization product when the 2,4,6-trimethoxy substituents were present in the aromatic ring of alkynone. As explained by the authors, the methoxy substituents in the 2- and 6-positions force the alkynone unit out of planarity with the methoxy substituted arene, thus preventing cyclization.

A new approach into the synthesis of 4-halophosphaisocoumarins **145** was described by Ding and co-workers.[48] This

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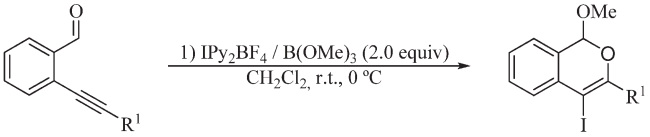
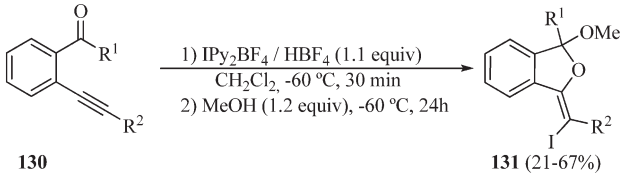
Scheme 56



127 **129** 79-88%

R^1 = Ph, *n*-Bu, 1-*c*-hexenyl

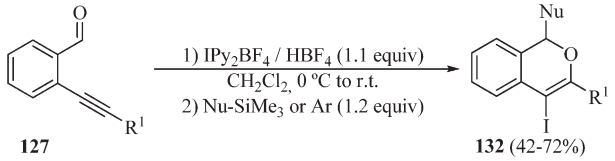
Scheme 57



130 **131** (21-67%)

R^1 = Me, Ph; R^2 = Ph, *n*-Bu

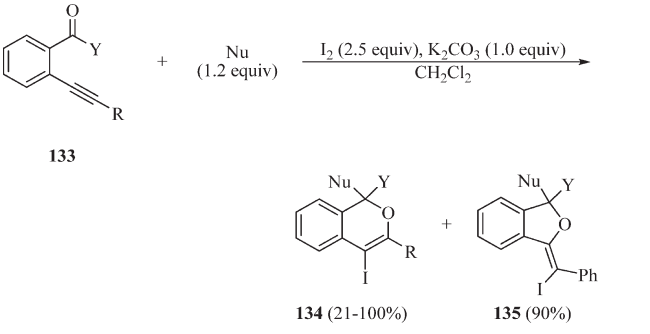
Scheme 58



127 **132** (42-72%)

Nu = allyl, *o*-vinyl, *o*-furyl; Ar = phenol, *N*,*N*-dimethyl-anilina, *p*-Me-phenol

Scheme 59



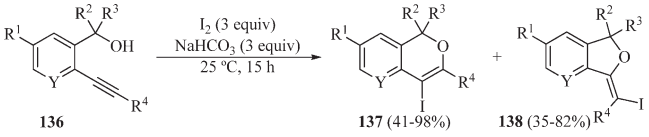
133

134 (21-100%) **135** (90%)

Y = H, Me; Nu = MeOH, EtOH, $PhNMe_2$, PhOH; R = H, *n*-Bu, Ph, 1-*c*-hexenyl, TMS

method led to 4-halophosphaisocoumarins **145** in good yields under mild conditions by the reaction of (1-alkynyl)phenylphosphonates **144** with I_2 in $CHCl_3$ and ICl in CH_2Cl_2 or by the reaction of 2-(1-alkynyl)phenylphosphonic acid monoesters with NBS or NCS in DMF (Scheme 63). The reaction was highly regioselective, since the six-membered ring phosphaisocoumarins were obtained in the complete absence of five-membered product. The authors assume that the mechanism of this process involves formation of the iodonium ion **146** through coordination of the triple bond of electrophile, followed by nucleophilic attack by the phosphonyl oxygen onto iodonium

Scheme 60



136 **137** (41-98%) **138** (35-82%)

Y = CH, N; R^1 = H, MeO, NO_2; R^2 = H, Et, *n*-Bu; R^3 = H, Et; R^4 = Ph, *p*-Me-C_6H_4, *p*-NO_2-C_6H_4, 3-thienyl

ion to give the intermediate **147**, which after a displacement of ethyl group by nucleophilic attack of the halogen atom delivers the product (Scheme 64).

Although electrophilic cyclization of alkynes represents the most common mode of reaction for halogens, NXS, and PhSeBr as electrophilic agents, other reagents serve as electrophilic source as well. For example, (bis-collidine) bromo and iodine hexafluorophosphates $[X^+(coll)_2PF_6^-]$ have been found to be very efficient in the formation of halo enol phostones **149** using acetylenic phosphonate monoesters **148** as staring materials (Scheme 65).[49] The cyclization was carried out at room temperature by reaction of a dichloromethane solution of $X^+(coll)_2PF_6^-$ (1.3 equiv) with monoester phosphonate (0.3 mmol). Depending on the number of carbons between the triple bond and the phosphorus atom, the cyclization gave exclusively 6-membered-ring via 6-endo-dig cyclization or a mixture of five (**150**) and eight (**151**) membered ring via both exo- and endo-dig cyclizations.

Recently, much attention has been paid to the synthesis of isoxazoles-containing natural products, which exhibit interesting biological activities.[50] Besides other strategies, 2-alkyn-1-one *O*-methyl oximes were smoothly converted to 3,5-disubstituted 4-halo(seleno)isoxazoles, as reported by Larock and co-workers.[51] In this way, the reaction of *O*-methyl oximes **152** with different electrophiles (ICl, I_2, Br_2, and PhSeBr) afforded isoxazoles **153** (Scheme 66). The best results were obtained with ICl in CH_2Cl_2 at room temperature, while the use of I_2 in CH_2Cl_2 resulted in lowered yields. Br_2 and PhSeBr were also utilized in the cyclization process; however, the reaction required more electrophile and longer reaction time. The effect on the yield of varying the nature of the group R^1, while R^2 was maintained as a phenyl group, was examined. The reaction worked well when R^1 was a hydrogen, an alkyl chain, or a bulky alkyl group. When R^2, attached in the alkyne, was a vinylic, alkyl, bulky *tert*-butyl, or TIPS group, the desired 4-iodoisoxazoles were also obtained in good yields. However, 2.0 equiv of ICl was required in the case of the TIPS group. This process can also be scaled up to provide multigram quantities of the desired product without sacrificing the yield or outcome of the methodology. In addition, subsequent palladium-catalyzed reactions of 4-iodoisoxazoles with various cross-coupling partners, such as commercially available boronic acid, acetylene, styrene, and amine, allowed for simple construction of a 51-member library of 3,4,5-trisubstituted isoxazoles.[52]

Recently, the electrophilic cyclization was used to prepare some pyranones with capacity to inhibit the in vitro growth of three human tumor cell lines, MCF-7 (breast adenocarcinoma), NCI-H460 (nonsmall cell lung cancer), and SF-268 (central nervous system cancer).[53] For instance, iodine in dichloromethane at room temperature promoted the cyclization of thiophene-2-carboxylates **154** to 3-aryl-4-iodobenzothieno[2,3-*c*]pyran-1-ones **155** in good yields (Scheme 67). The method was highly regioselective, since

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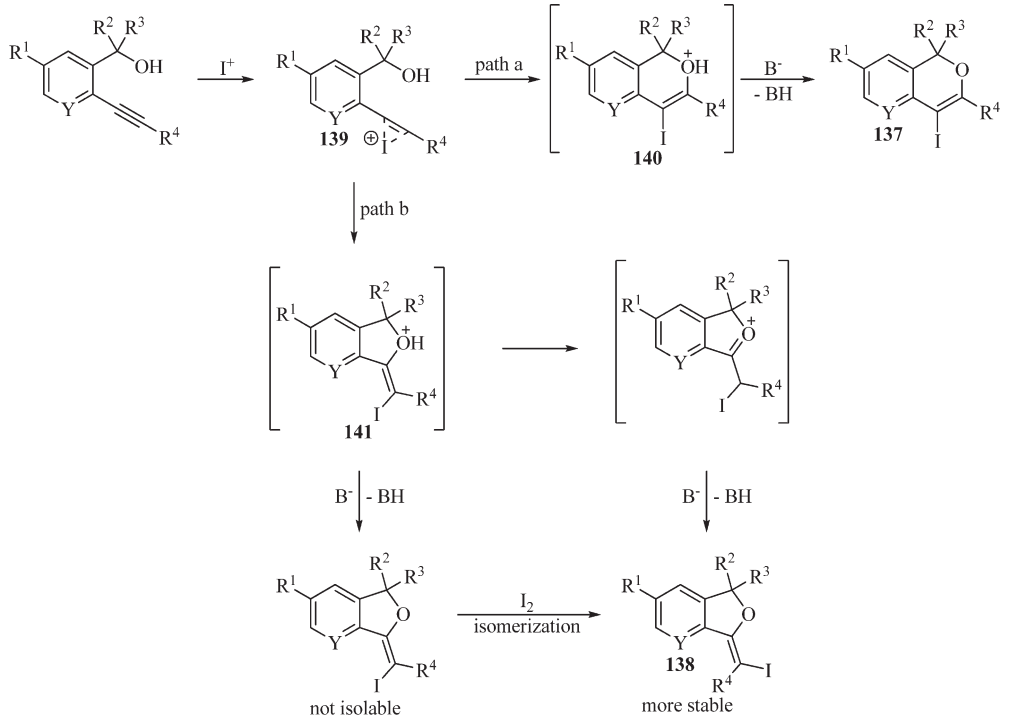
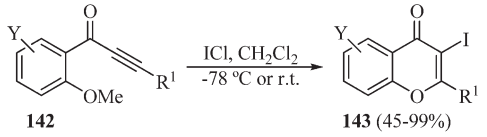
Scheme 61

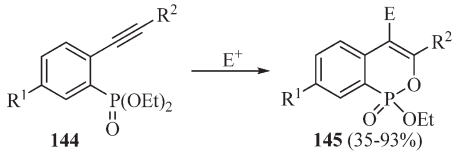


Scheme 62



Y = H, F, Br, MeO, NO_2; R^1 = Ph, *p*-Me-C_6H_4, *p*-MeO-C_6H_4, 3-thienyl, TMS, *n*-pentyl

Scheme 63

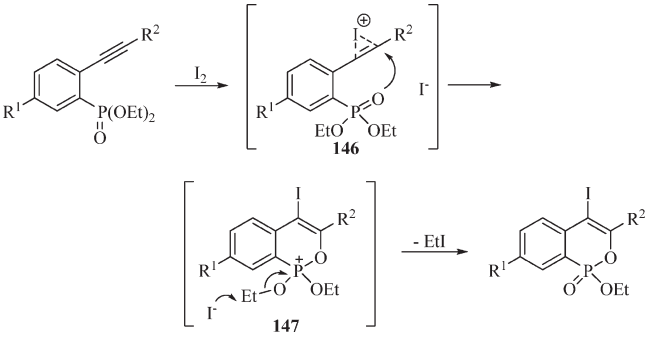


E^+ = I_2, ICl, NBS, NCS; R^1 = H, Cl, MeO; R^2 = H, Ph, *n*-Bu, $SiMe_3$, *p*-Et-C_6H_4

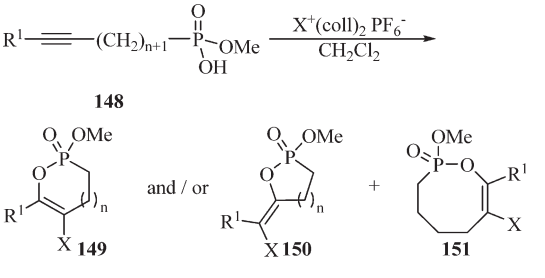
the 6-endo-dig products were obtained in total absence of 5-exo-dig patterns.

The cyclization of alkynyl carboxamides **156** in the presence of iodine and CH_2Cl_2 as solvent, in the absence of base, led to 3-iodopyrans **157** in good yields (Scheme 68), by exclusive attack of the oxygen of the carbonyl group on the activated iodonium intermediate to produce pyran salts **158**, and deprotonation of **158** by the iodide gave the products **157** (Scheme 69).[54] Other electrophiles, such as ICl, NBS, and NIS, were also tested; however, the results were unsatisfactory. For example, the use of NIS, in the presence or absence of bases, gave the 3-iodopyran

Scheme 64



Scheme 65

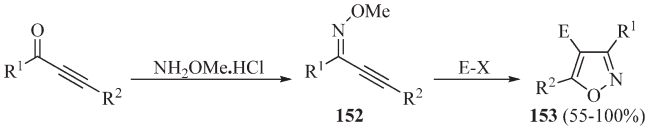


X = Br, I; R^1 = Me, *n*-C_4H_9, *n*-C_6H_{13}

derivatives **157** only in moderate yields, while the use of NBS or ICl failed to form the desired product. The results also revealed that the reaction significantly depended on the electronic effects

dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 66



E-X = I_2, ICl, Br_2, PhSeBr; R^1 = H, Ph, *n*-C_6H_{13}, *t*-Bu; R^2 = Ph, Me, *t*-Bu, TIPS

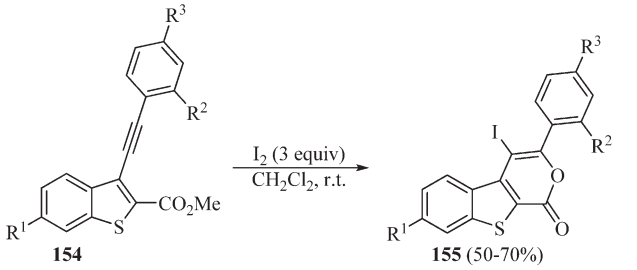
of substituent on the nitrogen atom. The presence of electron-withdrawing groups on the *N*-aromatic ring increased the yields and decreased the reaction times. On the other hand, the presence of an electron-donating group on the *N*-aromatic moiety lowered the yield.

The sequential cyclization−cycloaddition reactions of *o*-alkynyl-substituted benzaldehydes **159** in the presence of 2 equiv of I_2 and 2 equiv of $NaHCO_3$ in 3 mL of CH_2Cl_2 at room temperature represents an interesting method to prepare oxacyclic ring systems **160** (Scheme 70).[55] Concerning other electrophiles, I_2 and ICl promoted the reaction in similar yields, but NIS was not effective. The presence of bases was critical for the success of this cyclization reaction. The best results were achieved with $NaHCO_3$, K_2CO_3, and K_3PO_4. When the reaction was carried out in the absence or using stronger base, such as *t*-BuOK or CH_3ONa, the target products were not obtained. The mechanism shown in Scheme 71 was proposed for this process. It consists of the following key steps: formation of iodonium intermediate **161**, nucleophilic attack of oxygen on the activated iodonium intermediate to produce carbonyl oxabicyclic **162**, tandem [3 + 2] cycloaddition with alkene leading to oxabicyclic skeleton intermediate **163**, the intermediate **163** being trapped by the nucleophile HO^- present in the reaction to form hydroxyl-substituted intermediate **164**, and elimination of HI to generate the desired product **160**.

3. ELECTROPHILIC CYCLIZATION LEADING TO *N*-HETEROCYCLES VIA NITROGEN NUCLEOPHILE

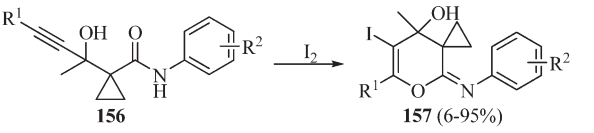
Nitrogen heterocycles are an important class of compounds due to their excellent biological effects, including antifungal, antiviral, and antiproliferative activities.[56] In addition, these compounds are very useful synthetic intermediates and can function as suitable building blocks to synthesize some other biologically active compounds, such as natural products. Many synthetic methods, including palladium-catalyzed intermolecular annulation[57] and transition-metal-catalyzed intramolecular cyclization,[58] have been successfully employed in the synthesis of nitrogen-containing heterocycles. However, some of these approaches are either incompatible with functionality or sometimes restricted by a lack of regioselectivity. More recently, significant advances have been made in the formation of nitrogen-containing heterocycles using electrophilic cyclization reactions. In this reaction, an appropriate unsaturated nitrogen compound acts as nucleophile partners with a number of electrophile-mediated carbon−nitrogen bond formations to give the heterocycle. As early as 1996, Noguchi and co-workers reported a remarkable systematic study on the preparation of functionalized imidazole derivatives by the iodocyclization of imidazolinones.[59] Depending on the substrate, the higher 5-exo, 6-exo, and 6-endo ratios were obtained with I_2 in DME either in the presence or absence of bases. For example, the cyclization of 2-anilino-3-(prop-2-ynyl)-l-imidazolinone **165**, which has a terminal alkyne and a phenyl substituent directly bonded to the nitrogen

Scheme 67



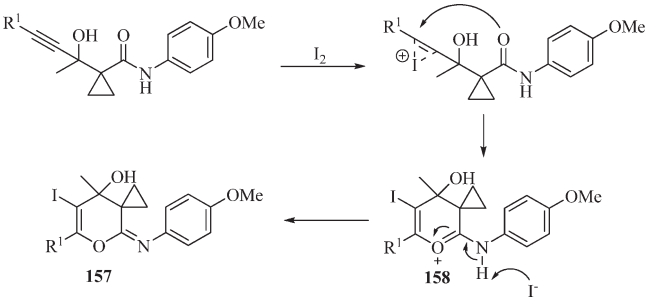
R^1 = H, MeO; R^2 = H, F; R^3 = H, MeO, F

Scheme 68

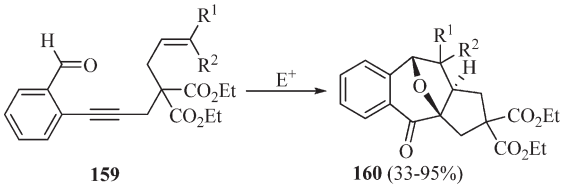


R^1 = Ph, *p*-Cl-C_6H_4, *p*-Br-C_6H_4, *n*-Pr, *n*-Pent; R^2 = H, Me, NO_2, MeO, Cl, Br

Scheme 69



Scheme 70



E^+ = I_2, ICl; R^1 = H, Me; R^2 = H, Me, Ph, *p*-Cl-C_6H_4, *p*-Br-C_6H_4, CO_2Et

atom, with iodine (3.0 equiv) in DME at room temperature, for 1 day, gave 5-exo cyclization product **166** in 77% yield (Scheme 72). When similar reaction conditions were applied to the imidazolinone **167**, with a naphthyl or tosyl substituent directly bonded to the nitrogen atom, a mixture of 5-exo cyclization product **168** together with a trace of diiodide **169** was obtained (Scheme 72). On the other hand, when in the imidazolinone structure the terminal alkyne was substituted by a Me group, the 5-exo cyclization product **170** and 6-endo one **171** were formed in 14 and 77% yields, respectively

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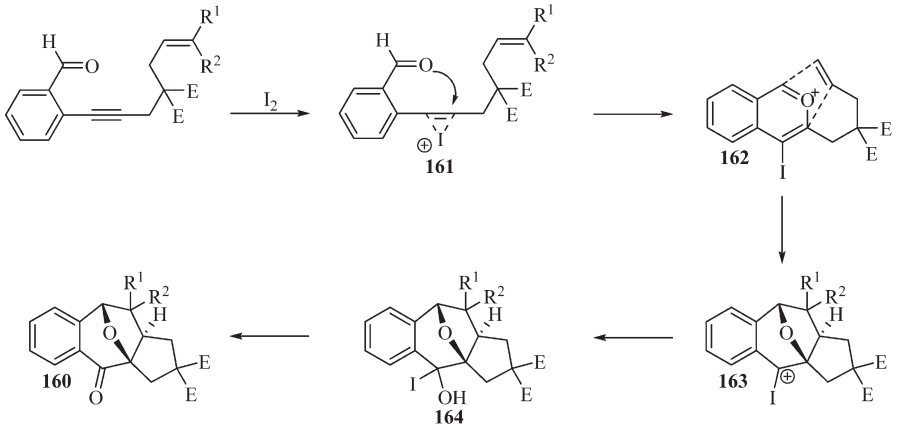
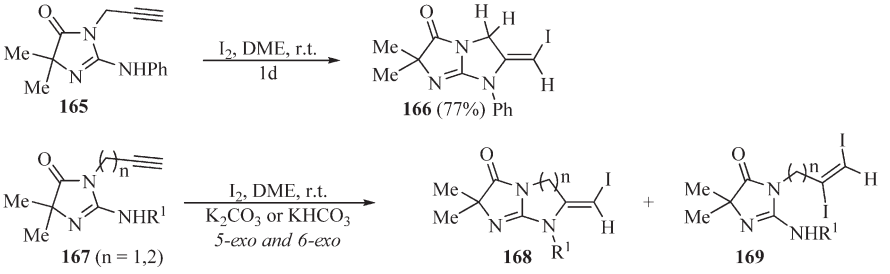
Scheme 71

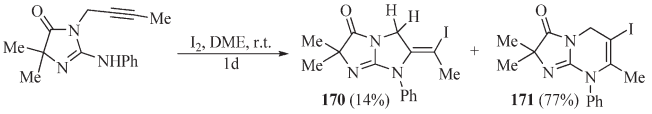


Scheme 72

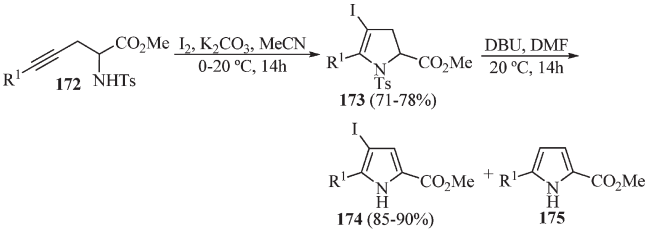


R^1 = *m*-Tolyl, Ts, 1-Naphthyl

Scheme 73



Scheme 74



R^1 = Ph, Et, 2-furyl, 2-thienyl

(Scheme 73). Furthermore, the presence of a phenyl in place of a methyl group at the terminal alkyne greatly favored the cyclization to give the 6-endo product exclusively in 86% yield.

