DOI: 10.1002/adsc.201300561

Regioselective One-Pot Synthesis of Isocoumarins and Phthalides from 2-Iodobenzoic Acids and Alkynes by Temperature Control

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Received: June 26, 2013; Revised: September 5, 2013; Published online: November 8, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300561.

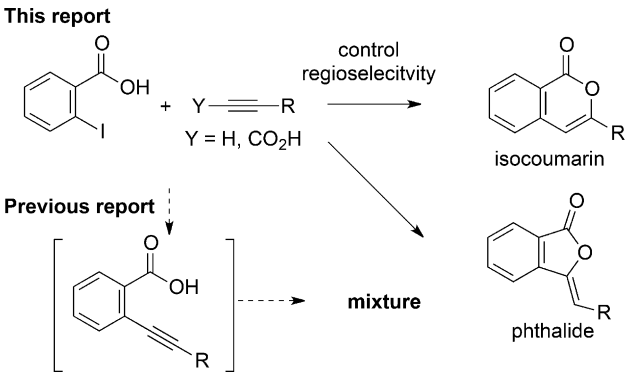
Abstract: Copper-catalyzed coupling reaction of 2-iodobenzoic acids and alkynes such as terminal acetylenes, alkynyl carboxylic acids, and trimethylsilylacetylene selectively afforded isocoumarins and phthalides in the presence of cesium carbonate (Cs_2CO_3) and dimethyl sulfoxide (DMSO). Among the regioselective products, only the 6-*endo-dig* product, isocoumarin, was formed at 100 °C, and the 5-*exo-dig* product, phthalide, was formed as a major product at 25 °C. A variety of alkynes produced the corresponding isocoumarins and phthalides in good yields. A mechanism is suggested in which the formation of 2-alkynylbenzoic acid as an intermediate *via* Sonogashira-type coupling was ruled out in the reaction pathway.

Keywords: alkynes; copper; decarboxylative coupling; isocoumarins; phthalides

Introduction

One of the most striking features in the synthesis of natural products and bioactive molecules is the control of the regioselectivity.[1] Regarding economy and diversity, it is important to synthesize a variety of compounds with similar structures from single starting materials through the control of the regioselectivity. For example, phthalide, which has a 5-membered ring, and isocoumarin, which has a 6-membered ring, can be obtained from the selective ring closing reactions of the same starting substrates. They are important building blocks in many biological and material molecules, as well as natural products. Isocoumarins exhibit bioactivities, such as antifungal,[2] antimicrobial,[3] anticancer,[4] anti-HIV[5] properties and enzyme inhibition activities.[6] Phthalides have also shown a wide range of biological activities acting as antispasmodic,[7] antifungal,[8] and pesticidic agents.[9]

Traditionally, phthalide-containing products can be prepared by the reaction of phthalic anhydride with acetic anhydride/acid at high temperature[10] and the condensation of phthalides (or phthalide phosphate) with aldehyde.[11] Isocoumarin-containing products are also obtained from similar traditional methods,[12] electrophilic,[13] or transition metal-catalyzed reactions.[14] Above all, the metal-catalyzed 5-*exo-dig* or 6-*endo-dig* cyclization of 2-alkynylbenzoic acid/esters, which are obtained[15] or generated *in situ*[16] from the Sonogashira-type coupling reaction, was one of the most attractive methods for the synthesis of phthalides and isocoumarins. Depending on the cyclization pathway, 5-*exo-dig* cyclization afforded phthalides and 6-*endo-dig* cyclization afforded isocoumarins. Despite having high substrate scopes, these methods often suffer from low regioselectivity. Even though additional methodologies have been reported to selectively synthesize either phthalide or isocoumarin, control of the regioselectivity has been lacking.[17] Uchiyama et al. reported that 5-*exo-dig* and 6-*endo-dig* products were selectively obtained from 2-phenylethynylbenzoic acid by using a weak base and strong acid, respectively. However, only one example of the substrate was shown, which was 2-phenylethynylbenzoic acid, and only the 6-*endo-dig* product was employed for the synthesis of natural products. The one-pot synthesis of isocoumarins from the copper-catalyzed coupling reaction of 2-iodobenzoic acid and terminal alkynes was described by Abarbri and Parrain et al. However, their system afforded a mixture of isocoumarins and phthalides with low regioselectivity. To the best of our knowledge, there is no report on the selective control of 5-*exo-dig* and 6-*endo-dig* modes from the coupling of 2-halobenzoic acids and corre-



Scheme 1. Synthesis of isocoumarins and phthalides.

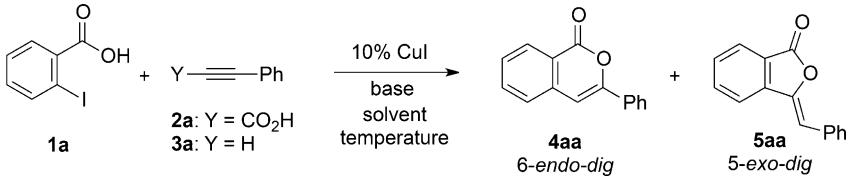
sponding alkynes *in situ*. Therefore, more studies for the development of a regioselective control method are desirable.

As part of our ongoing development of decarboxylative coupling reactions, the selective synthesis of isocoumarins and phthalides has retained our attention. We found that the 6-*endo-dig* product was only formed when 2-iodobenzoic acid and phenylpropiolic acid were reacted in the presence of Cs_2CO_3 and a copper catalyst. This result was different from a previous report in which a mixture of 5-*exo-dig* and 6-*endo-dig* products was formed in the presence of K_2CO_3. We envisioned that this transformation could be selectively controlled by tuning the reaction parameters. This has stimulated considerable effort to develop a selective control reaction method for 5-*exo-dig* and 6-*endo-dig* products by tuning the reaction parameters (Scheme 1).

