Published in final edited form as:
J Org Chem. 2006 January 6; 71(1): 236–243. doi:10.1021/jo051948k.

Synthesis of Naphthalenes and 2-Naphthols by the Electrophilic Cyclization of Alkynes

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Abstract

A wide variety of substituted naphthalenes are readily prepared regioselectively under mild reaction conditions by the 6-*endo*-dig electrophilic cyclization of appropriate arene-containing propargylic alcohols by ICl, I_2, Br_2, NBS, and PhSeBr. 3-Iodo-2-naphthols have also been prepared in excellent yields by the cyclization of analogous 1-aryl-3-alkyn-2-ones. This methodology readily accommodates various functional groups and has been successfully extended to the synthesis of substituted carbazoles and dibenzothiophenes.

Introduction

Polysubstituted naphthalenes and 2-naphthols have played an important role in the chemical and pharmaceutical industries.[1] The discovery of technologically promising electronic and optical properties in fused aromatic compounds underscores the importance of new synthetic routes to such systems.[2] Therefore, the development of new and efficient methodologies for the regioselective synthesis of polysubstituted naphthalene derivatives has attracted much attention.[3] A variety of methods have been reported, including (i) the traditional stepwise introduction of substituents through electrophilic aromatic substitutions;[4] (ii) [4+2] cycloaddition;[5] (iii) annulation of arenes bearing an unsaturated carbonyl side chain;[6] (iv) reaction of aryl halides or arylmetal compounds with alkynes using transition metals;[7] (v) annulation of arynes with alkynes;[8] (v) annulation via Fischer carbenes (the Dötz reaction);[9] and (vi) Lewis acid-catalyzed cyclization of carbonyl compounds or epoxides with alkynes.[10] These methods sometimes involve relatively harsh reaction conditions, expensive catalysts, and substrates which require multistep synthesis. In some cases, the reactions also produce a mixture of isomers.

Recently, we and others have developed efficient methods for the synthesis of various carbo- and heterocyclic compounds through electrophilic cyclization of appropriate *ortho*-functionalized aromatic acetylenes.[11] Relatively little work[12] has been carried out on the intramolecular electrophilic cyclization of alkynes onto arenes to prepare polycyclic aromatics. Barluenga has reported one example of the electrophilic carbocyclization of 1,4-diphenyl-1-butyne to 1,2-dihydronaphthalene utilizing expensive $I(py)_2BF_4$ (eq 1).[12a] The scope of this process has yet to be investigated, but the conversion of such 1,2-dihydronaphthalenes to naphthalenes is not always easy,[13] especially when considerable functionality is present.

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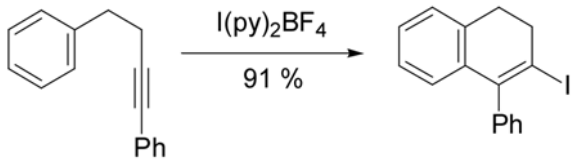

(1).

Herein, we report our results on the electrophilic cyclization of arylalkynes to naphthalenes and naphthols. This chemistry generally produces good to excellent yields of the desired arenes under very mild reaction conditions, accommodates various functional groups, and has been successfully extended to systems containing heterocyclic rings.

Results and Discussion

We envisioned that hydroxydihydronaphthalenes might be easily transformed to the corresponding naphthalenes through acid-catalyzed dehydration.[14] Thus, we chose to investigate the cyclization of appropriate benzylic-substituted propargylic alcohols, such as 1 (Scheme 1). These alcohols are easily prepared in excellent yields by the reaction of lithium acetylides and the corresponding 2-arylacetaldehydes.[15]

We first examined the reaction of alkynol 1 with I_2 and were delighted to find that the desired 2-iodonaphthalene 2 was formed exclusively in a 75% yield after 0.5 h when using 0.3 mmol of 1, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in MeCN at ambient temperature (Table 1, entry 1). None of the 5-*exo*-dig cyclization product was detected. Reducing the amount of I_2 to 2 equiv resulted in an incomplete reaction after 48 h. The addition of $NaHCO_3$ did improve the yield in this reaction (compare entries 1 and 2), although it is only a marginal effect.