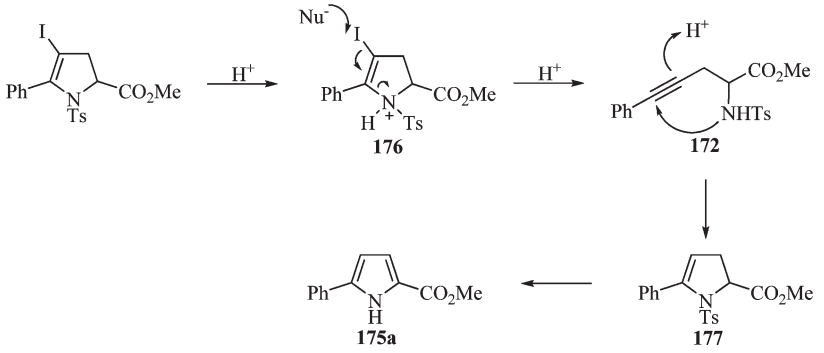
Starting from sulfonamides **172**, the construction of highly substituted iododihydropyrroles was developed by employing 3 equiv of I_2 and K_2CO_3 in dry MeCN (Scheme 74).[60] The reaction carried out at room temperature resulted in slow but clean cyclization to give excellent isolated yields of iododihydropyrroles. In addition, the dihydropyrroles **173** were converted to the corresponding iodopyrroles **174** by reaction with DBU in DMF at room temperature, via elimination of toluene-*p*-sulfinic acid. The authors found that the amount of base played an import role in this step. The best results were obtained using 2 equiv of base; if only 1 equiv was used, a 1:1 mixture of undesired pyrroles **175** and the expected products **174** was obtained. An elegant mechanistic study demonstrated that the side product **175** was obtained via *p*-toluenesulfinic acid, which acts as a proton source, causing a protonation of the nitrogen atom to give salt **176** with the iodine loss. Subsequently, the regenerated homopropargylic sulfonamide **172** affords the 2,3-dihydropyrrole **177** via an acid-induced cyclization, which after an elimination reaction gives the obtained 5-phenylpyrrole-2-carboxylate **175a** (Scheme 75).

Very recently an alternative intramolecular electrophilic cyclization of *Z*-alkenylamides **178** was reported by Abarbri and coworkers (Scheme 76).[61] In this study, pyrrolones **179** were obtained in good yields by reaction of *Z*-alkenylamides **178** with 3.1 equiv of ICl in CH_2Cl_2 at room temperature for 4 h in the presence of $NaHCO_3$ as base. The reaction proceeded via a 5-exo-dig process, giving only the six-membered ring having a preferential *Z*-exocyclic double bond. The authors proposed a mechanism initiated by the activation of the triple bond with iodine followed by a nitrogen nucleophilic attack on the activated triple bond with subsequent deprotonation to explain the cyclized products obtained (Scheme 76).

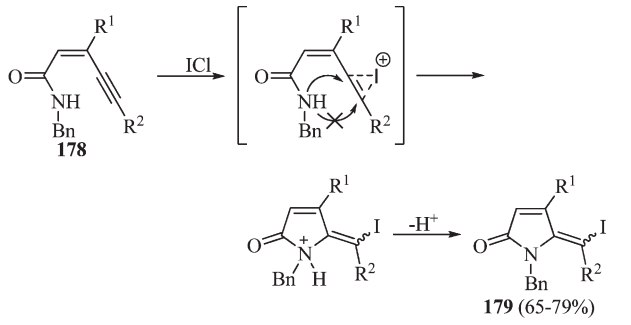
Much attention has been paid to the synthesis of indole-containing natural products, which exhibit important biological

dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 75

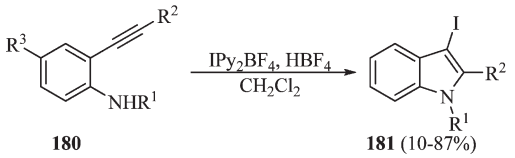


Scheme 76



R^1 = H, Me, R^2 = Ph, $SiMe_3$, $C(OH)Me_2$

Scheme 77

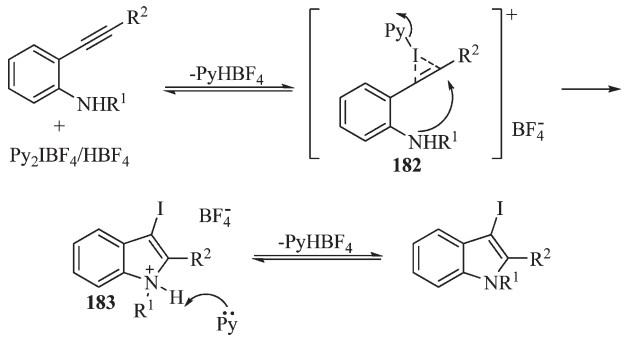


R^1 = SO_2Me, CO_2Me, CO_2t-Bu; R^2 = Ph, Bn, Bu, 3-thienyl; R^3 = H, Me

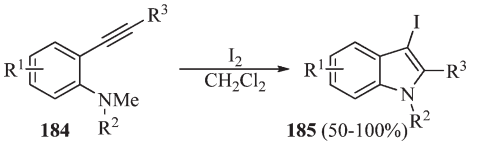
activities. Besides other strategies, the intramolecular electrophilic cyclization is one of the most important approaches for the construction of these heterocycles. In this way, *N*-protected *o*-(alkynyl)anilines **180** underwent electrophilic cyclization with IPy_2BF_4 as iodinating agent to give 2-substituted-3-iodoindoles **181** (Scheme 77).[62] *N*-Boc-(alkynyl)anilines, having a aryl or heteroaryl substituent at the alkyne, gave the indole derivatives in satisfactory yields; however, the application of this procedure to (alkynyl)anilines, having an alkyl or alkenyl group at the alkyne, proved to be difficult because of a significant decrease in yields. The proposed mechanism for this cyclization is shown in Scheme 78: the reaction of iodinating agent with alkyne gives the intermediate **182**, the nucleophilic attack of nitrogen leads to the cyclization, and pyridine removes the proton from the intermediate **183**, affording the indole derivatives.

3-Iodoindoles **185** were also achieved in excellent yields by coupling of terminal acetylenes with *N*,*N*-dialkyl-*o*-iodoanilines in the presence of a Pd/Cu catalyst, followed by an electrophilic

Scheme 78

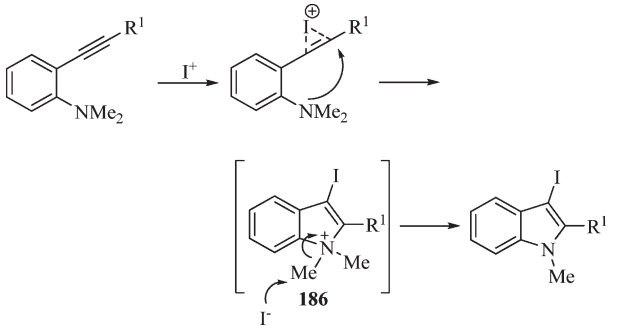


Scheme 79



R^1 = H, Me, MeO, NO_2, CO_2Et, CO_2Me; R^2 = Me, *n*-Bu, *c*-Hexyl, Ph; R^3 = *n*-C_6H_{13}, *t*-Bu, Ph, *c*-Hexenyl

Scheme 80



cyclization of the resulting *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines **184** using I_2 in CH_2Cl_2 (Scheme 79).[63] The proposed mechanism is illustrated in Scheme 80: the coordination of the alkyne to the

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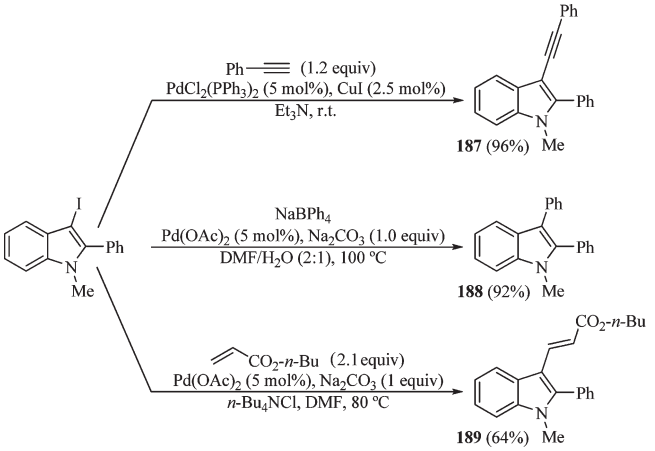
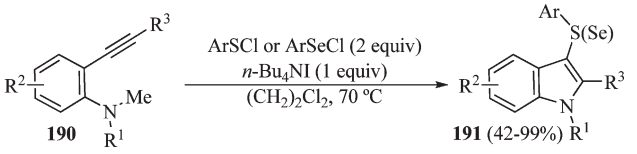
iodine to give an iodonium salt initiates a nucleophilic attack of the nitrogen to the carbon, leading to intermediate **186**, which loses an alkyl group via S_N2 substitution promoted by the iodide nucleophile present in the reaction mixture. The success of this reaction depends on the alkyl groups on the nitrogen atom, which make the nitrogen highly nucleophilic; the interaction between the two alkyl groups and the internal triple bond favors an orientation of the nitrogen with its lone pair of electrons pointing toward the triple bond, and the highly nucleophilic iodide ion formed after the cyclization facilitates removal of the alkyl group. In this way, the authors demonstrated that *N*,*N*-dimethyl-*o*-(1-alkynyl)anilines with substituents, which are in conjugation with the triple bond, such as the phenyl or vinyl group, cyclized more rapidly and generally produced higher yields of products. The bulky group tended to hinder cyclization and required a longer reaction time. The presence of electron-withdrawing cyano and chloro groups afforded lower yields than the simple alkyl-substituted alkyne. In addition, the presence of two different alkyl groups on the nitrogen of the aniline afforded interesting selectivity. In general, the less-hindered methyl group was more easily removed than was the *n*-butyl group, suggesting that alkyl cleavage is proceeding by an S_N2 process. Finally, aniline, containing a methyl and a phenyl group on the nitrogen, gave exclusively the expected *N*-phenylindole. The 3-iodoindoles produced by this methodology were functionalized by applying palladium-catalyzed coupling reactions. For example, *N*-methyl-2-phenyl-3-(phenylethynyl)indole **187**, *N*-methyl-2,3-diphenylindole **188**, and *n*-butyl *E*-3-(1-methyl-2-phenylindol-3-yl)propenoate **189** were obtained in 96, 92, and 64% overall yields, from 3-iodoindoles using Sonogashira, Suzuki, and Heck palladium cross-coupling reactions, respectively (Scheme 81).

In addition to 3-iodoindoles, Larock and co-workers also reported the preparation of 3-sulfenyl and 3-selenylindoles **191** by *n*-Bu_4NI-induced electrophilic cyclization of *N*,*N*-dialkyl-2-(1-alkynyl)anilines **190** using arylsulfenyl chlorides or arylselenyl chlorides as electrophilic sources (Scheme 82).[64] This procedure allowed simultaneous construction of the indole ring system and the installation of a sulfenyl or selenyl group in the 3-position of the indole nucleus. The authors suggested that the presence of *n*-Bu_4NI was crucial for this cyclization and it was necessary either to remove the methyl group from nitrogen via

Scheme 81

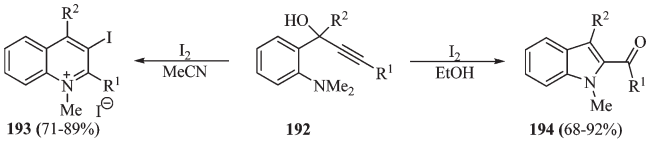


Scheme 82



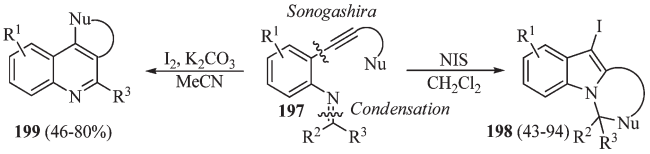
R^1 = Me, Ph; R^2 = H, Me, Br, CO_2Me; R^3 = Ph, *p*-MeO-C_6H_4, *o*-MeO-C_6H_4, *p*-NMe_2-C_6H_4, *p*-CN-C_6H_4, 3-thienyl; Ar = Ph, *p*-Me-C_6H_4, *p*-NO_2-C_6H_4, C_6F_5

Scheme 83



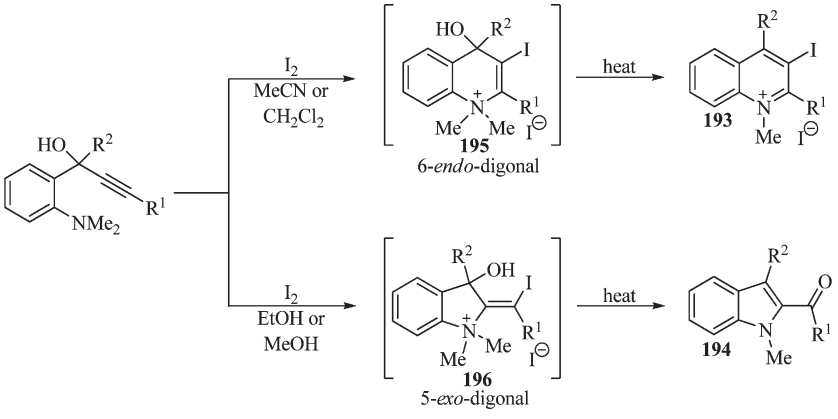
R^1 = *n*-Pr, *p*-MeO-C_6H_4; R^2 = H, Me

Scheme 85



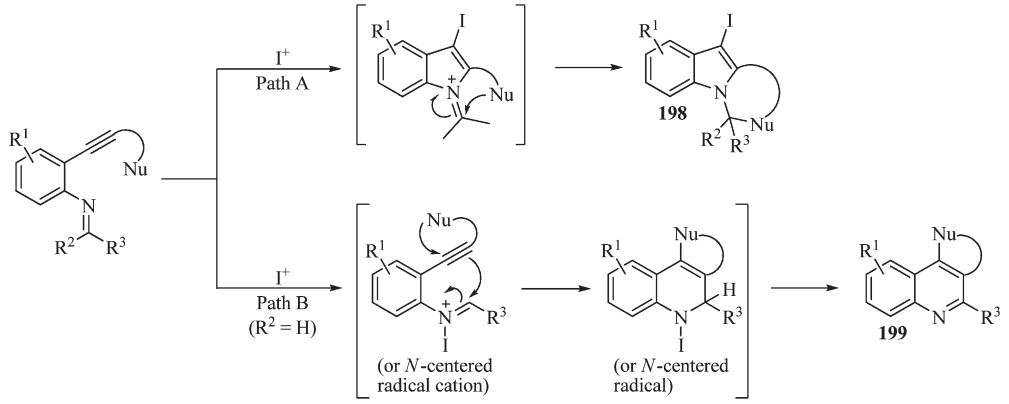
R^1 = H, Me, Ph; R^2 = H, Ph, *p*-MeO-C_6H_4; R^3 = OEt, Ph, *p*-Me-C_6H_4, *p*-MeO-C_6H_4

Scheme 84



dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 86

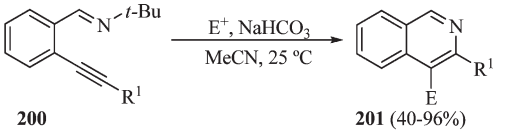


S_N2 displacement or to promote the activation of the arylchalcogenyl chlorides through halogen exchange, forming the arylchalcogenyl iodide.

Substituted quinolines are useful synthetic intermediates and also important structural elements in natural products having anti-inflammatory, antibacterial, antimalarial, anti-Alzheimer, and anti-HIV activity.[65] This fact stimulated a great interest for the development of general routes to such compounds, and the use of imines, iminoalkynes, hydrazides, and oximes as substrate in the electrophilic cyclization has extensively been described. In this way, quinolines and indoles were selectively prepared from *N*,*N*-dimethylaniline derivatives **192**, using iodine as electrophilic source, by a 6-endo-dig or a 5-exo-dig pathway, depending on the nature of the reaction conditions (Scheme 83).[66] The authors observed that the electrophilic cyclization carried out using acetonitrile or dichloromethane as solvent gave the quinoline **193** as products, via intermediate **195**. On the other hand, when the iodocyclization was performed in ethanol or methanol as solvent the 5-exo products **194** were obtained via intermediate **196** (Scheme 84). The same group also showed that *N*-(*o*-alkynylphenyl)imines **197** subjected to electrophilic cyclization delivered either ring-fused indoles **198** or quinolines **199**, depending on the electrophilic source used (Scheme 85).[67] For example, the reaction of *N*-(*o*-alkynylphenyl)imines with NIS in CH_2Cl_2 provided the formation of ring-fused indole compounds **198** via path A in Scheme 86. Simply by changing the electrophilic source to iodine, using the identical substrate, the reaction gave ring-fused quinoline compounds **199** via path B shown in Scheme 86.

The *tert*-butylimines of *o*-(1-alkynyl)benzaldehydes or analogous pyridinecarbaldehydes **200** were cyclized under very mild reaction conditions in the presence of I_2, ICl, PhSeCl, PhSCl, and *p*-$NO_2C_6H_4SCl$ to give the corresponding halogen-, selenium- and sulfur-containing disubstituted isoquinolines or naphthyridines **201** (Scheme 87).[68] In this study, the authors found some limitations, since considerable difficulties were found when they attempted to react alkyl-substituted *N*-(*o*-(1-alkynyl)benzylidene)-*tert*-butylamines with the electrophilic sources. However, they properly and elegantly solved the limitation using $AgNO_3$ or CuI as catalyst, which afforded decent yields of the corresponding isoquinolines. The following reaction pathway was proposed: the carbon−carbon triple bond of iminoalkyne **200** coordinates to the iodine to generate an iodonium intermediate **202**. This is followed by attack of the imine nitrogen on the activated triple bond to form intermediate **204**. Alternatively, the coordination of the iodine cation to the carbon−carbon triple bond may form

Scheme 87



E = I, PhS, *p*-NO_2-C_6H_4S, PhSe; R^1 = Ph, 1-*c*-Hexenyl, *c*-Hexyl, *n*-C_4H_9

a cationic intermediate like **203**, which cyclizes to intermediate **204**. The isoquinolinium salt **204** then presumably ionizes to produce the iodoisoquinoline **201** and a *tert*-butyl cation, which generates isobutylene (Scheme 88).