Results and Discussion

To investigate the effect of regioselectivity in the formation of phthalides and isocoumarins, the reaction of 2-iodobenzoic acid and phenylpropiolic acid (or phenylacetylene) was run in the presence of CuI (10 mol%) under various conditions. The results are summarized in Table 1. When Cs_2CO_3 and K_2CO_3 were used as bases, only the 6-*endo-dig* product was formed in 85% and 76% yields, respectively (entries 1 and 2). Et_3N, an organic base, showed a low yield of product mixtures with an 80/20 ratio of **4aa** and **5aa** (entry 3). With DMF and K_2CO_3, mixtures of product were formed, which was similar to the result reported by Muthusubramanian et al.[18] (entry 4). The use of

Table 1. Optimization of the selective synthesis of isocoumarin and phthalide.[a]



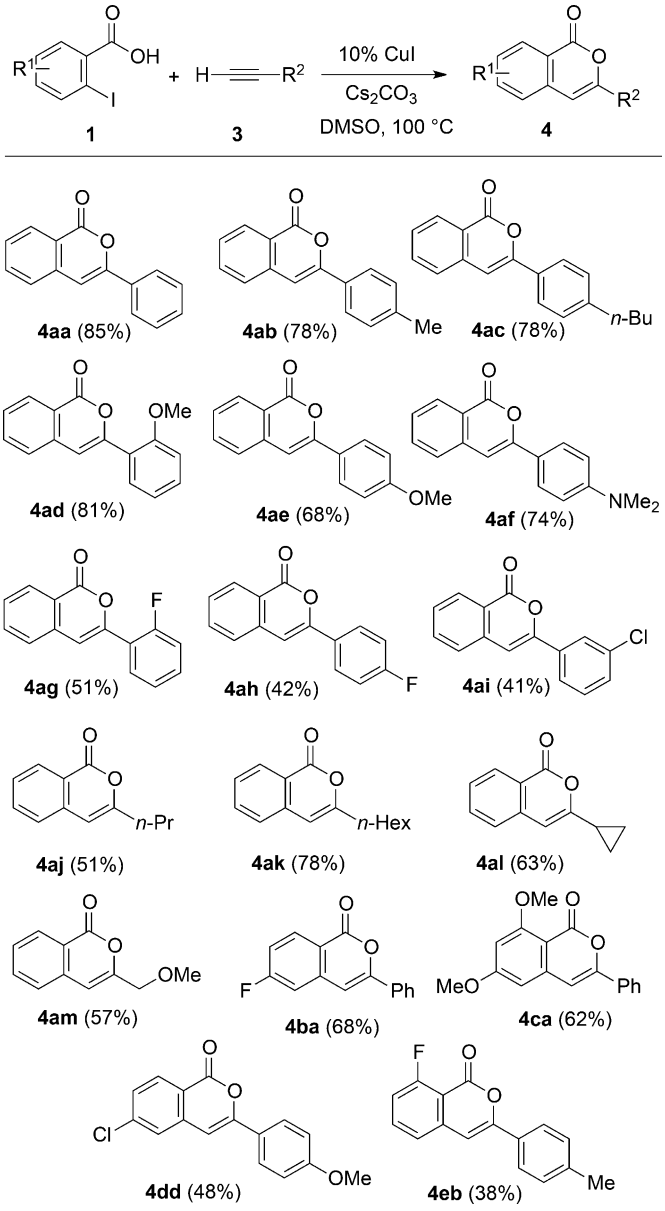
Entry	Alkyne	Base	Solvent	Temperature [°C]	Yield [%][b]	Ratio[c] of **4aa**/**5aa**
1	**2a**	Cs_2CO_3	DMSO	100	85	>99/0
2	**2a**	K_2CO_3	DMSO	100	76	>99/0
3	**2a**	Et_3N	DMSO	100	32	80/20
4	**2a**	K_2CO_3	DMF	100	58	61/39
5	**2a**	Cs_2CO_3	DMF	100	49	98/2
6	**2a**	Cs_2CO_3	DMSO	65	81	>99/0
7	**2a**	Cs_2CO_3	DMSO	25	71	9/91
8	**2a**	K_2CO_3	DMSO	25	61	8/92
9	**2a**	Cs_2CO_3	DMF	25	54	22/78
10	**2a**	Cs_2CO_3	CH_3CN	25	29	3/97
11	**2a**	Cs_2CO_3	CH_2Cl_2	25	34	1/99
12	**3a**	Cs_2CO_3	DMSO	100	88	>99/0
13	**3a**	Cs_2CO_3	DMSO	25	84	0/>99
14	**3a**	K_2CO_3	DMSO	100	62	23/77
15	**3a**	K_2CO_3	DMSO	25	75	50/50
16	**3a**	Cs_2CO_3	DMF	100	60	20/80
17	**3a**	Cs_2CO_3	DMF	25	32	13/87
18[d]	**3a**	Cs_2CO_3	DMSO	25, 100	84	0/>99

[a] *Reaction conditions:* **1a** (2.0 mmol), **2a** or **3a** (2.2 mmol), CuI (0.2 mmol) and base (4.0 mmol) for 12 h.
[b] Isolated yield.
[c] The ratio of **4aa**/**5aa** was determined by ^1H NMR.
[d] 25 °C for 12 h and then 100 °C for 6 h.

Cs_2CO_3 provided **4aa** as a major product with a ratio of 98/2, but its yield was low (entry 5). The regioselectivity of the product was not changed at 65 °C, but the yield was a bit decreased (entry 6). Interestingly, when the reaction temperature was reduced to 25 °C, the regioselectivity of the product showed an opposite trend in which **5aa** was formed as a major product with a small amount of **4aa** (entry 7). A similar trend was found in the case of K_2CO_3 (entry 8). Keeping Cs_2CO_3 as the base, we tried to screen a variety of solvents, but the formation of **4aa** was inevitable (entries 9–11). We then decided to employ phenylacetylene as a coupling reagent instead of phenylpropiolic acid. As expected, when Cs_2CO_3 was used in DMSO, the reaction at 100 °C afforded only **4aa** (entry 12). Surprisingly, only **5aa** was selectively formed when the reaction was conducted at 25 °C (entry 13). However, when other bases and solvents were used, all of them produced mixtures of products with low regioselectivity (entries 14–17). From these results, we found that DMSO and Cs_2CO_3 are important factors to obtain either **4aa** or **5aa** with high regioselectivity. Interestingly, to the best of our knowledge, there is no example of the employment of both Cs_2CO_3 and DMSO in the synthesis of phthalides and isocoumarins. This regioselectivity markedly in favor of the desired products **4aa** or **5aa** was dependent on the reaction temperature in the presence of Cs_2CO_3 and DMSO. In addition, we found that the yield and the regioselectivity of **5aa** were not changed, even though the reaction temperature was increased to 100 °C after the reaction was conducted at 25 °C for 12 h (entry 18). When the reactions were monitored by ^{1}H NMR, the formation of phthalide was detected at 25 °C and the formation of isocoumarin was detected at 100 °C.

