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Synthesis of Highly Substituted Furans by the Electrophile-Induced Coupling of 2-(1-Alkynyl)-2-alken-1-ones and Nucleophiles

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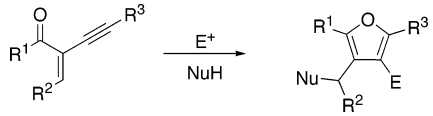

E = H (cat. $AuCl_3$); NuH = ROH, enol, ArH
E = I; NuH = ROH, RCO_2H, H_2O
E = PhSe; NuH = ROH

The coupling of 2-(1-alkynyl)-2-alken-1-ones with nucleophiles, either catalyzed by $AuCl_3$ or induced by an electrophile, provides highly substituted furans in good to excellent yields under very mild reaction conditions. Various nucleophiles, including functionally substituted alcohols, H_2O, carboxylic acids, 1,3-diketones, and electron-rich arenes, and a range of cyclic and acyclic 2-(1-alkynyl)-2-alken-1-ones readily participate in these cyclizations. Iodine, NIS, and PhSeCl have proven successful as electrophiles in this process. The resulting iodine-containing furans can be readily elaborated to more complex products using known organopalladium chemistry.

Introduction

Furans, one of the most important five-membered-ring heterocycles,[1] can be found in many naturally occurring compounds arising from plants and marine organisms.[2] For example, in a number of biologically significant natural products, such as pinguisone,[3] furodysinin,[4] and methyl vouacapenate,[5] a 2,3-disubstituted furan ring constitutes a distinctive structural feature. Furans are used as commercial pharmaceutical agents, flavor and fragrance compounds, insecticides, and antileukemic agents.[6] Polysubstituted furans can also be employed as building blocks for the total synthesis of complicated naturally occurring metabolites,[7] and as versatile starting materials for the preparation of a variety of heterocyclic and acyclic compounds.[8]

Their important biological activity and great utility have encouraged the search for ever newer, more efficient methods for the synthesis of furans.[9] The vast majority of the previous routes to furans have involved the chemical modification of acyclic precursors. A particularly effective approach to the synthesis of functionalized furans is through the transition metal-catalyzed cyclization of an alkynyl or allenyl ketone,[10] alcohol,[11] or epoxide,[12] or electrophilic cyclization of alk-3-yne-1,2-

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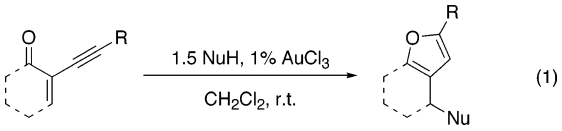
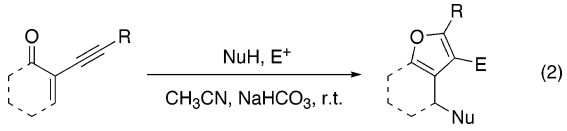
diols,[13] 2,4-dialkenyl-1,3-dicarbonyl compounds,[14] or 2-alkynyl carbonyl compounds.[15] No attention has been paid to 2-(1-alkynyl)-2-alken-1-ones as possible furan precursors, although they are more readily accessible and more easily manipulated than are alkynyl or allenyl ketones.[16] The utilization of 2-(1-alkynyl)-2-alken-1-ones for transition metal-catalyzed or electrophilic cyclization should significantly expand the range of suitable starting materials for the synthesis of functionally substituted furans.

Recently, we have communicated a $AuCl_3$-catalyzed synthesis of substituted furans from 2-(1-alkynyl)-2-alken-1-ones, which produces highly substituted furans in good to excellent yields (eq 1).[17] Now, we wish to report



(1)

a detailed study of the $AuCl_3$-catalyzed synthesis of substituted furans, together with a novel electrophile-induced three-component reaction, which produces tetrasubstituted furans in good to excellent yields (eq 2).



(2)

These unique cyclizations are particularly attractive, because *sequential nucleophilic domino attack onto an alkyne* affords multiply substituted furans through simultaneous formation of a C−O bond and a remote carbon−nucleophile bond. One of the advantages of this approach to furans is that the regioselective introduction of substituents about the furan ring comes down to the appropriate choice of the 2-(1-alkynyl)-2-alken-1-one and nucleophile, which allows for considerable versatility (Scheme 1). Furthermore, the electrophile-induced cyclization provides a general and efficient approach to the regioselective synthesis of tetrasubstituted furans, which is still today a challenge in organic synthesis.