To explore the scope of this chemistry, other electrophiles have also been examined (entries 3–6). The reaction with ICl was complete upon addition of the ICl and gave a higher yield of product 2 than the reaction with I_2 (entry 3). 2-Bromonaphthalenes can be obtained by using either Br_2 or NBS as the electrophile. An excellent 89% yield was provided by Br_2 at room temperature (entry 4). The reaction with NBS proceeded only at a higher temperature (50 °C) and afforded a lower yield of 3 (entry 5).

Cyclization with PhSeBr provided a 36% yield of 2-naphthyl phenyl selenide, together with a 53% yield of the product of simple addition of PhSeBr to the triple bond (entry 6).

Alkynes bearing an electron-rich aromatic ring and an acid-sensitive heterocycle, such as a thiophenyl group, reacted well with I_2 to provide the desired 1,2-disubstituted iodonaphthalenes in excellent yields (entries 7 and 10). None of the products of direct substitution on the electron-rich aromatic ring in these two examples were observed. Although the yield utilizing I_2 was only moderate for substrate 7 (entry 8), presumably because the ketone group decreases the electron-density of the aromatic ring, the desired conversion could be significantly improved by using ICl as the electrophile (entry 9). In the case of substrate 9, cyclization with 2 equiv of Br_2 resulted in a 45% yield of the monobrominated product 11 and a 36% yield of the dibromo product 12, which bears an extra Br on the 5-position of the thiophene (entry 11). The reaction with I_2 proceeded smoothly when a vinylic group was present on the alkyne terminus (entry 12). While only a 35% yield of 1-*n*-butyl-2-iodonaphthalene was isolated from the reaction of 1-phenyl-3-octyn-2-ol and I_2, a higher 75% yield was again obtained when ICl was employed (compare entries 13 and 14). An even better yield was obtained from an alkyne bearing a secondary alkyl group on the alkyne terminus (entry 15). The sterically hindered trimethylsilyl-substituted alkyne 19 failed to give any cyclization product using I_2 (entry 16), but was cyclized without difficulty when treated with

ICl (entry 17). However, the only product observed was 1,2-diiodonaphthlene in which the trimethylsilyl group was substituted by an iodine moiety. The synthesis of 1-ethoxy-2-iodonaphthalene from the corresponding ethoxy-substituted alkyne was not very successful using either I_2 or ICl as electrophiles under our standard reaction conditions (entries 17 and 18). Only low yields have been obtained. However, by lowering the reaction temperature of the ICl reaction, we were able to improve the yield to 54% (entry 19). No cyclization product was observed when the ester-substituted alkyne 24 was allowed to react with I_2 (entry 20).

To explore the effect of substituents in the side chain, a tertiary alcohol 26 was examined under our standard reaction conditions (entry 21). The presence of a methyl group did not hamper either the cyclization or the dehydration. Thus, regiospecific 2,3,4-trisubstituted naphthalenes can be readily synthesized in good yield in a single step using this methodology. The presence of methyl substitution on the benzylic position did not affect the overall yield either (entry 22). This allows a very direct approach to 1,2,4-trisubstituted naphthalene 29.

We next investigated the cyclization onto substituted arenes. Treatment of 1-(4-methoxyphenyl)-4-phenylbut-3-yn-2-ol (30) with I_2 under our standard reaction conditions afforded cyclization product 31 in a 90% yield (entry 23). A lower yield of bromonaphthalene 32 was obtained because of competitive *ipso*-cyclization to spirocycle 33.[16] Cyclization onto an aromatic ring substituted by a strong electron-withdrawing group, such as a fluorine group (entry 25), proceeded smoothly, affording an excellent yield of the desired naphthalene, even though the fluorine significantly lowers the nucleophilicity of the aromatic ring undergoing substitution. Iodocyclization onto a naphthalene ring afforded the corresponding 2-iodophenanthrene in a good yield (entry 26).