The electrophilic cyclization reaction of 2-alkynylbenzaldoximes **205** was used as a tool for the synthesis of isoquinoline *N*-oxides **206** (Scheme 89).[69] Best results were obtained when the electrophile (1.2 equiv) in 2 mL of CH_2Cl_2 was added dropwise to a solution of 2-alkynylbenzaldoxime (0.30 mmol) in 4 mL of CH_2Cl_2. Additionally, several variations in the organic group attached to alkyne in the alkynylbenzaldoximes were tolerated. The authors demonstrated that the best results were obtained with a neutral or electron-donating group on the aromatic ring bonded to the alkyne. Alkynylbenzaldoximes having alkyl- or propargylalkynes were also suitable to cyclization, giving the products in 85 and 64% yields, respectively. Concerning to electrophilic source, a slightly lower yield was observed when NBS or Br_2 was used in place of I_2, ICl, and NIS, while in the case of Br_2, ICl, or NIS, the reaction was faster (10 min) than that with NBS and I_2 (24 h). A plausible mechanism to this transformation is shown in Scheme 90: the coordination of the iodine to the alkyne activates the triple bond toward nucleophilic attack of the oxime nitrogen, leading to the iodoisoquinoline intermediate **207**. Subsequent elimination of a proton results in the formation of iodoisoquinoline *N*-oxide (Scheme 90).[70] A previous study by the same group used 2-alkynylbenzaldoximes **205** as substrate in the preparation of isoquinoline-based azomethine **208** via tandem electrophilic cyclization−[3 + 2] cycloaddition−rearrangement reactions (Scheme 91).[71]

Functionalized isoquinolines **210** were efficiently prepared from 2-alkynyl benzyl azides **219** using 5 equiv of iodine and 5 equiv of base in CH_2Cl_2 at room temperature (Scheme 92).[72] The azide cyclization mechanism is believed to proceed through the usual reaction of alkyne with I_2 to give the cyclic iodonium ion **212**. Nucleophilic attack of the azide at C2 from the activated

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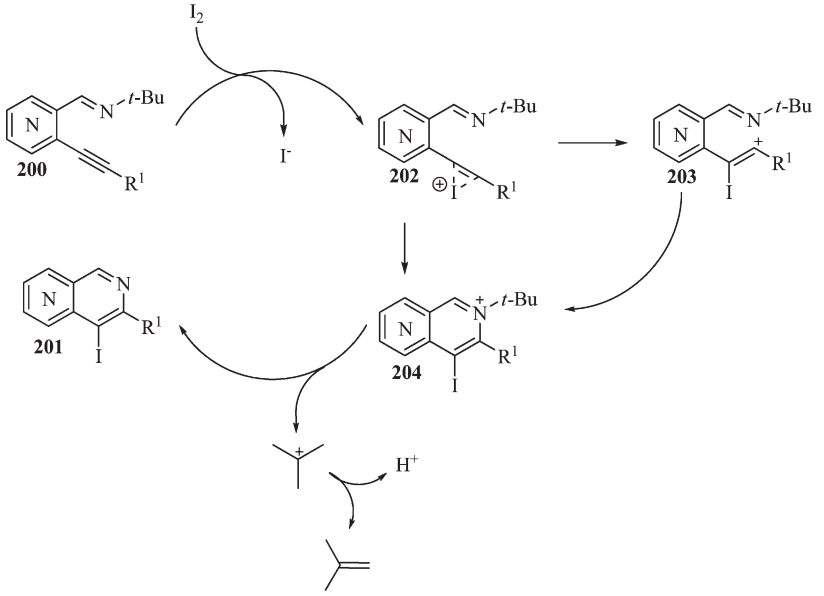
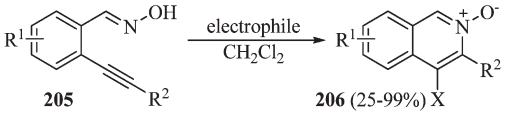
Scheme 88

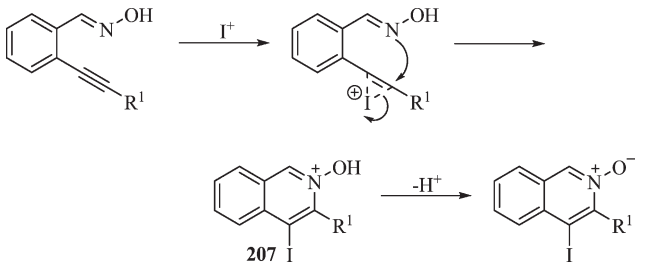


Scheme 89

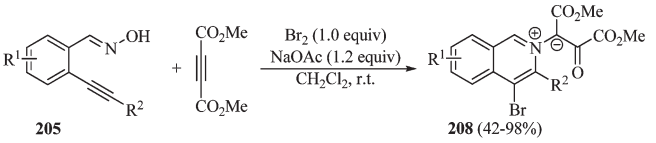


electrophile = I_2, ICl, NIS, Br_2, NBS; X = I, Br; R^1 = H, F; R^2 = Ph, *p*-MeO-C_6H_4, *n*-Bu, *c*-Pr

Scheme 90

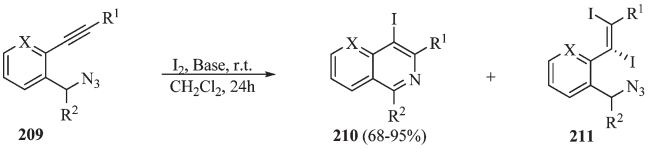


Scheme 91



R^1 = H, F; R^2 = Ph, *p*-MeO-C_6H_4, *n*-Bu, *c*-Pr

Scheme 92



X = CH, N; R^1 = H, Ph, *p*-MeO-C_6H_4, *p*-CF_3-C_6H_4; R^2 = H, Me, Ph

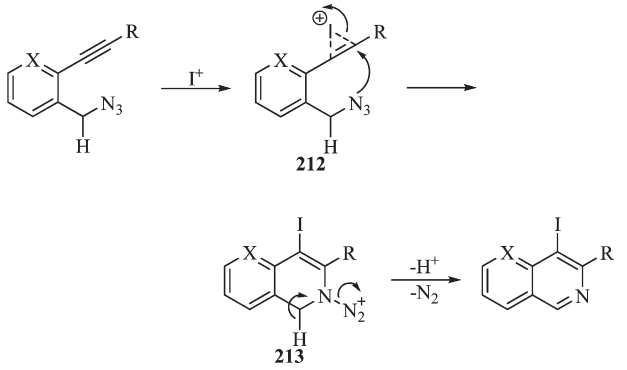
To **211** R^1 = 2-pyridinyl; R^2 = H; X = CH - 86%
R^1 = H; R^2 = H; X = CH - 56%

triple bond produces the intermediate **213**, which loses N_2 and H^+ to give the isoquinolines (Scheme 93). Only iodine promoted the reaction; other electrophilic sources were not effective. For example, ICl led to a mixture of iodine- and chloro-substituted isoquinolines, and NBS gave no conversion. It is important to point out that the choice of the base was also crucial for the outcome of the cyclization. While for primary azides, K_3PO_4 gave the best results, for secondary azides, the high yields were obtained using $NaHCO_3$ as base. With regard to the substitution pattern at the carbon−carbon triple bond, little influence in the yield was observed with phenyl or aryl group having either electron-donating or electron-withdrawing group. However, the authors reported some limitations in their methodology when they attempted to react 2-alkynyl benzyl azides having both terminal alkynes and a 2-pyridinyl group at the carbon−carbon triple bond. In these cases, they only observed the triple bond reduction product **211**, with no formation of desired product. In a closely related study, Yamamoto also found that 1-azido-2-(2-propynyl)benzenes **214** were converted to the corresponding substituted quinolines **215**, via electrophilic cyclization using I_2, Br_2, ICl, NBS, NIS, and $HNTf_2$ as electrophilic reagents in CH_3NO_2 at room temperature (Scheme 94).[73]

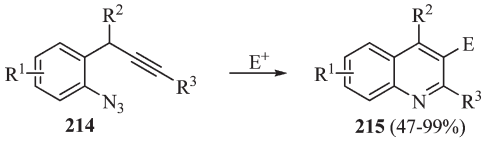
The same research group described an advance in the application of this methodology in the synthesis of norchelerythrine **216**, which exhibits potent pharmacological activities, such as antitumor and antiviral (Scheme 95).[74] The retrosynthetic analysis of the molecule involved the construction of a key fragment containing a 3,4-disubstituted isoquinoline **217**. To the synthesis of this fragment, it was initially necessary to prepare the diaryl acetylene **218**, which was achieved in good yield via the sequence Sonogashira cross-coupling, reduction, and

dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 93

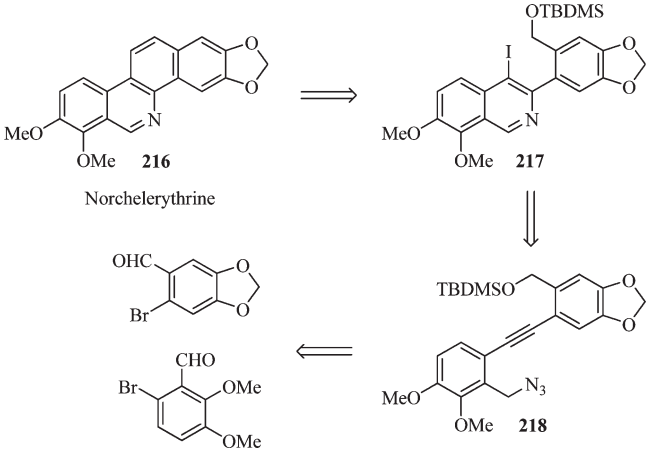


Scheme 94



E = H, Br, I; R^1 = H, Cl, Br; R^2 = H, AcO; R^3 = Me, *c*-hexyl, Ph

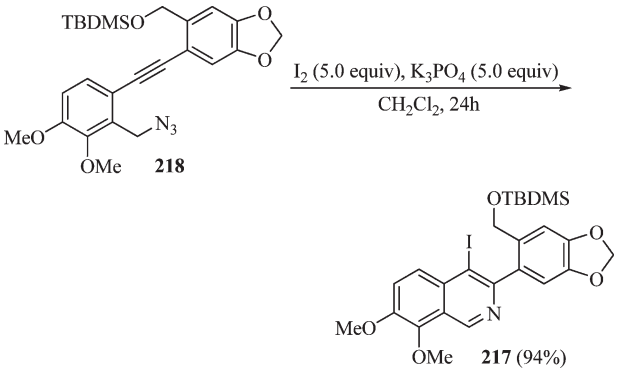
Scheme 95



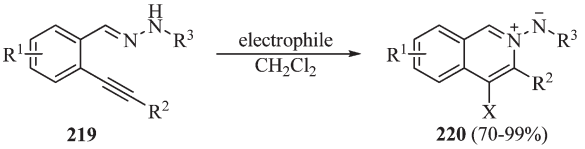
deprotection reactions. Further cyclization reaction of **218** using I_2 (5 equiv) and K_3PO_4 (5 equiv) in CH_2Cl_2 for 24 h gave the 3,4-disubstituted isoquinoline **217** in 94% yield (Scheme 96).[75]

Similar chemistry as that described for alkynylbenzaldoximes (Scheme 90) was used to prepare isoquinoline derivatives **220** via 6-endo-dig electrophilic cyclization reaction of hydrazides. The reaction was studied with *N*′-(2-alkynylbenzylidene)hydrazides **219** with I_2, Br_2, or ICl as electrophilic source, in dichloromethane at room temperature (Scheme 97).[76] In general, when the electrophilic source was changed from I_2 to Br_2 or ICl, no difference in the yields was found. The reaction was tolerant to several different functional groups in the alkyne, such as aryl, *n*-butyl, and cyclopropyl groups. The cyclization also worked well for a benzoyl or benzenesulfonyl group on the nitrogen in place of *N*′-(2-alkynylbenzylidene)hydrazide. In an extension of this previous study, Wu and co-workers recently disclosed a new approach

Scheme 96

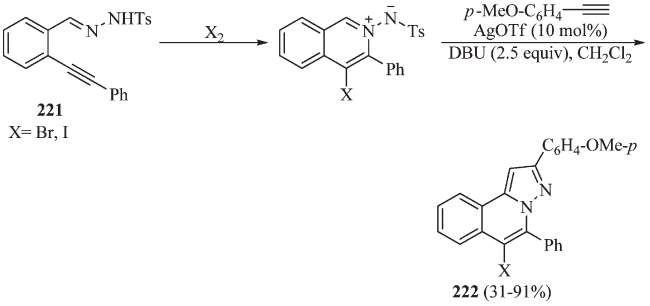


Scheme 97



electrophile = I_2, ICl, Br_2; X = I, Br; R^1 = H, F; R^2 = Ph, *n*-Bu, *c*-Pr
R^3 = Ts, SO_2Ph, COPh

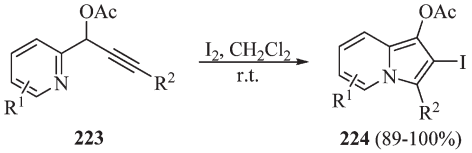
Scheme 98



for functionalized isoquinolines. This approach consisted of the sequential reactions of *N*′-(2-alkynylbenzylidene)hydrazides **221** with bromine-mediated electrophilic cyclization, followed by Ag-catalyzed alkyne nucleophilic addition (Scheme 98).[77] The advantages of this method are the easy availability of the halo-containing *H*-pyrazolo[5,1-*a*]isoquinoline compounds **222**, which are the precursors for the palladium-catalyzed cross-coupling reaction.

The nitrogen from pyridine derivatives is another functional group frequently used in electrophilic cyclization. For example,

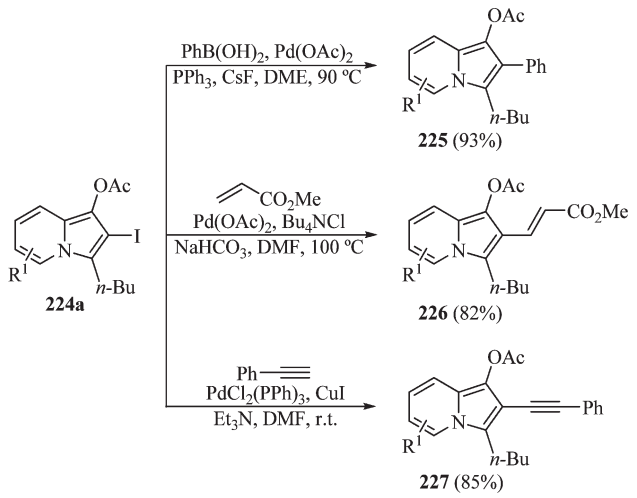
Scheme 99



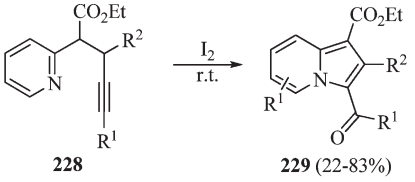
R^1 = H, Me; R^2 = *n*-Bu, *t*-Bu, Ph, 1-*c*-hexenyl, 3-furyl, $(CH_2)_2OTBS$, $(CH_2)_2OBn$

(pyridinyl)propynyl acetates **223** cyclized, via 5-endo-dig cyclization, in the presence of iodine and methylene chloride at room temperature to give indolizines **224** in excellent yields

Scheme 100



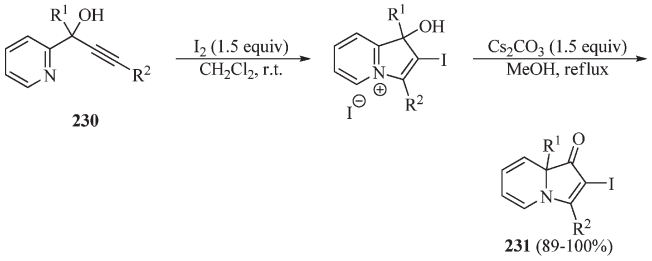
Scheme 101



R^1 = H, Me, *n*-pent, Ph, *p*-MeO-C_6H_4, *p*-Me-C_6H_4, *p*-F-C_6H_4; R^2 = H, Me, Et

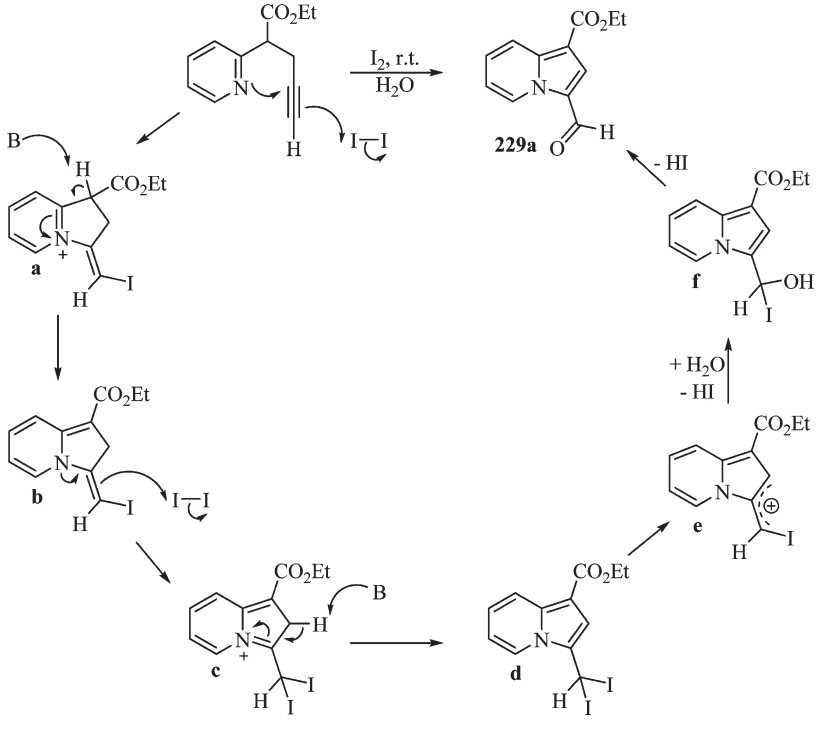
(Scheme 99).[78] The authors observed that other commonly used electrophiles, such as Br_2, NBS, and selenium electrophilic reagents, failed to initiate similar ring closure under the identical conditions. The potential of 2-iodoindolizines obtained as precursors for increasing molecular complexity via palladium-catalyzed reactions was also briefly investigated. In this study, the reaction of compound **224a** with phenylboronic acid, under Suzuki cross-coupling, gave the corresponding product **225** in 93% yield. Similarly, Heck reaction of **224a** with methyl acrylate cleanly afforded ester **226** in 82% yield. Finally, the phenylacetylene group was installed at C2 of **224a** via Sonogashira coupling to give **227** in 85% yield (Scheme 100). The same authors applied this cyclization to the synthesis of the 3-acylated indolizines **229** via 5-exo-dig iodocyclization of (pyridinyl)butynoate derivatives **228**, where a pyridinyl nitrogen also acted as an internal nucleophile (Scheme 101).[79] After several optimization studies, the authors found that the presence of external H_2O source was crucial for the outcome of the reaction. Thus, when (pyridinyl)butynoate was initially exposed to 3 equiv of iodine in CH_2Cl_2 at room temperature, the cyclized product was obtained in 10% yield, while a simple change in the solvent to CH_3CN—

Scheme 103



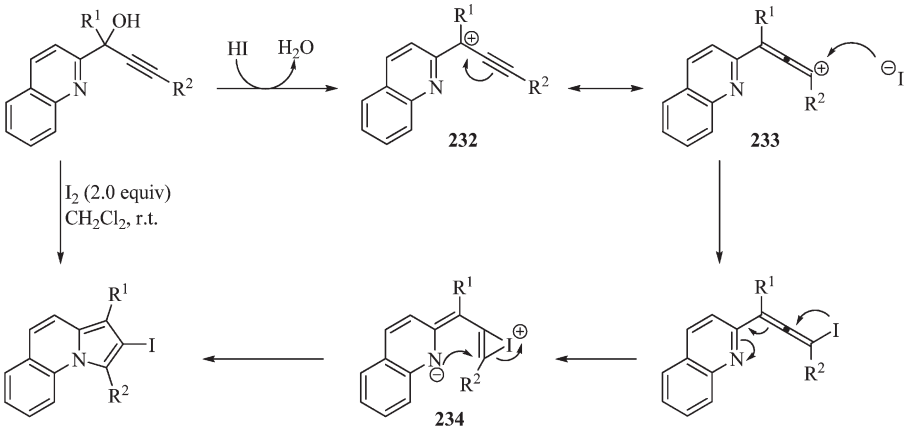
R^1 = Me, Et, Ph, Py; R^2 = *n*-Bu, *t*-Bu, Ph, 1-*c*-hexenyl, H, 3-thienyl

Scheme 102

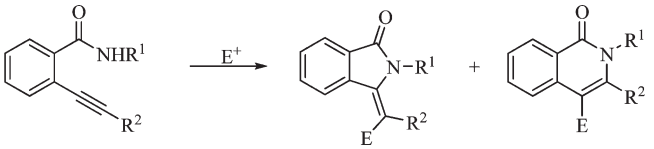


dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 104



Scheme 105



E^+ = ICl, I_2, NBS, *p*-NO_2-C_6H_4SCl, PhSeCl; R^1 = H, Me, Ph, Bn; R^2 = H, Ph, TMS, 1-*c*-hexenyl, *n*-C_5H_{11}

H_2O (10:1) increased the yield of the product to 83%. A mechanistic rationale was proposed to explain the use of H_2O and the excess of iodine. The newly generated carbonyl group at the 3-position of indole was assumed to come from an external source and the iodine was used for hydrative cyclization and oxidation to gain aromaticity. Thus, the iodocyclization initially generates vinyl iodide **a**, which after deprotonation would lead to **b**. Attack of another iodine upon the enamine would then produce the geminal diiodide **c**. Finally, diiodide **c** loses a proton to furnish 3-formylindolizine **d**, which after hydratation followed by elimination of HI, via cation **e**, gives the aldehyde **229** (Scheme 102).