Results and Discussion

Our preliminary studies have been carried out on the transition metal-catalyzed coupling of 2-phenylethynyl-2-cyclohexen-1-one (**1**) and methanol to afford furan **2** (Table 1). As we previously communicated, silver, copper, gold, and mercury salts afford good yields of furan **2** (Table 1, entries 1−4).[17] Among these salts, $AuCl_3$ is the most efficient catalyst based on reaction time and yield. This is consistent with previous work on the cyclization

SCHEME 1

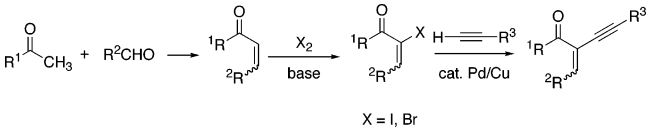
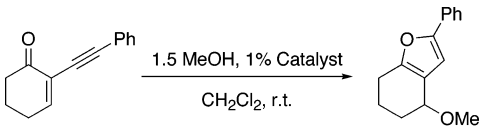


TABLE 1. Catalytic Cyclization and Coupling of 2-Phenylethynyl-2-cyclohexen-1-one (1) and Methanol[a]



1 **2**

entry	catalyst	time (h)	% yield of **2**[b]	% recovery of **1**
1	AgO_2CCF_3	10	87	0
2	$Cu(O_3SCF_3)_2$	9	81	0
3	**$AuCl_3$**	**0.5**	**90**[c]	**0**
4	$Hg(O_2CCF_3)_2$	8	86	0
5	$Pd(OAc)_2$	6	30[d]	65
6	$PtCl_2$	24	10	81
7	$Cu(NO_3)_2 \cdot 2.5H_2O$	24	27	68
8	$RuCl_3 \cdot 3H_2O$	24	0	95
9	$PtCl_2(PPh_3)_2$	24	18	71
10	$RhCl_3$	24	8	90
11	HBF_4	1	0	0

[a] Reaction conditions: **1** (0.1 mmol), catalyst (0.001 mmol), and MeOH (0.15 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. [b] Determined by ^1H NMR spectroscopic analysis. [c] Compound **2** can be obtained cleanly within 40 min in an 88% yield when using 0.1 mol % $AuCl_3$. Only a 30% yield of **2** was obtained after 24 h when 0.01 mol % of $AuCl_3$ was employed. [d] Pd black appeared.

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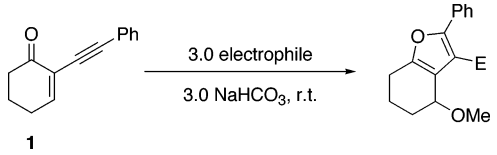
TABLE 2. Electrophile-Induced Cyclization and Coupling of 2-Phenylethynyl-2-cyclohexen-1-one (1) and Methanol[a]



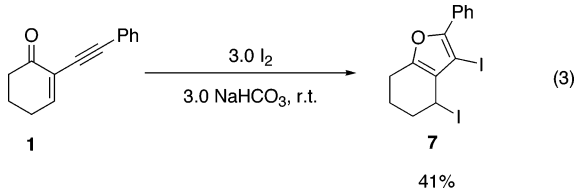
1

entry	electrophile	nucleophile	solvent	product		% yield[b]
1	I_2	MeOH	MeOH	E = I	**3**	70
2	I_2	3.0 MeOH	CH_3CN		**3**	50[c]
3	I_2	8.0 MeOH	CH_3CN		**3**	80
4	NIS	3.0 MeOH	CH_2Cl_2		**3**	60
5	NBS	3.0 MeOH	CH_2Cl_2	E = Br	**4**	0
6	PhSeCl	3.0 MeOH	CH_2Cl_2	E = PhSe	**5**	45
7	*p*-$O_2NC_6H_4SCl$	3.0 MeOH	CH_2Cl_2	E = *p*-$O_2NC_6H_4S$	**6**	~20[d]

[a] Reaction conditions: a solution of 0.2 mmol of **1**, 3 equiv of electrophile, the nucleophile indicated, and 3 equiv of $NaHCO_3$ in 2 mL of solvent was stirred at room temperature for 1 h. [b] Isolated yield. [c] Compound **7** was also isolated in a 17% yield. [d] An inseparable mixture with *p*-$O_2NC_6H_4SOMe$ was obtained. The yield was determined by ^1H NMR spectroscopic analysis.