The regioselectivity of this cyclization has also been explored. Cyclization onto 3-methoxyphenyl alkynol 38 was quite regioselective, affording a 7:1 regioisomeric mixture of 39 and 40 in an excellent overall yield (entry 27). The isomer 39 formed by cyclization onto the less hindered position *para* to the methoxy group is the major product. Only one isomer was observed in the cyclization of 2-naphthyl alkynol 41; ring closure occurred selectively on the one position of the naphthalene ring (entry 28). This is rather surprising, since analogous iodocyclization of 2-naphthyl-3-phenylpropargylamine gave exclusively the aromatic amine formed by cyclization onto the three position of the naphthalene.[12e] Clearly, electronic effects favor cyclization to 42 over cyclization to the less hindered 3-position of the naphthalene.

We were particularly interested in extending these cyclizations to alkynes containing important electron-rich heteroaromatic rings, such as benzothiophenes and indoles. As exemplified in entries 29 and 30, both benzothiophene derivatives 43 and 45 undergo I_2-induced carbocyclization to the corresponding dibenzothiophenes in excellent yields. However, only an 18% yield of iodocarbazole 48 was obtained under our standard I_2 cyclization conditions without formation of any significant side products (entry 31). The yield of this cyclization could be improved to 50% when ICl was used as the electrophile (entry 32). These benzannulations all start from readily available precursors, involve very simple synthetic manipulations with highly regiocontrolled ring formation, and provide the desired products in good to excellent yields.

Our protocol utilizing much more economical and convenient to handle I_2 can also be employed in the synthesis of 1,2-dihydronaphthalenes (entry 33), considerably simplifying the procedure developed earlier by Barluenga using an iodonium reagent.[12a] In comparison, the attempted cyclization to iodoindenes through a 5-*endo*-dig cyclization failed completely using either I_2 or ICl (entries 34–36). In all cases, 1,2-adducts formed by direct I_2 or ICl addition to the triple bond were obtained.

The facility with which this carbocyclization process occurs encouraged us to attempt a double cyclization. The double cyclization of diyne 55 afforded a 32% yield of diiodoanthracene 56 and a 20% yield diiodophenanthrene 57 in a decent overall yield.

A propargylic acetate 58 has also been successfully employed in this process, although more base and a longer reaction time were required (entry 38). None of the corresponding dihydronaphthalene acetate was detected.

The synthetic utility of this protocol has also been demonstrated in the preparation of iodotetrahydrophenanthrene 60. Both *cis*- and *trans*-2-phenyl-1-(phenylethynyl) cyclohexanols (59 and 61) can be efficiently cyclized under our standard reaction conditions to provide the desired arene 60 in a 72% (from the *cis*-cyclohexanol) or quantitative yield (from the *trans*-cyclohexanol) (entries 39 and 40). Furthermore, compound 60 can also be obtained from the corresponding methyl ethers of 59 and 61 in almost quantitative yields (entries 41 and 42). Obviously the relative stereochemistry of the alcohols or ethers in these systems has little effect on the overall success of these cyclizations. It should be pointed out that during these cyclizations no spots corresponding to the intermediate dihydronaphthalenes could be detected by TLC analysis. The starting materials were gradually consumed, while the desired product was generated at the same time. The anticipated dihydronaphthalenes either immediately undergo elimination by the I_2 during the reaction or by the silica gel during thin layer chromatographic analysis.

In comparison, the reaction of 1,4-diphenylbut-3-yn-1-ol bearing the OH group now on the benzylic position instead of the propargylic position became very sluggish under the I_2 cyclization conditions with or without base when starting from (entry 43). Most of the alkynol was left after 24 h and the desired naphthalene 2 was obtained in only a 20 % yield.

Interestingly, 3-iodo-4-phenyl-2-naphthol (65) can be readily prepared by analogous cyclization of the appropriate alkynone 64 (entries 44–46). An initial experiment using I_2 in the presence of base indicated a rather messy reaction with several unidentified side products (entry 44). We assume that those side products might have come from base-induced iodination of the ketone or the product and subsequently found that by simple removal of the base, the yield was improved dramatically to 78% (entry 45). An almost quantitative yield was obtained using ICl as the electrophile and no base (entry 46). However, only a trace of the bromonaphthol derivative 67 was generated when we employed Br_2 as the electrophile (entry 47). This is a general approach to iodonaphthols as it is also compatible with both vinylic and alkyl substitution on the alkyne (entries 48 and 49).

