$Cy_2NH{\cdot}HX$-Promoted Cyclizations of *o*-(Alk-1-ynyl)benzoates and (*Z*)-Alk-2-en-4-ynoate with Copper Halides to Synthesize Isocoumarins and α-Pyrone

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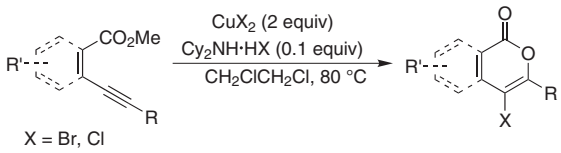
Abstract: $Cy_2NH{\cdot}HX$ was found to improve the cyclization reactions of *o*-(alk-1-ynyl)benzoates and (*Z*)-alk-2-en-4-ynoate with CuX_2 (X = Cl, Br) to synthesize the corresponding 4-haloisocoumarins and 5-bromo-2-pyrone, respectively. In the presence of two equivalents of $CuCl_2$, cyclization of methyl 2-(2-phenylethynyl)benzoate was conducted smoothly to afford the corresponding desired product in 83% yield after 24 hours, whereas the yield was enhanced to 91% in eight hours when 0.1 equivalent of $Cy_2NH{\cdot}HCl$ was added. Under the standard reaction conditions, a variety of *o*-(alk-1-ynyl)benzoates and (*Z*)-alk-2-en-4-ynoate underwent the cyclization reaction with CuX_2 to provide the corresponding 4-haloisocoumarins and 5-bromo-2-pyrone, respectively, in moderate to excellent yields.

Key words: cyclization, *o*-(alk-1-ynyl)benzoate, (*Z*)-alk-2-en-4-ynoate, 4-haloisocoumarin, 5-bromo-2-pyrone, $Cy_2NH{\cdot}HX$, copper(II) halide

Isocoumarins and α-pyrones[1] are found in numerous natural products[2] and synthetic compounds of vital medicinal value.[3] Accordingly, many excellent synthetic methods have been reported for their direct preparation.[4–6] Among these efficient methods, mainly the electrophilic cyclizations of 2-(alk-1-ynyl)benzoic acids, 5-substituted (*Z*)-alk-2-en-4-ynoic acids and their analogous esters to construct the corresponding isocoumarins and α-pyrones have been attractive. Thus, this method has been successful in the selective synthesis of many isocoumarins and α-pyrones containing diverse functional groups under mild and simple conditions.[4–6] In particular, isocoumarins and 2-pyrones with a halide group (I, Br or Cl) are of great value for the introduction of new groups in the synthesis of natural products.[4,5] However, recently much attention was focused on the synthesis of 4-iodoisocoumarins and 5-iodo-2-pyrones. Initially, a variety of 4-haloisocoumarins and 5-halo-2-pyrones were prepared by the halolactonization of the corresponding 2-(alk-1-ynyl)benzoic acids and 5-substituted (*Z*)-alk-2-en-4-ynoic acids with X_2 or NXS (X = I, Br, Cl), but the selectivity of these reactions was not satisfactory because a mixture of five- and six-member-ring products was formed.[4] Recently, Rossi and coworkers[5b,c] have disclosed the synthesis of 4-iodoisocoumarins and 5-iodo-2-pyrones via the iodocyclization of the corresponding acetylenic esters, but their selectivity still depended on both the electrophilic reagents (I_2 or ICl) and solvents (CH_2Cl_2 or MeCN). Larock and Yao[5d,e] have successfully employed both 2-(alk-1-ynyl)benzoates and 5-substituted (*Z*)-alk-2-en-4-ynoates as the starting materials in the iodolactonization reaction to selectively construct the corresponding 4-iodoisocoumarins and 5-iodo-2-pyrones in CH_2Cl_2. To the best of our knowledge, only two examples of 4-bromoisocoumarins by bromocyclization of the corresponding acetylenic esters using Br_2 and LiBr as the electrophilic reagents are known,[5a] and the synthesis of 4-chloroisocoumarins from a similar route remains unexplored. Thus, development of a new and simple method to selectively construct these 4-haloisocoumarins and 5-halo-2-pyrones (halo = Br Cl) is still significant. Here, we wish to report that 4-haloisocoumarins and 5-bromo-6-phenyl-2*H*-pyran-2-one were obtained in moderate to excellent yields using CuX_2 (X = Br, Cl) as the electrophilic reagent and the corresponding $Cy_2NH{\cdot}HX$ (X = Br, Cl) as the promoter (Equation 1).



Equation 1

The reaction of methyl 2-(2-phenylethynyl)benzoate (**1a**)[5e,7] with $CuCl_2$ in the presence of some additives was first tested as a model reaction, and the results are summarized in Table 1. Very recently, we have reported a novel and selective method for the synthesis of 2-disubstituted 3-halobenzo[*b*]furans in the presence of PdX_2 and CuX_2.[8] In that paper, $Et_3N{\cdot}HX$ was found as a switch to shift the selectivity. Thus, we applied these conditions in the cyclization of methyl 2-(2-phenylethynyl)benzoate (**1a**). As expected, 4-chloro-3-phenyl-1*H*-isochromen-1-one (**2a**), a target product, was isolated in 48% yield together with a 28% yield of a by-product **3a** in the presence of $PdCl_2$ (5 mol%), $CuCl_2$ (4 equiv) and $Et_3N{\cdot}HCl$ (0.1 equiv) (entry 1). However, the following results indicated that the presence of $PdCl_2$ and/or $Et_3N{\cdot}HCl$ disfavored the selectivity of **2a** (entries 1–3). Without $PdCl_2$, treatment of substrate **1a** with $CuCl_2$ and $Et_3N{\cdot}HCl$ provided the desired product **2a** regiospecifically in 77% yield in 12 hours (entry 2), whereas the yield of **2a** was enhanced to 83% in the ab-