In addition, a methodology using (pyridinyl)propargyl alcohol **230** was applied to the preparation of 2-iodoindolizinones **231** via a 5-endo-dig iodocyclization/1,2-shift sequence (Scheme 103).[80] The cyclization was carried out using 1.5 equiv of iodine in dichloromethane at room temperature, while the best conditions found for the 1,2-migration was the reaction of cyclized product with 1.5 equiv of cesium carbonate in methanol, at reflux for 6 h. Furthermore, the use of quinoline derivatives as starting material greatly favored the cyclization to give the pyrrol[1,2]quinolines instead of the corresponding 2-iodoindolizinones. A plausible mechanism to explain the exclusive formation of pyrrol product is the generation of the carbocation **232** via an initial loss of H_2O from propargyl alcohol. The iodide attacks the resonance-stabilized structure **232** to form iodoallene **233**. The intramolecular Michael-type addition of iodine group in **233** to the olefin gives the zwitterion **234**, which is subsequently cyclized via nucleophilic nitrogen attack to furnish the pyrrol-[1,2]quinolines (Scheme 104).

Isoindolinones **236** and isoquinolinones **237** were formed in high yields from *o*-(1-alkynyl)benzamides **235** through an electrophilic cyclization process that was carried out with 0.30 mmol of the *o*-(1-alkynyl)benzamide, 3 equiv of I_2, and 3 equiv of $NaHCO_3$ in 3 mL of CH_3CN stirred at room temperature (Scheme 105).[81] The authors reported that compared with the stronger electrophile ICl, the weaker electrophile I_2 showed better regioselectivity. The regioselectivity of this process also depended on the solvent employed in the reaction. The use of CH_3CN as the solvent afforded better regioselectivity and a higher yield than CH_2Cl_2 for 5-exo-dig cyclization products. In addition, the yield and selectivity can be further improved by adding $NaHCO_3$ to neutralize the acid generated in the reaction. According to the author's suggestion, the probable mechanism ran via the carbon−carbon triple bond activation by coordination to iodine and subsequent intramolecular nucleophilic attack by the nitrogen of the amide group on the carbon−carbon triple bond, followed by deprotonation to afford the cyclized products (Scheme 106). An effective application of this I_2-promoted cyclization of benzamides was the key step in the synthesis of the precursor of the alkaloid cepharanone B (**238**), which displays many pharmacological activities (Scheme 107).[82]

Pal and co-workers reported the conversion of *o*-(1-alkynyl)-arenesulfonamides **239** to 4-iodo-*2H*-benzo[1,2]thiazine derivatives **240** (Scheme 108).[83] After studying a number of solvents, such as ethanol, 1,4-dioxane, dichloromethane, and acetonitrile, and bases, such as triethylamine, $NaHCO_3$, Na_2CO_3, and K_2CO_3, a combination of acetonitrile/K_2CO_3 with 2.5 equiv of iodine at room temperature was found to be optimum with respect to the yield of product isolated. The optimized protocol tolerated a variety of functional groups, such as hydroxy, chloro, cyano, and methoxy, producing exclusively the six-membered heterocycles via 6-endo-dig mode of cyclization. Neither isomeric five-membered ring products nor the product involving the simple addition of iodine to the triple bond was detected under the conditions employed. In addition, it was found that either the use of less iodine or the omission of base lowered the yield of the cyclized product. When the reaction was carried out in the presence of other electrophiles (e.g., ICl, NBS), it led to products in poor yields. The applicability of the above cyclization product to the synthesis of more functionalized benzothiazine was demonstrated by transition-metal-catalyzed processes, such as Sonogashira, Suzuki, and Heck cross-coupling reactions. For instance, compound **240a** under Sonogashira, Heck, and Suzuki cross-coupling reactions gave the corresponding products **241**, **242**, and **243** in 84, 92, and 82% yields, respectively (Scheme 109).

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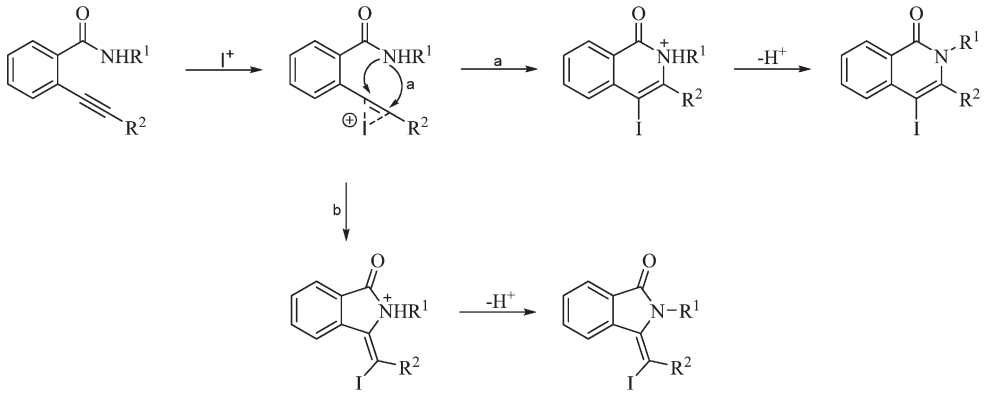
Scheme 106



The use of a nitrogen atom from the propargylic aziridines as a nucleophile in the electrophilic cyclization was also reported (Scheme 110).[84] Thus, 3-iodopyrroles **245** were prepared by the iodine-promoted electrophilic cyclization of propargylic aziridines **244** with simultaneous aromatization and introduction of an iodine at C-3 of pyrrole. The yields and selectivity in this system were strongly dependent on the solvent, temperature, and base. The best results were obtained using 2 equiv of iodine and 5 equiv of $NaHCO_3$, in dioxane at 100 °C for 10 min. While the use of THF at room temperature did not afford the cyclized product, dioxane at 100 °C, in the absence of base, gave the noniodinated pyrrole **246** as side product. The mechanism shown in Scheme 111 was proposed for this process. It consists of the following key steps: (1) coordination of the propargylic triple bond to iodine forms the cyclic iodonium ion **247**, (2) nucleophilic attack of the aziridine nitrogen on the iodonium ion produces the cyclized intermediate **248**, and (3) aromatization by elimination of the proton gives 3-iodopyrrole **245**.

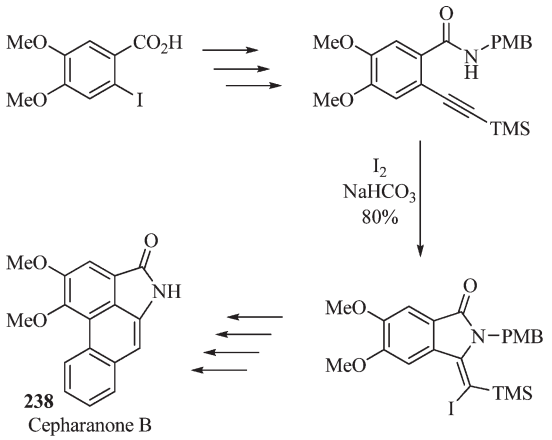
Recently, a series of studies on the use of alkynylamide derivatives in electrophilic cyclizations was carried out by Zard and co-workers.[85] They reported that the alkynylamides **249** readily afforded iodopyrrolinones **250**, after reaction with *N*-iodosuccinimide and a nucleophilic source, such as water and alcohols (Scheme 112). The proposed reaction pathway initiates by the formation of the iodonium species followed by the nitrogen nucleophilic attack to the active carbon−carbon bond to give cyclic enamide **251**. The second reaction with NIS gives the intermediate **252**, which reacts with nucleophile (water or alcohols) in the medium to afford diiodo compound **253**. The elimination of hydrogen iodide generates the observed iodopyrrolinone **250** (Scheme 113).

4. ELECTROPHILIC CYCLIZATION LEADING TO S-, SE-, AND TE-HETEROCYCLES

4.1. Via Sulfur Nucleophile

Chalcogenophene heterocycles (S, Se, Te) and their derivatives have numerous uses in the fields of biochemistry, physical organic chemistry, materials chemistry, and organic synthesis. For example, selenophene oligomers are compounds of current interest because many of them show photoenhanced biological activities[86] and crystalline polymerizations.[87] Thus, a wide variety of oligomers and related chalcogen compounds, including mixed thiophene−pyrrole oligomers, have been synthesized mainly with the expectation of obtaining excellent precursor compounds for molecular devices and electroconductive polymers.[88] In

Scheme 107



Scheme 108

R^1 = H, Me, Et, MeO; R^2 = *n*-Bu, *n*-C_6H_{13}, $(CH_2)_2OH$, Ph, tolyl; R^3 = Me, Et

addition, selenophenes are widely studied agents with a diverse array of biological effects, including antioxidant,[89] antinociceptive,[90] and anti-inflammatory properties,[91] as well as efficacy as maturation-inducing agents.[92] A great number of these heterocycles have been synthesized, and their chemistry has attracted a good deal of interest and activity from a variety of standpoints, such as structures, stereochemistry, reactivities, and applications to organic synthesis.[93] The electrophilic cyclization of alkynes bearing an organochalcogen moiety is a powerful approach to the preparation of several functionalized chalcogenophenes with high regioselectivity, particularly when one considers that there are many ways to transform selectively the resulting halogen, sulfur, selenium, and tellurium functionalities into a great number of interesting substituted heterocycles. As early as 1993, Turos and co-workers developed an elegant study on the regio- and stereochemistry for the electrophilic cyclization of benzyl

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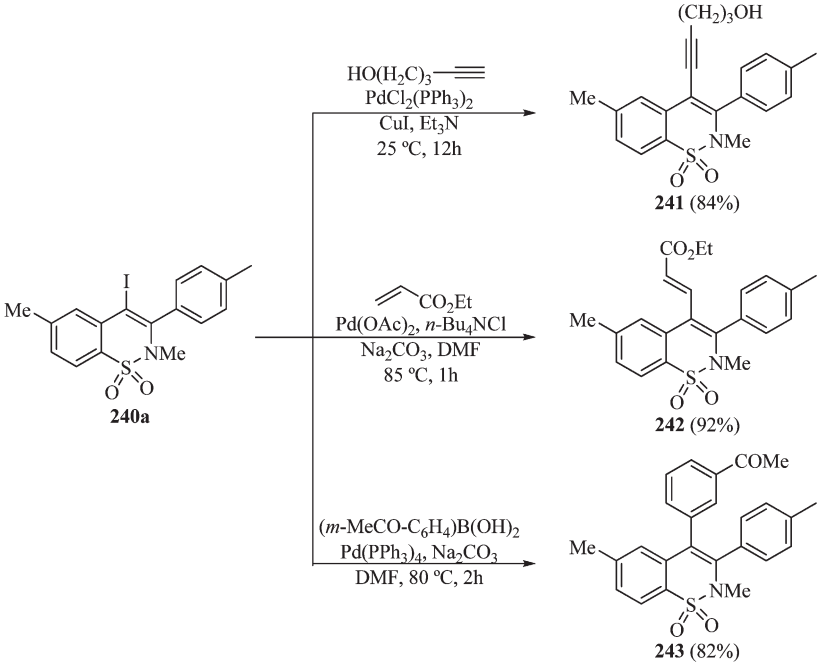
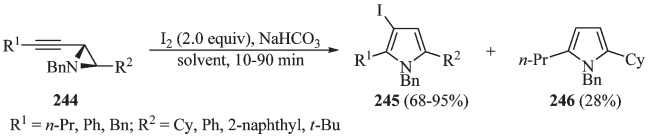
Scheme 109

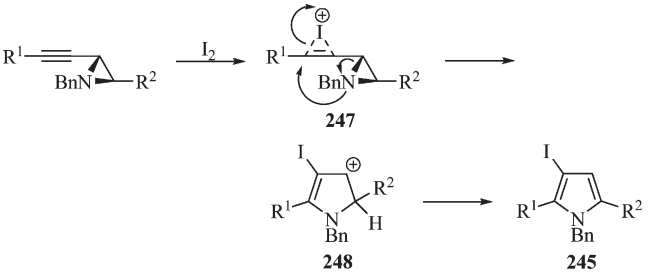


Scheme 110



R^1 = *n*-Pr, Ph, Bn; R^2 = Cy, Ph, 2-naphthyl, *t*-Bu

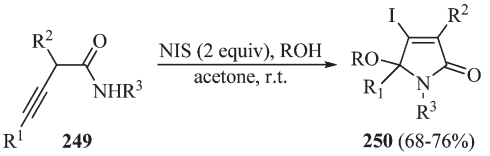
Scheme 111



alkynyl sulfides as a function of tether length, substituent, and electrophilic sources.[94] They observed that the reactions of benzyl alkynyl sulfides **254** with iodine gave equally high yields and regiochemical control, regardless of the tether length. Thus, 3-butynyl **254a** and 4-pentynyl sulfides **254b** cyclized cleanly to the five-membered ring, while 5-hexynyl sulfides **254c** gave exclusively the six-membered ring (Scheme 114).

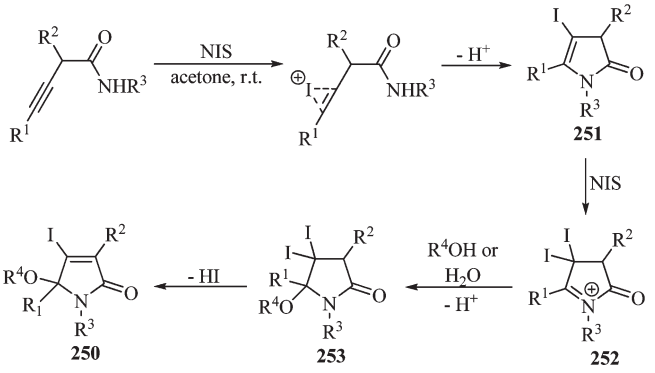
Turos and co-workers also reported the preparation of bicyclic β-lactams **256** via 5-endo electrophilic cyclization of acetylenic azetidinones **255** using 1 equiv of I_2 in CH_2Cl_2 at room temperature. The results showed that the cis isomer **255** cyclized easily, giving the desired product in 95% yield, while the trans isomer under the same reaction condition was recovered unchanged (Scheme 115). At the same time, it was demonstrated that the iodocyclization of the β-lactams **257** gave the

Scheme 112



R^1 = Ph; R^2 = *c*-Pr, *p*-Me-C_6H_4; R^3 = *t*-Bu, Bn

Scheme 113

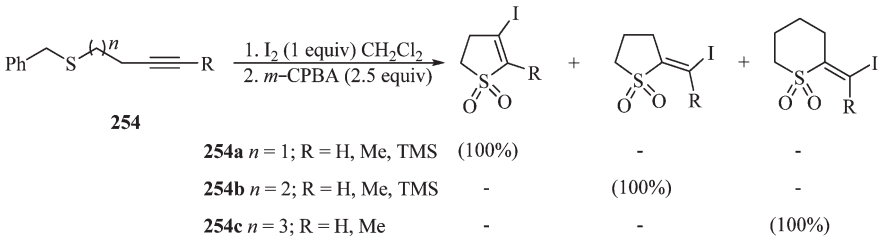


bicycloadducts **258** in moderated yields via a 5-exo-dig closure (Scheme 116).[95]

The intramolecular electrophilic cyclization of the 2-alkynylphenyl sulfide **259** to give benzothiophenium salts **260** was also described.[96] Although the reaction displayed a preference for cyclization through the 5-endo cyclization, it was observed that the substituent effects on the intramolecular cyclization afforded a mixture of products. Thus, the aryl-substituted alkynes afforded predominantly the cyclized 1-phenyl-3-iodobenzothiophenium salts, but methyl-substituted alkynes yielded a mixture of the cyclized salt **260** and the 1,2-addition product **261**

dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 114



254

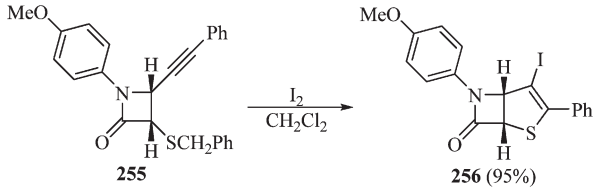
254a n = 1; R = H, Me, TMS	(100%)	-	-
254b n = 2; R = H, Me, TMS	-	(100%)	-
254c n = 3; R = H, Me	-	-	(100%)

(Scheme 117). The authors suggested that the benzothiophenium salts were formed via coordination of the carbon−carbon triple bond to the I_2 to generate the vinyl cation **262** or a bridged ion **263** followed by nucleophilic attack of sulfur atom (Scheme 118). In the case of methyl-substituted alkynes, the intramolecular cyclization competes with intermolecular attack of the counteranion. Since the addition of electrophiles occurs at the carbon β to the (phenylsulfanyl)phenyl group to give the vinyl cation **264** or an unsymmetrical bridged ion **265**, the intramolecular cyclization does not occur to produce the benzothiophenium ion but affords the addition products by intermolecular attack of halogen (Scheme 119).

An interesting study about electrophilic cyclization of *o*-(1-alkynyl)thioanisole **266** in the preparation of 2,3-disubstituted benzo[*b*]thiophenes **267**, using I_2, Br_2, NBS, *p*-$O_2NC_6H_4SCl$, and PhSeCl as electrophiles, was published by Larock and co-workers (Scheme 120).[97] The nature of the electrophile played an important role in these cyclization reactions. While I_2 and NBS cyclization reactions were most efficient and general, the Br_2 afforded the 3-bromobenzo[*b*]thiophenes in poor yields. In this study, they found some limitations in the methodology, since considerable difficulties were found when they attempted to react *o*-(1-alkynyl)thioanisole having a trimethylsilyl group at the alkyne. In this case, the reaction with Br_2 led to a mixture of 2,3-dibromobenzo[*b*]thiophene **270** and products of simple addition of the Br_2 to the carbon−carbon triple bond. They suggested that the formation of **270** occurs via bromocyclization in the desired manner followed by more rapid bromodesilylation by the mechanism described in Scheme 121, where the bromine first adds to the triple bond to form the simple addition product **268**. Attack of another 1 equiv of Br_2 on the simple addition product might then lead to cyclization and formation of a 2,3-dihydrobenzo[*b*]thiophene **269** bearing bromine atoms and a silyl group. Elimination of trimethylsilyl bromide would afford **270**. In addition, the carbon−halogen bond of 3-iodobenzo[*b*]thiophenes prepared by this method was efficiently used to generate a library, using parallel synthesis of multisubstituted benzo[*b*]thiophenes by palladium-catalyzed Suzuki−Miyaura, Sonogashira, Heck, and carboalkoxylation chemistry (Scheme 122).[98] Previous approaches to compound library synthesis of benzo[*b*]thiophenes were also published by Flynn and co-workers. Their earlier results are summarized in Scheme 123.[99] The resin-bound methyl phenyl sulfides **271** treated with elemental iodine in dichloromethane, at room temperature, gave the benzo[*b*]thiophene derivatives **272**. Subsequently, palladium-catalyzed Suzuki cross-coupling followed by reaction with trifluoroacetic acid in dichloromethane afforded 2,3-disubstituted benzo[*b*]thiophenes **273** in high purity and yields.

