Synthesis of substituted quinolines by the electrophilic cyclization of *n*-(2-alkynyl)anilines

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ABSTRACT

A wide variety of substituted quinolines are readily synthesized under mild reaction conditions by the 6-*endo-dig* electrophilic cyclization of *N*-(2-alkynyl)anilines by ICl, I_2, Br_2, PhSeBr, and *p*-$O_2NC_6H_4$SCl. The reaction affords 3-halogen-, selenium- and sulfur-containing quinolines in moderate to good yields in the presence of various functional groups. Analogous quinolines bearing a hydrogen in the 3-position have been synthesized by the Hg(OTf)$_2$-catalyzed ring closure of these same alkynylanilines.

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1. Introduction

The quinoline skeleton occurs in numerous natural products, especially in alkaloids.[1] Many quinolines display interesting physiological activities and have found applications as pharmaceuticals (e.g., antimalarial drugs, such as quinine or chloroquine) and agrochemicals, as well as being general synthetic building blocks.[2] Halogen-containing quinolines are of particular interest, because the halogen atom can play a crucial role in the compound's bioactivity and provides an avenue for further structure elaboration.[3] The isolation and synthesis of naturally-occurring quinoline derivatives have received considerable attention in the literature due to their biological and pharmaceutical importance.[4] Although simple 3-bromoquinolines can be obtained by the bromination of quinoline hydrochlorides,[5] the site-selective aromatic halogenation of substituted quinolines remains a synthetic challenge.[6] 3-Halo-

quinolines have also been synthesized by a photochemical route,[7] a modified Skraup quinoline synthesis employing halo-substituted acroleins and anilines,[8] and the Friedländer quinoline synthesis.[3c] Some of these methods suffer relatively low yields, poor regioselectivity, and/or rather lengthy synthetic sequences.

The cyclization of alkynes containing proximate nucleophilic centers promoted by electrophiles is currently of great interest and developing into a very effective strategy for carbo- and heterocyclic ring construction.[9] This chemistry provides a convenient approach to the synthesis of functionalized cyclic compounds through the regioselective addition of the nucleophile and the electrophile across the carbon–carbon triple bond. Successful examples of this process have been reported for the synthesis of isoquinolines,[10]
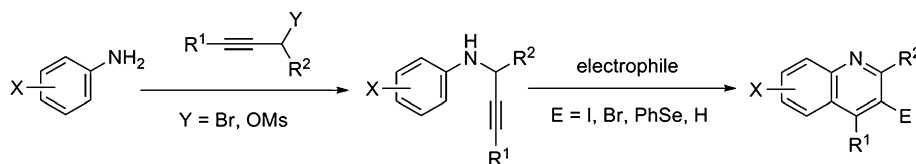
Scheme 1.

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benzothiophenes,[11] polycyclic aromatics,[12] indoles,[13] furopyridines,[14] isoindolin-1-ones,[15] isocoumarins,[16] isochromenes,[17] and benzofurans.[13d,18] However, no one prior to our recent communication[19] had employed this chemistry to synthesize quinolines. Herein, we wish to report the full details of this successful strategy for the synthesis of quinolines using very mild reaction conditions (Scheme 1).

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2. Results and discussion

During our early efforts to obtain 3-iodoquinolines, a two-step procedure was first examined (Scheme 2). Triflamide **1** with R=Ph was treated with ICl at −78 °C to afford a dihydroquinoline intermediate, which could be subsequently treated with base to achieve aromaticity.[20]
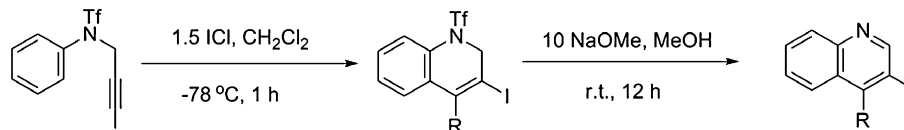
3-Iodo-4-phenylquinoline (**2**) was generated in a good yield using this approach (Table 1, entry 1). Thus, we have subsequently employed the reaction conditions developed here on a wide variety of other triflamides and the results are summarized in Table 1, entries 2–10. Good yields have been obtained when the group R on the alkyne is phenyl, as well as relatively electron-rich or electron-deficient aryl groups (entries 1–4). The cyclization of substrates
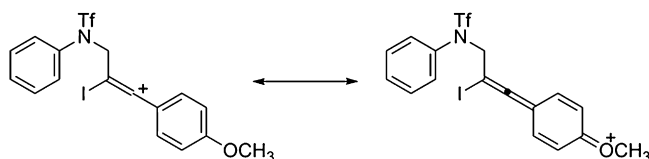
Scheme 2.

Table 1
Synthesis of quinolines from *N*-(2-alkynyl)triflamides[a]

Entry	Triflamide		Electrophile	Product		% Overall yield
1	R=Ph	**1**	ICl		**2**	88
2	R = (3-OCH₃-phenyl)	**3**	ICl		**4**	62
3	R = (4-CH₃-phenyl)	**5**	ICl		**6**	45
4	R = (4-COCH₃-phenyl)	**7**	ICl		**8**	51
5	R = (4-OCH₃-phenyl)	**9**	ICl		**10**	trace
6		**9**	I₂/AgClO₄		**10**	trace
7	R=n-Bu	**11**	ICl		**12**	25
8		**13**	ICl		**14**	trace
9		**15**	ICl	**17**		60+25
10		**18**	ICl		**19**	56
11		**20**	ICl		**2**	74

[a] All reactions were run using 0.30 mmol of the *N*-(2-alkynyl)sulfonamide and 1.5 equiv of ICl in 3 mL of CH₂Cl₂ at −78 °C for 1 h. After work-up, the solvent was removed, the crude mixture and 10 equiv of NaOMe were directly dissolved in MeOH and stirred overnight.

bearing both electron-donating and -withdrawing groups on the aniline moiety proved no difficulty when R is phenyl group (entries 9 and 10). When the 3-methoxyaniline derivative **15** was utilized, two isomeric quinoline products were obtained (entry 9). The product formed from cyclization onto the less sterically hindered position *para* to the methoxy group is the major isomer.