of 3-alkyn-1-ones to furans.[10i] $Pd(OAc)_2$ provided a low yield, mainly due to the facile reduction of Pd(II) to Pd(0) in the presence of the alcohol (Table 1, entry 5).[18] The addition of 2 equiv of PPh_3 to $Pd(OAc)_2$ did stabilize the Pd(II) salt, but slowed the reactions. $PtCl_2$, $Cu(NO_3)_2$, and $RuCl_3$ (Table 1, entries 6−8) are not efficient catalysts, in part due to their poor solubility in dichloromethane. $PtCl_2(PPh_3)_2$ does have good solubility, but shows poor catalytic activity (Table 1, entry 9). $RhCl_3$ is barely active in this reaction (Table 1, entry 10). Thus, $AuCl_3$ was chosen as the catalyst for the cyclization of a number of other substrates. When the reaction of **1** was performed in the absence of $AuCl_3$ or in the presence of a catalytic amount of HBF_4 instead of $AuCl_3$, no cyclization product **2** was obtained at all (Table 1, entry 11). These blank tests clearly indicate that $AuCl_3$ is required for the reaction to proceed.

To expand the scope of our Au-catalyzed process, we have examined the use of other electrophiles. Our study of the electrophile-induced cyclization has also been carried out on 2-phenylethynyl-2-cyclohexen-1-one (**1**) and methanol in the presence of $NaHCO_3$. Initially, when I_2 was employed as the electrophile, and methanol was utilized as both the solvent and the nucleophile, the reaction afforded the desired 3-iodofuran **3** in a 70% yield (Table 2, entry 1). To make the reaction more useful, 3 equiv of MeOH was used as the nucleophile together with acetonitrile as the solvent (Table 2, entry 2). Unfortunately, in addition to the desired 3-iodofuran **3** (50%), compound **7** (see eq 3), which is obviously formed by



1 7 41% (3)

nucleophilic attack of iodide on the anticipated carbocation intermediate (see the later discussion of the mechanism), was isolated in a 17% yield. This implied that I_2 could serve *as both an electrophile and a nucleophile* in the reaction. Indeed, when the reaction was carried out in CH_3CN without any MeOH, compound **7** was isolated in a 41% yield (eq 3). Thus, to totally trap the carbocation intermediate, an excess of MeOH is required. We were happy to see that when 8 equiv of MeOH was employed, the desired 3-iodofuran **3** was obtained in an 80% yield, without any of compound **7** being formed (Table 2, entry 3). NIS and PhSeCl can also be employed as electrophiles in this process, *albeit* in lower yields (Table 2, entries 4 and 6). The electrophile *p*-$O_2NC_6H_4SCl$ afforded an inseparable mixture of the desired furan product and *p*-$O_2NC_6H_4SOMe$ in low yield (Table 2, entry 7). Unfortunately, NBS did not afford any furan product (Table 2, entry 5).

With the optimized reaction conditions in hand, the effect on the yield of the substituents on the alkyne was examined next (Table 3, entries 1−11). Alkynes bearing either electron-rich or electron-poor aryl groups are readily accommodated in both the $AuCl_3$-catalyzed and I_2-induced cyclizations (entries 3−7). The presence of a vinylic group presents no difficulties in the $AuCl_3$-catalyzed cyclization (entry 8), but afforded only a modest 46% yield upon reaction with I_2/MeOH (entry 9). Interestingly, while the TMS-substituted alkyne did not afford any furan product in the $AuCl_3$-catalyzed cyclization (entry 10), a good yield of 2,3-diiodofuran **21** was obtained in the iodine-induced cyclization (entry 11). Obviously, iododesilylation of the TMS group takes place either prior to or soon after cyclization. Alkynes bearing H and alkyl groups have thus far failed to provide any of the desired products, using either $AuCl_3$ or I_2.