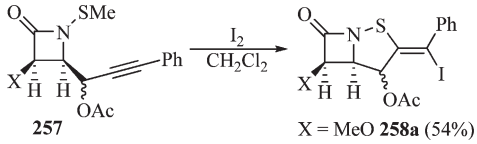
Flynn and co-workers published that, upon treatment with iodine in dichloromethane, at room temperature, benzyl sulfide **274** afforded 2,3-disubstituted benzo[*b*]thiophenes **275**. These authors developed this methodology and published an elegant

Scheme 115



255 **256** (95%)

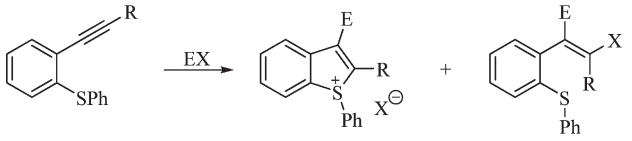
Scheme 116



257

X = MeO **258a** (54%)
X = *N*-phthalimidyl **258b** (61%)

Scheme 117



259 **260** (16-93%) **261** (10-60%)

E = H, Br, PhS; X = Cl, Br, BF_4, ClO_4; R = Me, Ph, *p*-Me-C_6H_4

application to the synthesis of some tubulin-binding agents, **276a**−**f** (Scheme 124).[100]

The intramolecular iodocyclization of *N*-[2-(methylthio)phenyl]propiolamides **277** is an attractive variation of the thiol cyclization applied to ring enlargement. Thus, the reaction of *N*-[2-(methylthio)phenyl]propiolamides **277** with electrophilic sources proceeded via both endo-dig and exo-dig cyclization to give 3-iodo-1,5-benzothiazepin-4-ones **278** and **279** (Scheme 125).[101] The reaction was performed at room temperature, and I_2, ICl, and NIS in CH_2Cl_2 were used as the electrophilic source; however, I_2 in CH_2Cl_2 provided the target products in the best yields. The results demonstrated that the selectivity between 6-exo-dig and 7-endo-dig cyclization was significantly influenced by both electronic and steric effects of the group directly bonded at the terminal alkyne. For example, propiolamides, bearing para-substituted aryl group, underwent the cyclization with I_2 to afford the endo-dig products **278**, exclusively. However, propiolamides, having an ortho- or meta-substituted aryl group, heteroaryl group, or terminal alkyne, provided a mixture of the endo-dig (**278**) and exo-dig (**279**) products. The 3-iodobenzothiazepins obtained by electrophilic cyclization are highly attractive as intermediates for the preparation of more highly

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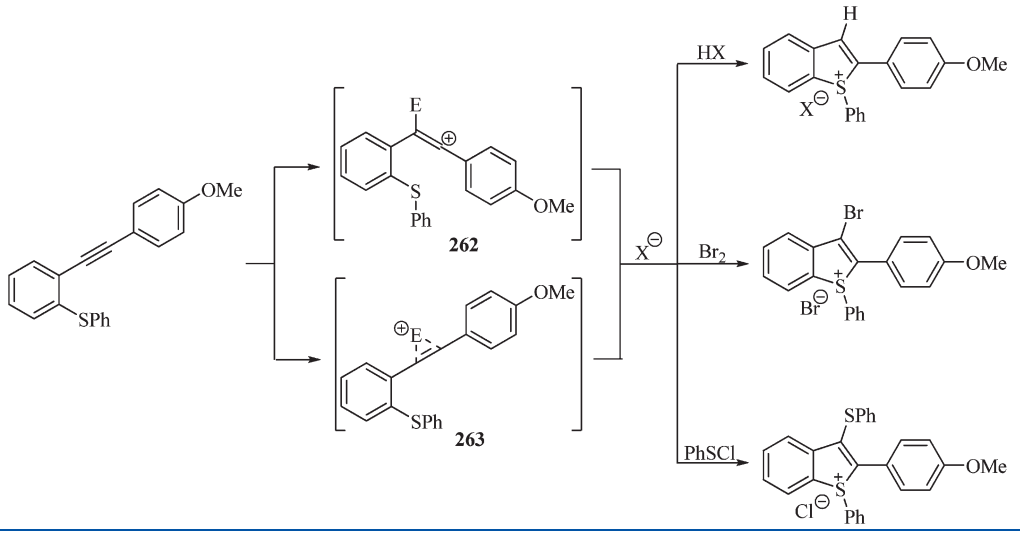
Scheme 118



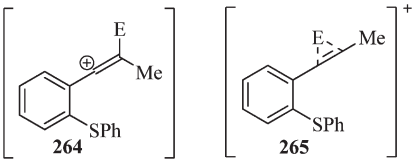
substituted benzothiazepin, particularly when one considers that there are many ways to transform the resulting halogen functionalities into other substituents. Thus, 3-iodobenzothiazepin **278a** was treated with $PhBF_3K$, $Pd(OAc)_2$, Ph_3P, and Cs_2CO_3, affording the Suzuki product **279** in 89% yield (Scheme 126). In addition, the palladium-catalyzed intramolecular oxidative coupling reaction of 3-iodobenzothiazepin **278b** was also carried out smoothly to afford the tetracyclic heterocycle **280** in 52% yield (Scheme 126).

4.2. Via Selenium Nucleophile

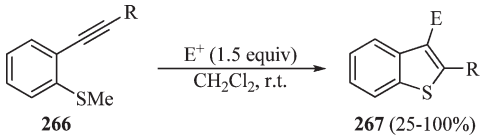
The introduction of a selenium group into organic molecules has found such wide utility because of its effects on an extraordinary number of very different reactions. They have become attractive synthetic targets because of their chemo-, regio- and stereoselective reactions,[102] use in a wide variety of functional groups, avoiding protection group chemistry, as well as useful biological activities.[103] The selenium group can be introduced in an organic substrate via both nucleophilic and electrophilic reagents. After being introduced in an organic substrate, the organoselenium groups can easily be removed by selenoxide syn elimination[104] and [2,3] sigmatropic rearrangement.[105] The carbon−selenium bond can also be replaced by a carbon−hydrogen,[106] carbon−halogen,[107] carbon−lithium,[108] or carbon−carbon bond.[109]

Heterocycles containing selenium play an important role in organic synthesis, especially in the development of methodologies for the synthesis of substituted selenophenes.[110] There are several reasons for this; they have a widely varied synthetic organochemical potential. The selenium atom exercises a stabilizing effect on neighboring positive as well as negative charges. This makes the carbon responsive toward both nucleophilic and electrophilic attack, an extremely useful feature for organic synthetic purposes. Larock and co-workers reported an elegant study on the preparation of 2,3-disubstituted benzo[*b*]selenophenes **282** by the electrophilic cyclization of various 1-(1-alkynyl)-2-(methylseleno)arenes **281** using Br_2, NBS, I_2, ICl, PhSeCl, and PhSeBr as electrophilic sources (Scheme 127).[111] This reaction tolerated many functional groups, including nitrile, hydroxyl, silyl, nitro, methoxyl, and ester. In this study, Larock and co-workers also evaluated the mechanistic details of this electrophilic cyclization. To determine the advanced intermediates of the reaction, the authors monitored the reaction by ^1H NMR spectroscopy. Among the data that could be obtained by ^1H NMR spectroscopy, the most relevant for the proposal was those shown in Scheme 128, where in the first step, the electrophile coordinates with the triple bond, followed by nucleophilic attack by selenium to generate a cationic intermediate **283**, which was detected by ^1H NMR. The cationic intermediate **283** can then undergo a facile removal of the methyl

Scheme 119

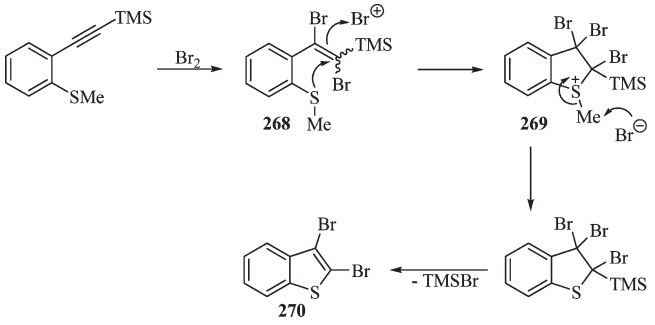


Scheme 120



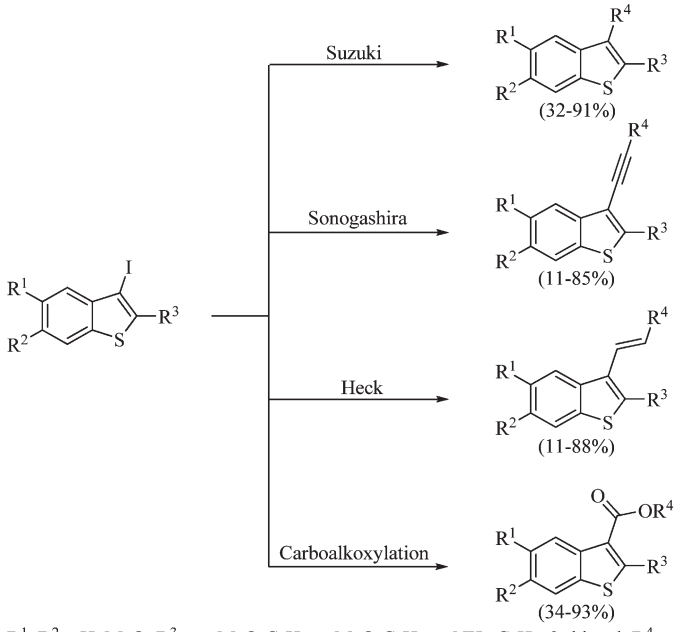
$E^+ = I_2$, Br_2, NBS, *p*-NO_2-C_6H_4SCl, PhSeCl
R = Ph, 1-*c*-hexenyl, *n*-C_8H_{17}, TMS

Scheme 121



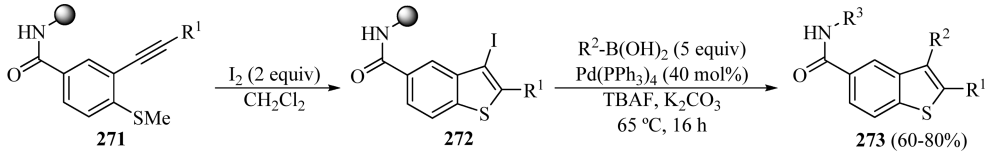
dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 122



R^1, R^2 = H, MeO; R^3 = *p*-MeO-C_6H_4, *o*-MeO-C_6H_4, *p*-NH_2-C_6H_4, 3-thienyl; R^4 = aryl, (Het)Ar, alcoxyl

Scheme 123



R^1 = Ph, *p*-MeO-C_6H_4, *p*-F-C_6H_4; R^2 = *p*-MeO-C_6H_4, *p*-F-C_6H_4, *p*-CN-C_6H_4, 3-thienyl; R^3 = H, resin

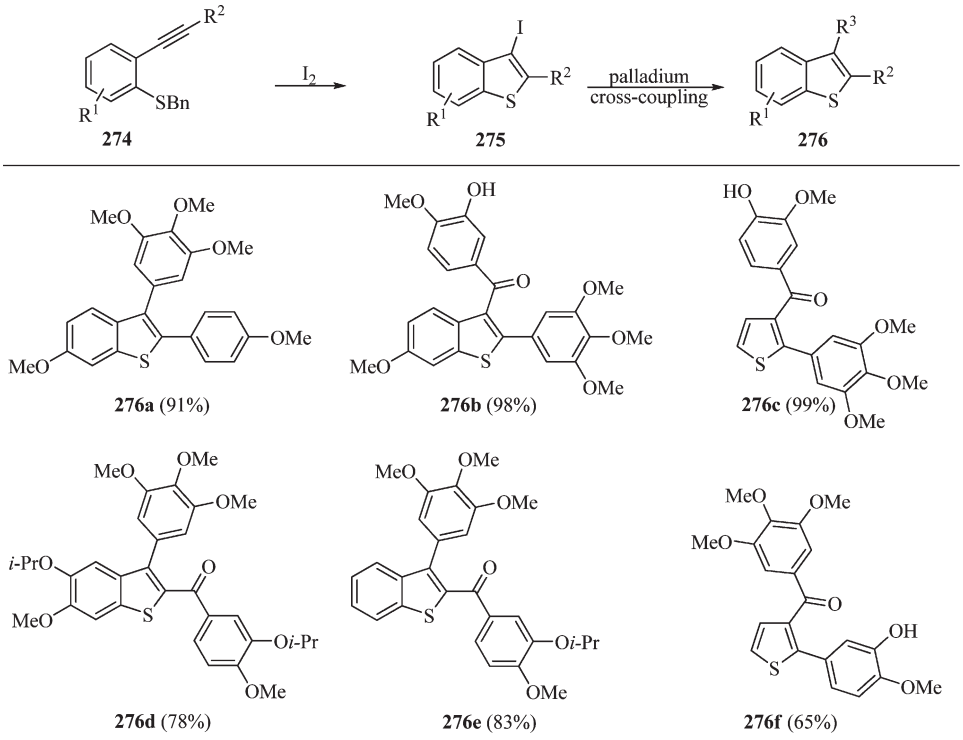
group via S_N2 displacement by the counterion bromide, generated in situ during the cyclization, to give MeBr (detected by ^1H NMR) and the cyclized product (Scheme 128). The same strategy was applied by Flynn and co-workers to the efficient solid-phase synthesis of benzo[*b*]selenophenes **285** via idocyclization of resin-bound substrates **284** (Scheme 129).[99]

We described a general approach to the preparation of 3-substituted selenophenes **287** via electrophilic cyclization reaction of (*Z*)-selenoenynes **286** (Scheme 130).[112] We observed that the nature of solvent and structure of (*Z*)-selenoenyne were important to the cyclization reaction. Regarding the influence of the solvent, better results were achieved using CH_2Cl_2, which furnished the desired product in high yields, after a very short reaction time. When THF, Et_2O, MeOH, hexane, and MeCN were used as solvent, good yields were also obtained; however, these reactions proceeded more slowly. In addition, our results also demonstrated that the efficiency of the selenophene formation was significantly dependent on the steric effects and that this cyclization reaction occurred only with selenoenynes having a Se−C(sp^3) bond. In order to complete our investigation and to further prove the potential of 3-iodoselenophene derivatives as precursors for increasing molecular complexity, we tested the reactivity of these compounds for the preparation of more highly substituted selenophenes. For instance, 3-iodoselenophene was treated under metal−halogen exchange conditions with *n*-BuLi, and trapping the intermediates with aldehydes provided the corresponding secondary alcohols **288** in good yields (Scheme 131). Conversely, using the palladium- or copper-catalyzed cross-coupling reactions with terminal alkynes, alkyl alcohols, boronic acids, and organozinc compounds, we were able to convert 3-iodoselenophene to Sonogashira (**289**), Suzuki (**290**), and Negishi (**291**) type products, respectively, in good yields (Scheme 131).[113]

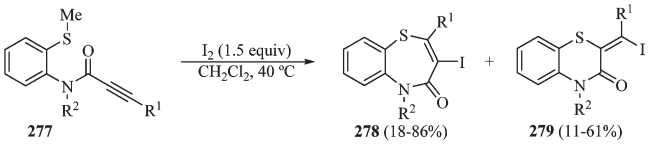
In a related study, we showed that 2,3-dihydroselenophenes **293** were formed from homopropargylic selenides **292** through electrophilic cyclization in a simple process employing I_2, ICl, and PhSeBr as electrophilic source, in CH_2Cl_2 as solvent and at room temperature (Scheme 132).[114] To identify the solvent potentially suitable for the cyclization, we first chose MeOH, hexane, MeCN, THF, and CH_2Cl_2. For this process, CH_2Cl_2 was the most effective solvent, giving the cyclized product in high yields. The study to screen the electrophilic source showed that ICl and PhSeBr gave the target products in lower yields than I_2. The cyclization turned out to be general with respect to a diverse array of functionalities. The experiments showed that the electrophilic cyclization of substrate, having an aromatic ring directly bonded to the terminal alkyne, was not sensitive to the electronic effects of the substituent. For example, the aromatic ring having either neutral, electron-donating, or electron-withdrawing substituent gave the cyclized products in very similar yields. By contrast, when the reaction was carried out with homopropargyl selenides with a hydrogen atom or an alkyl group in the terminal position, a little decrease in the yields was observed, and the cyclized products were obtained in moderated yields. We also

dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 124

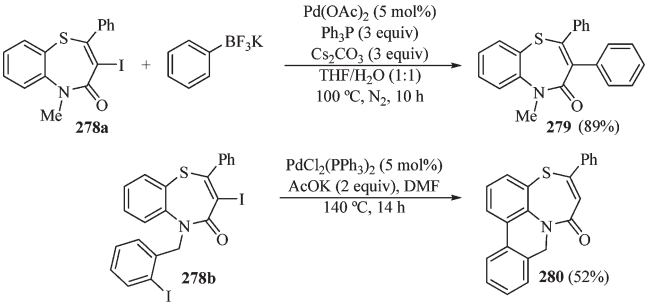


Scheme 125

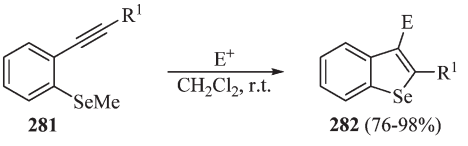


R^1 = H, Ph, *p*-Me-C_6H_4, *p*-NO_2-C_6H_4, *m*-CF_3-C_6H_4; R^2 = Me, Bn

Scheme 126

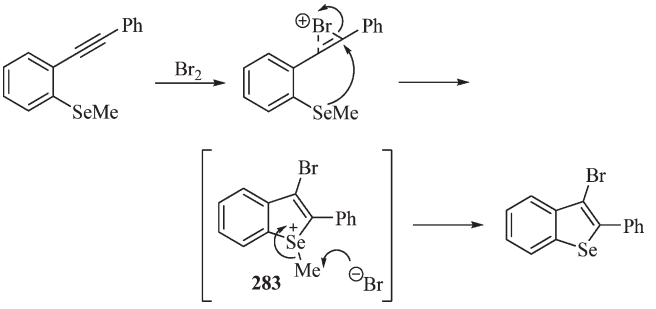


Scheme 127



E^+ = I_2, ICl, PhSeBr, PhSeCl, Br_2, NBS; R^1 = alkyl, vinyl, aryl

Scheme 128

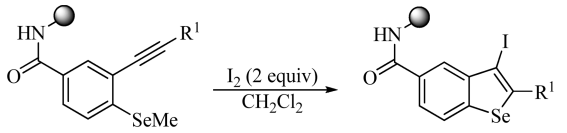


found that the reaction of 2,3-dihydroselenophenes **293** (1 equiv) with DDQ (2 equiv) in toluene at 90 °C gave the selenophene derivatives **294** in good yields (Scheme 133). In addition, 2,3-dihydroselenophene derivatives **293a** were submitted to a copper-catalyzed thiol cross-coupling reaction and Heck-type reaction, giving the desired products **295** and **296**, respectively, in moderate to good yields (Scheme 134).