The products of addition of ICl to the triple bond of the triflamides **9** and **13** were the major products observed under the above reaction conditions. These presumably are generated from the relatively stable cations formed by the electron-releasing MeO or vinylic groups, followed by trapping by the chloride anion generated from the ICl (Scheme 3).


Scheme 3.

It appears that the relatively stable iodovinylic cation is reluctant to undergo electrophilic attack on the *N*-substituted aromatic ring. Therefore, removal of the trifluoromethanesulfonyl group might be expected to increase the nucleophilicity of the aromatic ring and thus improve the yield of the desired cyclization. This has indeed proven to be the case. Furthermore, although this is a convenient and new approach to 3-iodo-1,2-dihydroquinolines, the failure of the reactions with substrates **9** and **13** and the poor yield from the reaction of the alkyl-substituted alkyne **11** encouraged us to search for a more general and straightforward synthetic approach to 3-iodoquinolines. Finally, the cyclization of methanesulfonamide **20** was also successful (entry 11). Obviously, one could obtain dihydroquinolines after the first step without further base-induced deprotection of the nitrogen if one so desired.

Aniline derivative **21** was next subjected to direct electrophilic cyclization (Scheme 4). A fair amount of the iodoquinoline **10** was generated upon reaction with ICl and subsequent treatment by the oxidizing agents nitrobenzene or DDQ. However, it was later found that the oxidation step was unnecessary, since **10** was formed in a good yield upon iodination with ICl plus NaHCO$_3$ without subsequent addition of an oxidant.
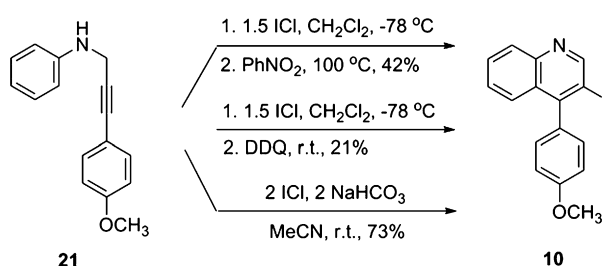
Scheme 4.

Figuring that the conversion of **21** to **10** by ICl might not be the simplest, most convenient and most general of transformations, we choose to optimize the reaction of aniline **22** using I$_2$ in the presence of various bases (Eq. 1).

(1)
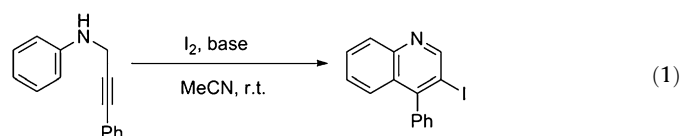
The results are summarized in Table 2. When a mixture of aniline **22**, 3 equiv of I$_2$ and 2 equiv of NaHCO$_3$ in MeCN was stirred at rt for

Table 2
Effect of I$_2$ stoichiometry and base on the cyclization of *N*-(3-phenyl-2-propynyl)aniline (**22**) (Eq. 1)[a]

Entry	Equiv of I$_2$	Base (equiv)	% Yield
1	3	NaHCO$_3$ (2)	76
2	2	NaHCO$_3$ (2)	44[b]
3	6	NaHCO$_3$ (2)	75
4	6	—	56[c]
5	3	NaOCO$_2$CH$_3$ (2)	72
6	3	Cs$_2$CO$_3$ (2)	71
7	3	pyridine (2)	35
8	3	Et$_3$N (2)	45

[a] All reactions were run under the following conditions unless otherwise stated: 0.3 mmol of **22**, I$_2$ and the base in 3 mL of MeCN were stirred at room temperature for 12 h.
[b] The reaction was not finished after 24 h; 40% of **22** was left.
[c] After 24 h, 25% of **22** was left.

0.5 h, the desired iodoquinoline **2** was obtained cleanly in a 76% yield (Table 2, entry 1). The reaction has also been run on a 2.0 mmol scale and product **2** was generated in a 75% yield, indicating the utility of this procedure on a larger scale. A much longer reaction time was required when decreasing the amount of I$_2$ from 3 to 2 equiv and the yield of **2** dropped substantially (entry 2). Essentially the same yield was obtained when using either 3 or 6 equiv of I$_2$ (compare entries 1 and 3). Thus, we chose to use 3 equiv of I$_2$ in the rest of our optimization work. The reaction was also dramatically slowed down when there was no base employed, even in the presence of 6 equiv of I$_2$ (entry 4). Other carbonate bases, such as Cs$_2$CO$_3$ and NaOCO$_2$CH$_3$, which have been successfully employed in our related isoquinoline synthesis,[10] gave a yield comparable to that of NaHCO$_3$ (entries 5 and 6). Organic bases, namely triethylamine and pyridine, actually lowered the yield (entries 7 and 8). The combination of 0.30 mmol of the *N*-(2-alkynyl)aniline, 3 equiv of I$_2$ and 2 equiv of NaHCO$_3$ in 3 mL of CH$_3$CN at room temperature was therefore chosen as our 'optimal' reaction conditions and the scope of this reaction was systematically investigated (Table 3).