An unprecedented set of nucleophiles can be employed in these cyclizations (Table 3, entries 12−30). Not only simple alcohols, like methanol and 2-propanol (Table 3, entries 12 and 13), but also labile alcohols, like allyl alcohol, benzylic alcohols, 3-phenyl-2-propyn-1-ol, and a protected D-pyranose, are effective nucleophiles in these cyclizations (Table 3, entries 14−20). Even though H_2O and acetic acid did not afford furan products in the $AuCl_3$-catalyzed process, they work well in the I_2-induced cyclization (Table 3, entries 21−24). It should be noted that the hydration of alkynes catalyzed by gold(I) and gold(III) has been reported previously,[19] which may explain the failure of H_2O in the $AuCl_3$-catalyzed cyclization, even though we did not observe any hydration products. Since iodide itself can serve as a nucleophile,

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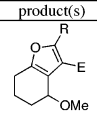
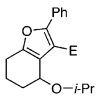
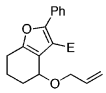
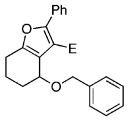
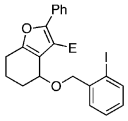
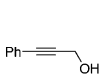
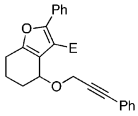
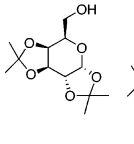
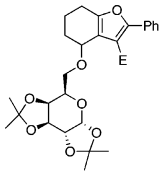
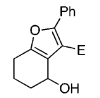
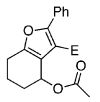
TABLE 3. Cyclization and Coupling of 2-(1-Alkynyl)-2-alken-1-ones and Various Nucleophiles[a]

entry	substrate	NuH	product(s)	E =		% yield
1	R = Ph (**1**)	MeOH		H	**2**	88
2				I	**3**	80
3	R = *p*-MeOC$_6$H$_4$ (**8**)			H	**9**	88
4				I	**10**	83
5	R = *p*-EtO$_2$CC$_6$H$_4$ (**11**)			H	**12**	91
6				I	**13**	83
7	R = *p*-O$_2$NC$_6$H$_4$ (**14**)			H	**15**	99
8	R = 1-cyclohexenyl (**16**)			H	**17**	80
9				I	**18**	46
10	R = TMS (**19**)			H	**20**	0
11			R = I	I	**21**	66
	R = Ph (**1**)	*i*-PrOH				
12				I	**22**	73
13				H	**23**	71
						
14				I	**24**	57
15				H	**25**	75
						
16				I	**26**	60
						
17				H	**27**	87
						
18				I	**28**	77
19				H	**29**	75
						
20				H	**30**	63
		H_2O				
21				I	**31**	77
22				H	**32**	0
		CH_3CO_2H				
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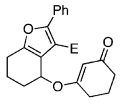
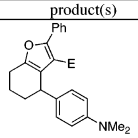
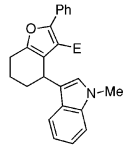
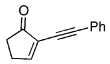
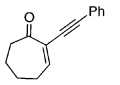
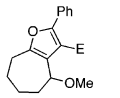
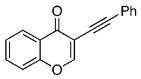
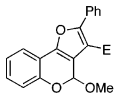
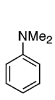
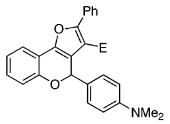
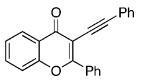
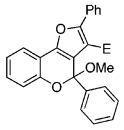
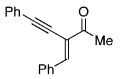
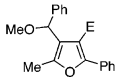
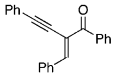
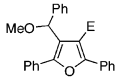
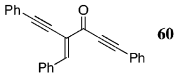
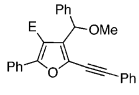
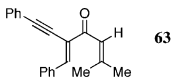
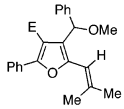
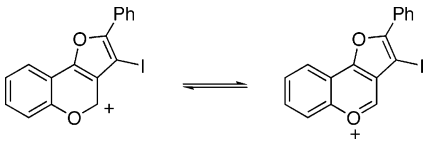
24				H	**34**	0
						
25				I	**35**	0
26				H	**36**	81

entry	substrate	NuH	product(s)	E =		% yield
						
27				I	**37**	0
28				H	**38**	52
						
29				I	**39**	0
30				H	**40**	90
	 **41**	MeOH				
31				I	**42**	74[b]
32				H	**43**	0
	 **44**					
33				I	**45**	76
34				H	**46**	82
	 **47**					
35				I	**48**	87[c]
36				H	**49**	62
						