We believe that this 6-*endo*-dig cyclization proceeds by *anti* attack of the electrophile and the aromatic ring on the alkyne to produce a cationic intermediate A (Scheme 2). Deprotonation of A affords the hydroxydihydronaphthalene B. Dehydration of the presumed intermediate B to the naphthalene is evidently rapid even in the presence of a base, since intermediates, such as B, have not been observed. The cyclization of alkynones is believed to follow the same pathway, except that tautomerization of the ketone intermediate to the naphthol affords the final product.

Halogenated naphthalenes and naphthols are very valuable intermediates in organic synthesis, a status much enhanced by recent developments in radical chemistry and especially in transition metal-catalyzed reactions.[17] For example, halonaphthalenes and halonaphthols are useful starting materials for palladium-catalyzed coupling reactions,[18] Pd migration to fused tricyclic compounds,[19] annulation to naphtha[2,3-*b*]furans[20] and polycyclic aromatic hydrocarbons, [21] carbonylation to benzo[*c*]flourenones,[22] and carbonylative annulation of alkynes to coumarins.[23] Some examples of the Pd migration and alkyne annulation chemistry utilizing substrates prepared in this study are illustrated in Scheme 3.

Conclusions

In summary, we have developed a new, very efficient protocol to effect the regioselective cyclization of simple aromatic acetylenes to multisubstituted 2-iodonaphthalenes and 3-halo-2-naphthols under very mild reaction conditions. This methodology accommodates various functional groups and generally affords the products in good yields. It has also been successfully applied to the cyclization of heterocyclic systems. Finally, the resulting halogen-containing products can be readily elaborated to more complex products using known organopalladium chemistry.

Experimental Section

General

The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). 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.

General procedure for the preparation of the alkynols

To a solution of the acetylene in anhydrous THF was added 1 equiv of *n*-BuLi at 0 °C under an Ar atmosphere. The resulting solution was stirred at that temperature for 1 h. Then 0.5 equiv of the α-arylacetaldehyde or α-arylacetone in THF was added by syringe. The reaction mixture was kept under the inert atmosphere and stirred for 12 h while it warmed up to ambient temperature. The mixture was then quenched by adding satd aq NH_4Cl and extracted twice with diethyl ether. The combined ether fractions were dried over $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel.

General Procedure for the Electrophilic Cyclization of Alkynols by I_2

0.3 Mmol of the alkynol, 3 equiv of I_2, 2 equiv of $NaHCO_3$, and 3 mL of CH_3CN were placed in a vial. The reaction mixture was stirred at room temperature, and the reaction was monitored by TLC to establish completion. The reaction mixture was diluted with 25 mL of ether, and washed with 20 mL of satd aq $Na_2S_2O_3$. 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.

General Procedure for the Electrophilic Cyclization of Alkynols by ICl, Br_2, and PhSeBr

0.30 Mmol of the alkynol, 2 equiv of $NaHCO_3$ and 2 mL of CH_3CN were placed in a vial. 2 Equiv of ICl, Br_2 or PhSeBr in 1 mL of CH_3CN 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 $Na_2S_2O_3$. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We gratefully acknowledge the National Institute of General Medical Sciences (GM 070620) for support of this research, and Kawaken Fine Chemicals Co., Ltd., and Johnson Matthey, Inc. for donations of palladium acetate.