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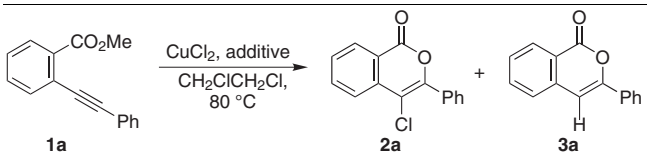
sence of both $PdCl_2$ and Et_3N·HCl after prolonging the reaction time (entry 3). Subsequently, a series of other additives, such as LiCl, K_3PO_4 and Cy_2NH·HCl, were evaluated to further enhance the selectivity toward to **2a** (entries 4–7). Gratifyingly, we found that both the selectivity and the rate could be promoted by Cy_2NH·HCl, but either LiCl or K_3PO_4 affected the reaction slightly. Treatment of substrate **1a** with $CuCl_2$ (4 equiv) and Cy_2NH·HCl (0.1 equiv) afforded the desired product **2a** in 91% yield in eight hours (entry 7), whereas only 72% or 68% yield of **2a** was obtained in the presence of LiCl and K_3PO_4, respectively (entries 4 and 6). We also discovered that the amount of $CuCl_2$ affected the reaction to some extent (entries 7–9). Identical results to those of entry 7 were observed in the presence of Cy_2NH·HCl when the amount of $CuCl_2$ was reduced to two equivalents (entry 8). However, the yield of **2a** was decreased to 55% when one equivalent of $CuCl_2$ was added (entry 9) and without $CuCl_2$ no reaction takes place even in the presence of four equivalents of LiCl (entry 5).

With the standard reaction conditions in hand, the scope of the substrates was then examined. As demonstrated in Table 2, the reaction tolerated a set of functional groups in the benzene rings or at the terminal of alkynes. To our delight, methyl 2-(2-phenylethynyl)benzoate (**1a**) could also react with $CuBr_2$ in the presence of Cy_2NH·HBr to give the corresponding desired product 4-bromo-3-phenyl-1*H*-isochromen-1-one (**4a**) in a 95% yield (entry 1). Other 2-ethynylbenzoates **1b–e** bearing different groups, such as long-chain alkyl, bulky alkyl, olefin and hydroxy groups, at the terminus of alkynes underwent both the chlorocyclization and bromocyclization reactions with $CuCl_2$ or $CuBr_2$ smoothly to selectively afford the corresponding products in good yields (entries 2–9). Gratifyingly the corresponding ethyl ester **1f** was also cyclized by $CuCl_2$ smoothly to generate the target product **2a** in a 93% yield (entry 10).

Table 1 Cyclization of Methyl 2-(2-Phenylethynyl)benzoate (**1a**) with Copper(II) Chloride[a]

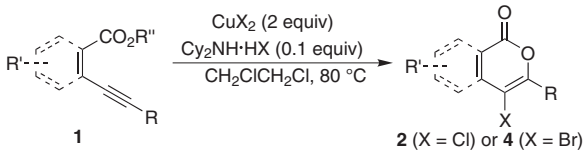


1a 2a 3a

Entry	Additive	Time (h)	Yield (%)[b]	
			2a	**3a**
1	$PdCl_2$ (5 mol%)/Et_3N·HCl (0.1 equiv)	8	48	28
2	Et_3N·HCl (0.1 equiv)	12	77	–
3	–	20	83	15
4	LiCl (2 equiv)	18	72	5
5[c]	LiCl (4 equiv)	24	–	–
6	K_3PO_4 (2 equiv)	18	68	10
7	Cy_2NH·HCl (0.1 equiv)	8	91	6
8[d]	Cy_2NH·HCl (0.1 equiv)	8	92	5
9[e]	Cy_2NH·HCl (0.1 equiv)	12	55	28

[a] Reaction conditions: **1** (0.3 mmol), $CuCl_2$ (4 equiv) and additive in CH_2ClCH_2Cl (3 mL) at 80 °C.
[b] Isolated yield.
[c] Without $CuCl_2$.
[d] With only 2 equivalents $CuCl_2$.
[e] With only 1 equivalent $CuCl_2$.