We were also able to prepare a range of fused 4-iodoselenopheno[2,3-*b*]thiophenes **298** by electrophilic cyclization of 2-alkylchalcogen-3-alkynylthiophenes **297** (Scheme 135).[115] Thus, the optimized reactions revealed that the optimum condition for this electrophilic cyclization reaction was the combination of 2-butylseleno-3-alkynylthiophenes (1 equiv) and electrophilic source (1.1 equiv) using CH_2Cl_2 (5 mL) as the solvent, at room temperature. Because the success of this reaction is probably dependent on the nature of the group directly linked to the selenium atom, we explored this influence using different alkyl, aryl, and benzyl groups. The results revealed that butyl and ethyl groups bonded at the selenium atom resulted in the formation of products in high yields after very short reaction times. The 2-benzylseleno-3-alkynylthiophene also gave the product in moderate yield, however, with longer reaction time. Nonetheless, by performing the reaction

dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 129



284 **285**

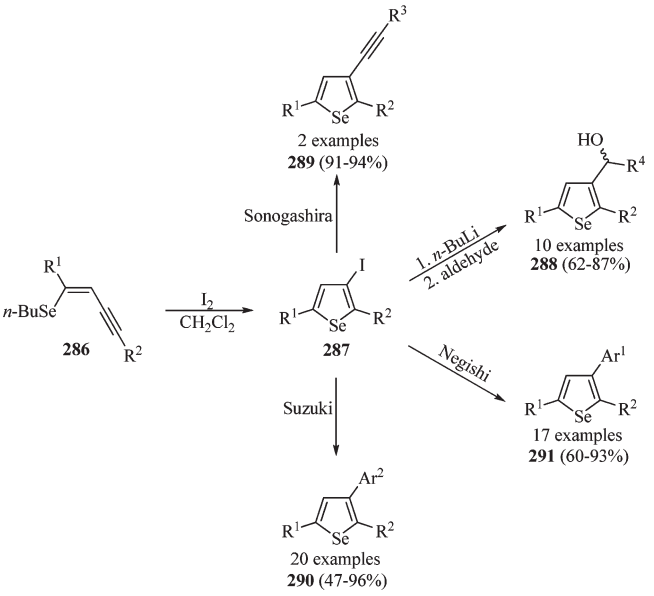
R = H, resin; R^1 = Ph, *p*-MeO-C_6H_4, *p*-F-C_6H_4; R^2 = *p*-MeO-C_6H_4, *p*-F-C_6H_4, *p*-CN-C_6H_4, 3-thienyl;

Scheme 130

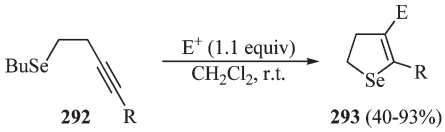
286 **287** (41-93%)

E = I, PhSe; R^1 = H, Ph, *n*-Bu, CH_2OH
R^2 = Ph, *n*-Bu, CH_2OH, *p*-Me-C_6H_4

Scheme 131



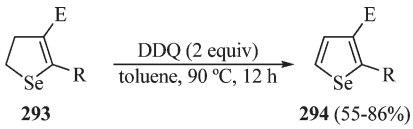
Scheme 132



292 **293** (40-93%)

E^+ = I_2, ICl, PhSeBr; R = aryl, alkyl, MeS, PhSe, BuSe, I, Br

Scheme 133

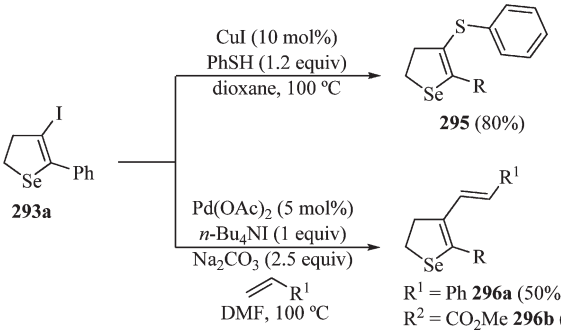


293 **294** (55-86%)

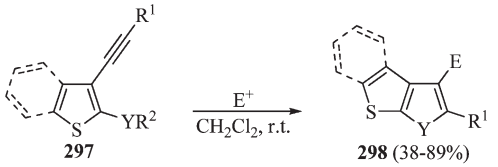
DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone

with 3-alkynylthiophene, having a phenyl group bonded at the selenium atom, the desired product was not observed, even under a long reaction time. The 4-iodoselenopheno[2,3-*b*]thiophene products can be further functionalized by palladium-catalyzed coupling reactions. In this way, the reaction of **298a** with aryl thiols, using just CuI as catalyst, in dioxane, afforded the resultant product **299**, in 66% isolated yield. In a similar manner, the reaction of **298a** with organoboron and organozinc species gave the corresponding Suzuki (**300**) and Negishi (**301**) products in 63% and 69% yields, respectively (Scheme 136).

Scheme 134

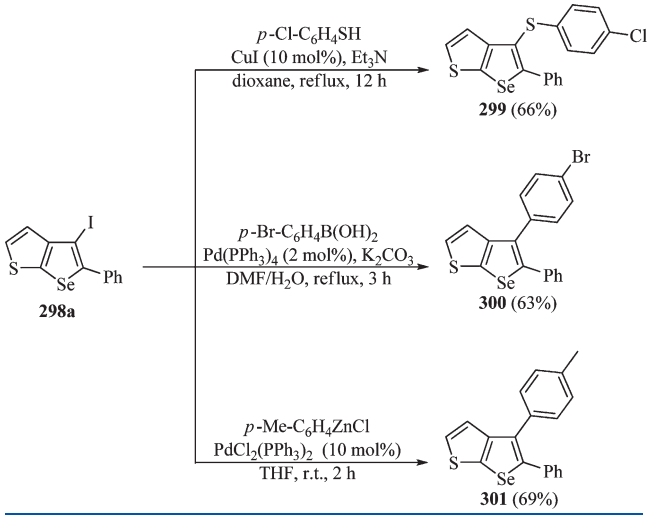


Scheme 135



Y = Se, Te; E^+ = I_2, ICl, PhSeBr; R^1, R^2 = alkyl, aryl

Scheme 136



Selenium β-lactams have also been synthesized using electrophilic cyclization. The selenium atom reacted as a nucleophile with alkyne selenoureas **302**, activated by the presence of an electrophilic source, to generate selenium β-lactams **303** (Scheme 137).[116] The cyclization was highly dependent on the type of electrophile and solvent used. When the reaction was carried out with NIS in THF, the desired selenium β-lactams were obtained along with side products. However, using iodine in THF, the selenium β-lactams **303** were exclusively produced in good isolated yields. The yields of

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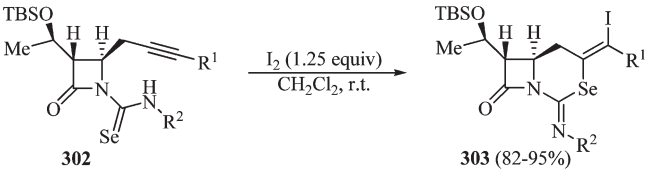
cyclization were improved to almost quantitative when the iodocyclization of alkyne selenoureas **302** was conducted with 1.25 equiv of iodine in CH_2Cl_2 at room temperature. The reaction was highly regioselective, although under these reaction conditions the six- or seven-membered ring β-lactams could be formed, only six-membered rings were detected. β-Lactams like **303a** offer an iodine substituent in the C-3 of the heterocycle, which provides a high degree of functionality and the possibility to exploit this residue to manipulate the heterocycle at a later stage. In this way, the reaction of compound **303a** with phenylacetylene using Sonogashira coupling conditions gave the corresponding coupling product **304** in 90% yield (Scheme 138).

We recently described the use of butyltellurium tribromide as an electrophilic source in the electrophilic cyclization of (*Z*)-chalcogenoenynes **305** to prepare 3-(butyltelluro)chalcogenophenes **306** (Scheme 139).[117] This study mainly focused on the introduction of a butyltelluro group at the C-3 of the selenophenes to be used as substrate in the palladium-catalyzed reactions.[118] We found that the butyltellurium bromide species did not work as electrophilic source; as a consequence, 3-(butyltelluro)selenophene was not obtained. With these disappointing results we turned our attention to use butyltellurium tribromide (*n*-BuTeBr$_3$), a tellurium(IV) species that is more electrophilic and more stable than *n*-BuTeBr. Thus, the reaction of 1.0 equiv of (*Z*)-selenoenyne and 1.1 equiv of *n*-BuTeBr$_3$ using MeCN as the solvent at room temperature and afterward treatment with $NaBH_4$ and EtOH gave the desired chalcogenophenes in high isolated yields. We believe that the mechanism of the tellurium cyclization reactions involves the following: (i) coordination of the carbon−carbon triple bond to the *n*-BuTeBr$_3$ to generate a telluronium intermediate **307**, (ii) anti attack of the selenium atom on the activated telluronium intermediate to produce the salt **308**, and (iii) facile removal of the alkyl group by the bromine present in the reaction mixture to generate the corresponding 3-[dibromo(butyl)tellanyl]selenophene **309** and one molecule of RBr. The reduction of **309** with $NaBH_4$ in EtOH gave the corresponding 3-(butyltellanyl)selenophene **306** as the product (Scheme 140). An advanced application of these tellurium compounds was carried out using the palladium-catalyzed cross-coupling. For example, compound **310** was successfully obtained in a 71% isolated yield by the Suzuki cross-coupling of **306a** with phenylethynyl trifluorborate (Scheme 141). In a similar manner, the cross-coupling of **306a** with 4-methoxyphenyl trifluorborate gave the corresponding selenophene derivative **311** in 68% yield (Scheme 141). These results were considered acceptable when compared to iodine analogues.[119]

4.3. Via Tellurium Nucleophile

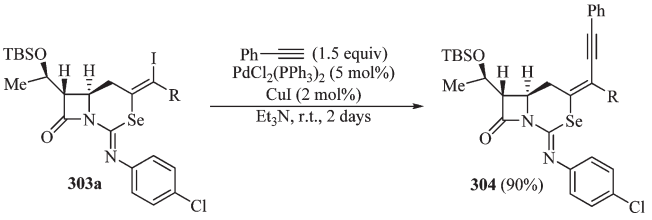
The use of tellurium species as nucleophile in the electrophilic cyclization reactions has been scarcely studied; in fact, only one example of such a transformation was reported in the literature by Daddoub and co-workers.[120] By studying the chemistry and application of the vinylic tellurides **312**, the authors discovered that they underwent the cleavage of the Te−C(sp^3) bond by reaction with iodine to produce 3-iodotellurophenes **313** as main products. The reaction was applicable to a series of tellurobutenynes, and the corresponding 3-iodotellurophenes **313** were isolated in good to excellent yields (Scheme 142). A mechanistic

Scheme 137

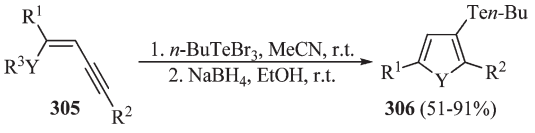


R^1 = H, Ph; R^2 = Ph, Bn, 2-naphthyl, *p*-Me-C_6H_4, *p*-Cl-C_6H_4

Scheme 138

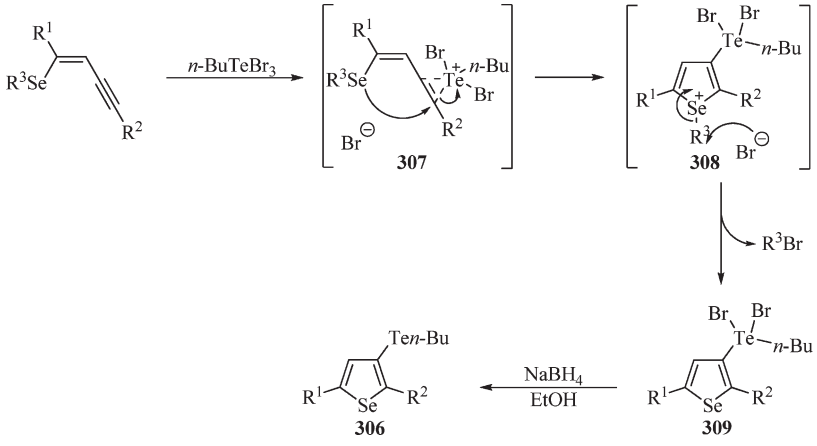


Scheme 139



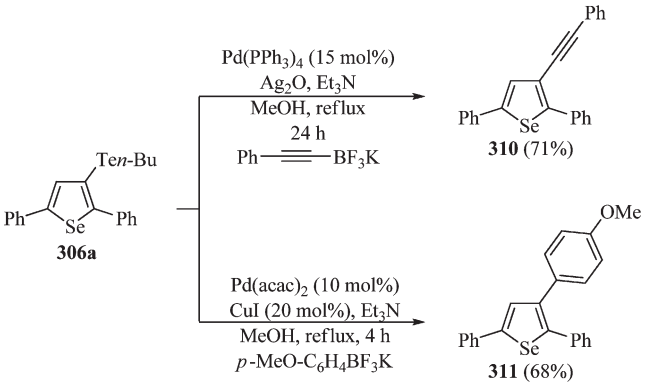
Y = Se, Te; R^1, R^2 = H, alkyl, aryl; R^3 = alkyl

Scheme 140

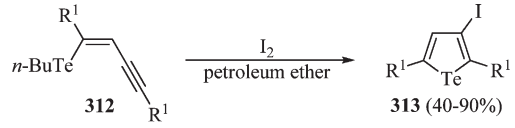


dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

Scheme 141



Scheme 142



R^1 = H, Me, Ph, *p*-Me-C_6H_4, *p*-MeO-C_6H_4

proposal was provided by the authors, which consists of an initial reaction of butyltelluroenyne with iodine to generate the iodonium intermediate **314**. The reaction with iodide gave origin to iodobutane and tellurenyl iodide **315**, which undergoes attack by an iodide at the iodine atom, followed by ring closure through opening of the iodonium ion (pathway a, Scheme 143). In another possibility, a direct ring closure can happen to give the dihalogenated tellurophene and iodobutane via intermediate **316** (pathway b, Scheme 143).

5. ELECTROPHILIC CYCLIZATION LEADING TO HETEROCYCLES VIA CARBON NUCLEOPHILE

The electrophilic cyclization of alkynes containing neighboring arenes provides a very valuable approach to a wide range of heterocycles. This process generally involves initial formation of an iodonium intermediate **317** by attack of the electrophile on the triple bond, followed by the attack of the electron cloud from the aromatic ring on the activated triple bond to produce the species **318**. Loss of a proton restores the aromatic ring, giving the cyclized product. Depending on the reaction conditions and the substrates, this process may involve the formation of spirocycles via ipso-cyclization through intermediate **319** (Scheme 144). Initial developments came from the Taniguchi group, who reported the successful conversion of *o*-aryloxyphenylalkynes **320** to dibenzoxepine derivatives by way of electrophilic cyclization using electrophiles, such as benzenesulfenyl chloride, bromine, and iodine monochloride.[121] The results revealed that the reaction was significantly dependent on the electronic effects of substituent in the aromatic ring of alkyne. While alkynes having an aromatic ring with a *p*-methoxy substituent reacted with ICl and PhSCl, giving the cyclized products **321** and **322** in 93 and 85% yields, respectively (Scheme 145), the alkynes having an aromatic ring without substituent gave a mixture of cyclized product **323** and 1,2-addition products **324** (Scheme 146). In addition to an aromatic ring, the reaction with alkyl group led to the exclusive formation of the 1,2-addition products **325** and **326** (Scheme 147).

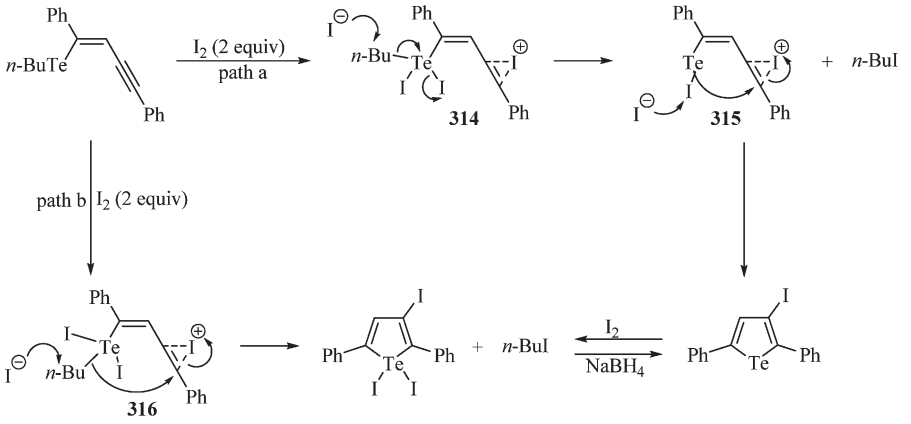
Larock and co-workers reported on the use of propargylic anilines **327** as precursors to quinolines **329**, substituted in the 3-position by an iodine or phenylseleno group (Scheme 148).[122] The optimal reaction conditions developed included stirring of 0.30 mmol of the propargylic aniline, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in 3 mL of CH_3CN at room temperature. The reaction took place under very mild reaction conditions and tolerated considerable functionality. In general, those alkyne substituents that can better stabilize an iodonium intermediate **328** increased the reactivity of the carbon−carbon triple bond and produced higher yields of the desired quinoline. Satisfactory results were obtained using substrates bearing either an electron-donating group on the phenyl ring of the side chain or an electron-withdrawing group on the aniline ring. The stronger electrophile ICl was also employed in this cyclization. The ICl reaction conditions included stirring of 0.30 mmol of the propargylic aniline, 2 equiv of ICl, and 2 equiv of $NaHCO_3$ in 3 mL of CH_3CN at room temperature. Once again, the best results were obtained at room temperature.

In a closely related investigation, Larock and co-workers also described that the electrophilic cyclization of substituted propargylic aryl ethers **330** by I_2, ICl, and PhSeBr produced 3,4-disubstituted 2*H*-benzopyrans **331** in excellent yields (Scheme 149).[123] This methodology resulted in vinylic halides or selenides under mild reaction conditions and tolerated a variety of functional groups, including methoxy, alcohol, aldehyde, and nitro groups. The introduction of substituent on the aryl groups had a considerable effect on the yield of the reaction. In addition, the presence of substituents on the aromatic ring attached to the alkyne showed that electron-donating groups, like Me and MeO in the para- or ortho-position, gave good yields, while an electron-withdrawing group, like a NO_2 group, gave relatively poor yields. The introduction of substituents onto the aromatic ring attached to the oxygen moiety also had a pronounced effect. Electron-donating groups, such as Me, *t*-Bu, and MeO, on the phenyl ring para to the oxygen gave better yields with I_2 as the electrophile than those obtained using ICl. To further prove the utility of this methodology, Larock carried out the palladium/copper-catalyzed reaction of the product **331a** with 5-ethynyl-2-fluorotoluene, obtaining **332** in an 87% yield. Palladium-catalyzed CO insertion in the product **331b** gave compound **333** in an overall 72% yield (Scheme 150).

