JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Intramolecular *ipso*-Halocyclization of 4-(*p*-Unsubstituted-aryl)-1-alkynes Leading to Spiro[4,5]trienones: Scope, Application, and Mechanistic Investigations

Bo-Xiao Tang,[‡] Yue-Hua Zhang,[‡] Ren-Jie Song,[†] Dong-Jun Tang,[‡] Guo-Bo Deng,[†] Zhi-Qiang Wang,[†,‡] Ye-Xiang Xie,[†] Yuan-Zhi Xia,[¶] and Jin-Heng Li*[,†]

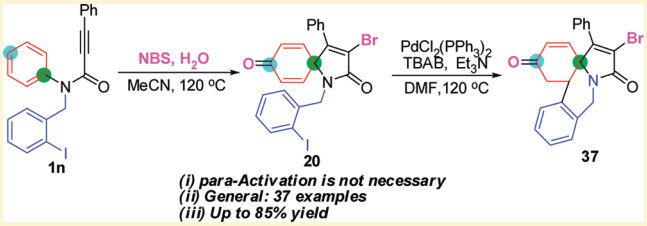
[†]State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China

[‡]Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research (Ministry of Education), Hunan Normal University, Changsha 410081, China

[¶]College of Chemistry and Materials engineering, Wenzhou University, Wenzhou, 325035, China

Supporting Information

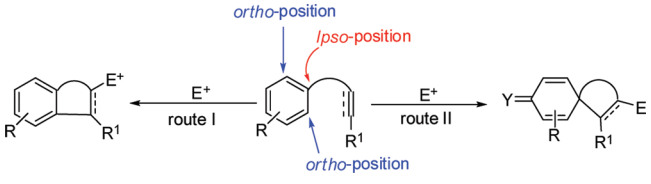
ABSTRACT: A new, general method for the synthesis of spiro[4,5]trienones is described by the intramolecular *ipso*-halocyclization of 4-(*p*-unsubstituted-aryl)-1-alkynes. In the presence of halide electrophiles, a variety of 4-(*p*-unsubstituted-aryl)-1-alkynes underwent the intramolecular *ipso*-halocyclization with water smoothly, affording the corresponding halo-substituted spiro[4,5]trienones in moderate to good yields. The obtained spiro[4,5]trienones can be applied in constructing the azaquaternary tricyclic skeleton via Pd-catalyzed Heck reaction. Notably, the prepared spiro[4,5]trienones and azaquaternary tricycles are of importance in the areas of pharmaceuticals and agrochemicals. The mechanism of the intramolecular *ipso*-halocyclization reaction is also discussed according to the ^{18}O-labeling experiments and DFT calculations.



INTRODUCTION

The intramolecular electrophilic cyclization reactions have emerged as one of the most important methods for constructing important carbocycles and heterocycles via the formation of both a carbon−carbon bond and a carbon−heteroatom bond in a single reaction.[1−4] Until now, there are two types of intramolecular electrophilic cyclization routes (Scheme 1): one involves the introduction of a substituent onto its *ortho*-position of the aromatic ring,[1−3] and the other is onto its *ipso*-position of the aromatic ring.[1,4−6] Although the latter is a useful tool for the synthesis of spiro-heterocycles, only a few papers have been reported. In 2003, Fanghänel and co-workers first described an interesting intramolecular electrophilic cyclization method that utilized the *ipso*-position of the aromatic ring in bis(4-methoxybenzylthio)acetylene as a reaction partner to react with ICl, Na_2CO_3, and H_2O, affording a spiro[4,5]trienone product (eq 1 in Scheme 2).[4] In 2005, Larock and Zhang developed a general intramolecular electrophilic *ipso*-cyclization protocol, which is compatible with a wide range of 4-(4-methoxyaryl)-1-alkynes to give the corresponding spiro[4,5]trienones in moderate to excellent yields using the ICl, I_2/$NaHCO_3$, or Br_2 electrophilic system (eq 2 in Scheme 2).[5a] Recently, we extended the intramolecular *ipso*-iodocyclization process to 4-(*p*-methylaryl)-1-alkynes (eq 3 in Scheme 2).[6b] However, these methods are restricted with arylalkynes bearing some *para*-substituents, such as methoxy, *N*,*N*-dimethylamino, or alkyl groups, on the aryl ring.[4,5,6a,b] Alternatively, a novel electrophilic *ipso*-cyclization of *para*-unsubstituted arylalkynes approach to spiro[4,5]trienyl acetates and ethers has been developed employing HOAc[6c] or polyfluoro alcohols[6d] as the cationic captors and NIS (*N*-iodosuccimide) as the electrophile (eq 4 in Scheme 2). To the best of our knowledge, however, a general route to 3-halo spiro[4,5]trienones by the electrophilic *ipso*-cyclization of *para*-unsubstituted arylalkynes with halide electrophiles has not yet been reported (eq 5 in Scheme 2). Moreover, the mechanism for the electrophilic *ipso*-cyclization method was not studied in detail.

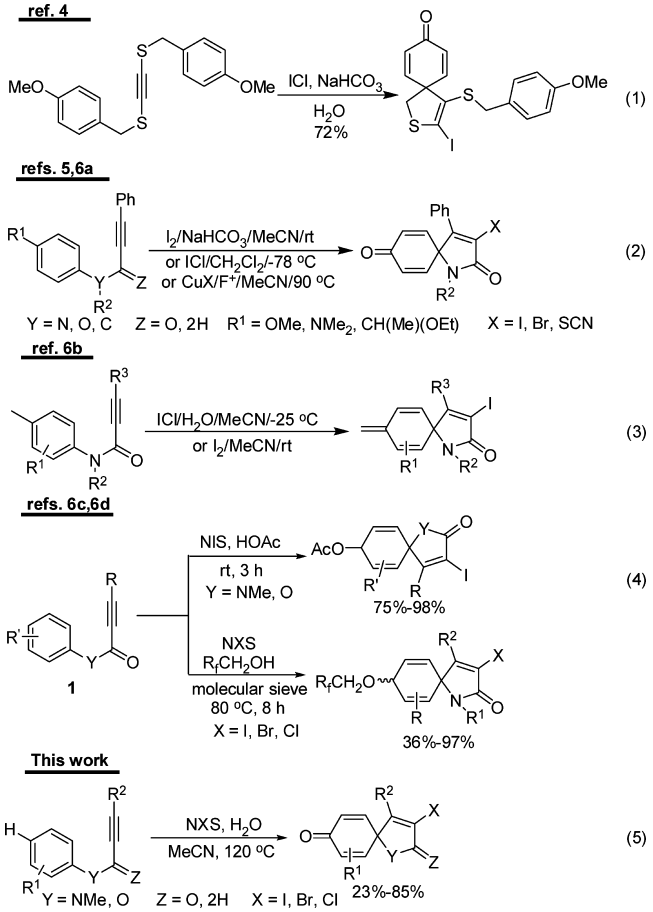
Scheme 1. Two Intramolecular Electrophilic Cyclization Routes



Received: January 11, 2012
Published: February 23, 2012

   dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

Scheme 2. The Intramolecular Electrophilic *ipso*-Cyclization Reactions



Spirocycles, particularly the primary *N*-containing spirocycle products described in this paper, are found in numerous biologically active molecules, such as the erythrina, amaryllidaceae, aspidosperma, and strychnos families (Figure 1).[7] Efforts to construct the core spirocyclic structure include intramolecular cyclization reactions, such as the radical cyclizations,[8] electrophilic substitution cyclizations on *N*-acyliminium intermediates or Pummerer-induced cyclizations,[9] transition metal-mediated cyclization reactions (often Heck reactions),[10,11] and anionic substitution reactions.[12] However, many methods are restricted to relatively harsh reaction conditions, inaccessible substrates, and/or expensive catalytic systems. Access to this class of compounds by the intramolecular electrophilic *ipso*-cyclization of arylalkynes would have advantages over the reported strategies because it would allow for easy variation of the aromatic component and introduction of new groups on the position of several preexisting functional groups (olefine and halo groups) in its products, facilitating the generation of analogues with a new structural feature for further elaboration.

Here, we report a new, general protocol for the synthesis of 3-halospirotrienones by the electrophilic *ipso*-cyclization of *para*-unsubstituted arylalkynes with halide electrophiles and water (eq 5 in Scheme 2). We have examined aspects of the electrophilic *ipso*-cyclization reaction by synthetic, applied, and mechanistic investigations. The synthetic and applied investigations will focus on (1) the 4-(*p*-unsubstituted-aryl)-1-alkyne scope for the electrophilic *ipso*-cyclization with halide electrophiles and water, (2) the development of an intramolecular Heck process for cyclization of 3-halo-1-(2-halobenzyl)-4-substituted-1-azaspiro[4.5]deca-3,6,9-triene-2,8-diones, constructing the erythratidinone analogues, and (3) the cross-coupling of the pre-existing olefinic and halo groups on the erythratidinone analogues. The mechanistic investigations will focus on (1) ^{18}O-labeling experiments under Larock's and our conditions in the presence of $H_2{}^{18}O$[13] and (2) a computational study including DFT calculations on each step for the related intermediates to understand the ^{18}O-labeling experiments.[14]

RESULTS AND DISCUSSION

Intramolecular *ipso*-Halocyclization of 4-(*p*-Unsubstituted-aryl)-1-alkynes. *N*-Methyl-*N*,3-diphenylpropiolamide (**1a**) was used as a model substrate, reacting with various halide electrophiles and water, to screen the optimal reaction conditions (Table 1). Initially, the reaction of substrate **1a** with NBS (*N*-bromosuccimide) and water was investigated (Table 1, entries 1−7). We found that the amount of water had a fundamental influence on the reaction (Table 1, entries 1−5). While 16.7 mmol H_2O gave the corresponding product **2** in a low yield (Table 1, entry 1), 2.8 mmol H_2O enhanced the yield to 76% (Table 1, entry 4). The yield of **2** was reduced to 56% when 1.5 mmol H_2O was added (Table 1, entry 5). It was found that the reactivity of substrate **1a** was lowered sharply at either 80 °C or 2 equiv of K_2CO_3 (Table 1, entries 6 and 7). Gratifyingly, the reaction of substrate **1a** with NIS and H_2O was also carried out smoothly at 120 °C, affording the corresponding product **3** in 73% yield (Table 1, entry 8). However, the yield was decreased to 50% when the reaction was conducted at 60 °C (Table 1, entry 9). Finally, the compatibility of the other electrophiles, including NCS (*N*-chlorosuccimide), ICl, I_2, and CuBr, was investigated, and the results demonstrated that they displayed less activity in the *ipso*-cyclization reaction (Table 1, entries 10−16): NCS, for instance, reacted with substrate **1a** and H_2O at 130 °C after 48 h to furnish the target product **4** in 33% yield (Table 1, entry 11). It is noteworthy that the structure of **3** was unambiguously confirmed by the X-ray single-crystal diffraction analysis.[15]

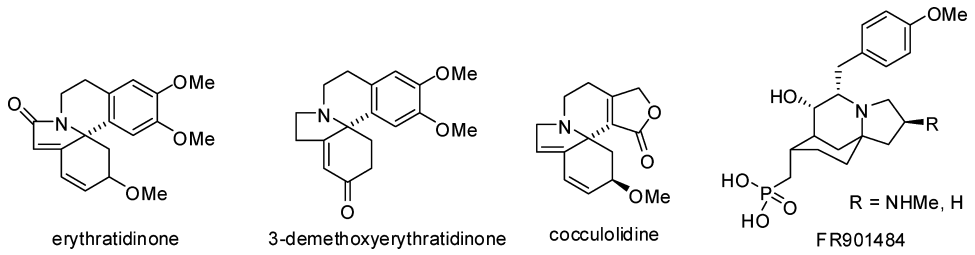
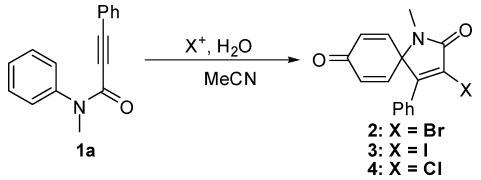


Figure 1. Representative biologically active spirocycles with curare-like, hypnotic, sedative, hypotensive, neuromuscular blocking, and CNS activity.

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

Table 1. Screening Optimal Conditions[a]



entry	X^+	H_2O (mmol)	T (°C)	time (h)	isolated yield (%)
1	NBS	16.7	120	24	35 (**2**)
2	NBS	11.1	120	24	68 (**2**)
3	NBS	5.6	120	24	64 (**2**)
4	NBS	2.8	120	24	76 (**2**)
5	NBS	1.5	120	24	56 (**2**)
6	NBS	2.8	80	24	35 (**2**)
7[b]	NBS	2.8	120	24	trace (**2**)
8[c]	NIS	2.8	120	8	73 (**3**)
9[c]	NIS	2.8	60	8	50 (**3**)
10	NCS	2.8	120	24	26 (**4**)
11	NCS	2.8	130	48	33 (**4**)
12	ICl	2.8	120	24	30 (**3**)
13	ICl	2.8	rt	24	5 (**3**)
14	I_2	2.8	120	24	trace (**3**)
15[d]	I_2	2.8	rt	24	21 (**3**)
16[e]	CuBr	2.8	120	24	trace (**2**)

[a]Reaction conditions: **1a** (0.3 mmol), X^+ (1.5 equiv), H_2O, and MeCN (1 mL). [b]K_2CO_3 (2 equiv). [c]NIS (2 equiv) was averagely added two times in 3 h. [d]$NaHCO_3$ (2 equiv) was added. [e]CuBr (3 equiv) combined with 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (1.5 equiv) was added.