Table 2 Cy$_2$NH·HX-Promoted Cyclization Reaction in the Presence of CuX_2[a]



1 2 (X = Cl) or 4 (X = Br)

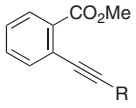
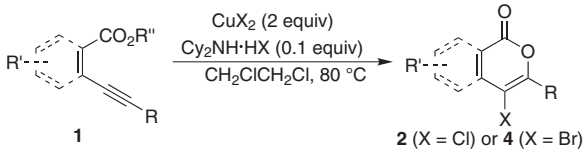
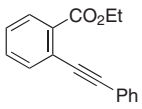
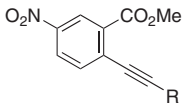
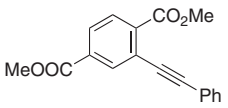
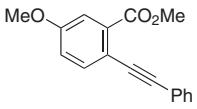
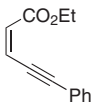
Entry	Substrate	Additive	Time (h)	Yield (%)[b]
1[c]	 R = Ph (**1a**)	$CuBr_2$/Cy_2NH·HBr	1	95 (**4a**)
2	R = *n*-C_8H_{17} (**1b**)	$CuCl_2$/Cy_2NH·HCl	5	99 (**2b**)
3	**1b**	$CuBr_2$/Cy_2NH·HBr	3	97 (**4b**)
4	R = *t*-Bu (**1c**)	$CuCl_2$/Cy_2NH·HCl	4	89 (**2c**)
5	**1c**	$CuBr_2$/Cy_2NH·HBr	1	78 (**4c**)

Table 2 $Cy_2NH{\cdot}HX$-Promoted Cyclization Reaction in the Presence of CuX_2[a] (continued)



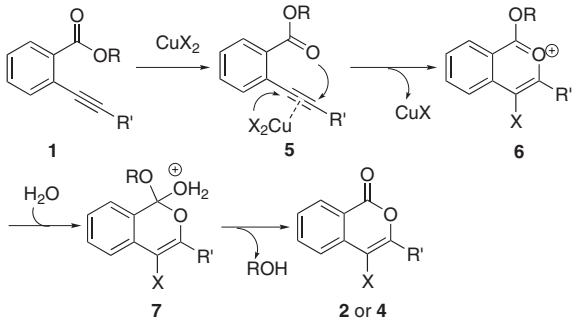
Entry	Substrate	Additive	Time (h)	Yield (%)[b]
6	R = cyclohex-1-enyl (**1d**)	$CuCl_2/Cy_2NH{\cdot}HCl$	20	99 (**2d**)
7[d]	**1d**	$CuBr_2/Cy_2NH{\cdot}HBr$	14	76 (**4d**)
8	R = CH_2OH (**1e**)	$CuCl_2/Cy_2NH{\cdot}HCl$	3	77 (**2e**)
9	**1e**	$CuBr_2/Cy_2NH{\cdot}HBr$	3	60 (**4e**)
10	 **1f**	$CuCl_2/Cy_2NH{\cdot}HCl$	8	93 (**2a**)
11	 R = Ph (**1g**)	$CuBr_2/Cy_2NH{\cdot}HBr$	3	88 (**4g**)
12	R = *n*-C_8H_{17} (**1h**)	$CuCl_2/Cy_2NH{\cdot}HCl$	26	87 (**2h**)
13[e]	**1h**	$CuBr_2/Cy_2NH{\cdot}HBr$	2	68 (**4h**)
14	 **1i**	$CuCl_2/Cy_2NH{\cdot}HCl$	6	90 (**2i**)
15[f]	**1i**	$CuBr_2/Cy_2NH{\cdot}HBr$	3	54 (**4i**)
16	 **1j**	$CuCl_2/Cy_2NH{\cdot}HCl$	6	99 (**2j**)
17	**1j**	$CuBr_2/Cy_2NH{\cdot}HBr$	3	77 (**4j**)
18	 **1k**	$CuBr_2/Cy_2NH{\cdot}HBr$	6	47 (**4k**)

[a] Reaction conditions: **1** (0.3 mmol), CuX_2 (2 equiv) and $Cy_2NH{\cdot}HX$ (0.1 equiv) in CH_2ClCH_2Cl (3 mL) at 80 °C under N_2.
[b] Isolated yield.
[c] The by-product **3a** was isolated in 4% yield.
[d] The by-product **3d** was isolated in 9% yield.
[e] The by-product **3h** was isolated in 29% yield.
[f] The by-product **3i** was isolated in 35% yield.

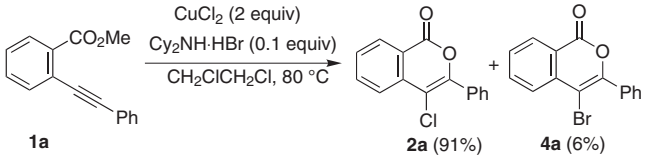
The substrates **1g–j** having an electron-withdrawing group or an electron-donating group on the benzene rings have also worked well with CuX_2 (X = Cl, Br), respectively, to give the target products in moderate to excellent yields (entries 11–17). For example, the cyclization of methyl 5-methoxy-2-(2-phenylethynyl)benzoate (**1j**) with $CuBr_2$ or $CuCl_2$ was conducted successfully to offer the corresponding products **2j** and **4j** in 99% and 77% yields, respectively (entries 16 and 17). Although the reactivity of $CuBr_2$ with (*Z*)-ethyl 5-phenylpent-2-en-4-ynoate (**1k**) was decreased to some extent, a moderate yield of the target product **4k** was still achieved (entry 18).

On the basis of the previous work[4,5,8] and our results, a working mechanism was proposed for the present reaction to elucidate the role of $Cy_2NH{\cdot}HX$ (Scheme 1). Firstly, the complex of CuX_2 with a C≡C bond on substrate **1** formed intermediate **5**, which was followed by the addi-

tion of intermediate **5** with X^- and oxygen to generate intermediate **6**. Intermediate **6** then reacted with water to yield products **2** or **4**. We deduced that Cy$_2$NH·HX may play two roles in the reaction, including: (1) phase-transfer catalyst for the CuX_2/solvent/substrate/product phases; (2) provide free active X^- to induce and improve the occurrence of the reaction (Equation 2). Further studies on the exact roles of Cy$_2$NH·HX is in progress.