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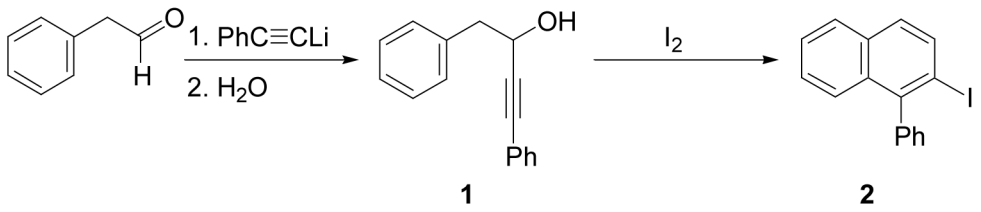
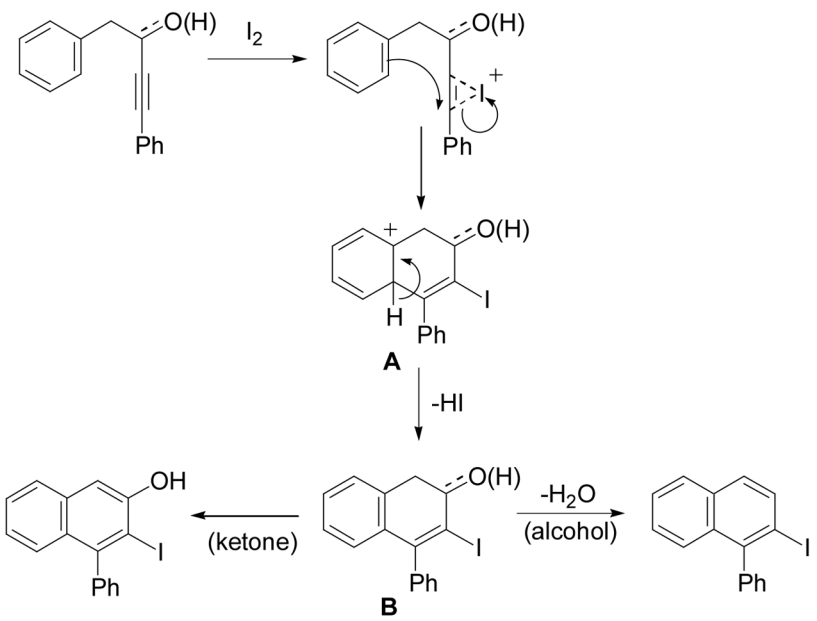
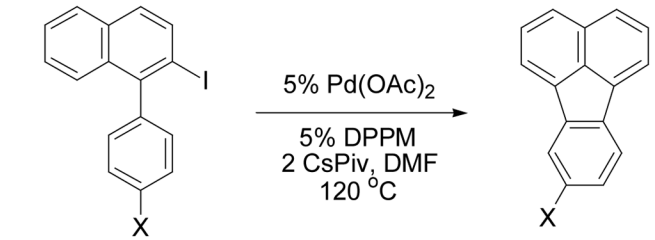


1 2

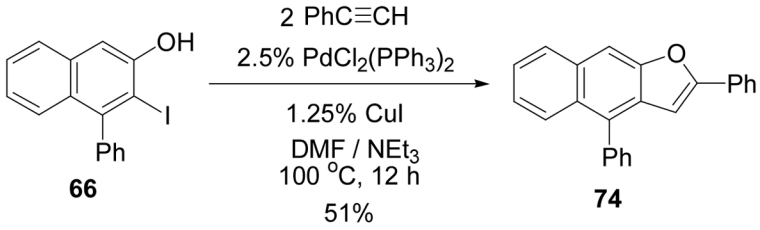
Scheme 1.



Scheme 2.



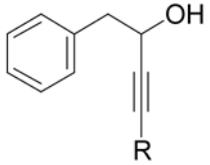
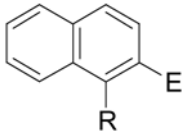
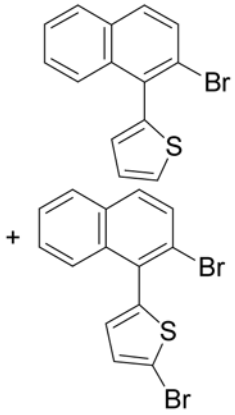
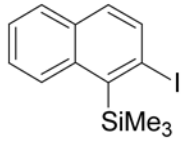
X	time (h)	% yield
OMe (**6**)	24	65 (**72**)
Ac (**8**)	84	64 (**73**)