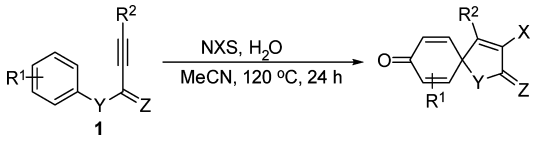
With the optimal reaction conditions in hand, the scope of 4-(*p*-substituted aryl)-1-alkynes for the *ipso*-cyclization reaction was explored (Table 2). The results demonstrated that several substituents, including aryl or aliphatic groups, at the terminal alkyne of propiolamide were tolerated well, and the order of substituent reactivity was electron-rich aryl groups and aliphatic groups > electron-deficient aryl groups (Table 2, entries 1−6). 4-Methoxyaryl-substituted substrate **1c**, for instance, was treated with NBS to give the desired product **6** in 75% yield (Table 2, entry 2). However, the reactivity of 4-nitroaryl alkyne **1e** was lowered, affording the corresponding **9** in 52% yield (Table 2, entry 5). It was noted that moderate yields were obtained from the reaction of substrate **1d** with either NBS or NIS in the presence of H_2O (Table 2, entries 3 and 4). Interestingly, a number of functional groups, such as methyl, chloro, bromo, and iodo groups, on the aryl moiety of *N*-arylpropiolamides **1g−1l** were compatible with the optimal conditions (Table 2, entries 7−14). For example, substrate **1h** with an *ortho*-methyl group was treated with either NBS or NIS smoothly, furnishing the corresponding products **13** and **14** in 83% and 65% yields, respectively (Table 2, entries 9 and 10). Good yields were still achieved from the reactions of substrates **1j−1l** with an *ortho*-chloro, bromo, or iodo groups (Table 2, entries 12−14). Gratifyingly, the analogous amides with the *N*-methyl group replaced by either a benzyl or a 2-iodobenzyl group were also suitable substrates to selectively afford the corresponding 1-azaspiro[4.5]deca-3,6,9-triene-2,8-diones **19−21** in good yields (Table 2, entries 15−17).

These encouraged us to examine the substituent effect on *N*-(2-halobenzyl)-*N*-arylpropiolamides **1o−1z** (Table 2, entries 18−29). Screening revealed that the optimal conditions were consistent with various substituents at the terminal propiolamide (Table 2, entries 18−21). Substrate **1p** with an *ortho*-MeO group, for instance, offered the desired product **23** in 57% yield (Table 2, entry 19). Using electron-withdrawing 4-acetoxy-susbtituted substrate **1q**, a moderate yield was still achieved (Table 2, entry 20). We were pleased to discover that aliphatic alkyne **1r** was also successful for the *ipso*-cycylzation with NBS (Table 2, entry 21). Subsequently, substitutents on the *N*-aryl ring were investigated in the presence of NBS and H_2O (Table 2, entries 22−25). While the electron-donating groups, methyl or methoxy group, on the aryl moiety of *N*-(2-halobenzyl)-*N*-arylpropiolamide were suitable for the reaction (Table 2, entries 22 and 23), the fluoro or iodo group on the *N*-aryl moiety led to low yields (Table 2, entries 24 and 25). The results disclosed that substrates **1w** and **1x**, having a Me or MeO group, on the aromatic ring of the *N*-(2-iodobenzyl) moiety could furnish the target products **30** and **31** in good yields (Table 2, entries 26 and 27). Interestingly, a heterocycle was introduced into this system, which also makes this methodology more useful for the preparation of pharmaceuticals and natural products (Table 2, entry 28). Notably, two substrates **1aa** and **1ab**, an amine and an ester, were also evaluated, and the results showed that they were consistent with the optimal conditions (Table 2, entries 30 and 31).

Intramolecular Heck Reaction of 3-Halo-1-(2-halobenzyl)-4-substituted-1-azaspiro[4.5]deca-3,6,9-triene-2,8-diones. The Heck reaction is one the most important methods for the formation of the carbon−carbon bond.[11] To construct the azaquaternary tricyclic skeleton, the product **20**, 3-bromo-1-(2-iodobenzyl)-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione, was employed to screen the optimal reaction conditions for the intramolecular Heck reaction (Table 3). We found that additives played important roles in the selectivity of the Heck reaction: while treatment of substrate **20** with $Pd(OAc)_2$ and Et_3N afforded two azaquaternary tricyclic products **36** and **37** in 17% and 18% yields, respectively (Table 3, entry 1), TBAB shifted the selectivity toward **37** with a 61% yield together with 20% yield of **36** (Table 3, entry 2). We were surprised to disclose that $Pd_3(dba)_2$ and $Pd(PPh_3)_4$ have no catalytic activity

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

Table 2. Intramolecular *ipso*-Halocyclization of 4-(*p*-Unsubstituted-aryl)-1-alkynes (1)[a]



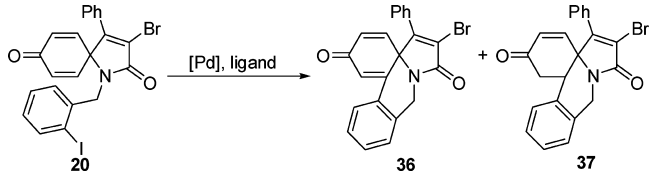
Entry	Substrate	X^+	Product		Yield (%)[b]
	R		R	X	
1	4-MeC_6H_4	**1b** NBS	4-MeC_6H_4	Br **5**	56
2	4-$MeOC_6H_4$	**1c** NBS	4-$MeOC_6H_4$	Br **6**	75
3	4-$CH_3COC_6H_4$	**1d** NBS	4-$CH_3COC_6H_4$	Br **7**	55
4[c]	4-$CH_3COC_6H_4$	**1d** NIS	4-$CH_3COC_6H_4$	I **8**	46
5	4-$NO_2C_6H_4$	**1e** NBS	4-$NO_2C_6H_4$	Br **9**	52
6	*n*-C_5H_{11}	**1f** NBS	*n*-C_5H_{11}	Br **10**	63
7	Ph	**1g** NBS	Ph	Br **11**	52
8[c]		NIS		I **12**	47
9	Ph	**1h** NBS	Ph	Br **13**	83
10[c]		NIS		I **14**	65
11	Ph	**1i** NBS	Ph, Br	**15**	61
12	Ph, Cl	**1j** NBS	Ph, Br, Cl	**16**	73
13	Ph, Br	**1k** NBS	Ph, Br, Br	**17**	80
14	Ph, I	**1l** NBS	Ph, Br, I	**18**	72
15	Ph, Bn	**1m** NBS	Ph, Br, Bn	**19**	58
16	Ph, I	**1n** NBS	Ph, X	Br **20**	85
17[c]		NIS		I **21**	78
	R, I		R, Br, I		
	R		R		
18	4-MeC_6H_4	**1o** NBS	4-MeC_6H_4	**22**	65
19	2-$MeOC_6H_4$	**1p** NBS	2-$MeOC_6H_4$	**23**	57
20	4-$CH_3COC_6H_4$	**1q** NBS	4-$CH_3COC_6H_4$	**24**	45
21	Me	**1r** NBS	Me	**25**	70
22	Ph, I	**1s** NBS	Ph, Br	**26**	83
23	Ph, I	**1t** NBS	Ph, Br	**27**	72
24	F, Ph, I	**1u** NBS	F, Ph, Br	**28**	42
25	I, Ph, I	**1v** NBS	I, Ph, Br	**29**	23
26	Ph, I	**1w** NBS	Ph, Br	**30**	60
27	Ph, MeO, I	**1x** NBS	Ph, Br, MeO	**31**	85
28	Ph, S, I	**1y** NBS	Ph, Br, S	**32**	53
29	Ph, Br	**1z** NBS	Ph, Br, Br	**33**	65
30	Ph, Tf	**1aa** NBS	Ph, Br, Tf	**34**	85
31[d]	Ph, O	**1ab** NBS	Ph, Br, O	**35**	51

[a]Reaction conditions: **1** (0.3 mmol), E^+ (1.5 equiv), H_2O (2.8 mmol), and MeCN (1 mL) at 120 °C for 24 h under argon atmosphere. [b]Isolated yield. [c]NIS (2 equiv) was averagely added two times in 3 h, and the reaction was then carried out for another 8 h. [d]For 48 h.

for the Heck reaction (Table 3, entries 3 and 4). Interestingly, the product **37** was obtained alone in 80% yield using the $PdCl_2(PPh_3)_2$/TBAB/Et_3N system (Table 3, entry 5). However, two other amine bases, $^iPr_2NH$ and *n*-Bu_3N, were less effective than Et_3N (Table 3, entries 6 and 7). Screening revealed that $Pd(OAc)_2$ combined with PPh_3 and TBAB was inferior to the $PdCl_2(PPh_3)_2$/TBAB/Et_3N system (Table 3, entry 8). To our delight, the selectivity was shifted toward the product **36** when the $Pd(OAc)_2/PPh_3/NaHCO_3$ system was used (Table 3, entry 9). However, two other inorganic bases,

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

Table 3. Screening Optimal Conditions for the Intramolecular Heck Reaction[a]



entry	[Pd] (mol %)	additive (equiv)	base (equiv)	time (h)	isolated yield (%)[b] 36	37
1	$Pd(OAc)_2$ (5)		Et_3N (2)	1.5	17	18
2	$Pd(OAc)_2$ (5)	TBAB (1)	Et_3N (2)	1.5	20	61
3	$Pd_3(dba)_2$ (5)	TBAB (1)	Et_3N (2)	1.5	trace	trace
4	$Pd(PPh_3)_4$ (5)	TBAB (1)	Et_3N (2)	1.5	trace	trace
5	$PdCl_2(PPh_3)_2$ (5)	TBAB (1)	Et_3N (2)	12	trace	80
6	$PdCl_2(PPh_3)_2$ (5)	TBAB (1)	$^iPr_2NH$ (2)	12	trace	40
7	$PdCl_2(PPh_3)_2$ (5)	TBAB (1)	Bu_3N (3)	12	trace	14
8	$Pd(OAc)_2$ (5)	TBAB (1)/PPh_3 (0.1)	Et_3N (2)	3	5	67
9	$Pd(OAc)_2$ (10)	PPh_3 (0.2)	$NaHCO_3$ (2)	1.5	78	15
10	$Pd(OAc)_2$ (10)	PPh_3 (0.2)	Na_2CO_3 (2)	1.5	58	5
11	$Pd(OAc)_2$ (10)	PPh_3 (0.2)	Cs_2CO_3 (2)	1.5	trace	trace

[a]Reaction conditions: **20** (0.2 mmol), [Pd], additive, and base in DMF (1 mL) at 120 °C under argon atmosphere. [b]Average yield in two runs.

Na_2CO_3 and Cs_2CO_3, lowered the reactivity of substrate **20** (Table 3, entries 10 and 11). Notably, the structure of **37** was also unambiguously confirmed by the X-ray single-crystal diffraction analysis.[15]

Consequently, the intramolecular Heck reaction was conducted in the presence of $PdCl_2(PPh_3)_2$, TBAB, and Et_3N, and the results are summarized in Table 4. The results demonstrated that substituents on the five-memebered ring affected the reaction. Substrate **21** bearing a 3-iodo group gave a trace of the desired product **38** in the presence of $PdCl_2(PPh_3)_2$, TBAB, and Et_3N (Table 4, entry 1), whereas substrates with a 3-bromo group were suitable for the intramolecular Heck reaction (Table 4, entries 2−11). Although 3-bromospirotrienones **22**, **24**, and **25** could successfully undergo the reaction, substituents at the 4-position have some effect on the yields: aryl group > aliphatic group (Table 4, entries 2−4). Subsequently, the effect of the substituents on the six-memebered ring was also examined under the standard conditions (Table 4, entries 5−8). In the presence of $PdCl_2(PPh_3)_2$, TBAB, and Et_3N, substrates **26**−**28** with a methyl or fluoro group at the 7-position gave the corresponding azaquaternary tricyclic products in good yields (Table 4, entries 5−7). However, substrate **29**, having an iodo group in the six-memebered ring moiety, offered the desired product **45** in a low yield (Table 4, entry 8). Substrate **31**, bearing a methoxy group, on the 2-iodobenzyl moiety was reacted with $PdCl_2(PPh_3)_2$, TBAB, and Et_3N smoothly in moderate yield (Table 4, entry 9). Using a heterocycle-contained substrate **32**, moderate yield was still achieved (Table 4, entry 10). Notably, 2-bromobenzyl 1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (**33**) could be cyclized in 71% yield after prolonging the reaction time using the $PdCl_2(PPh_3)_2$/TBAB/Et_3N system (Table 4, entry 11).

As shown in Scheme 3, another azaquaternary tricyclic skeleton was constructed in the presence of $Pd(OAc)_2$, PPh_3, and $NaHCO_3$. The results demonstrated that substrates **22** or **24** could react with $Pd(OAc)_2$, PPh_3, and $NaHCO_3$ to afford the corresponding products **48** and **49** in moderate yields.