First, various substituents on the end of the alkyne were examined. In general, electron-rich and electron-deficient aryl groups have generated quinolines in good to excellent yields, presumably because these substituents are capable of stabilizing a vinylic cation intermediate (entries 1, 5, and 10; Table 3). The yield dropped and a much longer reaction time was needed for the *p*-acetylphenyl-substituted alkyne **30** to react (24 h vs 0.5 h for alkyne **22**) (entry 11). Substrate **31** with a strong electron-withdrawing NO$_2$ group on the *para*-position of the arene failed to generate any cyclization product (entry 12). The yield of the pyridine derivative **34** also suffers, which might be the result of the coordination of I$^+$ to the nitrogen of the pyridine, further lowering the electron density of the pyridine ring (entry 13).[10] Interestingly, an amino group, generally believed to be a stronger nucleophile than a phenyl group, *ortho* to the alkynyl moiety remains untouched during the cyclization in contrast to our previously reported indole synthesis employing 2-(1-alkynyl)-anilines (entry 14).[13a] This indicates the need for an appropriate leaving group on the nitrogen in order to effect a successful indole synthesis. In fact, cyclization by I$_2$ proceeds in a decent yield even when the terminus of the carbon–carbon triple bond bears an alkyl group. Thus, 4-butyl-3-iodoquinoline (**12**) can be synthesized in a 43% yield, alongside a 26% yield of 4-butyl-3,6-diiodoquinoline, which is presumably formed by iodocyclization of *N*-(2-heptynyl)-4-iodoaniline formed by prior iodination of the aniline (entry 15). The desired cyclization did not occur when the acetylene bears a sterically-hindered silyl or *t*-Bu group, or a simple H atom on the triple bond (entries 17–19). Substitution of a vinylic group on the alkyne presents no problem as the 4-(1-cyclohexenyl)quinoline **14** was formed cleanly in an 80% yield

Table 3
Synthesis of quinolines by electrophilic cyclization of *N*-(2-alkynyl)anilines
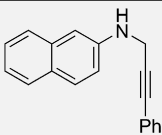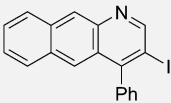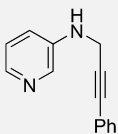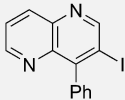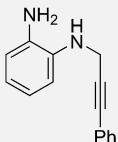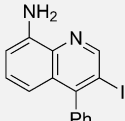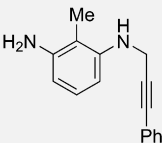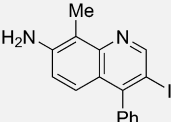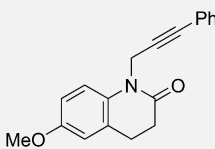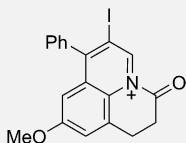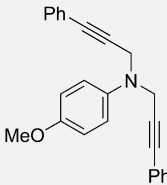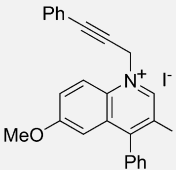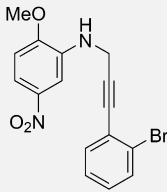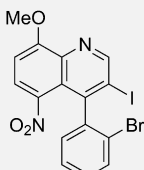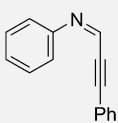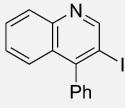
Entry	Propargylic amine		Electrophile	Product(s)			% Yield
				E			
1	R=Ph	**22**	I$_2$[a]	I		**2**	76
2			ICl[b]	I		**2**	83
3			PhSeBr[b]	PhSe		**23**	20
4			NBS[b]	Br		**24**	0[c]
5	R = —OMe	**21**	I$_2$[a]	I		**10**	71
6			ICl[b]	I		**10**	73
7			PhSeBr[b]	PhSe		**25**	74
8			Br$_2$[b]			**26**	51
9		**21**	*p*-O$_2$NC$_6$H$_4$SCl[b]	SC$_6$H$_4$NO$_2$-*p*		**27**	12
10	R = —F	**28**	I$_2$[a]	I		**29**	78
11	R = —COMe	**30**	I$_2$[a,d]	I		**8**	57
12	R = —NO$_2$	**31**	I$_2$[a]	I		**32**	trace
13	R =	**33**	I$_2$[a]	I		**34**	25
14	R =	**35**	I$_2$[a]			**36+37**	55+0
15	R=n-Bu	**38**	I$_2$[a]	I		**12**	43[e]
16			ICl[b]	I		**12**	30
17	R=SiMe	**39**	I$_2$[a]	I		**40**	trace
18	R=H	**41**	I$_2$[a]	I		**42**	0
19		**43**	I$_2$[a]			**44**	0

Table 3 (*continued*)

Entry	Propargylic amine		Electrophile	Product(s)		% Yield
20		**45**	I₂[a]		**14**	80
21		**46**	I₂[a]		**47**	38[f]
22		**48**	I₂[a]		**19**	63
23		**48**	PhSeBr[b]		**49**	75
24		**50**	I₂[a]	E = I	**51**	88
25			PhSeBr[b]	PhSe	**52**	56
26		**53**	I₂[a]		**54**	79
27		**55**	I₂[a]		**56**	75
28		**57**	I₂[a]		**58**	58[d]
29		**59**	I₂[a]		**16+17**	29+37
30		**60**	I₂[a]		**61+62**	71+8

(*continued on next page*)

Table 3 (continued)

Entry	Propargylic amine		Electrophile	Product(s)		% Yield
31		**63**	I_2[a]		**64**	75
32		**65**	I_2[a]		**66**	trace
33		**67**	I_2[a]		**68**	0
34		**69**	I_2[a]		**70**	35[g]
35		**71**	ICl[b,h]		**72**	50
36		**73**	I_2[a]		**74**	62
37		**75**	I_2[a]		**76**	80
38		**77**	I_2[a]		**2**	0

[a] All reactions were run under the following conditions unless otherwise stated: 0.3 mol of the propargylic aniline, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in 3 mL of CH_3CN were stirred at room temperature for 0.5 h.