37				I	**50**	80[c]
	 **51**	MeOH				
38				I	**52**	61[c]
39				H	**53**	0
	 **54**					
40				I	**55**	72[d]
41				H	**56**	60[e,f]
	 **57**					
42				I	**58**	71[d]
43				H	**59**	89[b,e]
	 **60**					
44				I	**61**	0
45				H	**62**	63
	 **63**					
46				I	**64**	0
47				H	**65**	63[b,e]

[a] For E = H, the following procedure was employed unless otherwise specified: a solution of 0.2 mmol of 2-(1-alkynyl)-2-alken-1-one, 1 mol % of $AuCl_3$, and 1.5 equiv of nucleophile in 1 mL of CH_2Cl_2 was stirred at room temperature for 1 h. For E = I, the following procedure was employed unless otherwise specified: a solution of 0.2 mmol of 2-(1-alkynyl)-2-alken-1-one, 3 equiv of I_2, 8 equiv of nucleophile, and 3 equiv of $NaHCO_3$ in 2 mL of CH_3CN was stirred at room temperature for 1 h. [b] The reaction took 4 h. [c] 1.5 equiv of nucleophile was used and CH_2Cl_2 was employed as the solvent. [d] The reaction took 50 h. [e] 2 mol % of $AuCl_3$ was used. [f] The reaction took 24 h.

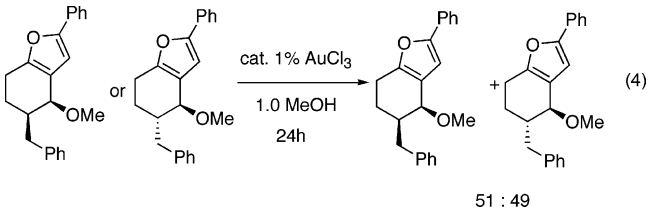
SCHEME 2



weak nucleophiles, like 1,3-cyclohexanedione and electron-rich arenes, did not afford coupling products in the I_2-induced process (Table 3, entries 25, 27, and 29). On the other hand, these weak nucleophiles work very well in the $AuCl_3$-catalyzed cyclization. Thus, the reaction of 1,3-cyclohexanedione afforded a high yield of the ether **36** in which the new bond has been formed between the β-carbon of the α,β-unsaturated ketone and the enol oxygen of the diketone (Table 3, entry 26). Electron-rich arenes, such as *N*,*N*-dimethylaniline and *N*-methylindole, can also be easily introduced completely regioselectively into furan products as carbon-based nucleophiles (Table 3, entries 28 and 30). *N*,*N*-Dialkylanilines can also be employed as benzene surrogates, since the direct deamination of *N*,*N*-dialkylanilines has recently been reported.[20] Overall, the $AuCl_3$-catalyzed and I_2-induced cyclizations compliment each other.[21] Together they provide a general and efficient route to highly substituted furans.

A range of 2-(1-alkynyl)-2-alken-1-ones readily participate in these cyclizations (Table 3, entries 31−47). In addition to the successful cyclization of 2-(1-alkynyl)-cyclohexenones **1** and **66** (see Scheme 3), 2-phenylethynyl-2-cyclopenten-1-one (**41**) afforded iodofuran **42** (74%) after an unusually long reaction time, but this alkyne was not reactive at all in the $AuCl_3$-catalyzed cyclization (Table 3, entries 31 and 32). A possible explanation is that the reaction is slowed because the carbonyl group is oriented away from the carbon−carbon triple bond. 2-Phenylethynyl-2-cyclohepten-1-one (**44**) (Table 3, entries 33 and 34) and chromone **47** (Table 3, entries 35−37) undergo smooth cyclizations. Interestingly, since the carbocation intermediates in the chromones are resonance stabilized by a neighboring oxygen (Scheme 2), *N*,*N*-dimethylaniline now proves to be an effective carbon-based nucleophile in the I_2-induced cyclization (Table 3, entry 37). Even sterically hindered chromone **51** afforded 3-iodofuran **52** in a good yield (Table 3, entry 38). Furthermore, acyclic 2-alken-1-ones also afford highly substituted furans in both the $AuCl_3$-catalyzed and I_2-induced cyclizations (Table 3, entries 40−43). Note that the acyclic substrates readily accommodate additional carbon−carbon double or triple bonds in the $AuCl_3$-catalyzed cyclizations, but not in the I_2-induced cyclizations (Table 3, entries 44−47). Again, these two cyclizations compliment each other.