Scheme 1



Equation 2 A control reaction was monitored by GC-MS analysis

In summary, we have described a simple and efficient protocol for the Cy$_2$NH·HX-promoted cyclizations of *o*-(alk-1-ynyl)benzoates and (*Z*)-alk-2-en-4-ynoate with CuX_2 (X = Cl, Br) to give the corresponding 4-haloisocoumarins and 5-bromo-2-pyrone in moderate to excellent yields. This represents a useful addition to the growing applications of isocoumarins and α-pyrones in preparative organic chemistry and medicinal industry.

NMR spectroscopy was performed on an INOVA-400 (Varian) spectrometer operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). TMS was used an internal standard and $CDCl_3$ was used as the solvent. All melting points are uncorrected.

Cy$_2$NH·HX-Promoted Cyclizations of *o*-(Alk-1-ynyl)benzoates and (*Z*)-Alk-2-en-4-ynoate with Copper Halides; General Procedure

A mixture of substrate **1** (0.3 mmol), CuX_2 (2 equiv), Cy$_2$NH·HCl (0.1 equiv) and CH_2ClCH_2Cl (3 mL) was stirred at 80 °C under N_2 for the desired time until complete consumption of starting material as monitored by TLC (Table 2). The mixture was filtered over a short column of silica gel and the solvent was evaporated. The residue was purified by flash column chromatography over silica gel (hexane–EtOAc) to afford the corresponding coupled products **2**, **3a**, **3d**, **3h** or **4**.

4-Chloro-3-phenyl-1*H*-isochromen-1-one (2a)[4a]

White solid; mp 150.0 °C.

IR (film): 1742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 8.0 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.88–7.84 (m, 3 H) 7.61 (t, *J* = 8.0 Hz, 1 H), 7.50–7.48 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 150.4, 135.9, 135.3, 131.4, 130.2, 129.8, 129.3, 129.1, 128.2, 124.0, 120.1, 111.3.

LRMS (EI, 20 eV): *m*/*z* (%) = 258 (M$^+$ + 2, 29), 256 (M$^+$, 84), 228 (57), 193 (M$^+$ – 28 – Cl, 61), 165 (48), 105 (68), 77 (100).

4-Chloro-3-octyl-1*H*-isochromen-1-one (2b)

Slightly yellow oil.

IR (CH_2Cl_2): 1716 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.6 Hz, 1 H), 7.81–7.77 (m, 2 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 2.77 (t, *J* = 7.6 Hz, 2 H), 1.76–1.72 (m, 2 H), 1.41–1.27 (m, 10 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 154.7, 135.5, 135.1, 129.7, 128.3, 123.1, 120.1, 110.9, 31.7, 31.2, 29.2, 29.1, 29.0, 26.7, 22.6, 14.0.

LRMS (EI, 20 eV): *m*/*z* (%) = 294 (M$^+$, 32) 292 (M$^+$, 93), 257 (M$^+$ – Cl, 11), 194 (64), 162 (52), 132 (77), 104 (100).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{21}{}^{35}ClO_2$ (M$^+$): 292.1230; found: 292.1229.

3-*tert*-Butyl-4-chloro-1*H*-isochromen-1-one (2c)

White solid; mp 137.0–138.2 °C.

IR (film): 1720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.4 Hz, 1 H), 7.89 (d, *J* = 8.4 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 1 H), 1.52 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 159.4, 136.7, 135.0, 129.3, 128.4, 123.2, 120.0, 110.7, 37.8, 28.2.

LRMS (EI, 20 eV): *m*/*z* (%) = 238 (M$^+$, 13), 236 (M$^+$, 39), 221 (28), 194 (42), 159 (M$^+$ – 42 – Cl, 100).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{13}{}^{35}ClO_2$ (M$^+$): 236.0604; found: 236.0604.

4-Chloro-3-cyclohexenyl-1*H*-isochromen-1-one (2d)

Yellow solid; mp 150.0–151.2 °C.

IR (film): 1740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.6 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.81 (t, *J* = 8.4 Hz, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 6.42 (t, *J* = 1.6 Hz, 1 H), 2.41–2.39 (m, 2 H), 2.27–2.25 (m, 2 H), 1.78–1.69 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 152.8, 136.2, 135.2, 135.1, 129.6, 128.5, 123.8, 120.3, 109.8, 26.3, 25.5, 22.3, 21.5, 18.2.

LRMS (EI, 20 eV): *m*/*z* (%) = 262 (M$^+$ + 2, 34), 260 (M$^+$, 100), 225 (M$^+$ – Cl, 32).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{13}{}^{35}ClO_2$ (M$^+$): 260.0604; found: 260.0603.

4-Chloro-3-(hydroxymethyl)-1*H*-isochromen-1-one (2e)

White solid; mp 151 °C.

IR (film): 1737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 7.2 Hz, 1 H), 7.81 (t, *J* = 6.4 Hz, 2 H), 7.58 (t, *J* = 8.4 Hz, 1 H), 4.75 (s, 2 H), 3.73 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 150.2, 135.4, 134.8, 128.7, 129.3, 124.0, 120.6, 112.1, 59.3.