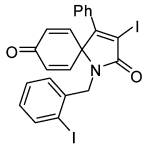
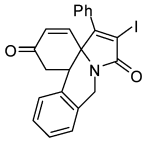
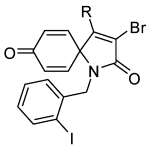
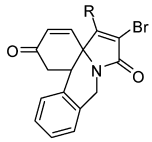
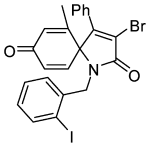
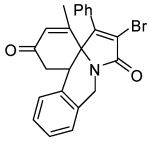
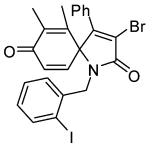
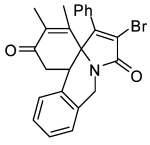
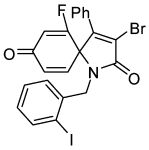
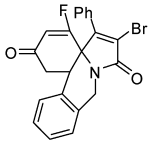
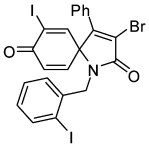
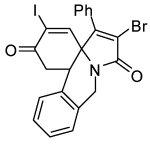
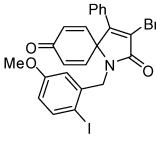
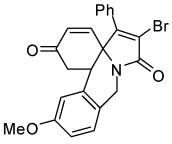
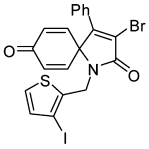
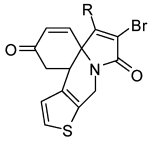
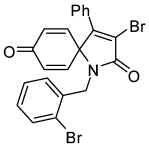
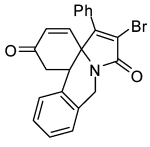
It is noteworthy that the above azaquaternary tricyclic products are still useful synthetic blocks because there are several functional groups, such as olefinic or bromo groups, in them. To verify it, the cross-coupling reactions of the azaquaternary tricyclic product **37** were investigated (Scheme 4).[16] The Sonogashira reaction of substrate **37** with phenylacetylene was conducted smoothly in 54% yield using the $PdCl_2(PPh_3)_2$/CuI catalytic system and Et_3N/THF as the media.[16a−c] Under our reported conditions, substrate **37** was reacted with *p*-tolylboronic acid or *tert*-butyl acrylate to afford the corresponding Suzuki product **51** or Heck product **52** in excellent yields.[16d]

Mechanistic Investigation ^{18}O-Labeling Experiments.[13] Fanghänel and Larock independently have proposed a possible mechanism for the *ipso*-cyclization of 4-(4-methoxyaryl)-1-alkynes.[3a,b] The main difference is the oxygen atom source of the ketone group in spiro[4,5]trienones: from water or the existing MeO group.

To elucidate the mechanism, ^{18}O-labeling experiments as listed in Scheme 5 were conducted in the presence of $H_2{}^{18}O$ under five types of reaction conditions including conditions **A**: NBS in MeCN at 120 °C; conditions **B**: NIS in MeCN at 120 °C; conditions **C**: NIS in MeCN at room temperature; conditions **D** (Larock's conditions): I_2 and $NaHCO_3$ in MeCN at room temperature; and conditions **E** (Larock's conditions): ICl in CH_2Cl_2 at −78 °C. Notably, the ^{18}O-labeling results were determined by GC−MS analysis. In the presence of $H_2{}^{18}O$, the electrophilic *ipso*-cyclization of *N*-methyl-*N*,3-diphenylpropiolamide (**1a**) with NBS or NIS afforded the ^{18}O-labeled product (conditions **A** and **B**). Identical results were obtained from *N*-(4-methoxyphenyl)-*N*-methyl-3-phenylpropiolamide (**1ac**) under conditions **A**−**D**, in which both the cleavage of C−OMe bond and a new C−O bond-forming take place. However, no ^{18}O-labeled product was observed when substrate **1ac** was reacted with ICl in the presence of $H_2{}^{18}O$ (conditions **E**). To verify these results, another substrate **1ad**, 1,1,1-trifluoro-*N*-(4-methoxyphenyl)-*N*-(3-phenylprop-2-ynyl)-methanesulfonamide, was tested with $H_2{}^{18}O$ under conditions **A**, **B**, **D**, and **E**. The results showed that the ^{18}O-labeled

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

Table 4. $PdCl_2(PPh_3)_2$-Catalyzed Heck Reaction in the Presence of TBAB and Et_3N[a]

Entry	Substrate	Product/Isolated yield (%)[b]
1	 **21**	 **38**/trace
2	 R = 4-MeC_6H_4 **22**	 R = 4-MeC_6H_4 **39**/85
3	R = 4-$CH_3COC_6H_4$ **24**	R = 4-$CH_3COC_6H_4$ **40**/92
4	R = Me **25**	R = Me **41**/53
5	 **26**	 **42**/76
6	 **27**	 **43**/96
7	 **28**	 **44**/92
8	 **29**	 **45**/38
9	 **31**	 **46**/62
10	 **32**	 **47**/40
11[c]	 **33**	 **37**/71

[a]Reaction conditions: **1a** (0.2 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), TBAB (1 equiv), and Et_3N (2 equiv) in DMF (1 mL) at 120 °C under argon atmosphere for 12 h. [b]Average yield in two runs. [c]For 48 h.

product was isolated under these conditions. Interestingly, one ^{16}O atom of CF_3SO_2 group was also replaced by ^{18}O under conditions **D**. It was noted that the ^{18}O-labeled product was also obtained from the reaction of ester **1ae**, 4-methoxyphenyl 3-phenylpropiolate, with $H_2{}^{18}O$ and I_2 (conditions **D**). These results indicate that the oxygen atom source of the ketone group in spiro[4,5]trienones depends on both substrates and the reaction conditions.

Consequently, a possible mechanism outlined in Scheme 6 was proposed.[4−6,14] Our experimental works showed that substrate **1a**, in which no *para*-methoxy group was contained, could also undergo the intramolecular *ipso*-halocyclization and lead to the ketone product **3**. They isolated an unstable intermediate, which was assigned to be intermediate **F** by GC−MS analysis.[17] DFT calculations supported the experiments well.[14] Intermediate **F** could be formed from the nucleophilic attack of H_2O to cation **E** via a transition state similar to **TS2-X** with an activation energy of 18 kcal/mol.[14] The following oxidation of alcohol **F** to ketone **3** is the rate-limiting step of the whole reaction, which requires an activation energy of 30 kcal/mol.

CONCLUSIONS

In summary, we have reported an efficient method for the intramolecular *ipso*-halocyclization of 4-(*p*-unsubstituted-aryl)-1-alkynes with halide electrophiles and water. This new method allows numerous *N*-arylpropiolamides, *N*-(prop-2-ynyl)anilines, and aryl propiolates to construct spiro[4,5]trienones in moderate to excellent yields. Importantly, the products, 3-halo spiro[4,5]trienones, are found in a wide range of biologically active molecules, such as the erythrina, amaryllidaceae, aspidosperma, and strychnos families,[4] and are valuable intermediates for easy introduction of new groups on the position of several preexisting functional groups (olefin and halo groups) to generate their analogues with a new structural feature for further elaboration. For example, the intramolecular Heck reaction of these 3-halo spiro[4,5]trienones was carried out for constructing the azaquaternary tricyclic skeleton. ^{18}O-labeling experiments have provided insight into the mechanism of the real oxygen atom source of the ketone moiety in spiro[4,5]trienones and show that the real oxygen atom source depends on both substrates and the reaction conditions. Our synthetic studies show that 4-aryl-1-alkynes with or without a substituent on their *para*-position are consistent with the optimal conditions, and their 3-halo spiro[4,5]trienone products with several attractive functional groups display some particular activities for introducing new groups. Additionally, the results of the GC−MS analysis demonstrate that 8-hydroxy-3-iodo-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-2-one (**F**) is generated, and it can be readily converted into the corresponding spiro[4,5]trienone (**3**). The computational studies predict these results and imply that this step is the rate-limiting step. Overall, these studies further expand our understanding of the intramolecular *ipso*-halocyclization process and how each of these contributes to the protocols derived from them.

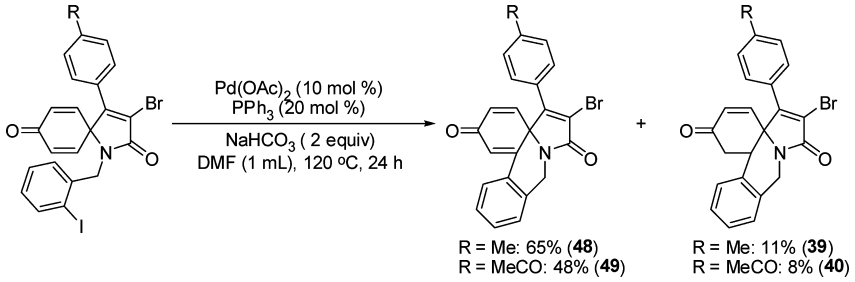
EXPERIMENTAL SECTION

The solvent of recrystallization for products **3** and **37** is a mixtue of ethyl acetate and hexane.

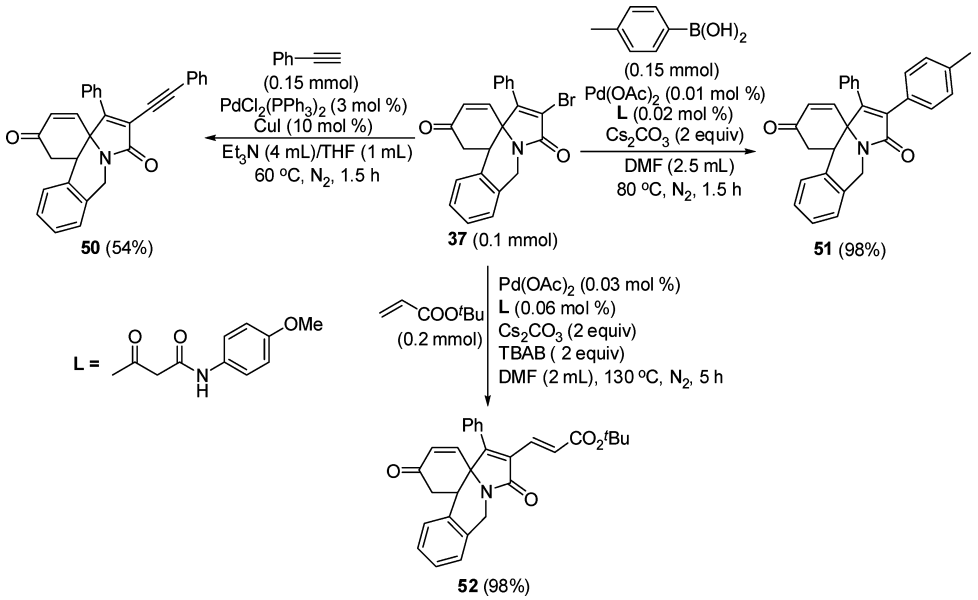
Typical Experimental Procedure for the Selective Synthesis 1-Azaspiro[4.5]deca-3,6,9-triene-2,8-diones. To a Schlenk tube were added amide **1** (0.2 mmol) and NBS (1.5 equiv), and then CH_3CN (1 mL) was added to the mixture at room temperature. Then the tube was stirred at 120 °C (oil bath temperature) for the indicated time until complete consumption of starting material as monitored by TLC and GC−MS analysis. After the reaction was finished, the reaction mixture was diluted in diethyl ether and washed with brine. The aqueous phase was re-extracted with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum,

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

Scheme 3. $Pd(OAc)_2/PPh_3$-Catalyzed Heck Reaction



Scheme 4. Cross-Coupling Reactions of Compound 37



and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1) to afford the corresponding 1-azaspiro[4.5]deca-3,6,9-triene-2,8-diones.

Typical Experimental Procedure for the $PdCl_2(PPh_3)_2$-Catalyzed Heck Reaction. To a Schlenk tube were added amide 1-azaspiro[4.5]deca-3,6,9-triene-2,8-diones (0.2 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), TBAF (0.2 mmol), and Et_3N (0.4 mmol), and then DMF (1 mL) was added to the mixture at room temperature. Then the tube was charged with Ar (1 atm) and was stirred at 120 °C (oil bath temperature) for the indicated time until complete consumption of starting material as monitored by TLC and GC−MS analysis. After the reaction was finished, the reaction mixture was diluted in diethyl ether and washed with brine. The aqueous phase was re-extracted with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in a vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4:1) to afford the corresponding products.

3-Bromo-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (2).[6a] White solid: mp 163.5−164.1 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.43−7.36 (m, 5H), 6.55−6.49 (m, 4H, spiro-ring-H), 2.94 (s, 3H); ^{13}C NMR (125 MHz) δ 183.7, 165.8, 151.3, 144.1, 133.5, 130.3, 130.2, 128.8, 127.8, 119.9, 68.3, 26.6; IR (KBr, cm^{-1}) 1701, 1670; LRMS (EI 70 eV) m/z (%) 331 (M^++2, 14), 329 (M^+, 15), 250 (45), 129 (100); HRMS (EI) for $C_{16}H_{12}BrNO_2$ (M^+) calcd. 329.0051, found 329.0054.

3-Iodo-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (3).[6a] Pale yellow solid: mp 195.5−197.3 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.40−7.35 (m, 3H), 7.30−7.27 (m, 2H), 6.53−6.45 (m, 4H, spiro-ring-H), 2.96 (s, 3H); ^{13}C NMR (125 MHz) δ 183.6, 167.3, 157.9, 144.0, 133.2, 131.8, 130.0, 128.6, 127.6, 98.1, 70.3, 26.9; IR (KBr, cm^{-1}) 1699, 1662; LRMS (EI 70 eV) m/z (%) 377 (M^+, 17), 250 (39), 129 (100); HRMS (EI) for $C_{16}H_{12}INO_2$ (M^+) calcd. 376.9913, found 376.9916.