We have also examined the stereochemistry of nucleophilic attack on the enone **66** (Scheme 3). This enone affords a mixture of cis and trans products in both cyclizations, with the latter predominating. Interestingly, when pureisomer **69** or **70** was subjected to our standard $AuCl_3$-catalyzed cyclization conditions, they were both readily isomerized to a 51:49 cis/trans mixture of **69** and **70** (eq 4).[22] Thus, the ratio of stereoisomers **69** and **70**



(4)

reported in Scheme 3 appears to roughly reflect the thermodynamic stability of the products. On the other hand, no isomerization of **67** or **68** was observed when they were subjected to our standard I_2-induced cyclization conditions.

This isomerization may occur through either Lewis acid-promoted ionization of the methyl ether to the corresponding cyclohexyl carbocation or electrophilic aromatic substitution of **69** or **70** by $AuCl_3$ to provide a furyl-gold species,[10i] which reverts back to starting material **66**, followed by $AuCl_3$-catalyzed recyclization of **66** to afford an equilibrium mixture of isomers (Scheme 4).

Further mechanistic studies have shown that neither of the above proposed mechanisms are correct (Scheme 5). When a 51:49 cis/trans mixture of **69** and **70** was subjected to our standard $AuCl_3$-catalyzed cyclization conditions using 5.0 equiv of CD_3OD as the nucleophile, no deuterium incorporation into the furan was observed, although the OCH_3 group was nearly completely replaced by OCD_3.

A reasonable pathway for this isomerization involves reversible abstraction of methoxide from **69** or **70** by oxophilic $AuCl_3$, as shown in Scheme 6.

At least two mechanisms are plausible for the gold-catalyzed cyclization (Scheme 7). In one (Cycle A), gold functions as both a Lewis acid and a transition metal.[23] $AuCl_3$ first acts as a Lewis acid, forming a complex with the carbonyl oxygen. This facilitates 1,4-addition of the nucleophile to the carbon−carbon double bond to produce **72**.[24] Subsequent coordination of the alkynyl moiety of the alkenynone **72** to $AuCl_3$ induces a cyclization of the carbonyl oxygen onto the triple bond, followed by elimination of a proton, and protonation of the resulting organogold intermediate to afford furan **2** with simultaneous regeneration of the $AuCl_3$ catalyst. An alternative mechanism in which $AuCl_3$ functions simply as a transition metal is also possible (Scheme 7, Cycle B).[10i] Coordination of the triple bond of **1** to $AuCl_3$ enhances the electrophilicity of the triple bond. Subsequent nucleophilic attack of the carbonyl oxygen on the electron-deficient triple bond generates carbocation **76**. Intermolecular nucleophilic attack on the carbocation and subsequent protonation of the carbon−gold bond afford

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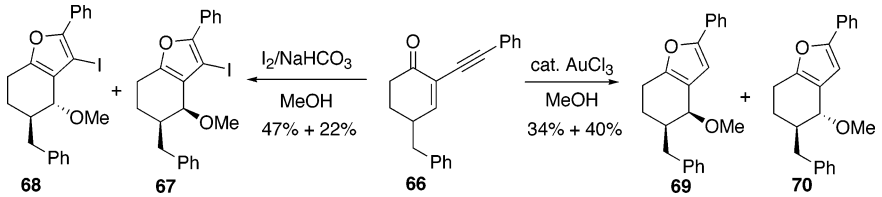
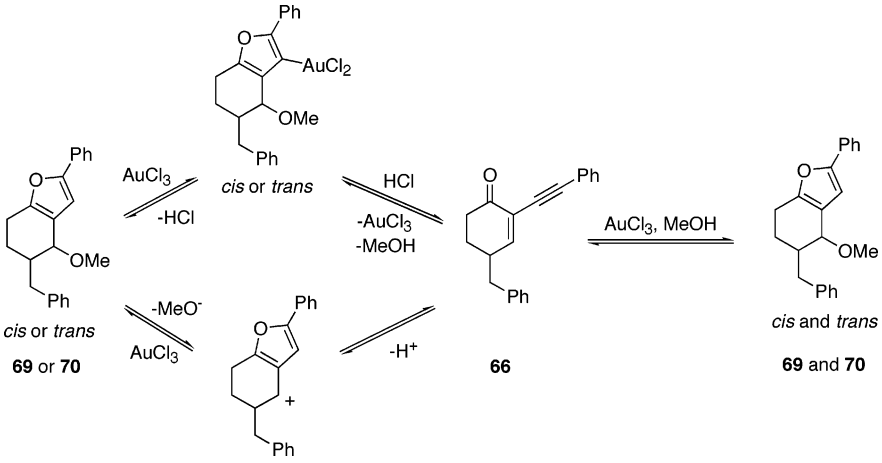
SCHEME 3