[b] Two equiv of ICl/Br_2/PhSeBr/p-$O_2NC_6H_4SCl$/NBS in 1 mL of CH_3CN were added dropwise to the solution of 0.3 mmol of propargylic aniline and 2 equiv of $NaHCO_3$ in 2 mL of MeCN over 10 min at rt and the solution was stirred for another 10 min.

[c] Only the product formed from bromination of the 4-position of the aniline ring was obtained.

[d] The reaction took 24 h.

[e] The product was obtained together with a 26% yield of 4-n-butyl-3,6-diiodoquinoline.

[f] Compound **2** was also generated in a 25% yield.

[g] 7-Amino-3,6-diiodo-8-methyl-4-phenylquinoline was also obtained in a 28% yield.

[h] ICl (4 equiv) in 1 mL of CH_2Cl_2 was added dropwise to the solution of 0.30 mmol of **71** in 2 mL of CH_2Cl_2 over 10 min at −78 °C and the solution was stirred for another 10 min.

(entry 20). Together with iodoquinoline **2**, formed in a 25% yield, the 2,3,4-trisubstituted quinoline **47** was obtained in a moderate yield. This quinoline is most likely generated by elimination of toluene during the aromatization step (entry 21).

An interesting feature of this cyclization is the fact that yields aren't significantly affected by the substituents on the aniline ring. para-Substituents ranging from a weak electron-withdrawing group, like a Br, to a strong electron-withdrawing group, like a NO_2,

along with an electron-donating MeO group, all generate the corresponding substituted quinoline derivatives in good yields (entries 22, 24, 26 and 27). A substrate with two methyl groups situated *meta* to the amino group also afforded a high yield of the corresponding quinoline, although a longer reaction time was needed (entry 28).

The regioselectivity of this cyclization has also been investigated. 3-Methoxyaniline **59** afforded the *ortho*-cyclization regioisomer **16** and the *para*-cyclization isomer **17** in 29% and 37% yields, respectively (entry 29). On the other hand, very interestingly, the 3-nitroaniline **60** afforded regioisomers **61** and **62** in a 79% combined yield with cyclization occurring primarily *ortho* to the nitro group (9:1 ratio of *ortho* to *para* cyclization) for reasons that are not obvious (entry 30). Excellent regioselectivity was achieved in the cyclization of 2-naphthylamine **63**, since only one isomer was observed. The ring closure occurred selectively in the less sterically-hindered 3-position of the naphthalene ring (entry 31). Unfortunately, cyclization onto a pyridine ring proved unsuccessful using our current reaction conditions (entry 32).

Other halogen electrophiles have also been successfully employed in this quinoline synthesis. For example, the stronger electrophile ICl has been utilized in this cyclization. Our 'optimal' ICl reaction conditions are the following: 0.30 mmol of the propargylic aniline, 2 equiv of ICl, and 2 equiv of $NaHCO_3$ in 3 mL of MeCN are stirred at room temperature. Three equiv of ICl were not necessary, since all of the alkynes were completely consumed when 2 equiv of ICl were employed. Lowering the temperature to 0 °C or −78 °C did not improve the yields. Yields comparable to those obtained using I_2 (compare entry 1 with 2, and entry 5 with 6, Table 3) have been obtained, but the reactions are much faster, being complete in about 5 min. However, using ICl as the electrophile was not helpful in improving the yields of the desired monoiodinated quinolines where I_2 only generated a moderate yield, as in entries 15 and 16. When 2 equiv of NBS in MeCN were added dropwise to a mixture of aniline **22** and 2 equiv of $NaHCO_3$ in MeCN, N-(3-phenyl-2-propynyl)-4-bromoaniline was obtained in quantitative yield, and no cyclization to the quinoline was observed after 2 h (entry 4). The reaction of Br_2 with alkynylaniline **22** was messy with the formation of mono-, di- and tribromoquinolines evident. In the case of aniline **21**, we were able to isolate dibromoquinoline **26** in a 51% yield (entry 8, Table 3).

Although PhSeCl and PhSeBr has been found to be effective electrophiles in our electrophilic cyclization of alkynes to isoquinolines,[10] isochromenes,[17] isocoumarins,[16] benzo[b]thiophenes,[11] and isoindolin-1-ones,[15] PhSeCl is not nearly as effective as PhSeBr in this current quinoline process (Eq. 2 and entries 1 and 3, Table 4). The reaction of PhSeCl plus 2 equiv of $NaHCO_3$ gave only a 38% yield of selenium-substituted quinoline (entry 1, Table 4). This reaction also provided a 19% yield of the 3,6-diselenium-substituted quinoline. No reaction occurred when using PhSeSePh (entry 2, Table 4). Interestingly, when PhSeBr was used as the electrophile, the desired 3-(phenylselenyl)quinoline **25** was obtained in a 74% yield (entry 3). Surprisingly, simply changing the base from $NaHCO_3$ to Na_2CO_3 resulted in a messy reaction and none of the desired quinoline **25** was observed (entry 4). Organic bases, such as NEt_3 and pyridine, provided lower yields (entries 5 and 6). The presence of a base to remove the side product HBr is crucial (entry 7). The reaction of **21** and PhSeBr without any base afforded none of the desired quinoline. Instead, a 42% yield of aniline **21** with a PhSe group *para* to the aniline nitrogen was obtained. It is important to emphasize that the dropwise addition of ICl and PhSeBr to the reaction vessel is very important in obtaining a clean reaction, but this is unnecessary when using I_2. Representative examples of the synthesis of selenium-containing quinolines are included in entries 3, 7, 23 and 25 in Table 3.