3-Chloro-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (4).[6a] Pale yellow solid: mp 201.7−203.5 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.48−7.46 (m, 2H), 7.42−7.39 (m, 3H), 6.53 (s, 4H, spiro-ring-H), 2.93 (s, 3H); ^{13}C NMR (125 MHz) δ 183.7, 165.2, 147.3, 144.4, 133.5, 130.4, 129.3, 128.8, 128.5, 127.8, 66.6, 26.4; IR (KBr, cm^{-1}) 1706, 1671; LRMS (EI 70 eV) m/z (%) 287 (M^++2, 21), 285 (M^+, 60), 25 (100); HRMS (EI) for $C_{16}H_{12}ClNO_2$ (M^+) calcd. 285.0557, found 285.0560.

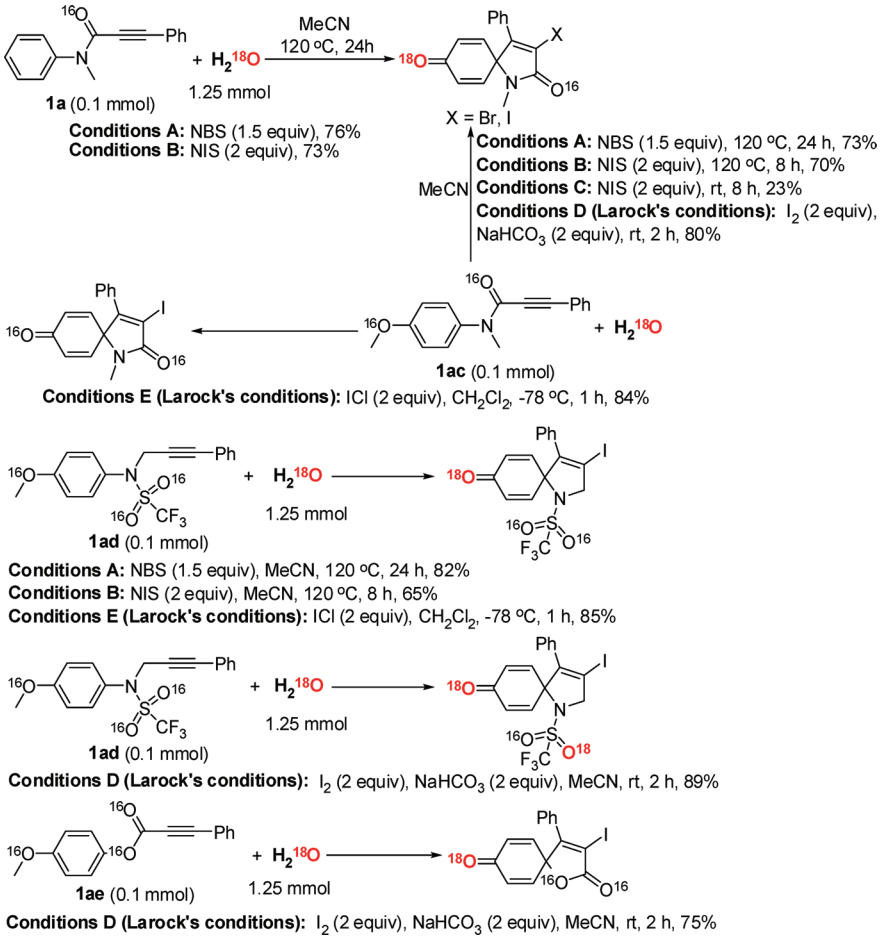
3-Bromo-1-methyl-4-*p*-tolyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (5). Pale yellow solid: mp 182.3−183.6 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.26−7.24 (m, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.46−6.41 (m, 4H, spiro-ring-H), 2.86 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz) δ 183.8, 165.9, 151.3, 144.4, 140.6, 133.4, 129.5, 127.6, 127.3, 119.2, 68.3, 26.6, 21.4; IR (KBr, cm^{-1}) 1711, 1687; LRMS (EI 70 eV) m/z (%) 345 (M^++2, 20), 343 (M^+, 17), 264 (20), 143 (100); HRMS (EI) for $C_{17}H_{14}BrNO_2$ (M^+) calcd. 343.0208, found 343.0211.

3-Bromo-4-(4-methoxyphenyl)-1-methyl-1-azaspiro[4.5]-deca-3,6,9-triene-2,8-dione (6).[6a] White solid: mp 165.7−166.9 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.47−7.44 (m, 2H), 6.90−6.87 (m, 2H), 6.55−6.50 (m, 4H, spiro-ring-H), 3.81 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (125 MHz) δ 183.7, 165.9, 160.9, 150.5, 144.6, 133.1, 129.2, 122.3, 118.2, 114.1, 68.0, 55.2, 26.4; IR (KBr, cm^{-1}) 1713, 1667; LRMS (EI 70 eV) m/z (%) 361 (M^++2, 28), 359 (M^+, 28), 280 (5.3), 159 (100); HRMS (EI) for $C_{17}H_{14}BrNO_3$ (M^+) calcd. 359.0157, found 359.0160.

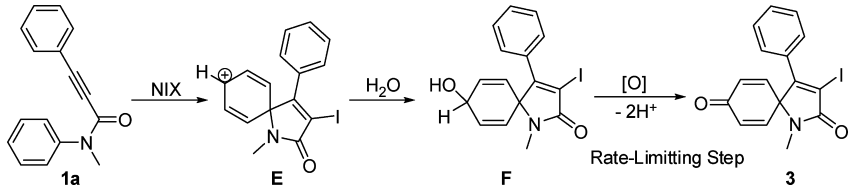
4-(4-Acetylphenyl)-3-bromo-1-methyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (7). White solid: mp 177.1−179.0 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.96−7.94 (m, 2H), 7.50−

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

Scheme 5. ^{18}O-Labeling Experiments in the presence of $H_2{}^{18}O$



Scheme 6. Reaction Mechanism for Substrate 1a



7.48 (m, 2H), 6.55−6.49 (m, 4H, spiro-ring-H), 2.95 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (125 MHz) δ 197.0, 183.3, 165.3, 150.2, 143.6, 138.0, 134.6, 133.6, 128.5, 128.1, 121.1, 68.2, 26.7, 26.6; IR (KBr, cm^{-1}) 1712, 1705, 1676; LRMS (EI 70 eV) m/z (%) 373 (M^++2, 25), 371 (M^+, 27), 292 (63), 171 (100); HRMS (EI) for $C_{18}H_{14}BrNO_3$ (M^+) calcd. 371.0157, found 371.0160.

4-(4-Acetylphenyl)-3-iodo-1-methyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (8).[6a] Pale yellow solid: mp 228.8−230.2 °C (uncorrected); ^1H NMR (500 MHz) δ 7.95 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 6.53 (d, J = 10.0 Hz, 2H, spiro-ring-H), 6.48 (d, J = 10.0 Hz, 2H, spiro-ring-H), 2.98 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (125 MHz) δ 197.0, 183.3, 167.0, 156.8, 143.6, 138.0, 136.4, 133.5, 128.5, 128.1, 99.4, 70.3, 27.0, 26.6; IR (KBr, cm^{-1}) 1706, 1702, 1670; LRMS (EI 70 eV) m/z (%) 419 (M^+, 17), 292 (36), 129 (29), 44 (100).

3-Bromo-1-methyl-4-(4-nitrophenyl)-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (9). Pale yellow solid: mp 199.3−201.8 °C (uncorrected); ^1H NMR (500 MHz) δ 8.26 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 9.0 Hz, 2H), 6.54 (s, 4H, spiro-ring-H), 2.98 (s, 3H); ^{13}C NMR (125 MHz) δ 183.0, 165.0, 149.0, 148.6, 143.3, 136.5, 134.0, 129.1, 124.0, 122.5, 68.2, 26.8; IR (KBr, cm^{-1}) 1710, 1693; LRMS (EI 70 eV) m/z (%) 376 (M^++2, 14), 374 (M^+, 15), 295 (100), 174 (70); HRMS (EI) for $C_{16}H_{11}BrN_2O_4$ (M^+) calcd. 373.9902, found 373.9905.

3-Bromo-1-methyl-4-pentyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (10). White solid: mp 111.1−113.2 °C (uncorrected); ^1H NMR (500 MHz) δ 6.56 (d, J = 10.0 Hz, 2H, spiro-ring-H), 6.36 (d, J = 10.0 Hz, 2H, spiro-ring-H), 2.90 (s, 3H), 2.17−2.13 (m, 2H), 1.48−1.44 (m, 2H), 1.30−1.25 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 183.9, 166.0, 153.6, 144.5, 133.4, 119.1, 68.5, 31.6, 27.6, 27.0, 26.9, 22.0, 13.7; IR (KBr, cm^{-1}) 1713, 1672; LRMS (EI 70 eV) m/z (%) 325 (M^++2, 7), 323 (M^+, 8), 244 (100); HRMS (EI) for $C_{15}H_{18}BrNO_2$ (M^+) calcd. 323.0521, found 323.0524.

3-Bromo-1,7-dimethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (11). White solid: mp 187.1−189.6 °C (uncorrected); ^1H NMR (500 MHz) δ 7.33−7.29 (m, 5H), 6.40 (s, 2H, spiro-ring-H), 6.22 (s, 1H, spiro-ring-H), 2.86 (d, J = 6.0 Hz, 3H), 1.87 (s, 3H); ^{13}C NMR (125 MHz) δ 184.5, 165.8, 151.7, 144.0, 140.7, 138.9, 133.2, 130.4, 130.1, 128.7, 127.8, 119.4, 68.9, 26.6, 15.9; IR (KBr, cm^{-1}) 1700, 1660; LRMS (EI 70 eV) m/z (%) 345 (M^++2, 8), 343 (M^+, 7), 264 (66), 129 (100); HRMS (EI) for $C_{17}H_{14}BrNO_2$ (M^+) calcd. 343.0208, found 343.0211.

3-Iodo-1,7-dimethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (12). Pale yellow solid: mp 172.7−174.8 °C

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

(uncorrected); ^{1}H NMR (500 MHz) δ 7.36−7.34 (m, 3H), 7.27−7.25 (m, 2H), 6.48−6.42 (m, 2H, spiro-ring-H), 6.29−6.27 (m, 1H, spiro-ring-H), 2.94 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz) δ 184.5, 167.3, 158.4, 143.9, 140.6, 138.8, 133.0, 132.1, 129.9, 128.6, 127.7, 97.7, 70.9, 26.9, 15.8; IR (KBr, cm^{-1}) 1693, 1666; LRMS (EI 70 eV) m/z (%) 391 (M$^+$, 32), 264 (25), 129 (100); HRMS (EI) for $C_{17}H_{14}INO_2$ (M$^+$) calcd. 391.0069, found 391.0072.

3-Bromo-1,6-dimethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (13). White solid: mp 193.3−195.4 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.42−7.40 (m, 3H), 7.40−7.38 (m, 2H), 6.54−6.49 (m, 2H, spiro-ring-H), 6.39 (m, 1H, spiro-ring-H), 2.87 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (125 MHz) δ 184.4, 166.3, 152.6, 151.3, 144.4, 132.9, 132.2, 130.4, 130.0, 128.9, 127.5, 119.7, 70.4, 26.2, 17.7; IR (KBr, cm^{-1}) 1708, 1660; LRMS (EI 70 eV) m/z (%) 345 (M$^+$+2, 29), 343 (M$^+$, 30), 264 (51), 129 (82), 44 (100); HRMS (EI) for $C_{17}H_{14}BrNO_2$ (M$^+$) calcd. 343.0208, found 343.0211.

3-Iodo-1,6-dimethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (14). Pale yellow solid: mp 167.3−169.7 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.41−7.35 (m, 3H), 7.34−7.31 (m, 2H), 6.48 (s, 2H, spiro-ring-H), 6.34 (s, 1H, spiro-ring-H), 2.87 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (125 MHz) δ 184.4, 167.9, 157.9, 152.4, 144.2, 132.8, 132.0, 131.6, 130.3, 128.8, 127.4, 97.9, 72.5, 26.5, 17.7; IR (KBr, cm^{-1}) 1701, 1661; LRMS (EI 70 eV) m/z (%) 391 (M$^+$, 12), 264 (52), 129 (100); HRMS (EI) for $C_{17}H_{14}INO_2$ (M$^+$) calcd. 391.0069, found 391.0072.

3-Bromo-1,6,9-trimethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (15). White solid: mp 182.0−182.9 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.35−7.28 (m, 5H), 6.27 (s, 1H, spiro-ring-H), 6.18 (s, 1H, spiro-ring-H), 2.75 (s, 3H), 1.88 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz) δ 185.1, 166.2, 152.3, 151.7, 140.2, 139.1, 131.9, 130.3, 130.2, 128.8, 127.5, 119.3, 71.0, 26.1, 17.4, 15.5; IR (KBr, cm^{-1}) 1712, 1674; LRMS (EI 70 eV) m/z (%) 359 (M$^+$+2, 33), 357 (M$^+$, 36), 278 (47), 129 (100); HRMS (EI) for $C_{18}H_{16}BrNO_2$ (M$^+$) calcd. 357.0364, found 357.0367.