LRMS (EI, 20 eV): *m*/*z* (%) = 212 (M$^+$ + 2, 12), 210 (M$^+$, 37), 181 (M$^+$ – H_2O, 100), 165 (M$^+$ – Cl, 38), 151 (46), 123 (84), 89 (38).

HRMS (EI): *m/z* calcd for $C_{10}H_7{}^{35}ClO_3$ (M^+): 210.0084; found: 210.0080.

4-Chloro-7-nitro-3-octyl-1*H*-isochromen-1-one (2h)
Yellow solid; mp 97 °C.

IR (film): 1740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 1 H), 8.60 (d, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 2.83 (d, *J* = 8.0 Hz, 2 H), 1.79–1.75 (m, 2 H), 1.42–1.25 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 158.8, 147.1, 140.3, 129.3, 125.7, 125.0, 120.7, 110.2, 31.8, 31.6, 29.2, 29.1 (2 C), 26.6, 22.6, 14.0.

LRMS (EI, 20 eV): *m/z* (%) = 339 (M^+ + 1, 2), 337 (M^+, 36), 302 (M^+ – Cl, 44), 239 (43), 57 (100).

HRMS (EI): *m/z* calcd for $C_{17}H_{20}{}^{35}ClO_4$ (M^+): 337.1081; found: 337.1080.

Methyl 4-Chloro-1-oxo-3-phenyl-1*H*-isochromene-6-carboxylate (2i)
White solid; mp 150.9–151.3 °C.

IR (film): 1738, 1727 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.60 (s, 1 H), 8.41 (d, *J* = 8.0 Hz, 1 H), 8.21 (d, *J* = 8.0 Hz, 1 H), 7.89–7.87 (m, 2 H), 7.51–7.50 (m, 3 H), 4.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 160.2, 151.1, 136.2, 136.1, 131.0, 130.5, 130.2, 129.4, 129.3, 128.3, 125.6, 123.3, 111.0, 52.9.

LRMS (EI, 20 eV): *m/z* (%) = 316 (M^+ + 2, 33), 314 (M^+, 99), 286 (38), 171 (24), 227 (30), 199 (16), 163 (M^+ – Cl, 32), 105 (62), 77 (70), 44 (100).

HRMS (EI): *m/z* calcd for $C_{17}H_{11}{}^{35}ClO_4$ (M^+): 314.0346; found: 314.0345.

4-Chloro-7-methoxy-3-phenyl-1*H*-isochromen-1-one (2j)
White solid; mp 170.0 °C.

IR (film): 1727 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.85 (m, 3 H), 7.76 (s, 1 H), 7.50–7.41 (m, 4 H), 3.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 160.2, 148.3, 131.5, 129.9, 129.5, 129.2, 128.2, 125.8, 125.6, 121.7, 111.3, 110.4, 55.9.

LRMS (EI, 20 eV): *m/z* (%): 288 (M^+ + 2, 33), 286 (M^+, 95), 256 (18), 258 (52), 223 (M^+ – 28 – Cl, 23), 215 (36), 152 (49), 105 (100), 77 (100).

HRMS (EI): *m/z* calcd for $C_{16}H_{11}{}^{35}ClO_3$ (M^+): 286.0397; found: 286.0396.

3-Phenyl-1*H*-isochromen-1-one (3a)[6m]
White solid; mp 88.0 °C (Lit.[5e] mp 87–89 °C).

IR (film): 1696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.4 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 7.68 (t, *J* = 7.2 Hz, 1 H), 7.47–7.39 (m, 5 H), 6.91 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 153.5, 137.4, 134.8, 131.8, 129.8, 129.5, 128.7, 128.0, 125.9, 125.1, 120.4, 101.7.

LRMS (EI, 20 eV): *m/z* (%) = 222 (M^+, 80), 194 (58), 105 (70), 77 (100).

3-Cyclohexenyl-1*H*-isochromen-1-one (3d)[9]
Slightly yellow oil.

IR (CH_2Cl_2): 1732 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.4 Hz, 1 H), 7.65 (t, *J* = 8.0 Hz, 1 H), 7.44–7.38 (m, 2 H), 6.82–6.80 (m, 1 H), 6.36 (s, 1 H), 2.30–2.25 (m, 4 H), 1.79–1.76 (m, 2 H), 1.67–1.65 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 154.3, 137.8, 134.6, 130.1, 129.5, 128.2, 127.5, 125.7, 120.5, 100.0, 25.6, 24.1, 22.2, 21.7.

LRMS (EI, 20 eV): *m/z* (%) = 226 (M^+, 100).

7-Nitro-3-octyl-1*H*-isochromen-1-one (3h)
Yellow solid; mp 54.1–56.0 °C.

IR (film): 1724 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.09 (s, 1 H), 8.48 (d, *J* = 8.8 Hz, 1 H), 7.52 (d, *J* = 8.8 Hz, 1 H), 6.38 (s, 1 H), 2.59 (t, *J* = 7.6 Hz, 2 H), 1.74–1.72 (m, 2 H), 1.39–1.25 (m, 10 H), 0.88 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 161.1, 146.5, 142.6, 128.9, 126.3, 125.6, 120.3, 102.2, 33.8, 31.7, 29.2, 29.1, 29.0, 26.7, 22.6, 14.0.

LRMS (EI, 20 eV): *m/z* (%) = 303 (M^+, 30), 205 (45), 57 (100);

HRMS (EI): *m/z* calcd for $C_{17}H_{21}NO_4$ (M^+): 303.1471; found: 303.1469.