SCHEME 4



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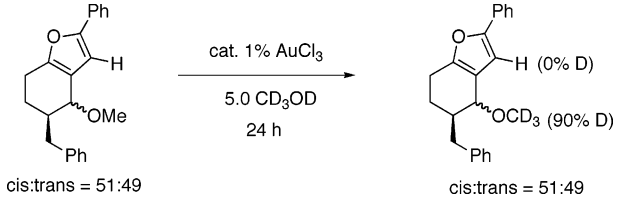
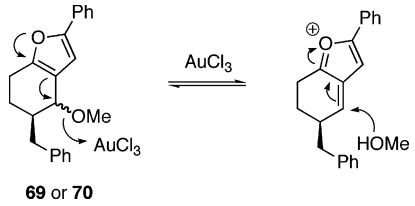
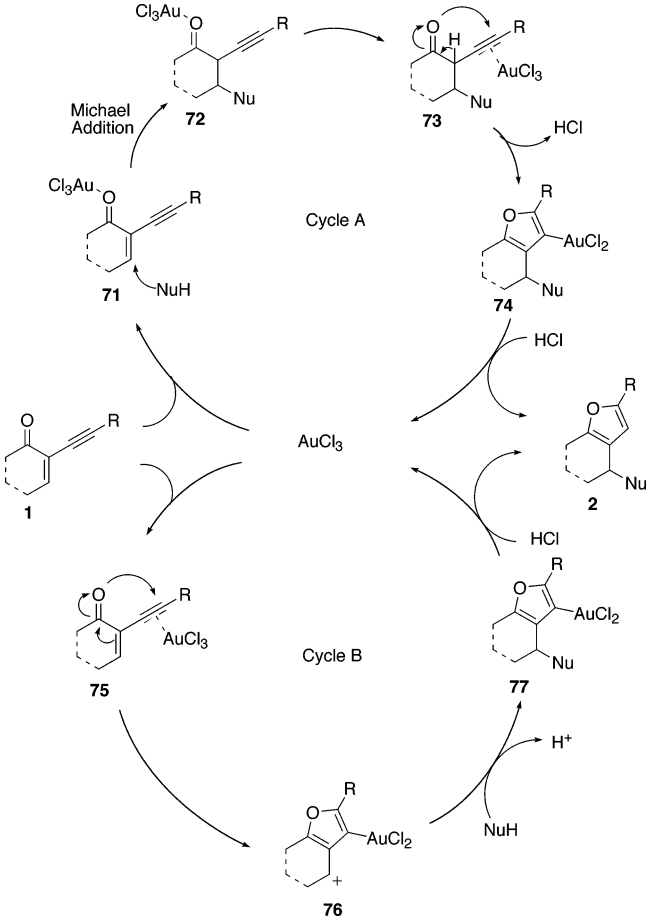


SCHEME 6

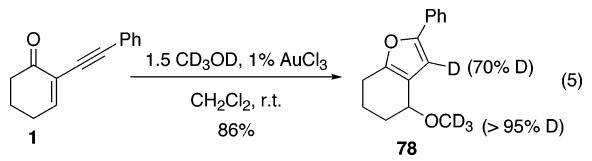


SCHEME 7



furan **2** and regenerate the catalyst $AuCl_3$. The mechanism illustrated in Cycle B appears more likely, since 1% $AuCl_3$ fails to catalyze the 1,4-addition of methanol to 2-cyclohexenone or methyl vinyl ketone under our standard reaction conditions.