3-Bromo-6-chloro-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (16). White solid: mp 191.3−192.7 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.44−7.38 (m, 3H), 7.36−7.34 (m 2H), 6.68 (s, 1H, spiro-ring-H), 6.60 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.53−6.51 (m, 1H, spiro-ring-H), 2.91 (s, 3H); ^{13}C NMR (125 MHz) δ 182.6, 166.0, 150.2, 150.0, 143.3, 133.1, 132.4, 130.5, 129.5, 128.9, 127.7, 121.4, 100.0, 71.4, 26.3; IR (KBr, cm^{-1}) 1722, 1662; LRMS (EI 70 eV) m/z (%) 365 (M$^+$+2, 31), 363 (M$^+$, 21), 284 (23), 129 (100); HRMS (EI) for $C_{16}H_{11}BrClNO_2$ (M$^+$) calcd. 362.9662, found 362.9665.

3,6-Dibromo-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (17). White solid: mp 205.6−208.0 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.44−7.40 (m, 5H), 6.94 (s, 1H, spiro-ring-H), 6.71 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.58−6.55 (m, 1H, spiro-ring-H), 2.92 (s, 3H); ^{13}C NMR (125 MHz) δ 181.8, 165.9, 150.5, 143.7, 143.0, 137.2, 132.3, 130.4, 129.4, 128.8, 127.8, 121.4, 71.9, 26.3; IR (KBr, cm^{-1}) 1716, 1670; LRMS (EI 70 eV) m/z (%) 411 (M$^+$+2, 18), 409 (M$^+$, 34), 330 (20), 328 (20), 249 (20), 129 (100); HRMS (EI) for $C_{16}H_{11}Br_2NO_2$ (M$^+$) calcd. 406.9157, found 406.9160.

3-Bromo-6-iodo-1-methyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (18). White solid: mp 213.3-214.9 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.44−7.39 (m, 5H), 7.24 (s, 1H, spiro-ring-H), 6.82 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.62−6.59 (m, 1H, spiro-ring-H), 2.89 (s, 3H); ^{13}C NMR (125 MHz) δ 180.6, 165.6, 151.1, 145.0, 143.2, 132.4, 130.4, 129.4, 128.8, 127.9, 123.9, 121.5, 72.7, 26.3; IR (KBr, cm^{-1}) 1717, 1667; LRMS (EI 70 eV) m/z (%) 457 (M$^+$+2, 60), 455 (M$^+$, 62), 376 (43), 330 (12), 328 (12), 249 (38), 129 (100); HRMS (EI) for $C_{16}H_{11}BrINO_2$ (M$^+$) calcd. 454.9018, found 454.9021.

1-Benzyl-3-bromo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (19).[6a] White solid: mp 140.9−142.1 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.30−7.27 (m, 3H), 7.26−7.23 (m, 7H), 6.37−6.26 (m, 4H, spiro-ring-H), 4.59 (s, 2H); ^{13}C NMR (125 MHz) δ 183.7, 165.9, 151.8, 144.1, 136.9, 132.5, 130.1, 130.0, 128.8, 128.5 (2C), 127.9, 127.8, 119.8, 68.7, 45.4; IR (KBr, cm^{-1}) 1708, 1665; LRMS (EI 70 eV) m/z (%) 407 (M$^+$+2, 71), 405 (M$^+$, 69), 193 (76), 165 (45), 91 (100); HRMS (EI) for $C_{22}H_{16}BrNO_2$ (M$^+$) calcd. 405.0364, found 405.0367.

3-Bromo-1-(2-iodobenzyl)-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (20).[6a] White solid: mp 145.7−147.3 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.74 (d, J = 7.5 Hz, 1H), 7.39−7.31 (m, 6H), 7.28−7.27 (m, 1H), 6.98−6.94 (m, 1H), 6.36−6.33 (m, 2H, spiro-ring-H), 6.27−6.24 (m, 2H, spiro-ring-H), 4.76 (s, 2H); ^{13}C NMR (125 MHz) δ 183.8, 166.0, 152.3, 143.4, 139.6, 139.3, 133.0, 130.2, 130.0 (2C), 129.7, 128.7, 128.6, 128.5, 128.3, 127.8, 119.6, 99.5, 68.7, 49.8; IR (KBr, cm^{-1}) 1720, 1699, 1667; LRMS (EI, 70 eV) m/z (%) 406 (100), 404 (94), 297 (36), 129 (20), 90 (22); HRMS (EI) for $C_{22}H_{15}BrINO_2$ (M$^+$) calcd. 530.9331, found 530.9334.

3-Iodo-1-(2-iodobenzyl)-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (21). White solid: mp 187.2−189.4 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.74 (d, J = 8.0 Hz, 1H), 7.39−7.32 (m, 4H), 7.28−7.20 (m, 3H), 6.99−6.93 (m, 1H), 6.35 (d, J = 10.0 Hz, 2H, spiro-ring-H), 6.22 (d, J = 10.0 Hz, 2H, spiro-ring-H), 4.76 (s, 2H); ^{13}C NMR (125 MHz) δ 183.8, 167.4, 158.7, 143.3, 139.4, 138.8, 132.6, 131.5, 130.0, 129.6, 128.9, 128.4, 128.1, 127.6, 99.5, 97.7, 70.5, 49.9; IR (KBr, cm^{-1}) 1703, 1667, 1618; LRMS (EI, 70 eV) m/z (%) 453 (24), 452 (100), 297 (20), 129 (36), 90 (21); HRMS (EI) for $C_{22}H_{15}I_2NO_2$ (M$^+$) calcd. 578.9192, found 578.9195.

3-Bromo-1-(2-iodobenzyl)-4-*p*-tolyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (22). White solid: mp 157.0−158.4 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.77−7.75 (m, 1H), 7.39−7.36 (m, 1H), 7.32−7.28 (m, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 6.97−6.94 (m, 1H), 6.33 (d, J = 10.0 Hz, 2H, spiro-ring-H), 6.27 (d, J = 10.0 Hz, 2H, spiro-ring-H), 4.75 (d, J = 4.5 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (125 MHz) δ 184.0, 166.1, 152.2, 143.6, 140.6, 139.5, 139.3, 132.9, 130.0, 129.7, 129.3, 128.7, 127.6, 126.9, 119.0, 99.5, 68.6, 49.7, 21.4; IR (KBr, cm^{-1}) 1716, 1671, 1634; LRMS (EI, 70 eV) m/z (%) 420 (97), 418 (100), 311 (36), 143 (34), 90 (34); HRMS (EI) for $C_{23}H_{17}BrINO_2$ (M$^+$) calcd. 544.9487, found 544.9490.

3-Bromo-1-(2-iodobenzyl)-4-(2-methoxyphenyl)-1-azaspiro-[4.5]deca-3,6,9-triene-2,8-dione (23). White solid: mp 159.9−161.2 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.77−7.74 (m, 1H), 7.62−7.60 (m, 1H), 7.38−7.35 (m, 2H), 7.30−7.28 (m, 2H), 6.97−6.94 (m, 1H), 6.84 (d, J = 8.5 HZ, 1H), 6.35 (d, J = 10.0 Hz, 2H, spiro-ring-H), 6.29 (d, J = 10.0 Hz, 2H, spiro-ring-H), 4.74 (d, J = 4.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz) δ 183.7, 165.8, 160.8, 157.1, 150.1, 143.8, 131.4, 139.5, 139.1, 132.9, 132.8, 132.7, 129.9, 129.7, 129.3, 128.6, 128.0, 123.2, 119.3, 114.0, 111.8, 111.5, 99.5, 68.4, 56.2, 55.2, 49.6; IR (KBr, cm^{-1}) 1712, 1663, 1626; LRMS (EI, 70 eV) m/z (%) 436 (17), 434 (18), 217 (12), 40 (100); HRMS (EI) for $C_{23}H_{17}BrINO_3$ (M$^+$) calcd. 560.9437, found 560.9440.

4-(4-Acetylphenyl)-3-bromo-1-(2-iodobenzyl)-1-azaspiro-[4.5]deca-3,6,9-triene-2,8-dione (24). White solid: mp 159.0−160.7 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.97 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.47−7.37 (m, 3H), 7.30−7.28 (m, 1H), 6.98−6.95 (m, 1H), 6.40 (d, J = 10.0 Hz, 2H, spiro-ring-H), 6.27 (d, J = 10.0, 2H, spiro-ring-H), 4.77 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (125 MHz) δ 196.9, 190.1, 183.4, 165.4, 151.1, 142.9, 142.8, 139.4, 138.9, 137.8, 134.3, 133.0, 132.9, 130.0, 129.7, 129.0, 128.6, 128.4, 128.3, 128.1, 99.5, 68.5, 49.7, 26.5; IR (KBr, cm^{-1}) 1716, 1699, 1683, 1654; LRMS (EI, 70 eV) m/z (%) 448 (18), 446 (74), 339 (27), 217 (21), 40 (100); HRMS (EI) for $C_{24}H_{17}BrINO_3$ (M$^+$) calcd. 572.9437, found 572.9440.

3-Bromo-1-(2-iodobenzyl)-4-methyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (25). White solid: mp 141.6−143.8 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.75 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 7.0 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 6.98−6.94 (m, 1H), 6.33 (d, J = 10.0 Hz, 2H, spiro-ring-H), 6.22 (d, J = 10.0 Hz, 2H, spiro-ring-H), 4.72 (s, 2H), 1.81 (s, 3H); ^{13}C NMR (125 MHz) δ 183.8, 165.8, 150.6, 143.9, 139.4, 139.1, 132.6, 130.1, 129.6, 128.4, 118.3, 99.4, 68.4, 49.8, 12.2; IR (KBr, cm^{-1}) 1720, 1669, 1683, 1654; LRMS (EI, 70 eV) m/z (%) 344 (13), 342 (13), 169 (13), 40 (100); HRMS (EI) for $C_{17}H_{13}BrINO_2$ (M$^+$) calcd. 468.9174, found 468.9177.

3-Bromo-1-(2-iodobenzyl)-6-methyl-4-phenyl-1-azaspiro-[4.5]deca-3,6,9-triene-2,8-dione (26). White solid: mp 152.1−153.2 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.74 (d, J = 7.5 Hz,

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

1H), 7.49−7.47 (m, 1H), 7.39−7.34 (m, 5H), 7.29−7.26 (m, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.30−6.26 (m, 2H, spiro-ring-H), 6.19 (d, J = 10.0 Hz, 1H, spiro-ring-H), 4.90 (d, J = 15.5 Hz, 1H), 4.47 (d, J = 15.5 Hz, 1H), 1.63 (s, 3H); ^{13}C NMR (125 MHz) δ 184.5, 166.6, 152.1, 151.4, 143.7, 139.3, 138.7, 132.7, 132.0, 130.3 (2C), 129.6, 128.7, 128.5, 127.4, 119.3, 99.6, 70.7, 49.4, 17.5; IR (KBr, cm^{-1}) 1720, 1699, 1667; LRMS (EI, 70 eV) m/z (%) 420 (45), 418 (46), 311 (15), 90 (17), 40 (100); HRMS (EI) for $C_{23}H_{11}BrINO_2$ (M^+) calcd. 544.9487, found 544.9490.

3-Bromo-1-(2-iodobenzyl)-6,7-dimethyl-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (27). White solid: mp 152.8−153.5 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.72 (d, J = 5.0 Hz, 1H), 7.51 (d, J = 5.5 Hz, 1H), 7.45−7.29 (m, 6H), 6.93−6.92 (m, 1H), 6.30 (d, J = 15.0 Hz, 2H, spiro-ring-H), 4.66 (d, J = 15.0 Hz, 2H), 1.76 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz) δ 184.1, 166.6, 152.7, 144.1, 142.9, 139.1, 139.0, 138.1, 131.9, 130.6, 130.1, 129.8, 129.5, 128.6 (2C), 128.5, 119.0, 99.6, 71.0, 49.3, 14.6, 11.6; IR (KBr, cm^{-1}) 1712, 1687, 1667; LRMS (EI, 70 eV) m/z (%) 434 (54), 432 (61), 325 (13), 129 (15), 40 (100); HRMS (EI) for $C_{24}H_{19}BrINO_2$ (M^+) calcd. 558.9644, found 558.9647.

3-Bromo-6-fluoro-1-(2-iodobenzyl)-4-phenyl-1-azaspiro-[4.5]deca-3,6,9-triene-2,8-dione (28). White solid: mp 155.1−156.7 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.81 (d, J = 8.0 Hz, 1H), 7.43−7.30 (m, 5H), 7.22 (d, J = 7.5 Hz, 2H), 7.01 (s, 1H, spiro-ring-H), 6.97 (d, J = 7.5 Hz, 1H), 6.42 (d, J = 7.0 Hz, 1H, spiro-ring-H), 6.38−6.35 (m, 1H, spiro-ring-H), 4.96 (d, J = 15.0 Hz, 1H), 4.68 (d, J = 15.0 Hz, 1H); ^{13}C NMR (125 MHz) δ 177.8, 165.6, 151.1 (2C), 143.8, 139.8, 139.0, 130.3, 130.2, 130.1, 129.9, 129.4, 128.9, 128.7, 127.7, 119.8, 108.3, 100.1, 71.4, 49.7; IR (KBr, cm^{-1}) 1716, 1699, 1654; LRMS (EI, 70 eV) m/z (%) 532 (71), 530 (63), 423 (12), 217 (27), 40 (100); HRMS (EI) for $C_{22}H_{14}BrFINO_2$ (M^+) calcd. 548.9237, found 548.9240.