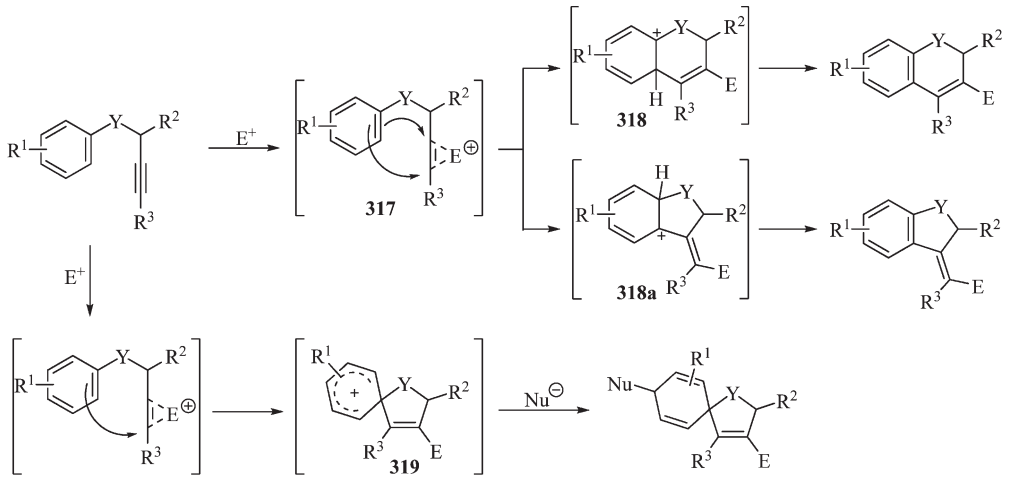
A somewhat different synthesis of benzopyrans and dihydroquinolines **335** from propargyl ethers or propargyl anilines **334** was studied by Barluenga and co-workers (Scheme 151).[124] In this case, the tetrafluoroborate of bis(pyridine)iodonium (IPy_2BF_4) reagent was employed as electrophilic source. The reaction provided a convenient method for the synthesis of a wide variety of benzofused heterocycles. The cyclization allowed additional substitution in the propargylic position, retaining the chirality and providing the possibility of carrying out the double and triple cyclizations (Scheme 152). In the case of aromatic rings having a para-donating group, MeO, the cyclization can proceed by initial ipso-substitution to give spirocycles that rearrange to benzopyrans.[125]

Two examples of 2-perfluoroalkyl quinolines preparation, by electrophilic iodocyclization of perfluoroalkyl propargyl imines/amines, were recently described.[126] One example, shown in Scheme 153, utilized the reaction of 2-perfluoroalkynyl imines **336** (0.5 mmol) with 2 equiv of I_2 and 2 equiv of CAN (ceric ammonium nitrate) in 0.1 M CH_3CN at room temperature to

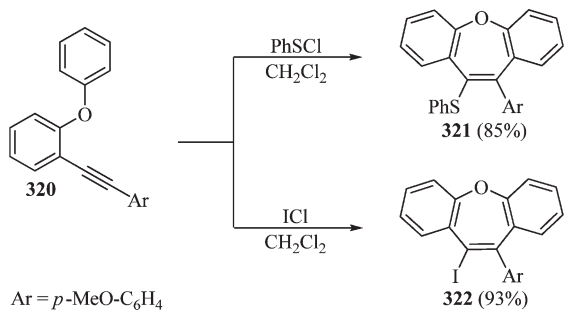
Scheme 143



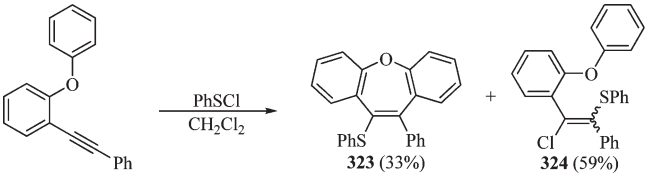
Scheme 144



Scheme 145



Scheme 146



afford quinoline derivatives **337** in 75−86% yields. While electron-donating, unsubstituted aniline and naphthylamine gave the desired products in good yields, the strongly electron-withdrawing fluorine failed to afford the product. In addition, methoxy perfluoroalkyl propargyl imine **338** gave the azaspiro compound **339** in 92% yield instead of the desired quinoline products (Scheme 153). The authors suggested that the presence of CAN is necessary to activate I_2, via reduction of Ce(IV) to Ce(III), which via electrophilic attack on the carbon−carbon triple bond of the propargylic aniline gives the iodonium intermediate **340**. The intramolecular ortho cyclization of the aniline aromatic ring with the triple bond results in the formation of perfluoroalkyl quinolines **337** (Scheme 154). Similarly, the formation of azaspiro compound **339** could involve the iodonium intermediate **341**, which undergoes intramolecular ipso-cyclization with the electron-rich aromatic ring. The subsequently nucleophilic attack of iodide on the methyl group bonded to the oxygen atom produces highly stabilized cyclized azaspiro product (Scheme 155). In the second example described in the paper, 2-perfluoroalkylquinolines **343** were also prepared in good yields via reaction of perfluoroalkyl propargyl amines **342** with 3 equiv of iodine in the presence of 2 equiv of $NaHCO_3$ in 0.1 M acetonitrile (Scheme 156). The mechanism of this cyclization reaction is believed to involve (i) coordination of the carbon−carbon triple bond to I_2 to generate an iodonium intermediate **344**, which activates the triple bond toward nucleophilic attack; (ii) nucleophilic attack of the aromatic ring on the activated iodonium intermediate to produce the 1,2-dihydroquinoline **345**;

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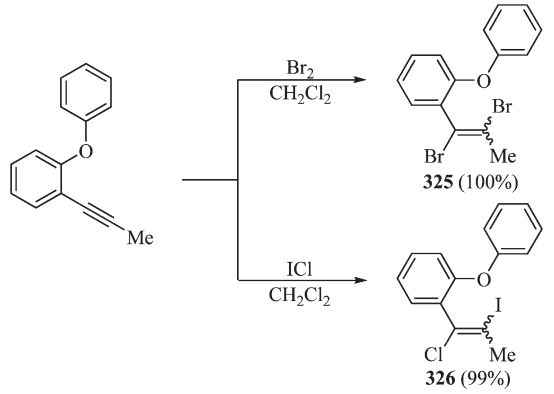
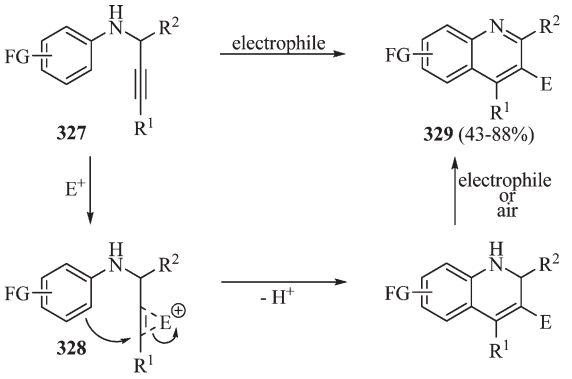
and (iii) facile oxidation of **345** by I_2 produces the corresponding quinolines **343** (Scheme 157).

Scheme 147

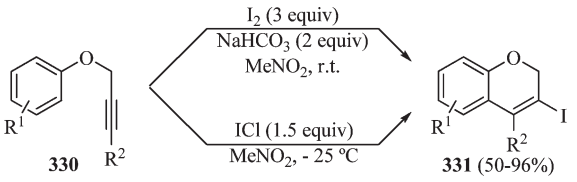


Scheme 148



E = I, PhSe; FG = H, CO_2Et, NO_2
R^1 = Ph, *p*-F-C_6H_4, *p*-Me-C_6H_4, *n*-Bu; R^2 = H, Me

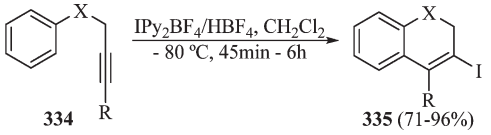
Scheme 149



R^1 = H, Me, *t*-Bu, MeO, Cl; R^2 = Ph, *p*-NO_2-C_6H_4, *p*-MeO-C_6H_4, Me

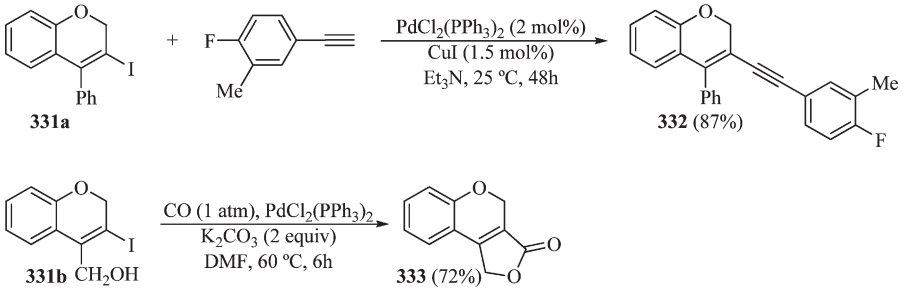
We utilized the intramolecular electrophilic cyclization of organochalcogen propargyl aryl ethers **346** to prepare functionalized 3-iodo-4-chalcogen-2*H*-benzopyrans **347** (Scheme 158).[127] We found that propargyl aryl ethers, bearing the chalcogen group, underwent highly selective intramolecular cyclizations when treated with I_2 or ICl, affording 3-iodo-4-chalcogen-2*H*-benzopyrans. Thus, the careful analysis of the optimized reactions revealed that the optimum condition for the I_2 cyclization was the addition of $NaHCO_3$ (0.5 mmol), at room temperature, to a solution of 0.25 mmol of selenophenyl propargyl aryl ether in 3 mL of THF. After that, 3 equiv of I_2 in 2 mL of THF was gradually added at room temperature. The large excess of I_2 required for the cyclization can be justified by the initial formation of an organochalcogen(IV) species **348** due to the great affinity of the chalcogen atom for I_2. It is well-reported that chalcogen alkynes react very fast and quantitatively with halogen to form a species of selenium(IV) known as dihalo organochalcogen.[128] For this reason, different from the mechanism proposed by the starting materials that were free of chalcogen atoms, we believe that the first step of this cyclization involves the usual reaction of organochalcogen propargyl aryl ethers with I_2 to give the selenium(IV) species **348**; after that the cyclization process follows: (i) coordination of the carbon−carbon triple bond to the electrophilic reagent to generate the iodonium intermediate **349**, (ii) attack of the electron from the aromatic ring on the activated triple bond to produce the species **350**, and (iii) the removal of a proton to restore the aromatic ring, giving the cyclized organochalcogen(IV) species **351**, which is reduced to organochalcogen(II) species by sodium thiosulfate (Scheme 159). We found the same limitation in our methodology when we used propargyl aryl ethers **352** having a tellurium group directly bonded at the triple bond. Unfortunately, in this case all conditions tested were found to be ineffective and neither I_2 nor ICl was effective to produce the cyclized product. This reaction gave as product the alkyne iodine **356** (Scheme 160). On the basis of these results and the knowledge that the C(sp)−tellurium bond exhibits an easier heterolytic cleavage than the carbon−sulfur and carbon−selenium bonds, due to the large volume and greater ionic character of the tellurium atom and the easy polarization of the bonds,[129] we assumed that the product **356** was formed via a tellurium(IV) intermediate **353**. Thus, the great affinity between tellurium and iodine atoms gives the telluride(IV)

Scheme 151



X = O, NMs, NTs; R = Me, Ph, Br, I, 3-thienyl

Scheme 150



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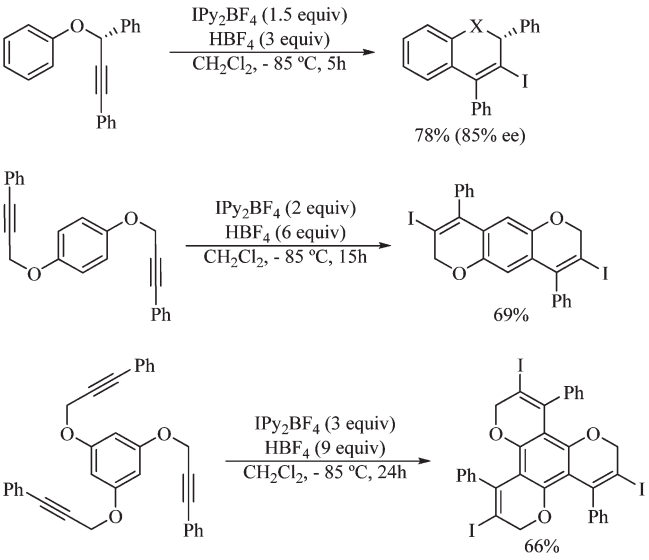
354;[130] nucleophilic attack of iodide on the alkyl group bonded to the tellurium atom produces a tellurium electrophilic species **355**, which via displacement of the stable tellurium tetraiodide affords the alkynyl iodide **356** (Scheme 160). Additional limitation in our method was observed when propargyl aryl ethers **357**, having a methoxyl group in the para-position of aromatic ring, reacted with I_2, giving as product an almost equimolar mixture of the two compounds, the cyclized in 50% yield and no cyclized **360** in 45% yield. In contrast, the reaction with propargyl aryl ether having a methoxyl group in the meta-position of the aromatic ring gave only the expected cyclized product in excellent yield and total stereoselection. Mechanistically, these results are a consequence of the two possible pathways, one of them involves the usual cyclization reactions as described in Scheme 159. The second mechanistic hypothesis involves the formation of hydroxylated uncyclized product **360**, via intermediates **358** and **359**, as shown in Scheme 161. The iodonium intermediate is formed followed by a nucleophilic attack of iodide on the methyl group bonded to the oxygen atom, producing the intermediate **359**, which is impeded to give the cyclized product.

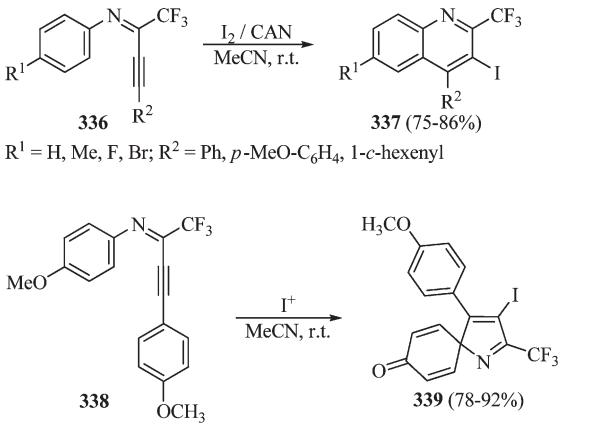
Larock and co-workers showed that the reaction of 2-(arylethynyl)biphenyl **361** with ICl at −78 °C afforded substituted polycyclic aromatic iodide **362** via ICl-induced intramolecular cyclization. Interestingly, this iodocyclization chemistry was successfully extended to heterocyclic systems.[131] For instance, treatment of benzofuran-containing acetylene **363** with ICl afforded the cyclization product **364** in a 91% yield and 2-(2-thiophenylethynyl)biphenyl **365** afforded the cyclization product **366** in good yield (Scheme 162). The regioselectivity in this iodocyclization chemistry was investigated. In the cyclization of thiophene **367**, the electronic effects control the regioselectivity, giving the product **368** as the major isomer. However, substantial amount of the product of substitution in the 4-position **369** was also observed (Scheme 163). In a closely related investigation, the same research group reported the cyclizations of alkynes containing electron-rich heteroaromatic rings, such as benzothiophenes and indoles. In this study, both benzothiophene derivatives **370** and **372** underwent I_2-induced carbocyclization to the corresponding dibenzothiophenes **371** and **373** in excellent yields. However, only an 18% yield of iodocarbazole **375** was obtained under I_2 cyclization conditions of **374**, but the yield of this cyclization was improved to 50% when ICl was used as the electrophile (Scheme 164).[132]

Intramolecular electrophilic cyclization of acetylenic malonates **376** was reported by Liang and co-workers. A procedure based on the use of 2.0 equiv of *t*-BuOK and 2.0 equiv of electrophile in THF at room temperature under argon converted acetylenic malonates **376** to the tricyclic lactone products **377** (Scheme 165).[133]

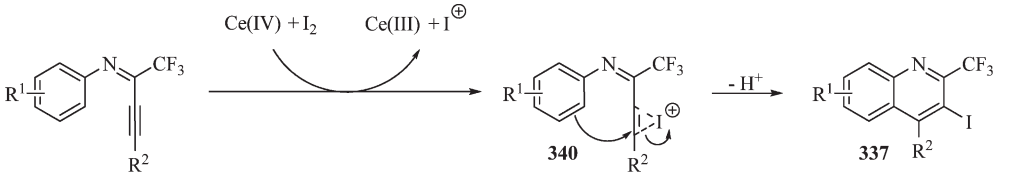
Scheme 152



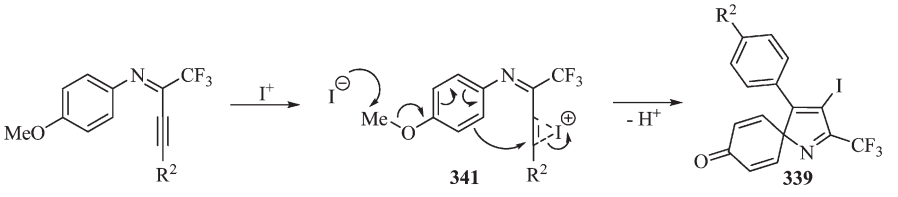
Scheme 153



Scheme 154



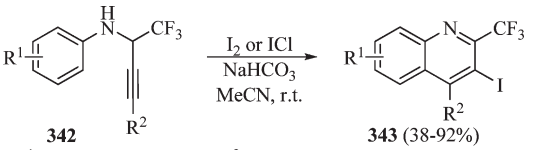
Scheme 155



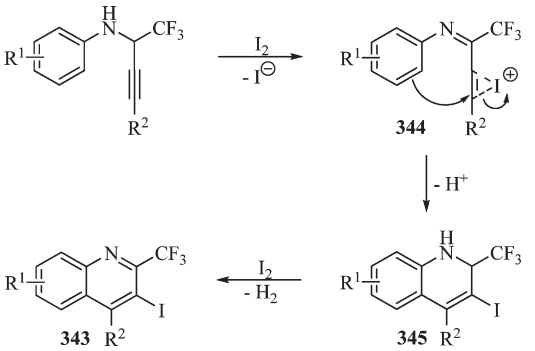
dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

The authors observed that the lactonization occurred after electrophilic cyclization, since in the absence of I_2 the lactones were not formed when acetylenic malonates **376** were treated with *t*-BuOK. In addition, the reactions of acetylenic malonates **376** with other electrophiles (ICl and NIS) were also studied. The 5-exo-dig cyclizations were consistent with a mechanism proposed, requiring initial coordination of iodine with carbon−carbon triple bond of acetylenic malonates to generate an iodonium intermediate **378**. The attack of the carbanion on the activated triple bond affords the cyclized product **379**, which after lactonization gives the tricyclic lactone products **377** (Scheme 166)

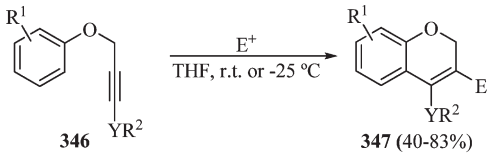
Scheme 156



Scheme 157

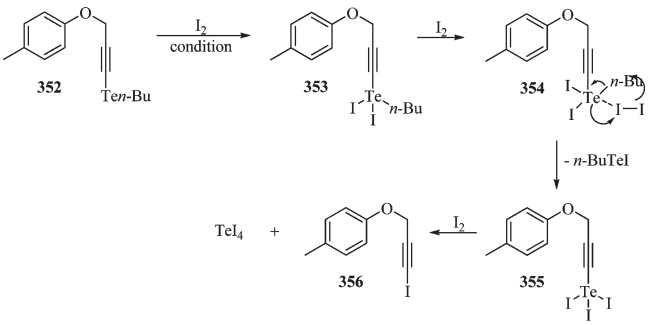


Scheme 158

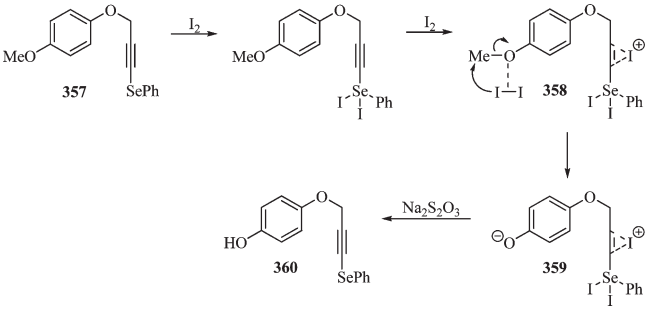


The intramolecular electrophilic cyclization of alkynes with functionally substituted aryl group via ipso-halocyclization provided a useful route to a wide variety of spirocycles. For example, Larock and Zhang described the preparation of the spirotrienones **381** by the reaction of triflamides **380** with electrophiles (Scheme 167).[134] The authors observed that, using ICl as electrophilic source, the substrates were efficiently cyclized when the reaction was carried out at −78 °C. When the cyclization of triflamides was performed at room temperature, the spirotrienone was obtained in a moderated yield together with the dihydroquinoline product **382**. The process was reasonably general with regard to the type of substituent on the remote end of the triple bond of the *N*-triflanilide. Electron-rich or electron-poor aryl- and alkyl-substituted alkynes were readily accommodated, producing the expected spirocyclic products in good yields. The presence of a sterically hindered silyl group presented no difficulty, and the reaction proceeded without desilylation. Iodine has also been employed successfully in this process as an electrophile; however, 2 equiv of $NaHCO_3$ were required to produce the spirotrienones in good yields. The mechanism shown in Scheme 168 is proposed