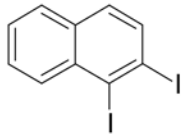
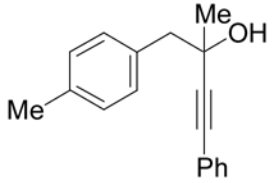
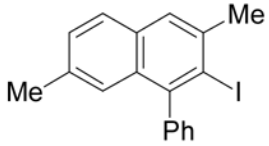
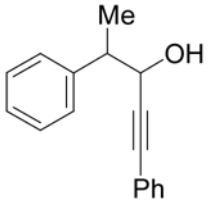
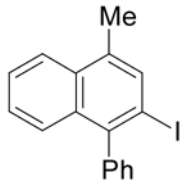
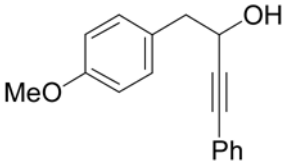
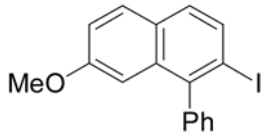
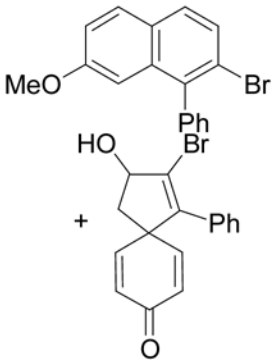


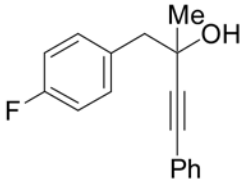
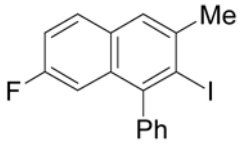
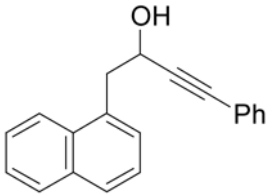
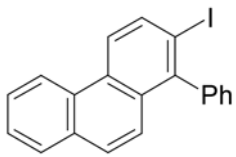
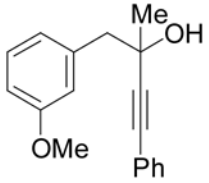
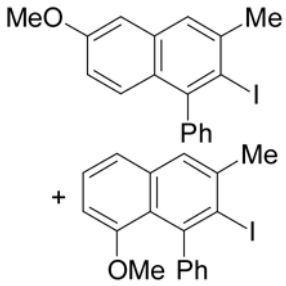
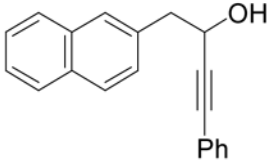
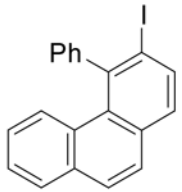
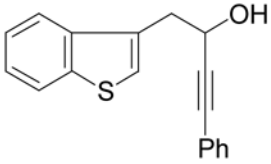
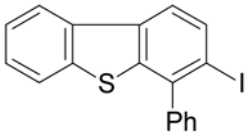
Scheme 3.

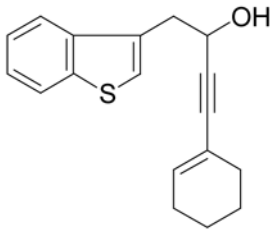
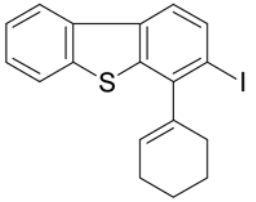
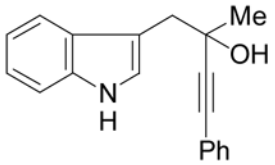
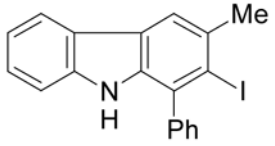
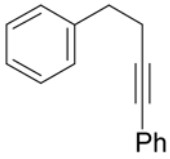
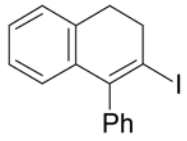
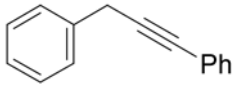
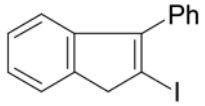
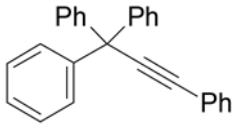
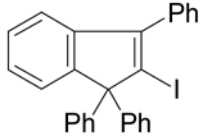
Table 1