3-Bromo-7-iodo-1-(2-iodobenzyl)-4-phenyl-1-azaspiro[4.5]-deca-3,6,9-triene-2,8-dione (29). White solid: mp 155.5−155.9 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.74 (d, J = 6.5 Hz,, 1H), 7.38−7.27 (m, 7H), 6.95 (s, 1H), 6.29−6.19 (m, 2H, spiro-ring-H), 5.98 (d, J = 12.0 Hz, 1H, spiro-ring-H), 4.86 (d, J = 15.5 Hz, 1H), 4.69 (d, J = 15.5 Hz, 1H); ^{13}C NMR (125 MHz) δ 185.5, 185.3, 166.5, 166.1, 150.1, 139.6, 139.3, 137.8, 131.8, 130.3, 130.1, 129.7, 129.0, 128.7, 128.4, 127.5, 120.6, 114.1, 114.0, 99.2, 68.8, 68.6, 49.7; IR (KBr, cm^{-1}) 1720, 1699, 1683, 1659; LRMS (EI, 70 eV) m/z (%) 424 (100), 422 (94), 315 (24), 183 (17), 129 (21); HRMS (EI) for $C_{22}H_{14}BrI_2NO_2$ (M^+) calcd. 656.8297, found 656.8300.

3-Bromo-1-(2-iodo-5-methylbenzyl)-4-phenyl-1-azaspiro-[4.5]deca-3,6,9-triene-2,8-dione (30). White solid: mp 156.7−157.8 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.39−7.33 (m, 2H), 7.29−7.27 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.07 (s, 1H), 7.01 (d, J = 7.0 Hz, 2H), 6.35 (d, J = 10.0 Hz, 2H, spiro-ring-H), 6.26 (d, J = 10.0 Hz, 2H, spiro-ring-H), 4.56 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz) δ 183.9, 165.9, 151.7, 144.2, 138.3, 136.7, 132.5, 130.1, 130.0, 129.6, 128.7, 128.6, 128.4, 127.8, 125.9, 119.9, 68.7, 45.4, 21.3; IR (KBr, cm^{-1}) 1716, 1699, 1650; LRMS (EI, 70 eV) m/z (%) 547 (18), 545 (17), 419 (14), 301 (25), 193 (16), 40 (100); HRMS (EI) for $C_{23}H_{17}BrINO_2$ (M^+) calcd. 544.9487, found 544.9490.

3-Bromo-1-(2-iodo-5-methoxybenzyl)-4-phenyl-1-azaspiro-[4.5]deca-3,6,9-triene-2,8-dione (31). White solid: mp 152.9−154.7 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.34−7.32 (m, 6H), 6.98 (s, 1H), 6.71−6.56 (m, 1H), 6.45 (d, J = 10.0 Hz, 2H, spiro-ring-H), 6.28 (d, J = 10.0 Hz, 2H, spiro-ring-H), 4.74−4.70 (m, 2H), 3.75 (s, 3H); ^{13}C NMR (125 MHz) δ 183.7 (2C), 165.8, 165.7, 159.9, 158.9, 152.1, 143.2, 139.8, 137.0, 133.2, 132.8, 132.7, 130.0, 128.4, 127.7, 119.3, 116.0, 115.3, 87.8, 68.5, 55.4, 44.7; IR (KBr, cm^{-1}) 1716, 1703, 1675, 1654; LRMS (EI, 70 eV) m/z (%) 436 (96), 434 (100), 327 (26), 165 (21), 129 (35); HRMS (EI) for $C_{23}H_{17}BrINO_3$ (M^+) calcd. 560.9437, found 560.9440.

3-Bromo-1-((3-iodothiophen-2-yl)methyl)-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (32). White solid: mp 163.1−165.5 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.42−7.28 (m, 6H), 7.05−7.00 (m, 1H), 6.42−6.29 (m, 4H, spiro-ring-H), 4.58−4.47 (m, 2H); ^{13}C NMR (125 MHz) δ 183.8, 165.7, 152.3, 143.1, 143.0, 141.6, 137.8, 133.2, 132.9, 131.9, 130.9, 130.2, 129.8, 128.6 (2C), 128.3, 127.7, 119.4, 116.8, 68.4, 41.8; IR (KBr, cm^{-1}) 1716, 1699, 1683, 1654; LRMS (EI, 70 eV) m/z (%) 538 (12), 536 (12), 492 (23), 490 (40), 412 (13), 298 (15), 191 (18), 40 (100); HRMS (EI) for $C_{20}H_{13}BrINO_2S$ (M^+) calcd. 536.8895, found 536.8898.

3-Bromo-1-(2-bromobenzyl)-4-phenyl-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (33). White solid: mp 147.2−147.8 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.41 (d, J = 7.5, 1H), 7.37−7.30 (m, 6H), 7.24 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.37 (d, J = 12.5, 2H, spiro-ring-H), 6.24 (d, J = 12.5 Hz, 2H, spiro-ring-H), 4.79 (s, 2H); ^{13}C NMR (125 MHz) δ 183.6, 165.7, 152.0, 143.2, 136.0, 132.6(2C), 130.5, 130.0, 129.7, 129.5, 128.4(2C), 127.6, 123.8, 119.3, 68.4, 44.6; IR (KBr, cm^{-1}) 1720, 1704, 1683, 1654; LRMS (EI, 70 eV) m/z (%) 406 (21), 404 (20), 297 (7), 129 (9), 40 (100); HRMS (EI) for $C_{22}H_{15}Br_2NO_2$ (M^+) calcd. 482.9470, found 482.9473.

3-Bromo-4-phenyl-1-trifluoromethanesulfonyl-1-azaspiro-[4,5]-deca-3,6,9-trien-2,8-dione (34). White solid: mp 143.6−144.9.1 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.38−7.31 (m, 3H), 7.09−7.07 (m, 2H), 6.88 (d, J = 9.5 Hz, 2H, spiro-ring-H), 6.23 (d, J = 10.5 Hz, 2H, spiro-ring-H), 4.73 (s, 2H); ^{13}C NMR (125 MHz) δ 183.5, 144.1, 138.2, 130.5, 129.6, 129.5, 129.1, 119.6 (d, J = 321.6 Hz, 1C), 118.4, 115.6, 74.1, 59.4; IR (KBr, cm^{-1}) 1671, 1389; LRMS (EI 70 eV) m/z (%) 435 (M^++2, 3), 432 (1), 302 (47), 300 (48), 221 (100); HRMS (EI) for $C_{16}H_{11}BrF_3NO_3S$ (M^+) calcd. 432.9595, found 432.9598.

3-Bromo-6-methyl-4-phenyl-1-oxaspiro[4.5]deca-3,6,9-triene-2,8-dione (35). Pale yellow solid: mp 120.0−124.6 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.51−7.47 (m, 3H), 7.44−7.41 (m, 2H), 6.64 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.43−6.41 (m, 1H, spiro-ring-H, spiro-ring-H), 6.29 (s, 1H, spiro-ring-H), 1.92 (s, 3H); ^{13}C NMR (125 MHz) δ 184.1, 167.3, 159.7, 150.8, 141.9, 131.9, 131.5, 130.7, 129.1, 128.4, 127.2, 112.1, 84.9, 17.2; IR (KBr, cm^{-1}) 1771, 1675; LRMS (EI 70 eV) m/z (%) 332 (M^++2, 8), 330 (M^+, 8), 251 (18), 129 (100); HRMS (EI) for $C_{16}H_{11}BrO_3$ (M^+) calcd. 329.9892, found 329.9895.

6-Bromo-5-phenyl-2*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*)-dione (36).[6a] White solid: mp 208.5−211.9 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.55−7.37 (m, 6H), 7.33−7.29 (m, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.75 (d, J = 9.5 Hz, 1H, spiro-ring-H), 6.39 (s, 1H, spiro-ring-H), 6.24 (d, J = 9.5 Hz, 1H, spiro-ring-H), 5.19 (d, J = 15.5 Hz, 1H), 4.17 (d, J = 15.5 Hz, 1H); ^{13}C NMR (125 MHz) δ 184.1, 171.3, 171.1, 157.1, 150.6, 145.9, 135.9, 132.6, 131.4, 131.0, 129.9, 129.1, 129.0, 128.8, 128.5, 128.3, 126.1, 124.9, 121.0, 72.1, 44.8; IR (KBr, cm^{-1}) 1716, 1703, 1671; LRMS (EI, 70 eV) m/z (%) 405 (M^++2, 15), 403 (M^+, 14), 324 (39), 129 (100); HRMS (EI) for $C_{22}H_{14}BrNO_2$ (M^+) calcd. 403.0208, found 403.0211.

6-Bromo-5-phenyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7-(9*H*,13*bH*)-dione (37).[6a] White solid: mp 218.0−223.3 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.51−7.46 (m, 3H), 7.36−7.34 (m, 2H), 7.23−7.17 (m, 4H), 6.55 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.22 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.32 (d, J = 17.5 Hz, 1H), 4.37 (d, J = 17.0 Hz, 1H), 3.61 (s, 1H, spiro-ring-H), 2.91 (d, J = 16.5 Hz, 1H, spiro-ring-H), 2.25 (d, J = 16.5 Hz, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 195.1, 163.5, 155.6, 143.5, 134.9, 132.1, 132.0, 131.3, 130.0, 129.2, 127.8 (2C), 127.2, 126.9, 126.5, 120.4, 66.5, 41.3, 40.3, 39.1; IR (KBr, cm^{-1}) 1716, 1663; LRMS (EI, 70 eV) m/z (%) 407 (M^++2, 14), 405 (M^+, 56), 326 (100), 298 (24), 129 (74); HRMS (EI) for $C_{22}H_{16}BrNO_2$ (M^+) calcd. 405.0364, found 405.0367.

6-Iodo-5-phenyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7-(9*H*,13*bH*)-dione (38). White solid: mp 210.6−214.7 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.49 (d, J = 13.5 Hz, 3H), 7.31−7.17 (m, 6H), 6.52 (d, J = 10.0, 1H, spiro-ring-H), 6.21 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.34 (d, J = 17.5 Hz, 1H), 4.39 (d, J = 17.0 Hz, 1H), 3.60−3.59 (m, 1H, spiro-ring-H), 2.90 (d, J = 16.5 Hz, 1H, spiro-ring-H), 2.21 (d, J = 16.5 Hz, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 195.2, 165.0, 162.3, 143.7, 134.7, 134.2, 132.0, 131.4, 130.0, 129.2, 127.8, 127.7, 127.2, 127.0, 126.5, 99.2, 68.4, 41.2, 40.6, 39.2; IR (KBr, cm^{-1}) 1707, 1683; LRMS (EI, 70 eV) m/z (%) 454 (M^++1, 24), 453 (M^+, 99), 326 (70), 129 (100); HRMS (EI) for $C_{22}H_{16}INO_2$ (M^+) calcd. 453.0226, found 453.0229.

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

6-Bromo-5-*p*-tolyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*,13*bH*)-dione (39). White solid: mp 223.5−225.9 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.28 (d, J = 8.0 Hz, 2H), 7.24−7.15 (m, 6H), 6.54 (d, J = 10.0, 1H, spiro-ring-H), 6.22 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.32 (d, J = 17.5 Hz, 1H), 4.37 (d, J = 17.5 Hz, 1H), 3.59−3.58 (m, 1H, spiro-ring-H), 2.91 (d, J = 17.0 Hz, 1H, spiro-ring-H), 2.42 (s, 3H), 2.31 (d, J = 17.0 Hz, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 195.3, 163.6, 155.7, 143.6, 140.3, 134.9, 132.1, 131.3, 129.9, 129.1, 127.8, 127.6, 127.2, 127.0, 126.5, 120.1, 66.5, 41.4, 40.3, 39.2, 21.4; IR (KBr, cm^{-1}) 1716, 1699, 1654; LRMS (EI, 70 eV) m/z (%) 421 (M$^+$+2, 58), 419 (M$^+$, 58), 340 (90), 312 (22), 143 (100); HRMS (EI) for $C_{23}H_{18}BrNO_2$ (M$^+$) calcd. 419.0521, found 419.0524.

5-(4-Acetylphenyl)-6-bromo-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*,13*bH*)-dione (40). White solid: mp 247.8−249.3 °C (uncorrected); ^{1}H NMR (500 MHz) δ 8.07 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.24−7.18 (m, 4H), 6.58 (d, J = 10.0, 1H, spiro-ring-H), 6.25 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.33 (d, J = 17.0 Hz, 1H), 4.39 (d, J = 17.0 Hz, 1H), 3.65−3.64 (m, 1H, spiro-ring-H), 2.94 (d, J = 17.0 Hz, 1H, spiro-ring-H), 2.66 (s, 3H), 2.22 (d, J = 17.0 Hz, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 197.0, 194.6, 163.1, 154.4, 143.2, 137.9, 136.8, 135.1, 132.0 (2C), 131.1, 129.0, 128.5, 128.3, 127.4, 126.6, 121.4, 66.6, 41.3, 40.4, 39.2, 26.6; IR (KBr, cm^{-1}) 1716, 1703, 1683; LRMS (EI, 70 eV) m/z (%) 449 (M$^+$+2, 71), 447 (M$^+$, 59), 368 (100), 340 (26), 171 (49), 117 (58), 43 (71); HRMS (EI) for $C_{24}H_{18}BrNO_3$ (M$^+$) calcd. 447.0470, found 447.0473.