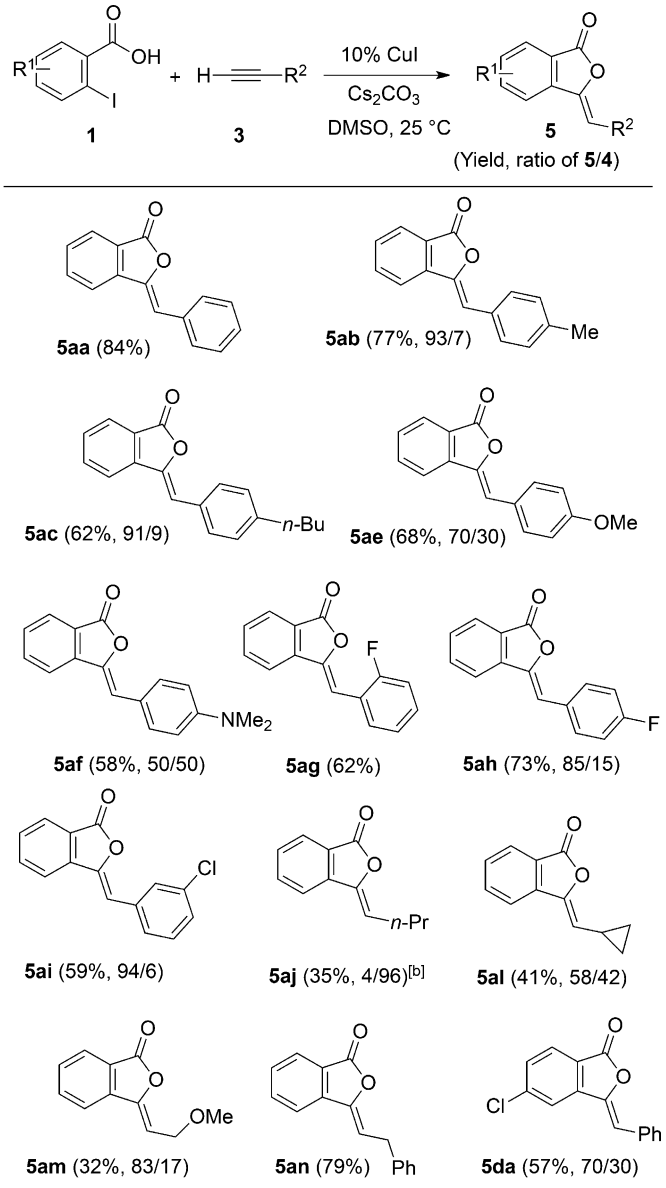
To evaluate this catalytic system for the regioseletive synthesis of isocoumarin, a variety of 2-iodobenzoic acids and terminal alkynes were reacted with Cs_2CO_3 in DMSO at 100 °C. The results are summarized in Scheme 2.

The reaction of 2-iodobenzoic acid and phenylacetylene afforded the phenylisocoumarin **4aa** in 85% yield. Alkyl-, alkoxy-, and amine-substituted phenylacetylenes produced the corresponding isocoumarins **4ab**, **4ac**, **4ad**, **4ae**, and **4af** in good yields. Phenylacetylenes bearing halide groups such as fluoride and chloride showed yields in the range of 41 to 51%. Alkyl-substituted terminal alkynes, such as pent-1-yne (**3j**), oct-1-yne (**3k**), ethynylcyclopropane (**3l**), and 3-methoxyprop-1-yne (**3m**) produced only corresponding 6-*endo-dig* products in 51%, 78%, 63%, and 57% yields, respectively. When halo- or methoxy-substituted 2-iodobenzoic acids **1b** and **1c** were reacted with phenylacetylenes, the corresponding isocoumarins were obtained in good yields. However, substituted phenylacetylene showed lower yields than others in the reaction with halo-substituted 2-iodobenzoic acids **1d** and **1e**.



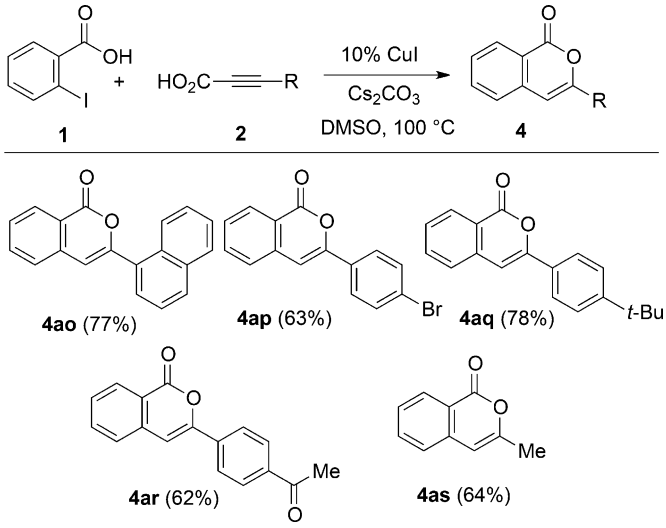
Scheme 2. Synthesis of isocoumarins from the coupling reactions of 2-iodobenzoic acids and terminal alkynes. *Reaction conditions:* **1** (2.0 mmol), **3** (2.2 mmol), CuI (0.2 mmol) and Cs_2CO_3 (4.0 mmol) at 100 °C for 12 h.

Next, to obtain the 5-*exo-dig* product, the phthalide, as a major product, the coupling reactions were carried out at 25 °C. As shown in Scheme 3, phenylacetylene afforded only phthalide **5aa** in 84% yield. Arylalkynes, which have an electron-donating group at the phenyl group, produced phthalides as the major product, but they all gave the corresponding isocoumarins as by-products. 2′-Fluorophenylacetylene (**3g**) produced only phthalide **5ag** in 62% yield. Other halide-substituted phenylacetylenes such as **3h** and **3i**



[a] Major product was **4aj**.

Scheme 3. Synthesis of phthalides from the coupling reactions of 2-iodobenzoic acids and terminal alkynes. *Reaction conditions:* **1** (2.0 mmol), **3** (2.2 mmol), CuI (0.2 mmol) and Cs_2CO_3 (4.0 mmol) at 25 °C for 12 h.



Scheme 4. Synthesis of isocoumarins from the coupling reactions of 2-iodobenzoic acids and alkynyl carboxylic acids. *Reaction conditions:* **1** (2.0 mmol), **2** (2.2 mmol), CuI (0.2 mmol) and Cs_2CO_3 (4.0 mmol) at 100 °C for 12 h.