(2)
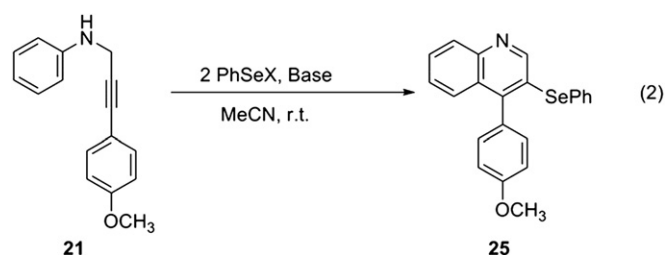
Table 4
Effect of organoselenium electrophiles on the cyclization of aniline **21** (Eq. 2)[a]

Entry	Electrophile	Base (equiv)	% Yield of 25
1	PhSeCl	$NaHCO_3$ (2)	38[b]
2	PhSeSePh	$NaHCO_3$ (2)	0
3	**PhSeBr**	**$NaHCO_3$ (2)**	**74**
4	PhSeBr	Na_2CO_3 (1)	0
5	PhSeBr	NEt_3 (3)	40
6	PhSeBr	Pyridine (3)	48
7	PhSeBr	—	0[c]

[a] Two equivalents of PhSeX in 1 mL of MeCN was added dropwise to a solution of 0.3 mmol of propargylic aniline and the base in 2 mL of MeCN at rt.
[b] A 19% yield of 3,6-di(phenylselenyl)quinoline was also obtained.
[c] Compound **21** bearing a PhSe group *para* to the amino group was obtained in a 42% yield.

When N,N-disubstituted anilines and derivatives were employed in the reaction with ICl or I_2, quinolinium salts can be obtained (entries 35 and 36, Table 3). Thus, the dipropargylic aniline **73** gave a good yield of the isoquinolinium salt **74**, when allowed to react with I_2 (Eq. 3). None of the double cyclization product was observed. In a similar fashion, amide **71** reacted with ICl to give isoquinolinium salt **72** (Table 3, entry 35).

(3)
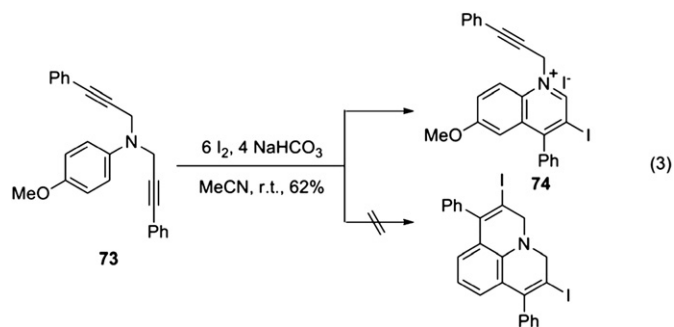
The highly substituted aniline **75** gave an excellent yield of the highly functionalized quinoline **76** (entry 37). An analogous approach to quinolines might be to cyclize N-(3-phenyl-2-propynylidene)aniline, which can be easily generated by the condensation of aniline with 3-phenylpropynal. However, under our standard I_2 reaction conditions, none of the desired iodoquinoline **2** was generated. Instead, the imine starting material decomposed (entry 38, Table 3).

We propose the following mechanism for this iodocyclization process (Scheme 5): (1) the carbon–carbon triple bond of the propargylic aniline coordinates to the iodine cation generating an iodonium intermediate **A**, (2) intramolecular nucleophilic attack of the aromatic ring of the aniline on the activated triple bond forms dihydroquinoline **B**, (3) in the presence of I_2 or ICl, the dihydroquinoline **B** is oxidized to the corresponding quinoline.[20] It is also possible that the dihydroquinoline is not oxidized to the quinoline until it is exposed to air during the work-up.

Scheme 5.
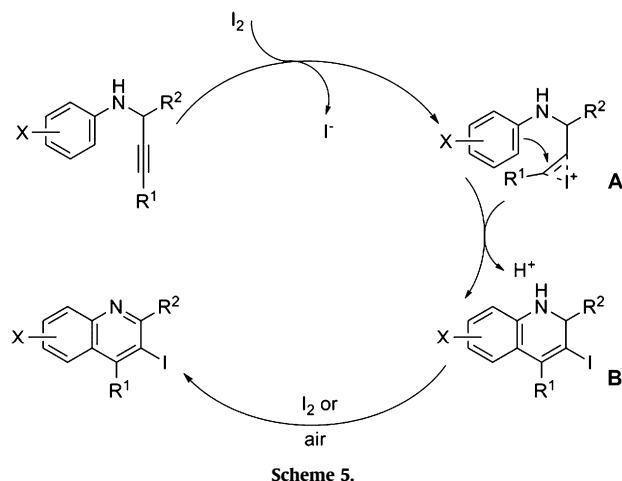
Recently, considerable attention has focused on metal catalysts, which can effectively activate unsaturated bonds toward intramolecular electrophilic attack on arenes. Various heterocycles and carbocycles have been successfully synthesized using this strategy.[21–26] However, the direct cyclization of simple propargylic anilines to quinolines has not yet been achieved. Our interest in the synthesis of quinolines bearing a hydrogen in the 3-position encouraged us to first screen those reagents and catalysts previously reported to be active in this kind of chemistry (Eq. 4). The results are summarized in Table 5.