6-Bromo-5-methyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*,13*bH*)-dione (41). White solid: mp 215.4−219.3 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.34 (d, J = 7.5 Hz, 1H), 7.28−7.22 (m, 2H), 7.16 (d, J = 7.5 Hz, 1H), 6.28 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.19 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.25 (d, J = 17.0 Hz, 1H), 4.32 (d, J = 17.5 Hz, 1H), 3.57−3.56 (m, 1H, spiro-ring-H), 3.38 (d, J = 17.5 Hz, 1H, spiro-ring-H), 3.25 (d, J = 17.5 Hz, 1H, spiro-ring-H), 2.29 (s, 3H); ^{13}C NMR (125 MHz) δ 194.8, 163.8, 153.4, 145.6, 134.0, 132.1, 131.4, 127.8, 127.3, 126.8, 126.6, 119.8, 65.9, 40.8, 40.3, 39.7, 15.0; IR (KBr, cm^{-1}) 1707, 1683; LRMS (EI, 70 eV) m/z (%) 345 (M$^+$+2, 25), 343 (M$^+$, 27), 264 (42), 236 (16), 43 (100); HRMS (EI) for $C_{17}H_{14}BrNO_2$ (M$^+$) calcd. 343.0208, found 343.0211.

6-Bromo-4-methyl-5-phenyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*,13*bH*)-dione (42). Pale yellow solid: mp 223.2−226.4 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.48−7.38 (m, 4H), 7.22−7.18 (m, 5H), 6.12 (d, J = 4.5 Hz, 1H, spiro-ring-H), 5.35 (d, J = 17.5 Hz, 1H), 4.21 (d, J = 17.5 Hz, 1H), 3.66−3.65 (m, 1H, spiro-ring-H), 2.91 (d, J = 17.0 Hz, 1H, spiro-ring-H), 2.21 (d, J = 17.0 Hz, 1H, spiro-ring-H), 1.93 (s, 3H); ^{13}C NMR (125 MHz) δ 194.8, 164.4, 155.7, 151.7, 133.6, 132.1, 131.9, 131.3, 130.8, 130.1, 129.2, 129.0, 128.5, 128.4, 128.0, 127.8, 127.5, 127.2, 126.7, 126.5, 126.1, 125.1, 120.2, 69.1, 41.7, 40.4, 38.8, 17.8; IR (KBr, cm^{-1}) 1699, 1663; LRMS (EI, 70 eV) m/z (%) 419 (M$^+$, 72), 404 (6), 340 (51), 129 (69), 43 (100); HRMS (EI) for $C_{23}H_{18}BrNO_2$ (M$^+$) calcd. 419.0521, found 419.0524.

6-Bromo-3,4-dimethyl-5-phenyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*,13*bH*)-dione (43). White solid: mp 214.2−216.3 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.49−7.44 (m, 3H), 7.24−7.14 (m, 6H), 5.33 (d, J = 17.5 Hz, 1H), 4.11 (d, J = 17.5 Hz, 1H), 3.58−3.57 (m, 1H, spiro-ring-H), 2.94 (d, J = 16.5 Hz, 1H, spiro-ring-H), 2.21 (d, J = 16.5, 1H, spiro-ring-H), 1.84 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (125 MHz) δ 194.3, 164.3, 156.4, 143.9, 139.2, 132.3, 132.2, 131.5, 130.0, 129.2, 127.7, 127.4, 127.1, 126.7, 126.4, 119.9, 69.8, 41.2, 40.3, 38.5, 14.6, 12.1; IR (KBr, cm^{-1}) 1699, 1650; LRMS (EI, 70 eV) m/z (%) 435 (M$^+$+2, 91), 433 (M$^+$, 95), 354 (52), 129 (100), 115 (49); HRMS (EI) for $C_{24}H_{120}BrNO_2$ (M$^+$) calcd. 433.0677, found 433.0680.

6-Bromo-4-fluoro-5-phenyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*,13*bH*)-dione (44). White solid: mp 206.2−210.9 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.52 (d, J = 6.5 Hz, 3H), 7.31 (d, J = 6.0 Hz, 2H), 7.27−7.21 (m, 4H), 6.01 (d, J = 13.5 Hz, 1H, spiro-ring-H), 5.33 (d, J = 17.5 Hz, 1H), 4.32 (d, J = 17.5 Hz, 1H), 3.68−3.67 (m, 1H, spiro-ring-H), 2.93 (d, J = 16.5 Hz, 1H, spiro-ring-H), 2.17 (d, J = 16.5 Hz, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 194.4, 194.3, 168.8 (d, J_{C-F} = 293.8 Hz), 163.8, 153.3, 131.4, 131.3, 131.0, 130.3, 129.4, 128.0, 127.6 (2C), 126.8, 126.7, 121.4, 115.4 (d, J_{C-F} = 8.8 Hz), 66.9, 66.7, 40.6, 40.5, 40.2, 39.5; IR (KBr, cm^{-1}) 1732, 1761, 1683, 1654; LRMS (EI, 70 eV) m/z (%) 425 (M$^+$+2, 94), 423 (M$^+$, 100), 344 (79), 324 (41), 129 (97); HRMS (EI) for $C_{22}H_{15}BrFNO_2$ (M$^+$) calcd. 423.0270, found 423.0273.

6-Bromo-3-iodo-5-phenyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*,13*bH*)-dione (45). Pale yellow solid: mp 206.5−211.4 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.53−7.47 (m, 3H), 7.35 (d, J = 8.0, 2H), 7.23−7.17 (m, 3H), 6.54 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.23 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.33 (d, J = 17.5 Hz, 1H), 4.38 (d, J = 17.0 Hz, 1H), 3.61−3.60 (m, 1H, spiro-ring-H), 2.91 (d, J = 17.0 Hz, 1H, spiro-ring-H), 2.25 (d, J = 17.0, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 195.1, 163.5, 155.6, 143.5, 135.0, 132.2, 132.0, 131.3, 130.1, 129.2, 127.9, 127.8, 127.3, 127.0, 126.6, 120.5, 66.6, 41.4, 40.4, 39.2; IR (KBr, cm^{-1}) 1716, 1703, 1683; LRMS (EI, 70 eV) m/z (%) 534 (M$^+$+3, 3), 532 (M$^+$+1, 3), 407 (29), 405 (33), 326 (51), 129 (53), 43 (100); HRMS (EI) for $C_{22}H_{15}BrINO_2$ (M$^+$) calcd. 530.9331, found 530.9334.

6-Bromo-11-methoxy-5-phenyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*,13*bH*)-dione (46). White solid: mp 249.2−253.1 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.48 (d, J = 13.5 Hz, 3H), 7.34 (d, J = 6.0 Hz, 2H), 7.13 (d, J = 9.0 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.67 (s, 1H), 6.52 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.22 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.29 (d, J = 17.5 Hz, 1H), 4.33 (d, J = 17.0 Hz, 1H), 3.76 (d, J = 11.0 Hz,, 3H, spiro-ring-H), 3.56 (s, 1H), 2.86 (d, J = 17.0 Hz, 1H, spiro-ring-H), 2.22 (d, J = 17.0 Hz, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 195.3, 163.5, 158.4, 155.7, 143.3, 134.9, 132.7, 132.2, 130.1, 129.2, 128.1, 127.8, 124.0, 120.3, 114.2, 111.0, 66.7, 55.3, 40.9, 40.5, 39.2; IR (KBr, cm^{-1}) 1712, 1683, 1658; LRMS (EI, 70 eV) m/z (%) 437 (M$^+$+2, 61), 435 (M$^+$, 63), 356 (100), 328 (21), 129 (56); HRMS (EI) for $C_{23}H_{18}BrNO_3$ (M$^+$) calcd. 435.0470, found 435.0473.

6-Bromo-5-phenyl-1*H*-pyrrolo[1,2-*j*]thieno[3,4-*c*]quinoline-2,7(9*H*,12*bH*)-dione (47). White solid: mp 220.5−227.4 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.50−7.46 (m, 3H), 7.33−7.31 (m, 2H), 7.24−7.23 (m, 1H), 6.83 (d, J = 5.5 Hz, 1H), 6.52 (d, J = 10.5 Hz, 1H, spiro-ring-H), 6.25 (d, J = 10.5 Hz, 1H, spiro-ring-H), 5.29 (d, J = 17.0 Hz, 1H), 4.23 (d, J = 17.0 Hz, 1H), 3.73−3.72 (m, 1H, spiro-ring-H), 2.62 (d, J = 17.5 Hz, 1H, spiro-ring-H), 2.16 (d, J = 17.5 Hz, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 194.1, 163.9, 154.9, 143.0, 134.8, 134.7, 131.8 (2C), 130.2, 129.2, 127.9, 125.8, 124.8, 120.1, 67.0, 41.1, 40.2, 39.1; IR (KBr, cm^{-1}) 1716, 1703, 1683; LRMS (EI, 70 eV) m/z (%) 413 (M$^+$+2, 55), 411 (M$^+$, 51), 332 (64), 129 (33), 123 (100); HRMS (EI) for $C_{20}H_{14}BrNO_2S$ (M$^+$) calcd. 410.9929, found 410.9932.

6-Bromo-5-*p*-tolyl-2*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*)-dione (48). White solid: mp 225.2−229.4 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.51 (d, J = 7.5 Hz, 1H), 7.44−7.41 (m, 2H), 7.32−7.30 (m, 1H), 7.18 (d, J = 7.5 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.40 (s, 1H, spiro-ring-H), 6.23 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.18 (d, J = 15.5 Hz, 1H), 4.15 (d, J = 15.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (125 MHz) δ 184.3, 171.5, 157.3, 150.8, 146.2, 140.2, 136.0, 132.8, 131.3, 131.0, 129.2 (2C), 129.0, 128.6, 126.2, 126.1, 124.9, 120.9, 72.2, 44.8, 21.4; IR (KBr, cm^{-1}) 1728, 1658; LRMS (EI, 70 eV) m/z (%) 419 (M$^+$+2, 13), 417 (M$^+$, 11), 338 (25), 143 (100); HRMS (EI) for $C_{23}H_{16}BrNO_2$ (M$^+$) calcd. 417.0364, found 417.0367.

5-(4-Acetylphenyl)-6-bromo-2*H*-pyrrolo[2,1-*e*]phenanthridine-2,7(9*H*)-dione (49). White solid: mp 245.0−247.1 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.96 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.5 Hz, 1H), 7.47−7.44 (m, 2H), 7.32 (d, J = 7.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.40 (s, 1H, spiro-ring-H), 6.27 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.20 (d, J = 15.5 Hz, 1H), 4.18 (d, J = 15.5 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (125 MHz) δ 197.0, 184.0, 171.0, 156.1, 150.7, 145.6, 137.9, 135.9, 133.9, 132.5, 131.6, 131.2, 129.2 (2C), 128.6, 128.3, 126.2, 125.0, 121.7, 71.9, 44.9, 26.6; IR (KBr, cm^{-1}) 1719, 1687, 1650; LRMS (EI, 70 eV) m/z (%) 447 (M$^+$+2, 56), 445 (M$^+$, 61), 367 (53), 169 (76),

dx.doi.org/10.1021/jo300037n | J. Org. Chem. 2012, 77, 2837−2849

129 (100); HRMS (EI) for $C_{24}H_{16}BrNO_3$ (M^+) calcd. 445.0314, found 445.0317.

5-Phenyl-6-(phenylethynyl)-1*H*-pyrrolo[2,1-*e*]-phenanthridine-2,7(9*H*,13*bH*)-dione (50). White solid: mp 208.8−209.7 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.57−7.55 (m, 2H), 7.50−7.48 (m, 3H), 7.40−7.39 (m, 2H), 7.32−7.19 (m, 7H), 6.63 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.27 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.35 (d, J = 17.0 Hz, 1H), 4.34 (d, J = 17.5 Hz, 1H), 3.56−3.55 (m, 1H, spiro-ring-H), 2.93 (d, J = 17.0, 1H, spiro-ring-H), 2.44 (d, J = 17.0 Hz, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 195.5, 165.2, 159.5, 134.8, 133.1, 132.5, 132.0, 131.6, 130.1, 129.1, 128.9, 128.2, 128.0, 127.8, 127.2, 127.1, 126.6, 122.1, 121.3, 98.5, 80.2, 71.8, 65.1, 41.9, 40.0, 39.3; IR (KBr, cm^{-1}) 1716, 1695, 1683; LRMS (EI, 70 eV) m/z (%) 428 (M^++1, 33), 427 (M^+, 100), 398 (20), 370 (17), 356 (10), 202 (12), 115 (27); HRMS (EI) for $C_{30}H_{21}NO_2$ (M^+) calcd. 427.1572, found 427.1575.

5-Phenyl-6-*p*-tolyl-1*H*-pyrrolo[2,1-*e*]phenanthridine-2,7-(9*H*,13*bH*)-dione (51). White solid: mp 193.7−195.1 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.37−7.35 (m, 3H), 7.28−7.18 (m, 8H), 7.03 (d, J = 8.0 Hz, 2H), 6.60 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.22 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.37 (d, J = 17.5 Hz, 1H), 4.36 (d, J = 17.0 Hz, 1H), 3.66−3.65 (m, 1H, spiro-ring-H), 2.88 (d, J = 17.0 Hz, 1H, spiro-ring-H), 2.28 (s, 3H), 2.22−2.17 (m, 1H, spiro-ring-H); ^{13}C NMR (125 MHz) δ 195.8, 167.3, 152.5, 145.6, 138.3, 134.4, 134.2, 134.0, 133.8, 133.0, 132.0, 129.4, 129.1, 128.8, 128.6, 128.5, 127.6, 127.2, 127.0, 126.6, 64.5, 41.4, 39.9, 39.4, 21.0; IR (KBr, cm^{-1}) 1695, 1679, 1613; LRMS (EI, 70 eV) m/z (%) 418 (M^++1, 24), 417 (M^+, 100), 389 (28), 360 (22), 115 (22); HRMS (EI) for $C_{29}H_{23}NO_2$ (M^+) calcd. 417.1729, found 417.1732.