Methyl 1-Oxo-3-phenyl-1*H*-isochromene-6-carboxylate (3i)
White solid; mp 199.0 °C.

IR (film): 1739, 1724 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 8.0 Hz, 1 H), 8.19 (s, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 7.6 Hz, 2 H), 7.49–7.46 (m, 3 H), 7.02 (s, 1 H), 4.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 161.6, 154.4, 137.5, 135.7, 131.5, 130.3, 130.0, 128.9, 128.2, 127.5, 125.3, 123.3, 101.5, 52.8.

LRMS (EI, 20 eV): *m/z* (%) = 282 (M^+ + 2, 5), 280 (M^+, 100), 252 (60), 105 (35), 77 (40) 44 (90).

HRMS (EI): *m/z* calcd for $C_{17}H_{12}O_4$ (M^+): 280.0736; found: 280.0735.

4-Bromo-3-phenyl-1*H*-isochromen-1-one (4a)[4a]
White solid; mp 99.5–101.0 °C (Lit.[11] mp 100.0–101.5 °C).

IR (film): 1739 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.0 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.85 (t, *J* = 8.8 Hz, 1 H), 7.81–7.78 (m, 2 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.48 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 151.8, 136.6, 135.4, 132.8, 130.2, 129.8, 129.6, 129.1, 128.1, 126.6, 120.6, 101.3.

LRMS (EI, 20 eV): *m/z* (%) = 332 (M^+ + 2, 80), 330 (M^+, 86), 304 (36), 302 (37), 223 (M^+ – 28 – Br, 26), 152 (54), 105 (100).

4-Bromo-3-octyl-1*H*-isochromen-1-one (4b)
Slightly yellow oil.

IR (CH_2Cl_2): 1723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.8 Hz, 2 H), 7.54–7.50 (m, 1 H), 2.81 (t, *J* = 7.2 Hz, 2 H), 1.77–1.72 (m, 2 H), 1.40–1.27 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 155.7, 136.3, 135.2, 129.6, 128.4, 125.6, 120.2, 101.1, 33.4, 31.7, 29.2, 29.1, 29.0, 26.8, 22.6, 14.0.

LRMS (EI, 20 eV): *m/z* (%) = 338 (M^+ + 2, 70), 336 (M^+, 72), 257 (M^+ – Br, 35), 159 (100).

HRMS (EI): *m/z* calcd for $C_{17}H_{21}{}^{79}BrO_2$ (M^+): 336.0725; found: 336.0723.

4-Bromo-3-*tert*-butyl-1*H*-isochromen-1-one (4c)
White solid; mp 123.0–125.5 °C.

IR (film): 1731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.0 Hz, 1 H), 7.95 (d, *J* = 8.4 Hz, 1 H), 7.79 (t, *J* = 8.4 Hz, 1 H), 7.53 (t, *J* = 8.4 Hz, 1 H), 1.56 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1, 160.1, 137.4, 135.1, 129.3, 128.5, 125.8, 120.1, 100.4, 38.5, 28.5.

LRMS (EI, 20 eV): *m*/*z* (%): 282 (M^+ + 2, 25), 280 (M^+, 24), 267 (8), 285 (9), 201 (26), 159 (M^+ – Br, 100).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{13}{}^{79}BrO_2$ (M^+): 280.0099; found: 280.0098.

4-Bromo-3-cyclohexenyl-1*H*-isochromen-1-one (4d)
Yellow solid; mp 105.0 °C.

IR (film): 1736 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.6 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 1 H), 7.81 (t, *J* = 8.4 Hz, 1 H), 7.54 (t, *J* = 8.0 Hz, 1 H), 6.32–6.29 (m, 1 H), 2.38–2.36 (m, 2 H), 2.26–2.23 (m, 2 H), 1.78–1.76 (m, 2 H), 1.76–1.69 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 154.3, 136.8, 135.2, 135.1, 131.1, 129.6, 128.6, 126.5, 120.5, 99.9, 26.3, 25.3, 22.2, 21.5.

LRMS (EI, 20 eV): *m*/*z* (%) = 306 (M^+ + 2, 100), 304 (M^+, 100), 252 (34), 250 (33), 197 (96), 179 (M^+ – 56 – Br, 50).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{13}{}^{79}BrO_2$ (M^+): 304.0099; found: 304.0099.

4-Bromo-3-(hydroxymethyl)-1*H*-isochromen-1-one (4e)
White solid; mp 124.5 °C.

IR (film): 1733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 7.6 Hz, 1 H), 7.83 (d, *J* = 4.0 Hz, 2 H), 7.62–7.58 (m, 1 H), 4.78 (s, 2 H), 2.88 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 151.8, 135.6 (2 C), 129.9, 129.5, 126.2, 120.8, 102.0, 61.5.

LRMS (EI, 20 eV): *m*/*z* (%) = 256 (M^+ + 2, 18), 254 (M^+, 19), 227 (29), 229 (32), 197 (26) 195 (26), 169 (53), 167 (55), 147 (M^+ – 29 – Br, 48), 88 (100).

HRMS (EI): *m*/*z* calcd for $C_{10}H_7{}^{79}BrO_3$ (M^+): 253.9579; found: 253.9578.

4-Bromo-7-nitro-3-phenyl-1*H*-isochromen-1-one (4g)
Yellow solid; mp 187.0–191.0 °C.