either MeCN or CH_2Cl_2 as the solvent at rt (entries 13 and 14). Lowering the amount of $Hg(OTf)_2$ or changing the solvent or addition of an oxidant are all detrimental to the reaction (entries 8–12). This reaction is believed to proceed in a stepwise manner, because compound **79** could be separated from the reaction mixture after half an hour and it was gradually converted to compound **78** when stirred in the presence of air, but the absence of mercury salts (Eq. 5). However, analogous dihydroquinoline intermediates have not been observed in the iodine-promoted ring closure process (Table 3).
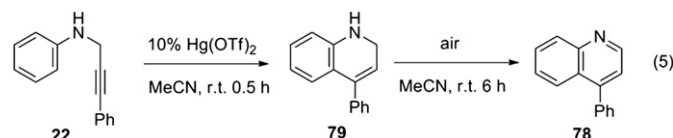
The scope of this metal-catalyzed process using the above 'optimal' reaction conditions was subsequently examined. The compatibility of substrates is very similar to that of the I_2 cyclization process. With phenyl and p-MeOC$_6$H$_4$ groups on the end of the alkyne, the desired quinolines were generated in excellent yields (Table 6, entries 1 and 2). An analogous 3,5-dimethylaniline derivative was also cyclized in good yield (entry 4). Only 4% $Hg(OTf)_2$ was needed for the cyclization of substrate **59** with a *meta*-methoxy substituent (entry 5). Regioisomers **83** and **84** were obtained in a 73% overall yield. The yield of isomer **84** is slightly higher than that of **83**. On the other hand, cyclization of the 2-naphthyl derivative **63** afforded a high yield of a single product in which cyclization occurs exclusively in the 1-position of the naphthalene (entry 6). Note that the regiochemistry here is completely the opposite of that of the corresponding iodocyclization (Table 3, entry 31). When an electron-withdrawing ester group was incorporated into the *para*-position of the aniline, only a 53% yield of quinoline **86** could be obtained employing 20 mol% of $Hg(OTf)_2$ (entry 7). The reaction was not as efficient when the distal

Table 5
Metal-catalyzed cyclization of aminoalkyne **22** (Eq. 4)

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	% Yield of **78** (**22**)	Ref.
1	5% $AuCl_3$	EtOH	75	48	10 (75)	21
2	5% $AuCl_3$/ 15% AgOTf	MeCN	70	72	15 (70)	22
3	5% $RuCl_3$/ 15% AgOTf	$ClCH_2CH_2Cl$	65	48	8 (90)	23
4	5% $PtCl_4$	$ClCH_2CH_2Cl$	70	48	38 (51)[a]	24
5	5% $PtCl_2$	toluene	80	48	5 (80)	25
6	3% $Cu(OTf)_2$	CH_2Cl_2	rt.	48	0	—
7	3% $Hg(O_2CCF_3)_2$	MeCN	rt.	48	trace	—
8	3% $Hg(OTf)_2$/ 15% TMU	MeCN	rt.	24	55 (35)[a]	—
9	5% $Hg(OTf)_2$	MeCN	rt.	48	50 (45)[a]	—
10	3% $Hg(OTf)_2$	MeCN	50	168	40 (50)[a]	—
11	4% $Hg(OTf)_2$	DMSO	100	48	10 (71)	—
12	5% $Hg(OTf)_2$/ 1.2 MnO_2	MeCN	rt.	24	< 1	—
13	**10% $Hg(OTf)_2$**	**MeCN**	**rt**.	**6**	**96**	—
14	10% $Hg(OTf)_2$	CH_2Cl_2	rt.	24	95	—

[a] The yield did not improve when the reaction was run a longer time.

$AuCl_3$ and $Au(OTf)_3$, which have been shown to be effective catalysts for the cyclization of imines derived from carbonyl compounds and propargylic amines,[21] and the hydroarylation of alkynes[22] were ineffective in this quinoline process (Table 5, entries 1 and 2). The reaction of aniline and 3-phenylpropynal was also messy under the reaction conditions of entry 1. Unsatisfactory results were also obtained from RuCl3/AgOTf, PtCl4, and PtCl2 salts, although they have been shown to affect the cyclization of N-protected anilines to hydroquinolines (entries 3–5).[23–25] While both $Cu(OTf)_2$ and $Hg(O_2CCF_3)_2$ are inactive (entries 6–8), $Hg(OTf)_2$ was found to be the catalyst of choice. Thus, 10% $Hg(OTf)_2$ promotes the cyclization of **22** to quinoline **78** in a 95–96% yield using

end of the triple bond was substituted by either an alkyl or vinylic group (entries 3, 8 and 9). However, we were able to efficiently cyclize substrates bearing electron-rich aromatic rings and either a butyl or cyclohexenyl group on the alkyne, and the amount of catalyst could be reduced to 5 mol% in both cases (entries 8 and 9, Table 6). It is particularly noteworthy that a C-C double bond is readily accommodated in this later process.