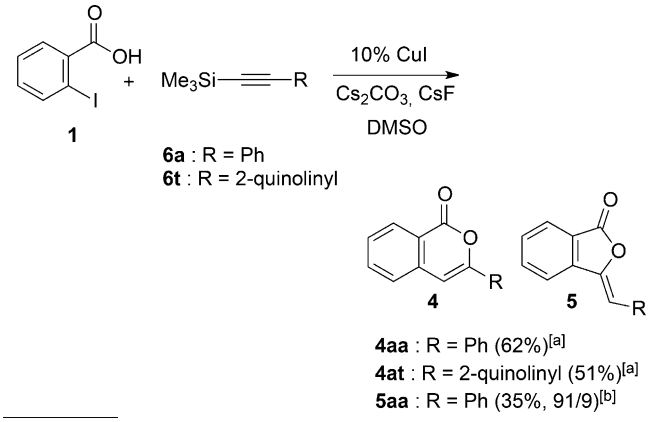
afforded the phthalides **5ah** and **5ai** as major products, but the corresponding isocoumarin was formed as a minor product.

In the case of the alkyl-substituted alkynes, some substrates showed the reversed regioselectivity. Pent-1-yne (**3j**) produced a trace amount of phthalide **5aj**, however, the corresponding isocoumarin **4aj** was formed as major product. Ethynylcyclopropane (**3l**) afforded the mixture of **5al** and **4al** with a ratio of 58/42. 3-Methoxyprop-1-yne (**3m**) gave the desired phthalide **5am** as major product. Benzylacetylene gave only phthalide **5an** in 79% yield. When halo-substituted 2-iodobenzoic acids **1b** and **1c** were reacted with terminal acetylenes at room temperature, they produced mixtures of phthalides and isocoumarins.

Instead of arylalkynes, the employment of arylalkynyl carboxylic acids has several advantages. They are easily prepared from the coupling reaction with aryl halides and propiolic acid. Alkynyl carboxylic acids with low molecular weight were used as good alkyne sources, because their terminal alkynes are too volatile to handle. A variety of alkynyl carboxylic acids were reacted with 2-iodobenzoic acid at 100 °C. As shown in Scheme 4, they all provided only isocoumarins in good yields. Particularly, but-2-ynoic acid, which is a propyne surrogate, gave the isocoumarin **4as** in 64% yield. When the alkynyl carboxylic acids were reacted with 2-iodobenzoic acid at 25 °C for the synthesis of phthalides, the desired product was not formed, because the decarboxylative coupling of alkynyl carboxylic acid requires a high temperature.

In addition, protected terminal alkynes such as trimethylsilylalkynes also provided the isocoumarins when the reaction was conducted with CuI, Cs_2CO_3, and CsF at 100 °C. As shown in Scheme 5, isocoumarins **4aa** and **4at** were formed in 62% and 51% yields, respectively. At 25 °C, phthalide **5aa** was formed as major product.

This reaction consists of the Sonogashira-type coupling and the addition of carboxylic acid to the coupled alkyne to produce the cyclized product. To investigate the reaction pathway and the regioselectivity, we first studied the Sonogashira coupling reaction of phenyl iodide (**7**) and phenylpropiolic acid (**2a**) or phenylacetylene (**3a**) in this catalytic system. As shown in Table 2, only phenylpropiolic acid afforded

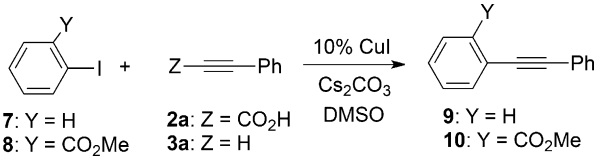


[a] Reaction temperature was 100 °C.

[b] Reaction temperature was 25 °C. **5aa** was the major product.

Scheme 5. Synthesis of isocoumarins from the coupling reactions of 2-iodobenzoic acids and trimethylsilylacetylenes. *Reaction conditions:* **1** (2.0 mmol), **3** (2.2 mmol), CuI (0.2 mmol), CsF (2.0 mmol) and Cs_2CO_3 (4.0 mmol) for 12 h.

Table 2. Sonogashira coupling reactions under this catalytic system.[a]



Entry	ArI	Alkyne	Temperature [°C]	Product	Yield [%][b]
1	**7**	**2a**	100	**9**	37
2	**7**	**2a**	25	**9**	0
3	**7**	**3a**	100	**9**	4
4	**7**	**3a**	25	**9**	0
5	**8**	**2a**	100	**10**	0
6	**8**	**3a**	100	**10**	0

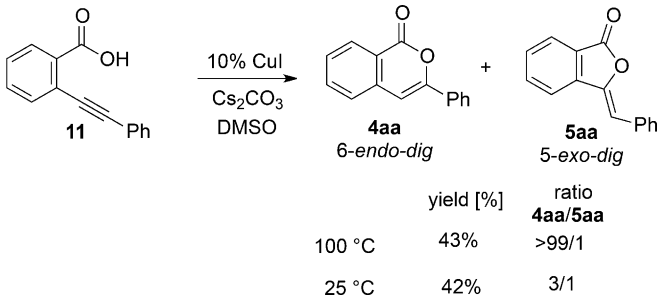
[a] *Reaction conditions:* **7** or **8** (2.0 mmol), **2a** or **3a** (2.2 mmol), CuI (0.2 mmol) and Cs_2CO_3 (4.0 mmol).

[b] Determined by ^{1}H NMR.

the coupled product **9** in 37% yield at 100 °C. Phenylacetylene did not give any coupled product at either 100 °C or 25 °C. In addition, an aryl iodide bearing an electron-withdrawing group, methyl 2-iodobenzoate (**8**), did not give any coupled product at 100 °C.

Next, we investigated the yields and the regioselectivity of the product. As shown in Scheme 6, 2-(phenylethynyl)benzoic acid (**11**), which has been reported as an intermediate in the reaction of 2-halobenzoic acid and alkyne, was employed under this catalytic system.

When 2-(phenylethynyl)benzoic acid (**11**) was employed under this catalytic system at 100 °C and 25 °C,



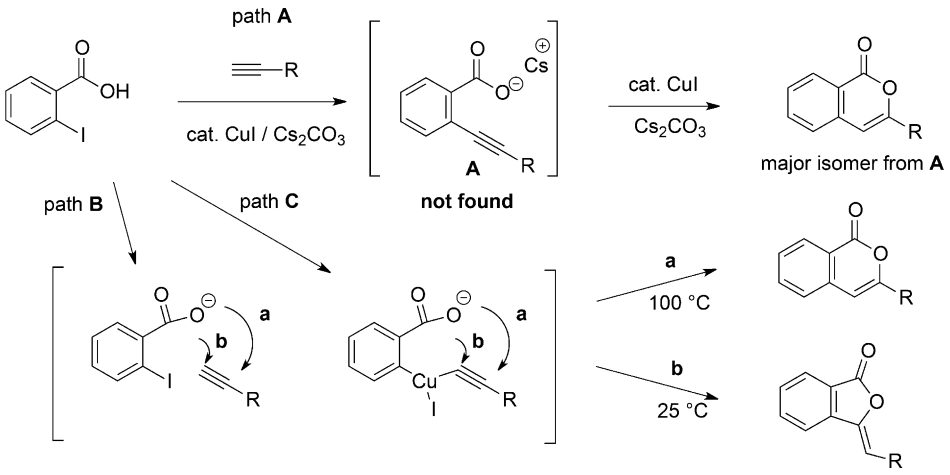
Scheme 6. Cyclization of 2-(phenylethynyl)benzoic acid under this catalytic system.

both cases showed the same regioselectivity and produced **4aa** as major product. The regioselectivity of this transformation at 25 °C was opposite to that of the coupling reaction of 2-iodobenzoic acid and phenylacetylene or phenylpropiolic acid.