IR (film): 1733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (s, 1 H), 8.63 (d, *J* = 8.8 Hz, 1 H), 8.17 (d, *J* = 8.8 Hz, 1 H), 7.85–7.82 (m, 2 H), 7.54–7.52 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 155.2, 147.5, 141.5, 131.9, 131.1, 129.7, 129.4, 128.5, 128.3, 125.6, 121.1, 99.8.

LRMS (EI, 20 eV): *m*/*z* (%) = 347 (M^+ + 2, 100), 345 (M^+, 89), 319 (42), 317 (40), 273 (21), 271 (23), 192 (M^+ – 74 – Br, 39), 163 (52), 105 (64), 77 (100).

HRMS (EI): *m*/*z* calcd for $C_{15}H_8{}^{79}BrNO_4$ (M^+): 344.9637; found: 344.9637.

4-Bromo-7-nitro-3-octyl-1*H*-isochromen-1-one (4h)
Yellow solid; mp 71.2–72.0 °C.

IR (film): 1729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11 (s, 1 H), 8.58 (d, *J* = 8.8 Hz, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H), 2.87 (t, *J* = 8.0 Hz, 2 H), 1.79–1.76 (m, 2 H), 1.43–1.31 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 159.6, 147.1, 141.1, 129.3, 127.5, 125.6, 120.7, 99.9, 33.9, 31.8, 29.2, 29.1, 29.0, 26.8, 22.6, 14.0.

LRMS (EI, 20 eV): *m*/*z* (%) = 383 (M^+ + 2, 18), 381 (M^+, 17), 302 (M^+ – Br, 42), 204 (46), 86 (55), 57 (100).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{20}{}^{79}BrNO_4$ (M^+): 381.0576; found: 381.0575.

Methyl 4-Bromo-1-oxo-3-phenyl-1*H*-isochromene-6-carboxylate (4i)
White solid; mp 156.0–156.6 °C.

IR (film): 1738, 1730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (s, 1 H), 8.40 (d, *J* = 8.0 Hz, 1 H), 8.20 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 7.2 Hz, 2 H), 7.51–7.49 (m, 3 H), 4.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 160.4, 152.5, 136.8, 136.3, 132.4, 130.4, 130.2, 129.6, 129.4, 128.2, 123.4, 100.9, 52.9.

LRMS (EI, 20 eV): *m*/*z* (%) = 360 (M^+ + 2, 100), 358 (M^+, 95), 332 (45), 330 (46), 273 (22), 271 (23), 192 (M^+ – Br, 12), 163 (22), 105 (96), 77 (88).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{11}{}^{79}BrO_4$ (M^+): 357.9841; found: 357.9839.

4-Bromo-7-methoxy-3-phenyl-1*H*-isochromen-1-one (4j)
White solid; mp 162.0–164.0 °C.

IR (film): 1732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 9.2 Hz, 1 H), 7.81–7.78 (m, 2 H), 7.76 (s, 1 H), 7.48–7.45 (m, 3 H), 7.41 (d, *J* = 9.2 Hz, 1 H), 3.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 160.3, 149.7, 132.8, 130.2, 129.9, 129.7, 128.5, 128.1, 124.7, 121.7, 110.4, 101.2, 56.0.

LRMS (EI, 20 eV): *m*/*z* (%) = 302 (M^+ – 28, 86), 300 (M^+ – 28, 85), 274 (52), 272 (50), 193 (M^+ – 58 – Br, 60), 165 (63), 105 (78), 77 (100).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{11}{}^{79}BrO_3$ (M^+): 329.9892; found: 329.9891.

5-Bromo-6-phenyl-2*H*-pyran-2-one (4k)[10]
White solid; mp 93.0–94.5 °C (Lit.[10] mp 91–92 °C).

IR (film): 1732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 2 H), 7.51–7.47 (m, 4 H), 6.23 (d, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 158.2, 148.5, 131.6, 130.9, 129.0, 128.3, 115.2, 98.0.

LRMS (EI, 20 eV): *m*/*z* (%) = 252 (M^+ + 2, 13), 250 (M^+, 14), 224 (59), 222 (58), 195 (7), 193 (7), 115 (M^+ – 55 – Br, 37), 105 (60), 77 (100).

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References

(1) For reviews, see: (a) Barry, R. D. *Chem. Rev.* **1964**, *64*, 229. (b) Shusherina, N. P. *Russ. Chem. Rev.* **1974**, *43*, 851. (c) Posner, G. H.; Afarinkia, K.; Vinader, V.; Nelson, T. D. *Tetrahedron* **1992**, *48*, 9111. (d) Kvita, V.; Fischer, W. *Chimia* **1992**, *46*, 457. (e) Kvita, V.; Fischer, W. *Chimia* **1993**, *47*, 3.

(2) (a) Larsen, T. O.; Breinholt, J. *J. Nat. Prod.* **1999**, *62*, 1182. (b) Dumontet, V.; Hung, N. V.; Adeline, M.-T.; Riche, C.; Chiaroni, A.; Sevenet, T.; Gueritte, F. *J. Nat. Prod.* **2004**, *67*, 858.