These functionally-substituted quinolines, particularly the iodo derivatives, offer considerable potential for further elaboration. For example, iodoquinoline **29** undergoes a facile Suzuki reaction[26] with styrylboronic acid to afford the styryl-substituted quinoline **93** in a 73% yield (Scheme 6). Quinoline **93** is an analog of a CHMG-CoA

Table 6
Synthesis of quinolines by the Hg(OTf)$_2$-catalyzed cyclization of *N*-(2-Alkynyl)anilines in MeCN[a]

Entry	Substrate		Hg(OTf)$_2$ (mol %)	Time (h)	Product		% Yield
1	R=Ph	**22**	10	6		**78**	96
2	R=ρ-MeOC$_6$H$_4$	**21**	10	6		**80**	88
3	R=n-Bu	**38**	15	12		**81**	50
4		**57**	10	6		**82**	79
5		**59**	4	6		**83** +**84**	35 +38
6		**63**	10	12		**85**	65
7		**50**	20	24		**86**	53
8		**87**	5	3		**88**	75
9		**89**	5	5		**90**	73
10		**45**	30	24		**91**	38
11		**75**	20	12		**92**	65

[a] To a solution of 0.3 mmol of the propargylic aniline in 3 mL of CH$_3$CN was added a catalytic amount of Hg(OTf)$_2$. The reaction mixture was stirred at room temperature for the indicated time.

reductase inhibitor.[3c] Iodoquinoline **36** readily undergoes an intra-molecular palladium-catalyzed Buchwald–Hartwig amination[27] to produce the interesting tetracyclic diamine **94** in a 65% yield.
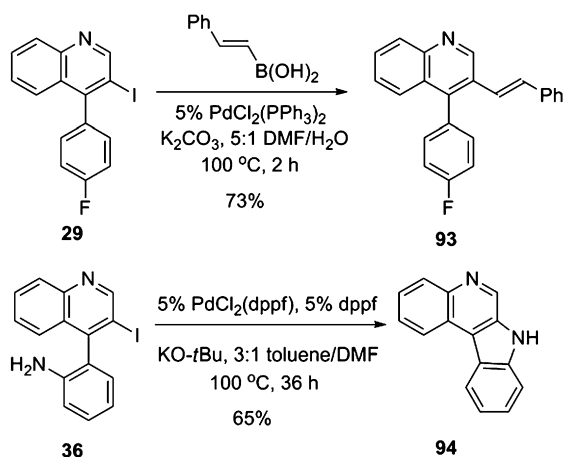
Scheme 6.

3. Conclusions

A wide variety of 3-halogen-, selenium- and sulfur-containing quinolines have been readily synthesized under mild reaction conditions by the 6-endo-dig electrophilic cyclization of N-(2-alkynyl)anilines by ICl, I$_2$, Br$_2$, PhSeBr and ArSCl as electrophiles. The reaction affords quinolines in moderate to good yields and various functional groups are readily accommodated. Dihydroquinoline derivatives can be obtained when triflamides are used as the starting materials. Quinolinium salts can be obtained when N-alkyl-N-(2-alkynyl)anilines are employed. Quinolines bearing a hydrogen in the 3-position have been synthesized by the Hg(OTf)$_2$-catalyzed ring closure of these same alkynylanilines. Finally, further conversion of the iodine moiety in these iodoquinolines to other functionally-substituted quinolines has been illustrated.

4. Experimental section

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. All melting points are uncorrected. High resolution mass spectra were recorded on a MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. All reagents were used directly as obtained commercially unless otherwise noted.

4.2. General procedure for the electrophilic cyclization of n-triflamides by ICl

To a solution of N-phenyl-N-(3-phenylprop-2-ynyl)trifluoro-methanesulfonamide (102 mg, 0.30 mmol) in CH$_2$Cl$_2$ (3.0 mL) at −78 °C was added ICl (58.5 mg, 0.36 mmol) in CH$_2$Cl$_2$ (0.5 mL) and the resulting solution was stirred at this temperature for 0.5 h. The reaction mixture was washed with satd aq Na$_2$S$_2$O$_3$ (20 mL) and the organic layer dried over Na$_2$SO$_4$, filtered, and the solvent removed under reduced pressure. To the crude solution of 3-iodo-4-phenyl-1-trifluoromethanesulfonyl-1,2-dihydroquinoline in MeOH (10 mL) was added NaOMe (3.0 mmol, 162 mg) and the mixture was stirred at rt in the presence of air for 12 h. The reaction mixture was diluted with diethyl ether (50 mL) and washed with brine (50 mL). The organic layer was dried (Na$_2$SO$_4$), filtered, and the solvent removed

under reduced pressure. The residue was purified by column chromatography on a silica gel column.

4.2.1. 3-Iodo-4-(3-methoxyphenyl)quinoline (4). The reaction mixture was chromatographed using 5:1 hexane/EtOAc to afford the product as a white solid in a 62% yield: 117–118 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.84 (s, 3H), 6.78 (s, 1H), 6.81–6.83 (m, 1H), 7.03–7.06 (m, 1H), 7.41–7.50 (m, 3H), 7.68–7.72 (m, 1H), 8.08–8.10 (d, J=6.6 Hz, 1H), 9.22 (s, 1H); ^{13}C NMR (CDCl$_3$, 75 Hz) δ 55.43, 96.11, 114.26, 114.66, 121.40, 126.78, 127.43, 128.90, 129.48, 129.76, 129.86, 141.60, 147.17, 152.24, 156.65, 159.70; IR (CHCl$_3$) 2837, 1613, 1513, 1483, 1246 cm^{-1}; HRMS m/z 360.9972 (calcd for C$_{16}$H$_{12}$INO, 360.9964); Anal. Calcd for C$_{16}$H$_{12}$INO: C, 53.1; H, 3.3; N 3.9; Found: C, 53.1; H, 3.9; N, 3.5.[27]