Based on these results, we proposed the reaction pathway as shown in Scheme 7. We do not suggest that the path **A**, which is the formation of 2-(phenylethynyl)benzoic acid through Sonogashira coupling reaction, is a major pathway. Unfortunately, we failed to isolate any intermediate compounds in this reaction pathway. Instead, we propose that the addition of the carboxylic acid of 2-iodobenzoic acid to the alkyne proceeds first (path **B**) or at the same time with the Sonogashira-type coupling reaction (path **C**). In these pathways, path **a** might be the predominant route at 100 °C, and path **b** might be the predominant route at 25 °C. The detailed reaction mechanism is currently being studied in our laboratory.

Conclusions

In summary, we have developed a simple copper catalytic system for the regioselective synthesis of isocoumarins and phthalides from the coupling reaction of 2-iodobenzoic acids and alkynes. The isocoumarins were obtained at 100 °C, and the phthalides were obtained at 25 °C in the presence of Cs_2CO_3 and DMSO. We found that: (i) the electronic properties of different substituents on the aryl rings did not affect the formation of isocoumarins at high temperature very much, but it did affect the formation of phthalide at low temperature; (ii) arylalkynyl carboxylic acid, and trimethylsilylacetylene were also good substrates for the formation of isocoumarins; (iii) this reaction pathway might be different from the previously reported one, and the formation of a previously reported intermediate, 2-alkynylbenzoic acid, might not be in the major pathway; (iv) the survival of halide groups such as bromide and chloride offered an opportunity for further functionalization; (v) this copper-catalyzed reaction system does not need any ligand.



Scheme 7. Proposed the reaction pathway.

Experimental Section

General Procedure for Synthesis of Isocoumarin from Terminal Alkynes or Alkynyl Carboxylic Acids

2-Iodobenzoic acid derivative (2.0 mmol) and Cs_2CO_3 (1.30 g, 4.0 mmol) were added in a vial containing anhydrous DMSO (8 mL), followed by addition of the appropriate acetylene derivative (2.2 mmol) and CuI (38 mg, 0.2 mmol). The suspension was stirred for 12 h at 100 °C. After cooling, the mixture was poured into the EtOAc (50 mL) and washed with water (2×25 mL), brine (2× 25 mL), then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography (hexane: EtOAc = 20:1) or re-crystallized from hexane to afford the final product.

3-Phenyl-1*H*-isochromen-1-one (4aa):[15c] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and phenyl acetylene (225 mg, 2.2 mmol) afforded **4aa** as a pale yellow solid; yield: 377 mg (1.70 mmol, 85%); mp 80–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30 (m, 1H), 7.88–7.85 (m, 2H), 7.77 (m, 1H), 7.50–7.40 (m, 5H), 6.94 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 153.6, 137.5, 134.8, 131.9, 129.9, 129.6, 128.8, 128.1, 125.9, 125.2, 120.5, 101.8.

3-*p*-Tolyl-1*H*-isochromen-1-one (4ab):[19] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-4-methylbenzene (255 mg, 2.2 mmol) afforded **4ab** as white solid; yield: 368 mg (1.56 mmol, 78%); mp 107–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (m, 1H), 7.75–7.65 (m, 3H), 7.47–7.41 (m, 2H), 7.26-7.21 (m, 2H), 6.86 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 153.7, 140.1, 137.6, 134.7, 129.5, 129.4, 129.0, 127.8, 125.8, 125.0, 120.3, 101.0, 21.3.

3-(4-Butylphenyl)-1*H*-isochromen-1-one (4ac): 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-butyl-4-ethynylbenzene (348 mg, 2.2 mmol) afforded **4ac** as a pale-yellow solid; yield: 434 mg (1.56 mmol, 78%); mp 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.66 (m, 1H), 7.42 (m, 2H), 7.25–7.20 (m, 2H), 6.85 (s, 1H), 2.66 (t, J = 7.6 Hz, 2H), 1.63 (m, 2H), 1.36 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 153.7, 145.1, 137.6, 134.7, 129.4, 129.2, 128.7, 127.7, 125.7, 125.0, 120.2, 100.9, 35.4, 33.2, 22.3, 13.8; HR-MS (APCI): m/z = 279.1382, calcd. for $C_{19}H_{19}O_2$ $[M+H]^+$: 279.1385.

3-(2-Methoxyphenyl)-1*H*-isochromen-1-one (4ad):[20] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-2-methoxybenzene (291 mg, 2.2 mmol) afforded **4ad** as a white solid; yield: 408 mg (1.62 mmol, 81%); mp 115–117 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (m, 1H), 7.96 (dd, J = 7.9, 1.7 Hz, 1H), 7.68 (m, 1H), 7.49–7.41 (m, 2H), 7.41–7.31 (m, 2H), 7.11–6.92 (m, 2H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6, 157.2, 150.4, 138.0, 134.6, 130.7, 129.4, 128.8, 127.9, 126.3, 120.8, 111.3, 106.9, 55.6.

3-(4-Methoxyphenyl)-1*H*-isochromen-1-one (4ae):[19] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-4-methoxybenzene (291 mg, 2.2 mmol) afforded **4ae** as a pale yellow solid; yield: 343 mg (1.36 mmol, 68%); mp 112–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, J = 0.7 Hz, 1H), 7.81 (d, J = 9.1 Hz, 2H), 7.67 (m, 1H), 7.47–7.41 (m, 2H), 6.96 (d, J = 9.1 Hz, 2H), 6.82 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 161.0, 153.7, 137.9, 134.8, 129.6, 127.7, 126.8, 125.7, 124.5, 120.2, 114.2, 100.2, 55.4.