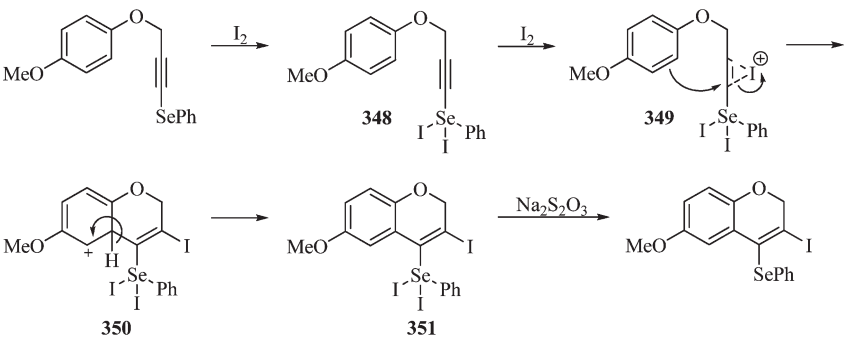
Scheme 160



Scheme 161

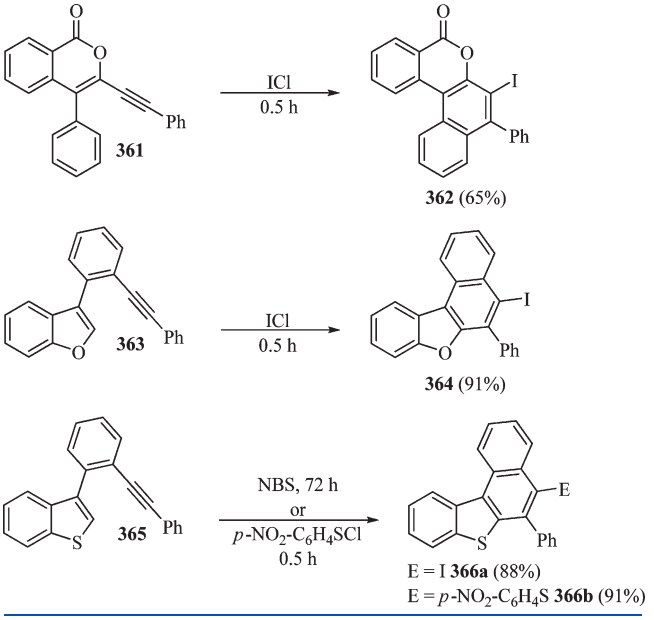


Scheme 159

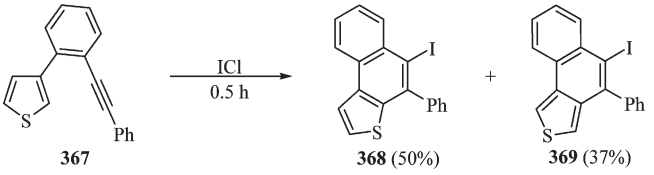


dx.doi.org/10.1021/cr100214d |*Chem. Rev.* 2011, 111, 2937–2980

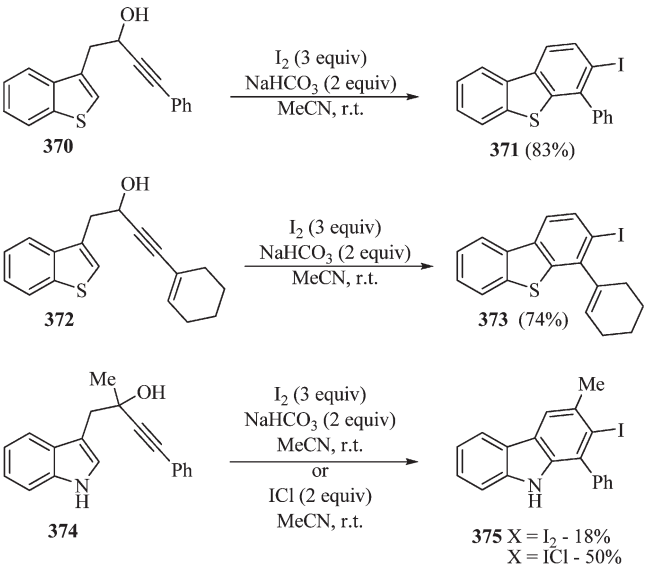
Scheme 162



Scheme 163

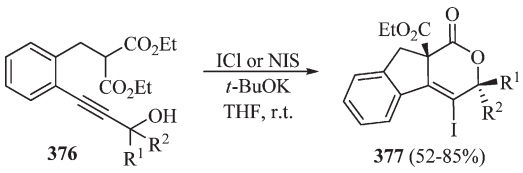


Scheme 164



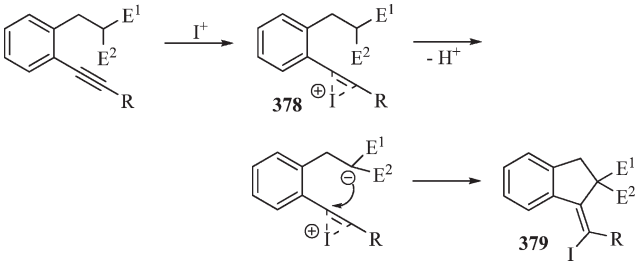
for this process. It consists of the following key steps: (1) an initial interaction of electrophilic iodine with the alkyne residue to give the iodonium intermediate **383**, (2) **383** can then undergo intramolecular ipso-attack on the electron-rich aromatic ring to form intermediate **384**, (3) the methyl group of **384** is removed via nucleophilic displacement by the X^- and HCO_3^- present in the reaction mixture.

Scheme 165



R^1 = H, Me, Ph, *p*-Me-C_6H_4, furyl; R^2 = H, Me

Scheme 166



Li and co-workers recently described two elegant examples of the electrophilic cyclization via ipso-halocyclization mentioned earlier. In one example, shown in Scheme 169, they utilized para-unactivated arylalkynes **385** to prepare spiro[4,5]trienyl acetates **386** using NIS and HOAc.[135] The reaction was carried out using arylalkynes (0.4 mmol), NIS (0.6 mmol), and HOAc (1 mL) at room temperature for 3 h. In the second example, they used para-activated *N*-(4-methylphenyl)propiolamides **387** as substrate in the synthesis of 8-methyleneazaspiro[4,5]trienes **388** (Scheme 170).[136] In this case, both ICl and iodine were used as electrophilic source. When ICl was used as electrophilic source, the best condition was the use of propiolamide (0.3 mmol) in MeCN (3 mL), ICl (1.5 equiv), and H_2O (0.1 mL) at −25 °C (0.5 h). The use of iodine required the propiolamide (0.3 mmol) in MeCN (3 mL) and I_2 (2 equiv) at room temperature for 24 h. The differentiation between the mechanism of this two methodologies is shown in Scheme 171. In one way, the mechanism proposed for the formation of spiro-[4,5]trienyl acetates involves the key intermediate **389**, which is attacked by the nucleophile HOAC to afford the cyclized product. In the other way, the 8-methyleneazaspiro[4,5]trienes are formed via intermediates **390** and **391**. The intermediate **391** is the most stable and undergoes the β-H elimination process to give the corresponding product. Analogous reaction conditions were applied by the same group to prepare the 8-(polyfluoroalkoxy)-azaspiro[4,5]trienes **393** from para-unactivated *N*-arylpropynamides **392**, using *N*-halosuccinimides as electrophilic source and 2,2,2-trifluoroethanol as nucleophilic reagents (Scheme 172).[137] The author found that the temperature, the use of molecular sieves, and the electrophilic sources had a fundamental influence on the reaction. The best results were achieved by using room temperature, 100 mg of 3 Å molecular sieves, and *N*-iodosuccinimide as electrophile.

Li and co-workers also reported the first electrophilic ipso-halocyclization using an electrophilic exchange process between CuX and electrophilic fluoride reagents.[138] They found that the reaction of *N*-(*p*-methoxyaryl)propiolamides or 4-methoxyphenyl 3-phenylpropiolates **394** with CuX (X = I, Br, SCN) and 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate **396** or *N*-fluoro-*N*′-(chloromethyl)triethylenediamine bis(tetrafluoroborate) **397** gave the corresponding spiro[4.5]decenones **395** in moderate to

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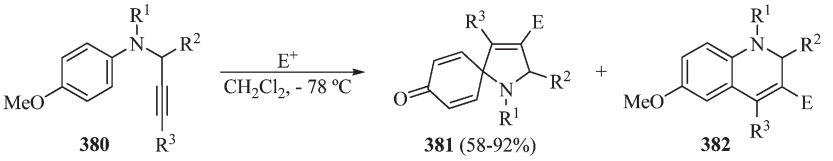
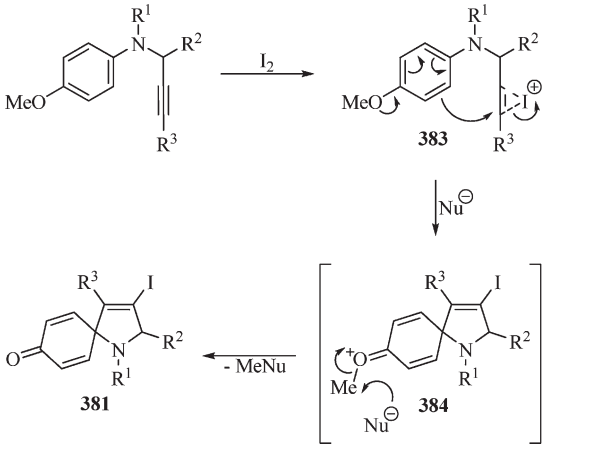
Scheme 167

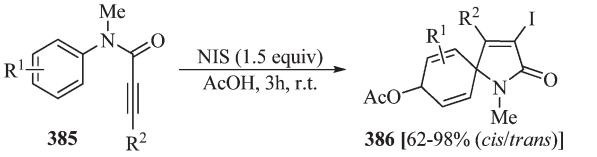


E = I, Br; R^1 = H, Tf, C(O)Me; R^2 = H, Me; R^3 = Ph, *p*-MeO-C_6H_4, *n*-Bu, TMS

Scheme 168

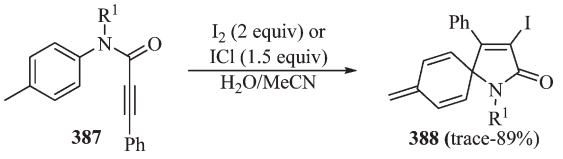


Scheme 169



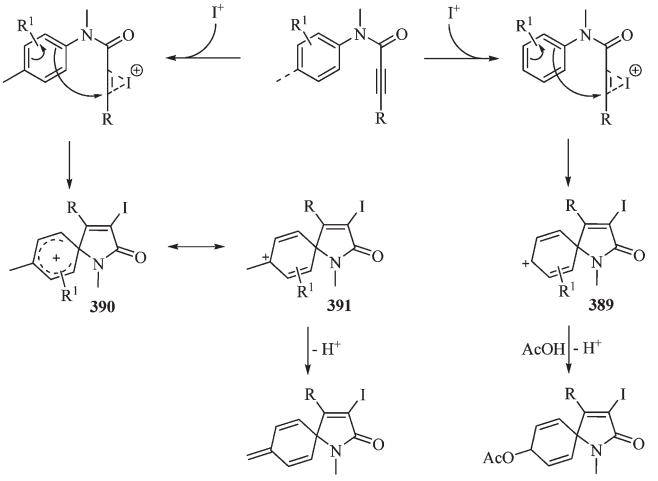
R^1 = Me, Ph, *p*-Me-C_6H_4, *p*-MeO-C_6H_4; R^2 = H, Me, Br, Cl, I, C(O)Me

Scheme 170

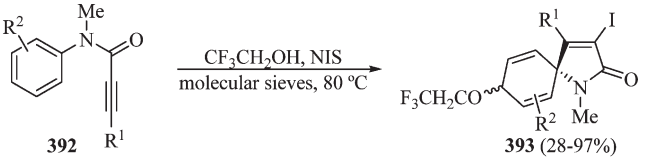


R^1 = H, Me, Ac, Bn

Scheme 171

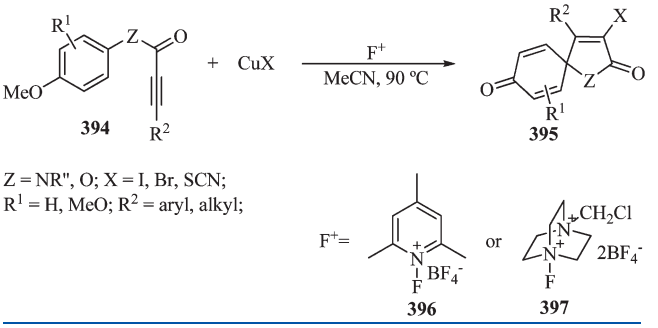


Scheme 172



R^1 = H, Me, Ph, *p*-MeO-C_6H_4, *p*-NO_2-C_6H_4; R^2 = H, Me, MeO, Cl, Br, I

Scheme 173



Z = NR", O; X = I, Br, SCN;
R^1 = H, MeO; R^2 = aryl, alkyl;

good yields (Scheme 173). The proposed mechanism is represented in Scheme 174: (i) the electrophilic source is first formed in situ by the reaction of copper salt with the fluoride reagents; (ii) coordination of the carbon−carbon triple bond to electrophile generates an onium intermediate **398**, which activates the triple bond toward nucleophilic attack; (iii) intramolecular ipso-cyclization gives the intermediates **399** and **400**; and (iv) facile removal of the alkyl group by the nucleophilic reagents, present in the reaction mixture, generates the spiro[4.5]decenones.

Fanghänel and co-workers described a very interesting ortho/ipso competition in the electrophilic cyclization.[139] They studied the cyclization of bis(4-methoxybenzylthio)acetylenes **401** with iodine monochloride in the presence or absence of nucleophiles. In these reactions, the cation **402** intermediate was assumed to participate in both cases. In this way, when the reaction of bis(4-methoxybenzylthio) acetylene with iodine monochloride was carried out in the absence of nucleophile, the 3-iodo-6-methoxy-4-(4-methoxybenzylthio)-1*H*-benzothiopyran **403** was formed in good yields. On the other hand, the reaction conducted in the presence of nucleophile, such as

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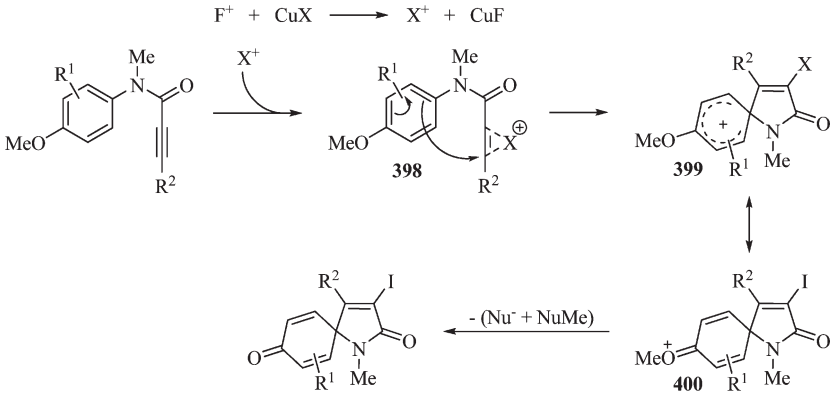
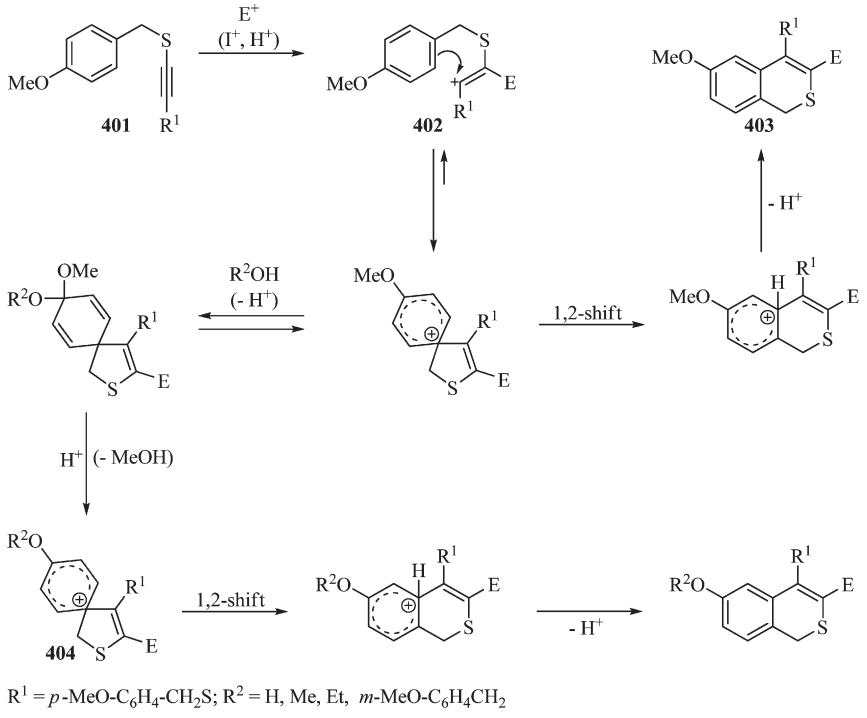
Scheme 174



Scheme 175



water or alcohols, gave the spirocyclohexadienone dihydrothiophenes **404** (Scheme 175).

6. CONCLUSIONS

In this review, we presented numerous very useful processes for the synthesis of heterocycles that involve electrophilic cyclization reactions via addition of the electrophilic source to the C(sp) bond of alkynes. The resulting functionalized heterocycles can undergo a variety of very useful subsequent transformations to give highly substituted heterocycles. In this methodology, halogen can usually be used as electrophilic source; however, organoselenium and organotellurim have proved to be the very effective for the electrophilic source, particularly when one considers that there are many ways to transform the resulting chalcogen functionalities into other substituents. These cyclization reactions proceed under relatively mild reaction conditions and tolerate a wide variety of functional groups, thus avoiding protection group chemistry. Most electrophilic cyclization-based methodology proceeds stereo- and regioselectively in excellent yields. Recently, an impressive increase in the number of publications on the preparation of heterocycles via electrophilic cyclization appeared in the literature. In fact, many efforts and developments have transformed heterocyclic chemistry into a very broad and exciting field with many opportunities for research and development of applications. Definitely, much more remains to be done in this field, and in the next few years, we will see many new, exciting findings in electrophilic cyclizations, mainly in the study of the applications of organochalcogen either as electrophilic source or substrate as well as studies in the toxicological and pharmacological aspects of new heterocycles containing chalcogenides. Thus, we hope with

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this review to have provided appropriate background for such developments and the encouragement to synthetic organic chemists to employ this valuable methodology in important new heterocyclic and medicinal chemistry.

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BIOGRAPHIES

Benhur Godoi was born in Santa Cruz do Sul, RS, Brazil, in 1985. He received his B.S. in Industrial Chemistry in 2007 and his M.S. degree in 2008 from the Federal University of Santa Maria (South Brazil), working under the direction of Prof. Gilson Zeni. After that, he started, in the same group, his Ph.D. studies on the synthesis of organochalcogen propargyl aryl ethers and their application in electrophilic cyclization reactions. His research interests are focused on the synthesis of heterocyclic compounds using electrophilic agents, transition metals, and Lewis acids in intramolecular cyclization reactions.

Ricardo F. Schumacher was born in 1984 in Santa Cruz do Sul, RS, Brazil. He received his B.S. degree in 2007 and his M.S. degree in 2008, from the Federal University of Santa Maria (Brazil), working under the direction of Prof. Dr. Gilson Zeni. After that, he started, in the same group, his Ph.D. studies on the synthesis of selenophene derivatives and Pd-catalyzed cross-coupling reactions. His research interests are focused on the synthesis of heterocycles and improvement of cross-coupling reactions using organochalcogen compounds.

Gilson Zeni was born in Irai, Brazil. He received his M.S. degree from the Federal University of Santa Maria-RS (South Brazil) in 1996, working under the direction of Prof. A. L. Braga, and his Ph.D. (1999) under the direction of Prof. J. V. Comasseto (the University of São Paulo). He then moved to the Federal University of Santa Maria, where he is now a professor. In 2003, he received a CNPq Postdoctoral Fellowship to work with Prof. R. C. Larock at Iowa State University. His current research interests center around the synthesis and reactivity of organochalcogen compounds, the development of new synthetic methods to application of organochalcogen substrates in the electrophilic cyclization reactions, and novel iron catalysts for cross-coupling reactions of organochalcogens.

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