(3) For selected recent examples, see: (a) Abraham, W. R.; Arfmann, H. A. *Phytochemistry* **1988**, *27*, 3310. (b) Schlingmann, G.; Milne, L.; Carter, G. T. *Tetrahedron* **1988**, *54*, 13013. (c) Simon, A.; Dunlop, R. W.; Ghisalberti, E. L.; Sivasithamparam, K. *Soil Biol. Biochem.* **1988**, *20*, 263. (d) Vara Prasad, J. V. N.; Para, K. S.; Lunney, E. A.; Ortwine, D. F.; Dunbar, J. B. Jr.; Ferguson, D.; Tummino, P. J.; Hupe, D.; Tait, B. D.; Domagala, J. M.; Humblet, C.; Bhat, T. N.; Liu, B.; Guerin, D. A. M.; Baldwin, E. T.; Erickson, J. W.; Sawyer, T. K. *J. Am. Soc. Chem.* **1994**, *116*, 6989. (e) Shi, X.; Leal, W. S.; Liu, Z.; Schrader, E.; Meinwald, J. *Tetrahedron Lett.* **1995**, *36*, 71. (f) Thaisrivongs, S.; Romero, D. L.; Tommasi, R. A.; Janakiraman, M. N.; Strohbach, J. W.; Turner, S. R.; Biles, C.; Morge, R. R.; Johnson, P. D.; Aristoff, P. A.; Tomich, P. K.; Lynn, J. C.; Horng, M.-M.; Chong, K.-T.; Hinshaw, R. R.; Howe, W. J.; Finzel, B. C.; Watenpaugh, K. D. *J. Med. Chem.* **1996**, *39*, 4630. (g) Hagen, S. E.; Vara Prasad, J. V. N.; Boyer, F. E.; Domagala, J. M.; Ellsworth, E. L.; Gajda, C.; Hamilton, H. W.; Markoski, L. J.; Steinbaugh, B. A.; Tait, B. D.; Lunney, E. A.; Tummino, P. J.; Ferguson, D.; Hupe, D.; Nouhan, C.; Gracheck, S. J.; Saunders, J. M.; VanderRoest, S. *J. Med. Chem.* **1997**, *40*, 3707. (h) Judge, T. M.; Phillips, G.; Morris, J. K.; Lovasz, K. D.; Romines, K. R.; Luke, G. P.; Tulinsky, J.; Tustin, J. M.; Chrusciel, R. A.; Dolak, L. A.; Mizsak, S. A.; Watt, W.; Morris, J.; Vander Velde, S. L.; Strohbach, J. W.; Gammill, R. B. *J. Am. Chem. Soc.* **1997**, *119*, 3627. (i) Deck, L. M.; Baca, M. L.; Salas, S. L.; Hunsaker, L. A.; Vander Jagt, D. L. *J. Med. Chem.* **1999**, *42*, 4250.

(4) For papers on the synthesis of isocoumarins and α-pyrones by electrophilic cyclization of the corresponding acids, see: (a) Nagarajan, A.; Balasubramanian, T. R. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1988**, *27*, 380. (b) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 2859. (c) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857.

(5) For papers on the synthesis of isocoumarins and α-pyrones by electrophilic cyclization of the corresponding esters, see: (a) Oliver, M. A.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 558. (b) Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023. (c) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067. (d) Yao, T.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 7401. (e) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936.

(6) For selected recent papers on the synthesis of isocoumarins and α-pyrones by other methods, see: (a) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145. (b) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770. (c) Fringuelli, F.; Piermatt, O.; Pizzo, F. *Heterocycles* **1999**, *50*, 611. (d) Sashida, H.; Kawamukai, A. *Tetrahedron* **2000**, *56*, 4777. (e) Rossi, R.; Bellina, F.; Biagetti, M.; Catanese, A.; Mannina, L. *Tetrahedron Lett.* **2000**, *41*, 5281. (f) Kotrestou, S. I.; Georgiadis, M. P. *Org. Prep. Proced. Int.* **2000**, *32*, 161. (g) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533. (h) Thibonnet, J.; Abarbri, M.; Parrain, J.-L.; Duchene, A. *J. Org. Chem.* **2002**, *67*, 3941. (i) Nakamura, Y.; Ukita, T. *Org. Lett.* **2002**, *4*, 2317. (j) Ma, S.; Yu, S.; Yin, S. *J. Org. Chem.* **2003**, *68*, 8996. (k) Cherry, K.; Parrain, J.-L.; Thibonnet, J.; Duchene, A.; Abarbri, M. *J. Org. Chem.* **2005**, *70*, 6669. (l) Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778. (m) Zhu, X.-F.; Schaffner, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977. (n) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437. (o) Wang, Y.; Burton, D. J. *J. Org. Chem.* **2006**, *71*, 3859.

(7) *o*-(Alk-1-ynyl)benzoates **1a–i** were prepared from the reaction of the corresponding 2-iodobenzoates with terminal alkynes and (*Z*)-alk-2-en-4-ynoate(**1j**) was obtained from the reaction of (*Z*)-2-iodo-1-phenylalkene with ethynyl propionate by known procedures, see: (a) Arcadi, A.; Marinelli, F. *Synthesis* **1986**, 749. (b) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

(8) Liang, Y.; Tang, S.; Zhang, X.-D.; Mao, L.-Q.; Xie, Y.-X.; Li, J.-H. *Org. Lett.* **2006**, *8*, 3017.

(9) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3711.

(10) Patel, M. G.; Sethna, S. *J. Indian Chem. Soc.* **1962**, *39*, 595.

(11) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459.