3-[4-(Dimethylamino)phenyl]-1*H*-isochromen-1-one (4af):[21] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 4-ethynyl-*N,N'*-dimethylaniline (319 mg 2.2 mmol) afforded **4af** as a greenish yellow solid; yield: 392 mg (1.48 mmol, 74%); mp 171–174 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (m, 1H), 7.77–7.68 (m, 2H), 7.63 (m, 1H), 7.43–7.34 (m, 2H), 6.72 (d, J = 1.2 Hz, 2H), 6.69 (s, 1H), 3.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 154.6, 151.3, 138.5, 134.6, 129.5, 126.9, 126.4, 125.3, 119.7, 119.3, 111.7, 98.4, 40.1.

3-(2-Fluorophenyl)-1*H*-isochromen-1-one (4ag):[21] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-2-fluorobenzene (264 mg, 2.2 mmol) afforded **4ag** as a white solid; yield: 244 mg (1.02 mmol, 51%); mp 110–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 (d, J = 7.3 Hz, 1H), 8.00 (m, 1H), 7.76 (m, 1H), 7.54–7.48 (m, 2H), 7.40 (m, 1H), 7.26 (m, 1H), 7.20 (s, 1H), 7.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.0, 160.0 (d, $J_{C,F}$ = 252.6 Hz), 148.0 (d, $J_{C,F}$ = 5.1 Hz), 137.4, 134.9, 131.1 (d, $J_{C,F}$ = 9.0 Hz), 129.5, 128.6,

128.4, 126.4, 124.6 (d, $J_{C,F}$=3.6 Hz), 120.8, 120.1 (d, $J_{C,F}$= 10.0 Hz), 116.4 (d, $J_{C,F}$=22.9 Hz), 107.2 (d, $J_{C,F}$=15.6 Hz).

3-(4-Fluorophenyl)-1*H*-isochromen-1-one (4ah):[21] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-4-fluorobenzene (264 mg, 2.2 mmol) afforded **4ah** as a white solid; yield: 201 mg (0.84 mmol, 42%); mp 127–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.29 (m, 1H), 7.87-7.82 (m, 2H), 7.70 (m, 1H), 7.50- 7.45 (m, 2H), 7.16–7.09 (m, 2H), 6.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=163.7 (d, $J_{C,F}$= 244.6 Hz), 162.0, 152.7, 137.4, 134.9, 129.7, 128.2, 127.3, 127.2, 125.9, 120.3, 116.1 (d, $J_{C,F}$=22.0 Hz), 115.8, 101.5 (d, $J_{C,F}$=1.6 Hz).

3-(3-Chlorophenyl)-1*H*-isochromen-1-one (4ai):[21] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-3-chlorobenzene (300 mg, 2.2 mmol) afforded **4ai** as a white solid; yield: 210 mg (0.82 mmol, 41%); mp 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.31 (m, 1H), 7.86 (m, 1H), 7.75–7.72 (m, 2H), 7.53–7.48 (m, 2H), 7.41–7.37 (m, 2H), 6.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=161.9, 152.1, 137.1, 135.0, 133.7, 130.1, 129.9, 129.8, 128.6, 126.1, 125.3, 123.3, 120.7, 102.7.

3-Propyl-1*H*-isochromen-1-one (4aj):[15b] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and pent-1-yne (150 mg, 2.2 mmol) afforded the **4aj** as a pale yellow oil; yield: 192 mg (1.02 mmol, 51%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.21 (m, 1H), 7.63 (m, 1H), 7.43 (m, 1H), 7.33 (d, J=7.8 Hz, 1H), 6.22 (s, 1H), 2.46 (m, 2H), 1.71 (m, 2H), 0.96 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=163.1, 157.9, 137.5, 134.6, 129.4, 127.5, 124.9, 120.0, 102.9, 35.3, 20.2, 13.4.

3-Hexyl-1*H*-isochromen-1-one (4ak):[16d] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and oct-1-yne (242 mg, 2.2 mmol) afforded **4ak** as a pale yellow solid; yield: 359 mg (1.56 mmol, 78%); mp 122–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.23 (m, 1H), 7.6 (m, 1H), 7.39 (m, 1H), 7.35 (m, 1H), 6.25 (s, 1H), 2.50 (m, 2H), 1.68 (m, 2H), 1.38–1.27 (m, 6H), 0.88 (m, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ= 162.7, 157.9, 137.3, 134.4, 129.0, 127.1, 124.7, 119.7, 102.5, 33.2, 31.2, 28.4, 26.5, 22.2, 13.7.

3-Cyclopropyl-1*H*-isochromen-1-one (4al):[22] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-cyclopropane (145 mg, 2.2 mmol) afforded **4al** as a pale yellow oil; yield: 234 mg (1.26 mmol, 63%); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.18 (d, J=8.0 Hz, 1H), 7.63 (m, 1H), 7.37 (m, 1H), 7.30 (m, 1H), 6.28 (s, 1H) 1.79 (m, 1H), 1.05 (m, 2H), 0.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=162.5, 158.1, 137.7, 134.5, 129.2, 126.8, 124.4, 119.6, 101.2, 13.6, 6.8.

3-(Methoxymethyl)-1*H*-isochromen-1-one (4am):[16b] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 3-methoxyprop-1-yne (154 mg, 2.2 mmol). afforded **4am** as a pale yellow solid; yield: 217 mg (1.14 mmol, 57%); mp 48–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.18 (m, 1H), 7.66 (m, 1H), 7.42 (m, 1H), 7.35 (d, J=7.8 Hz, 1H), 6.47 (s, 1H), 4.20 (d, J=0.9 Hz, 2H), 3.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=162.0, 153.4, 136.6, 134.7, 129.4, 128.1, 125.5, 120.5, 103.7, 70.3, 58.8.

6-Fluoro-3-phenyl-1*H*-isochromen-1-one (4ba):[14k] 4-Fluoro-2-iodobenzoic acid (532 mg, 2.0 mmol) and ethynylbenzne (224 mg, 2.2 mmol) afforded **4ba** as a white solid; yield: 326 mg (1.36 mmol, 68%); mp 158–161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.29 (dd, J=8.7, 5.6 Hz, 1H), 7.86–7.82 (m, 2H), 7.47–7.40 (m, 3H), 7.13 (m, 2H), 6.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=166.6 (d, $J_{C,F}$=256.3 Hz), 161.3, 154.8, 140.1(d, $J_{C,F}$=10.9 Hz), 132.9 (d, $J_{C,F}$=10.4 Hz), 131.5, 130.3, 128.8, 125.3, 116.9 (d, $J_{C,F}$=2.0 Hz), 116.4 (d, $J_{C,F}$=23.3 Hz), 116.5 (d, $J_{C,F}$=22.6 Hz), 101.1 (d, $J_{C,F}$= 2.9 Hz).