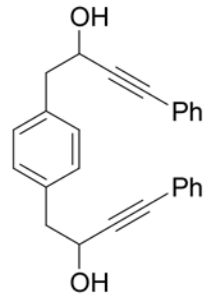
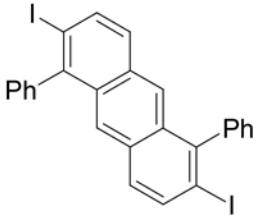
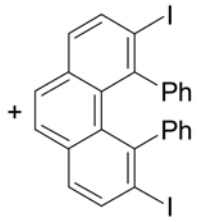
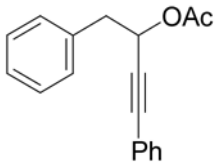
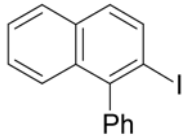
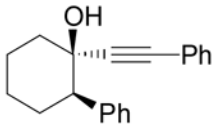
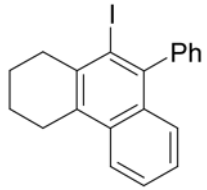
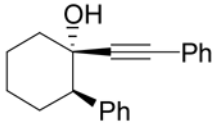
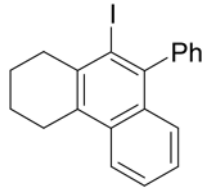
Synthesis of Naphthalenes and Naphthols by Electrophilic Cyclization

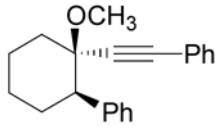
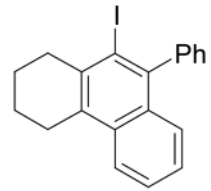
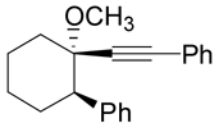
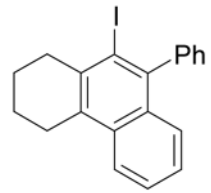
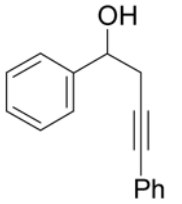
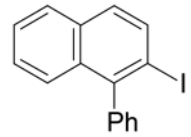
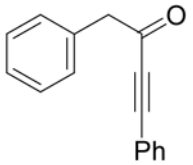
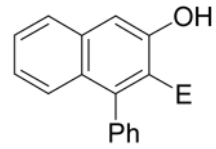
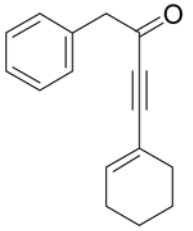
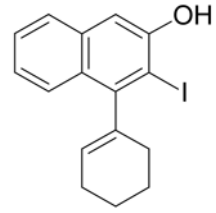
entry	substrate		electrophile	product(s)			% yield
							
					E		
1	R = Ph	**1**	I_2[a]		I	**2**	75
2			I_2[b]		I	**2**	71
3			ICl[c]		I	**2**	93
4			Br_2[d]		Br	**3**	89
5			NBS[e]		Br	**3**	40
6			PhSeBr[d]		PhSe	**4**	36[f]
7	R = *p*-$MeOC_6H_4$	**5**	I_2[a]		I	**6**	75
8	R = *p*-$CH_3COC_6H_4$	**7**	I_2[a]		I	**8**	54[g]
9			ICl		I	**8**	92
10	R =2-thienyl	**9**	I_2[a]		I	**10**	94
11	R = 2-thienyl	**9**	Br_2[d]			**11**+**12**	45+36
12	R = 1-cyclohexenyl	**13**	I_2[a]		I	14	69
13	R = *n*-Bu	**15**	I_2[a]		I	**16**	35
14			ICl[c]		I	**16**	75
15	R = cyclohexyl	**17**	ICl[c]		I	**18**	90
16	R = $SiMe_3$	**19**	I_2[a]			**20**	0