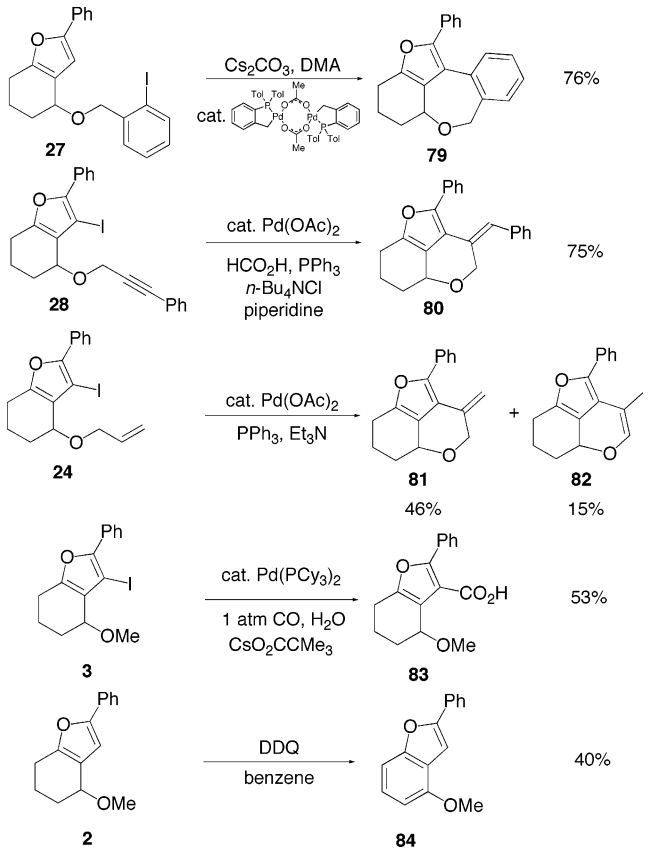
An experiment using fully deuterated methanol as the nucleophile, although it cannot distinguish between Cycle A and Cycle B in Scheme 7, produced furan **78** with 70% deuterium incorporation into the furan (eq 5). The proton-



(5)

containing furan product is apparently formed by inadvertent introduction of water into the deuterated methanol and/or the solvent. Using 3.0 equiv of fully deuterated methanol improved the deuterium incorporation in the furan to 85%.

SCHEME 8



The mechanism of the I_2-induced cyclization is presumably similar to that shown in Cycle B (Scheme 7). Coordination of the electrophile to the triple bond promotes nucleophilic attack of the carbonyl oxygen on the triple bond, generating a carbocation intermediate, which then undergoes nucleophilic attack to afford the furan product.

We have also investigated further transformations of the furan products (Scheme 8). For example, palladium-catalyzed intramolecular arylation,[25] intramolecular hydroarylation,[26] intramolecular Heck reaction,[27] and carbonylation[28] have afforded the anticipated products in modest to good yields. Benzofuran **84** can also be prepared through the DDQ-promoted dehydrogenation of **2**,[29] thus providing a regioselective method for the preparation of 4-substituted benzofurans.

Conclusion

An efficient synthesis of highly substituted furans has been developed through the cyclization of 2-(1-alkynyl)-2-alken-1-ones in the presence of various nucleophiles. If $AuCl_3$ is used as a catalyst, a proton is introduced into the 3 position of the furan. An iodide is readily introduced into the 3 position by using I_2 as the electrophile. Selenium and sulfur electrophiles can also be utilized, but the yields are low. An unprecedented range of nucleophiles can be employed in these processes, which are often complementary. This methodology accommodates various functional groups and affords the anticipated furans in good to excellent yields under very mild reaction conditions. The resulting iodine-containing products can be readily elaborated to more complex products using known organopalladium chemistry.

Experimental Section

Representative Procedure for the $AuCl_3$-Catalyzed Cyclizations. A solution of $AuCl_3$ (30.3 mg) in MeCN (970 mg) was prepared. To the appropriate 2-(1-alkynyl)-2-alken-1-one (0.2 mmol) and nucleophile (1.5 equiv) in CH_2Cl_2 (1 mL) was added the above $AuCl_3$ solution (20 mg, 1 mol %). The mixture was stirred at room temperature for 1 h unless otherwise specified. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel.

Representative Procedure for the I_2-Induced Cyclizations. To a mixture of the appropriate 2-(1-alkynyl)-2-alken-1-one (0.2 mmol), I_2 (3.0 equiv), and $NaHCO_3$ (3.0 equiv) was added a solution of the nucleophile (8.0 equiv) in MeCN (2 mL). The resulting mixture was stirred at room temperature for 1 h unless otherwise specified. The mixture was diluted with ether (25 mL), washed with saturated $Na_2S_2O_3$ (25 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and the National Institute of General Medical Sciences (GM070620) for partial support of this research.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0510585

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