6,8-Dimethoxy-3-phenyl-1*H*-isochromen-1-one (4ca):[23] 2-Iodo-4,6-dimethoxybenzoic acid (616 mg, 2.0 mmol) and ethynylbenzene (224 mg, 2.2 mmol) afforded **4ca** as a white solid; yield: 350 mg (1.24 mmol, 62%); mp 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.83 (m, 2H), 7.40–7.37 (m, 2H), 7.30 (m, 1H), 6.73 (d, J=1.8 Hz, 1H), 6.44 (d, J= 1.7 Hz, 1H), 6.32 (s, 1H), 3.96 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.0, 164.8, 159.6, 144.9, 144.5, 133.2, 130.1, 128.7, 128.4, 128.3, 106.7, 100.1, 94.8, 56.2, 56.0.

6-Chloro-3-(4-methoxyphenyl)-1*H*-isochromen-1-one (4dd): 4-Chloro-2-iodobenzoic acid (565 mg, 2.0 mmol) and 1-ethynyl-4-methoxybenzene (291 mg, 2.2 mmol) afforded **4dd** as a white solid; yield: 275 mg (0.96 mmol, 48%); mp 132–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.19 (d, J= 8.4 Hz, 1H), 7.79 (d, J=9.1 Hz, 2H), 7.42 (m, 2H), 6.96 (d, J=9.1 Hz, 2H), 6.73 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=161.7, 161.4, 155.0, 141.4, 139.3, 131.3, 128.1, 127.0, 125.1, 124.0, 118.3, 114.3, 99.2, 55.4; HR-MS (APCI): m/z=287.0477, calcd. for $C_{16}H_{12}ClO_3$ $[M+H]^+$: 287.0475.

8-Fluoro-3-*p*-tolyl-1*H*-isochromen-1-one (4eb): 2-Fluoro-6-iodobenzoic acid (532 mg, 1.61 mmol) and 1-ethynyl-4-methylbenzene (255 mg, 2.2 mmol) afforded **4eb** as a white solid; yield: 193 mg (0.76 mmol, 38%); mp 161–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.79–7.76 (m, 2H), 7.69 (m, 1H), 7.29–7.25 (m, 3H), 7.16 (m, 1H), 6.89 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=163.0 (d, $J_{C,F}$= 266.3 Hz), 154.8, 140.7, 140.3, 136.1 (d, $J_{C,F}$=10.1 Hz), 129.6, 128.7, 125.3, 121.6, 121.5, 114.9 (d, $J_{C,F}$=21.3 Hz), 100.4 (d, $J_{C,F}$=3.1 Hz), 21.4; HR-MS (APCI); m/z=255.0822, calcd. for $C_{16}H_{12}FO_2$ $[M+H]^+$: 255.0821.

3-(Naphthalen-1-yl)-1*H*-isochromen-1-one (4ao):[20] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 3-(napthalen-2-yl) propiolic acid (431 mg, 2.2 mmol) afforded **4ao** as a white solid; yield: 419 mg (1.54 mmol, 77%); mp 150–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.40 (m, 1H), 8.27 (m, 1H), 7.96–7.89 (m, 2H), 7.79–7.74 (m, 2H), 7.59-7.51 (m, 5H), 6.91(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=162.6, 154.7, 137.4, 134.9, 133.7, 130.5, 129.7, 128.6, 128.4, 127.7, 127.1, 126.3, 125.9, 125.1, 120.5, 107.1.

3-(4-Bromophenyl)-1*H*-isochromen-1-one (4ap):[24] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 3-(4-bromophenyl)-propiolic acid (495 mg, 1.76 mmol) afforded **4ap** as a white solid; yield: 378 mg (1.26 mmol, 63%); mp 133–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.30 (m, 1H), 7.75–7.67 (m, 3H), 7.58 (m,1H), 7.56 (m, 1H), 7.52–7.46 (m, 2H), 6.93 (s, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ=162.0, 152.5, 137.2, 134.9, 132.0, 130.9, 129.7, 128.4, 126.7, 126.0, 124.3, 120.6, 102.1.

3-(4-*tert*-Butylphenyl)-1*H*-isochromen-1-one (4aq): 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 3-(4-*tert*-butylphenyl)propiolic acid (445 mg, 2.2 mmol) afforded **4aq** as a white solid; yield: 434 mg (1.56 mmol, 78%); mp 121–125 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.27 (m, 1H), 7.80 (m, 2H), 7.67 (m, 1H), 7.47–7.41 (m, 4H), 6.89 (s, 1H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=162.4, 153.7, 153.3, 137.6, 134.7, 129.5, 129.0, 127.8, 125.8, 125.7, 124.9, 120.3,

101.1, 34.8, 31.1; HR-MS (APCI): $m/z = 279.1384$, calcd. for $C_{19}H_{19}O_2$ $[M+H]^+$: 279.1385.

3-(4-Acetylphenyl)-1*H*-isochromen-1-one (4ar): 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 3-(4-acetylphenyl)propiolic acid (414 mg, 2.2 mmol) afforded **4ar** as a white solid; yield: 327 mg (1.24 mmol, 62%); mp 140–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.33$ (m, 1H), 8.04–7.95 (m, 4H), 7.74 (m, 1H), 7.54–7.51 (m, 2H), 7.07 (s, 1H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.3$, 161.9, 152.3, 137.7, 136.9, 136.0, 135.1, 129.8, 128.8, 126.3, 125.3, 120.9, 103.6, 26.7; HR-MS (APCI): $m/z = 265.0865$, calcd. for $C_{17}H_{13}O_3$ $[M+H]^+$: 265.0865.

3-Methyl-1*H*-isochromen-1-one (4as):[14m] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and but-2-ynoic acid (186 mg, 2.2 mmol) afforded **4as** as a white solid; yield: 205 mg (1.02 mmol, 64%); mp 70–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.20$ (m, 1H), 7.62 (m, 1H), 7.40 (m, 1H), 7.28 (d, $J = 7.9$ Hz, 1H), 6.21 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.9$, 154.4, 137.5, 134.7, 129.3, 127.4, 124.8, 119.7, 103.4, 19.5.

General Procedure for Synthesis of Isocoumarins from Trimethylsilylacetylenes

2-Iodobenzoic acid derivative (2.0 mmol), CsF (304 mg, 2.0 mmol) and Cs_2CO_3 (1.30 g, 4.0 mmol) were added to a vial containing anhydrous DMSO (8 mL), followed by addition of appropriate the trimethylsilylacetylene derivative (2.2 mmol) and CuI (38 mg, 0.2 mmol). The suspension was stirred for 12 h at 100 °C. After cooling, the mixture was poured into the EtOAc (50 mL) and washed with water (2 × 25 mL), brine (2 × 25 mL), then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography (hexane: EtOAc = 20:1) or re-crystallized from hexane to afford the final product.