(*E*)-*tert*-Butyl 3-(2,7-Dioxo-5-phenyl-2,7,9,13b-tetrahydro-1*H*-pyrrolo[2,1-*e*] phenanthridin-6-yl) Acrylate (52). Yellow solid: mp 178.7−179.8 °C (uncorrected); ^{1}H NMR (500 MHz) δ 7.50−7.45 (m, 3H), 7.36−7.20 (m, 7H), 7.19−7.08 (m, 1H), 6.51 (d, J = 10.0 Hz, 1H, spiro-ring-H), 6.21 (d, J = 10.0 Hz, 1H, spiro-ring-H), 5.33 (d, J = 17.5 Hz, 1H), 4.33 (d, J = 17.0 Hz, 1H), 3.56−3.55 (m, 1H, spiro-ring-H), 2.89 (d, J = 17.0 Hz, 1H, spiro-ring-H), 2.23 (d, J = 17.0 Hz, 1H, spiro-ring-H), 1.46 (s, 9H); ^{13}C NMR (125 MHz) δ 195.3, 166.4, 166.2, 158.5, 144.3, 134.8, 132.5, 132.1, 131.6, 131.3, 130.0, 129.5, 129.2, 128.3, 127.7, 127.2, 127.0 (2C), 126.6, 80.7, 71.8, 64.6, 41.4, 39.6, 39.0, 28.0; IR (KBr, cm^{-1}) 1716, 1699, 1683; LRMS (EI, 70 eV) m/z (%) 454 (M^++1, 13), 453 (M^+, 37), 397 (100), 380 (27), 352 (22), 324 (14), 115 (39); HRMS (EI) for $C_{29}H_{27}NO_4$ (M^+) calcd. 453.1940, found 453.1943.

■ ASSOCIATED CONTENT

Supporting Information

Computational details, crystal data (CIF files), and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jhli@hnu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (No. 20872112 and 21172060) and Fundamental Research Funds for the Central Universities (Hunan University) for financial support.

■ REFERENCES

(1) For reviews, see: (a) Larock, R. C. *Acetylene Chem.* **2005**, 51. (b) Luo, P.; Tang, R.; Zhong, P.; Li, J. *Chin. J. Org. Chem.* **2009**, *29*, 1924. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *Aldrichimica Acta* **2011**, *44*, 27. (d) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937.

(2) For selected recent papers on the electrophilic halogenocyclizations of alkynes, see: (a) Stein, A. L.; da Rocha, J.; Menezes, P. He.; Zeni, G. *Eur. J. Org. Chem.* **2010**, 705. (b) Verma, A. K.; Aggarwal, T.; Rustagi, V.; Larock, R. C. *Chem. Commun.* **2010**, 4064. (c) Schumacher, R. F.; Rosario, A. R.; Souza, A. C. G.; Menezes, P. H.; Zeni, G. *Org. Lett.* **2010**, *12*, 1952. (d) Huo, Z.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2010**, *75*, 1266. (e) Zhang, X.; Yao, T.; Campo, M. A.; Larock, R. C. *Tetrahedron* **2010**, *66*, 1177. (f) Chen, Y.; Cho, C.-H.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 6802. (g) Manarin, F.; Roehrs, J. A.; Mozzaquatro Gay, R.; Brandao, R.; Menezes, P. H.; Nogueira, C. W.; Zeni, G. *J. Org. Chem.* **2009**, *74*, 2153. (h) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141. (i) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173. (j) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 15720. (k) Wen, S.-G.; Liu, W.-M.; Liang, Y.-M. *J. Org. Chem.* **2008**, *73*, 4342. (l) Xie, Y.-X.; Liu, X.-Y.; Wu, L.-Y.; Han, Y.; Zhao, L.-B.; Fan, M.-J.; Liang, Y.-M. *Eur. J. Org. Chem.* **2008**, 1013. (m) Just, Z. W.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 2662. (n) Du, H.-A.; Zhang, X.-G.; Tang, R.-Y.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 7844. (o) Jiang, T.-S.; Zhang, X.-G.; Li, J.-H. *Synthesis* **2009**, 3029. (p) Crone, B.; Kirsch, S. F.; Umland, K.-D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4661. (q) Majumdar, K. C.; Ansary, I.; Sinha, B.; Roy, B.; Sridhar, B. *Synthesis* **2011**, 3287. (r) Du, H.-A.; Tang, R.-Y.; Deng, C.-L.; Liu, Y.; Li, J.-H.; Zhang, X.-G. *Adv. Synth. Catal.* **2011**, *353*, 2739. (s) Ouyang, H.-C.; Tang, R.-Y.; Zhong, P.; Zhang, X.-G.; Li, J.-H. *J. Org. Chem.* **2011**, *76*, 223. (t) Zora, M.; Kivrak, A.; Yazici, C. *J. Org. Chem.* **2011**, *76*, 6726. (u) Chen, X.; Lu, P.; Wang, Y. *Chem.—Eur. J.* **2011**, *17*, 8105. (v) Yang, F.; Ji, K.-G.; Zhu, H.-T.; Shaukat, A.; Liu, X.-Y.; Liang, Y.-M. *Chem.—Eur. J.* **2011**, *17*, 4986. (w) Ali, S.; Zhu, H.-T.; Xia, X.-F.; Ji, K.-G.; Yang, Y.-F.; Song, X.-R.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 2598. (x) Yang, F.; Jin, T.; Bao, M.; Yamamoto, Y. *Chem. Commun.* **2011**, *47*, 4541. (y) Ji, K.-G.; Zhu, H.-T.; Yang, F.; Shaukat, A.; Xia, X.-F.; Yang, Y.-F.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2010**, *75*, 5670. (z) Zhu, H.-T.; Ji, K.-G.; Yang, F.; Wang, L.-J.; Zhao, S.-C.; Ali, S.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 684. (aa) Likhar, P. R.; Racharlawara, S. S.; Karkhelikara, M. V.; Subhasa, M. S.; Sridharb, B. *Synthesis* **2011**, 2407. (ab) Majumdar, K. C.; Ghosh, T.; Shyam., P. K. *Synlett* **2011**, 2657.

(3) For special papers, see: (a) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028. (b) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *Org. Lett.* **2003**, *5*, 4121. (c) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (d) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3140. (e) Barluenga, J.; Palomas, D.; Rubio, E.; Gonzalez, J. M. *Org. Lett.* **2007**, *9*, 2823 and references cited therein.

(4) Appel, T. R.; Yehia, N. A. M.; Baumeister, U.; Hartung, H.; Kluge, R.; Ströhl, D.; Fanghänel, E. *Eur. J. Org. Chem.* **2003**, 47.

(5) (a) Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230. (b) Li, C.-W.; Wang, C.-I.; Liao, H.-Y.; Chaudhuri, R.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 9203. (c) Okitsu, T.; Nakazawa, D.; Kobayashi, A.; Mizohata, M.; In, Y.; Ishida, T.; Wada, A. *Synlett* **2010**, 203.

(6) (a) Tang, B.-X.; Yin, Q.; Tang, R.-Y.; Li, J.-H. *J. Org. Chem.* **2008**, *73*, 9008. (b) Yu, Q.-F.; Zhang, Y.-H.; Yin, Q.; Tang, B.-X.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *J. Org. Chem.* **2008**, *73*, 3658. (c) Tang, B.-X.; Tang, D.-J.; Tang, S.; Yu, Q.-F.; Zhang, Y.-H.; Liang, Y.; Zhong, P.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1063. (d) Wang, Z.-Q.; Tang, B.-X.; Zhang, H.-P.; Wang, F.; Li, J.-H. *Synthesis* **2009**, 891.

(7) (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley-Interscience: New York, 1983; Vol. 5, p 264. (b) Yoneda, K.; Yamagata, E.; Nakanishi, T.; Nagashima, T.; Kawasaki, I.; Yoshida, T.; Mori, H.; Miura, I. *Phytochemistry* **1984**, *23*, 2068. (c) Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanishi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37. (d) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691. (e) Blackman, A. J.; Li, C.; Hockless,

D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645. (f) Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463 and references cited therein. (g) Amagata, T.; Minoura, K.; Numata, A. *J. Nat. Prod.* **2006**, *69*, 1384. (h) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (i) Chawla, A. S.; Kapoor, V. K. In *The Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1995; Vol. 9, p 86. (j) Tsuda, Y.; Sano, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1996; Vol. 48, p 249. (k) Cha, J. Y.; Huang, Y.; Pettus, T. R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9519.

(8) (a) Kende, A. S.; Koch, K. *Tetrahedron Lett.* **1986**, *27*, 6051. (b) Miranda, L. D.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 1135. (c) Chikaoka, S.; Toyao, A.; Ogasawara, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 312. (d) Inui, M.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 469. (e) Gonzalez-Lopez de Turiso, F.; Curran, D. P. *Org. Lett.* **2005**, *7*, 151. (f) Lanza, T.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Zanardi, G. *Angew. Chem., Int. Ed.* **2008**, *48*, 9439.

(9) (a) Gajewski, R. P. *Tetrahedron Lett.* **1976**, *17*, 4125. (b) Kawashima, T.; Naganuma, K.; Okazaki, R. *Organometallics* **1998**, *17*, 367. (c) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053. (d) Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* **2003**, *68*, 5429. (e) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739. (f) Wardrop, D. J.; Landrie, C. L.; Ortíz, J. A. *Synlett* **2003**, 1352. (g) Wardrop, D. J.; Burge, M. S. *J. Org. Chem.* **2005**, *70*, 10271. (h) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224. (i) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (j) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353. (k) Allin, S. M.; Streetley, G. B.; Slater, M.; James, S. L.; Martin, W. P. *Tetrahedron Lett.* **2004**, *45*, 5493. (l) Allin, S. M.; James, S. L.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2002**, *67*, 9464. (m) Padwa, A.; Lee, H. I.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2004**, *69*, 8209. (n) Katritzky, R. A.; He, H.-Y.; Jiang, R. *Tetrahedron Lett.* **2002**, *43*, 2831. (o) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (p) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. (q) Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292. (r) Padwa, A.; Lee, H. I.; Rashatasakhon, P.; Rose, M. *J. Org. Chem.* **2004**, *69*, 8209. (s) Nakazaki, A.; Kobayashi, S. *Synlett* **2009**, 1605.

(10) (a) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834. (b) Rigby, J. H.; Deur, C.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 6887. (c) Kim, G.; Kim, J. H.; Lee, K. Y. *J. Org. Chem.* **2006**, *71*, 2185. (d) Mori, M.; Kuroda, S.; Zhang, C.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (e) Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633. (f) Takano, S.; Inomata, K.; Ogasawara, K. *Chem. Lett.* **1992**, 443. (g) Pigge, F. C.; Coniglio, J. J.; Rath, N. P. *Org. Lett.* **2003**, *5*, 2011. (h) Pigge, F. C.; Coniglio, J. J.; Rath, N. P. *Organometallics* **2005**, *24*, 5424. (i) Pigge, F. C.; Coniglio, J. J.; Dalvi, R. *J. Am. Chem. Soc.* **2006**, *128*, 3498. (j) Pigge, F. C.; Dhanya, R.; Swenson, D. C. *Organometallics* **2009**, *28*, 3869. (k) Haack, R. A.; Beck, K. R. *Tetrahedron Lett.* **1989**, *30*, 1605. (l) Nagao, Y.; Lee, W. S.; Jeong, I.-Y.; Shiro, M. *Tetrahedron Lett.* **1995**, *36*, 2799. (m) Boyle, F. T.; Hares, O.; Matusiak, Z. S.; Li, W.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2707. (n) Blay, G.; Cardona, L.; Collado, A. M.; García, B.; Morcillo, V.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 7294. (o) Pearson, A. J.; Wang, X.; Dorange, I. B. *Org. Lett.* **2004**, *6*, 2535.

(11) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem.* **1972**, *14*, 2320. (c) *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, 2009.

(12) (a) Dréau, M.-A.; Desmaële, D.; Dumas, F.; d'Angelo, J. *J. Org. Chem.* **1993**, *58*, 2933. (b) Warrener, R. N.; Liu, L.; Russell, R.; Tiekink, E. R. T. *Synlett* **1998**, 387. (c) Wang, Z.; Xi, Z. *Synlett* **2006**, 1275. (d) Liu, L.; Wang, Z.; Zhao, F.; Xi, Z. *J. Org. Chem.* **2007**, *72*, 3484.

(13) See the detailed data of the ^{18}O-labeling experiments determined by GC−MS analysis in the Supporting Information (Figure S1).

(14) For detailed descriptions of all DFT calculation methods, see the Supporting Information.

(15) See the detailed ORTEP diagram of the single-crystal X-ray structure of compounds **3** and **37** in the Supporting Information.

(16) The Sonogashira cross-couping reaction: (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Diek, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259. (c) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253. The Suzuki cross-couping reaction: (d) Li, J.-H.; Zhang, Y.-H.; Song, R.-J.; Xie, Y.-X.; Deng, C.-L.; Liang, Y. *Synthesis* **2007**, 2957.

(17) See GC−MS analysis data of intermediate **F** in Figure S2 of the Supporting Information.