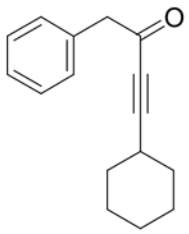
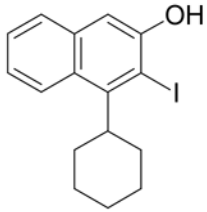
entry	substrate		electrophile	product(s)		% yield
		19	ICl[c]		**21**	50
17	R = OEt	**22**	I_2[a]	I	**23**	22
18		**22**	ICl[c]	I	**23**	30
19		**22**	ICl[h]	I	**23**	54
20	R = CO_2Et	**24**	I_2[a]	I	**25**	0
21		**26**	I_2[a]		**27**	78
22		**28**	I_2[a]		**29**	76
23		**30**	I_2[b]		**31**	90
24		**30**	Br_2[b]		**32**+**33**	55+25

entry	substrate		electrophile	product(s)		% yield
25		**34**	I_2[a]		**35**	79
26		**36**	I_2[a]		**37**	70
27		**38**	I_2[a]		**39**+**40**	**83**+**12**
28		**41**	I_2[a]		**42**	75
29		**43**	I_2[a]		**44**	83

entry	substrate		electrophile	product(s)		% yield
30		**45**	I_2[a]		**46**	74
31		**47**	I_2[a]		**48**	18
32		**47**	ICl[b]		**48**	50
33		**49**	I_2[a]		**50**	76
34		**51**	I_2[a]		**52**	0
35		**51**	ICl[b]		**52**	0
36		**53**	ICl[b]		**54**	0

entry	substrate		electrophile	product(s)		% yield
37		**55**	I_2[a]	 	**56**+**57**	**32**+**20**
38		**58**	I_2[a,i]		**2**	51
39		**59**	I_2[a]		**60**	72
40		**61**	I_2[a]		**60**	99

entry	substrate		electrophile	product(s)			% yield
41		**62**	I_2[a]			**60**	99
42		**63**	I_2[a]			**60**	90
43		**64**	I_2[a]			**2**	20
44		**65**	I_2[a]		I	**66**	45
45			I_2[b]		I		78
46			ICl[b]		I		98
47			Br_2[b]		Br	**67**	trace
48		**68**	ICl[b]			**69**	65

entry	substrate		electrophile	product(s)		% yield
49		**70**	ICl[b]		**71**	79

[a] The reactions were run under the following conditions: 0.3 mmol of the propargylic alcohol, 3 equiv of I_2, and 2 equiv of $NaHCO_3$ in 3 mL of CH_3CN were stirred at room temperature.

[b] No $NaHCO_3$ was employed.

[c] 2 Equiv of ICl in 1 mL of CH_3CN was added dropwise to 0.3 mmol of propargylic alcohol and 2 equiv of $NaHCO_3$ in 2 mL of CH_3CN at room temperature.

[d] 2 Equiv of Br_2 or PhSeBr in 1 mL of CH_3CN was added dropwise to 0.3 mmol of propargylic alcohol and 2 equiv of $NaHCO_3$ in 2 mL of CH_3CN at room temperature.

[e] 0.9 Mmol of NBS and 0.3 mmol of propargylic alcohol in 5 mL of CH_3CN were stirred at 50 °C for half an hour.

[f] The product formed from simple addition of PhSeBr to the triple bond was obtained in a 53% yield.

[g] The reaction took 48 h.

[h] 2 Equiv of ICl in 1 mL of CH_2Cl_2 was added dropwise to 0.3 mmol of propargylic alcohol **21** and 2 equiv of $NaHCO_3$ in 2 mL of CH_2Cl_2 at −78 °C.

[i] 3 Equiv of $NaHCO_3$ was employed.

J Org Chem. Author manuscript; available in PMC 2008 September 9.