Compounds **38**, **39**, **41**, **43**, **46**, **48**, **53**, **55**, **59**, and **65** were prepared by reaction of the appropriate aniline (2 equiv) and the corresponding propargylic mesylate at room temperature in CH$_3$CN.[28]

4.2.2. N-(2-Heptynyl)aniline (38). To a solution of the methanesulfonate[29] of 2-heptyn-1-ol (950 mg, 5.0 mmol) in 50 mL of CH$_3$CN was added aniline (930 mg, 10.0 mmol). After being stirred for 20 h under N$_2$, the reaction was quenched by adding brine. The reaction mixture was extracted with Et$_2$O (2×30 mL). The extracts were dried over MgSO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (10:1 hexane/EtOAc) on silica gel to afford 589 mg of the product (63% yield) as a light yellow oil. The spectral properties were identical with those previously reported.[30]

4.3. General procedure for the electrophilic cyclization of N-(2-Alkynyl)anilines by I$_2$

In a vial was placed 0.3 mmol of the propargylic aniline, 3 equiv of I$_2$, 2 equiv of NaHCO$_3$, and 3 mL of CH$_3$CN. The reaction mixture was stirred at room temperature, and the reaction was monitored by TLC to establish completion. When finely ground iodine powder was employed, all reactions were complete in 0.5 h. The reaction mixture was then diluted with 25 mL of ether and washed with 20 mL of satd aq Na$_2$S$_2$O$_3$. The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined organic layers were dried over MgSO$_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

4.4. General procedure for the electrophilic cyclization of N-(2-Alkynyl)anilines by ICl, Br$_2$, PhSeBr or p-O$_2$NC$_6$H$_4$SCl

In a vial was placed 0.3 mmol of the propargylic aniline, 2 equiv of NaHCO$_3$ and 2 mL of CH$_3$CN. Two equivalents of ICl, Br$_2$, PhSeBr or p-O$_2$NC$_6$H$_4$SCl in 1 mL of CH$_3$CN were added dropwise to the vial. The reaction mixture was stirred at room temperature for 5 min. The reaction mixture was then diluted with 25 mL of ether, and washed with 20 mL of satd aq Na$_2$S$_2$O$_3$ (for the reaction of ICl and Br$_2$) or satd aq NaCl (for the reactions of PhSeBr and p-O$_2$NC$_6$H$_4$SCl). The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined organic layers were dried over MgSO$_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

4.4.1. 4-(4-Methoxyphenyl)-3-(phenylseleno)quinoline (25). The reaction mixture was chromatographed using 3:1 hexane/EtOAc to afford 86 mg (74%) of the product as a yellow solid: mp 93–94 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.91 (s, 3H), 7.06 (d, J=6.0 Hz, 2H), 7.26–7.32 (m, 5H), 7.43–7.57 (m, 3H), 7.63–7.68 (m, 1H), 7.68–7.73 (m, 1H), 8.05 (d, J=8.4 Hz, 1H), 8.67 (s, 1H); ^{13}C NMR (CDCl$_3$, 75 Hz) δ 55.57, 114.25, 126.23, 127.22, 127.34, 128.44, 128.47, 129.16, 129.61,

129.70, 129.74, 129.85, 130.87, 134.81, 147.08, 148.27, 152.43, 159.99; IR (CHCl$_3$) 2923, 2851, 1736, 1250 cm^{-1}; HRMS m/z 391.0482 (calcd for C$_{22}$H$_{17}$NOSe, 391.0475).

4.5. General procedure for the Hg(OTf)$_2$-catalyzed cyclization of *N*-(2-alkynyl)anilines

To a vial containing a solution of 0.3 mmol of the propargylic aniline in 3 mL of CH$_3$CN was added a catalytic amount of Hg(OTf)$_2$. The reaction mixture was stirred at room temperature, and the reaction was monitored by TLC to establish completion. The reaction mixture was then diluted with 25 mL of ether, and washed with 20 mL of satd aq NaI. The organic layer was separated and the aqueous layer was extracted with another 25 mL of ether. The combined organic layers were washed further with 25 mL of satd aq NaCl. The organic layer was dried over MgSO$_4$ and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

*4.5.1. 4-(4-Methoxyphenyl)quinoline (**80**).* The reaction mixture was chromatographed using 10:1 hexane/EtOAc to afford 62 mg of the product (88%) as a light yellow oil: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 3.91 (s, 3H), 7.05–7.08 (d, J=8.7 Hz, 2H), 7.32–7.33 (d, J=4.2 Hz, 2H), 7.44–7.53 (m, 3H), 7.70–7.75 (m, 1H), 7.96–7.99 (d, J=8.4 Hz, 1H), 8.15–8.18 (d, J=8.4 Hz, 1H), 8.92–8.93 (d, J=4.5 Hz, 1H); ^{13}C NMR (CDCl$_3$, 100 Hz) δ 55.46, 114.11, 121.34, 125.97, 126.54, 127.00, 129.30, 129.89, 130.33, 130.86, 148.26, 148.80, 150.06, 159.91; IR (CHCl$_3$) 3060, 2930, 2849, 1617 cm^{-1}; HRMS m/z 235.1001 (calcd for C$_{16}$H$_{13}$NO, 235.0997).

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.12.012.

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