3-(Quinolin-2-yl)-1*H*-isochromen-1-one (4at): 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 2-((trimethylsilyl)ethynyl)-quinoline (384 mg, 2.2 mmol) afforded **4at** as a white solid; yield: 278 mg (1.02 mmol, 51%); mp 163–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.32$ (d, $J = 2.3$ Hz, 1H), 8.72 (d, $J = 2.2$ Hz, 1H), 8.35 (m, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 7.92 (d, $J = 8.1$ Hz, 1H), 7.76-7.73 (m, Hz, 2H), 7.63-7.52 (m, 3H), 7.18 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 161.9$, 151.2, 148.2, 146.7, 137.0, 135.2, 132.7, 130.7, 129.9, 129.3, 128.8, 128.6, 127.6, 127.4, 126.3, 124.9, 120.8, 103.1; HR-MS (APCI): $m/z = 274.0869$, calcd. for $C_{18}H_{12}O_2$ $[M+H]^+$: 274.0868.

General Procedure for Synthesis of Phthalides from Terminal Alkynes

2-Iodobenzoic acid derivative (2.0 mmol) and Cs_2CO_3 (1.30 g, 4.0 mmol) were added to a vial containing anhydrous DMSO (8 mL), followed by addition of the appropriate acetylene derivative (2.2 mmol) and CuI (38 mg, 0.2 mmol). The suspension was stirred for 12 h at 25 °C. After cooling, the mixture was poured into the EtOAc (50 mL) and washed with water (2 × 25 mL), brine (2 × 25 mL), then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography (hexane: EtOAc = 20:1) or re-crystallized from hexane to afford the final product.

(*Z*)-3-Benzylideneisobenzofuran-1(3*H*)-one (5aa):[19] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and phenylacetylene (225 mg, 2.2 mmol) afforded **5aa** as a pale yellow solid; yield: 373 mg (1.68 mmol, 84%); mp 82–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.92$ (m, 1H), 7.85–7.81 (m, 2H), 7.77–7.67 (m, 2H), 7.55–7.50 (m, 1H), 7.42–7.37 (m, 2H), 7.32 (m, 1H), 6.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 167.0, 144.5, 140.6, 134.5, 133.0, 130.1, 129.8, 128.7, 128.4, 125.6, 123.4, 119.8, 107.0.

(*Z*)-3-(4-Methylbenzylidene)isobenzofuran-1(3*H*)-one (5ab):[19] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-4-methylbenzene (255 mg, 2.2 mmol) afforded a mixture of **5ab** and **4ab** in the ratio of 93:7 as a pale yellow solid; yield: 363 mg (1.54 mmol, 77%); mp 147–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (m, 1H), 7.73–7.65 (m, 4H), 7.50 (m, 1H), 7.19 (d, $J = 8.0$ Hz, 2H), 6.37 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.1$, 143.9, 140.6, 138.6, 134.3, 130.2, 130.0, 129.5, 127.8, 125.4, 123.2, 119.6, 107.1, 21.2; (*peaks for **4ab**:* 134.8, 127.8, 125.8, 125.1, 101.1).

(*Z*)-3-(4-Butylbenzylidene)isobenzofuran-1(3*H*)-one (5ac): 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-butyl-4-ethynylbenzene (348 mg, 2.2 mmol) afforded a mixture of **5ac** and **4ac** in the ratio of 91:9 as a pale yellow solid; yield: 345 mg (1.24 mmol, 62%); mp 152–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.84$ (m, 1H), 7.72–7.68 (m, 2H), 7.67–7.62 (m, 2H), 7.46 (m, 1H), 7.17 (d, $J = 8.3$ Hz, 2H), 6.33 (s, 1H), 2.61 (m, 2H), 1.59 (m, 2H), 1.35 (m, 2H), 0.92 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.9$, 143.7, 143.4, 140.4, 134.6, 130.3, 129.9, 129.3, 128.6, 125.2, 122.9, 119.5, 107.0, 35.4, 33.2, 22.2, 13.8, (*peaks for **4ac**:*162.1, 153.6, 145.0, 137.5, 134.5, 127.6, 125.7, 125.0, 120.1, 100.9); EI-MS: $m/z = 278$ (M^+, 100), 250 (75), 235 (100), 207 (50), 178 (40), 89 (30); anal calcd. for $C_{19}H_{18}O_2$: C 81.99, H 6.52; found: C 82.12, H 6.41.

(*Z*)-3-(4-Methoxybenzylidene)isobenzofuran-1(3*H*)-one (5ae):[15d] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-4-methoxybenzene (291 mg, 2.2 mmol) afforded **5ae** and **4ae** in the ratio of 70:30 as a white solid; yield: 343 mg (1.36 mmol, 68%); mp 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (m, 1H), 7.80–7.75 (m, 2H), 7.71 (m, 1H), 7.54–7.43 (m, 2H), 6.95-6.91 (m, 2H), 6.36 (s, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.2$, 159.7, 143.1, 140.8, 134.3, 131.7, 129.2, 126.8, 125.8, 125.5, 123.1, 119.5, 114.2, 106.9, 55.3, (*peaks for **4ae**:* 162.4, 161.0, 153.7, 137.9, 134.8, 129.6, 127.6, 125.7, 124.5, 120.1, 114.2, 101.2, 55.4).

(*Z*)-3-[4-(Dimethylamino)benzylidene]isobenzofuran-1(3*H*)-one (5af):[25] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 4-ethynyl-*N,N*′-dimethylaniline (319 mg 2.2 mmol) afforded **5af** and **4af** in the ratio of 50:50 as a pale yellow solid; yield: 307 mg (1.16 mmol, 58%); mp 121–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.87$ (m, 1H), 7.76–7.73 (m, 2H), 7.63 (m, 1H), 7.46–7.41 (m, 2H), 6.72–6.70 (m, 2H), 6.35 (s, 1H), 3.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 167.6, 150.3, 141.6, 141.1, 134.1, 131.6, 128.5, 125.4, 122.7, 121.1, 119.2, 111.8, 112.1, 108.1, 108.1, 40.2, (*peaks for **4af**:* 162.8, 154.7, 151.4, 138.5, 134.7, 129.6, 126.9, 126.5, 125.4, 119.7, 119.3, 98.4, 40.2).

(*Z*)-3-(2-Fluorobenzylidene)isobenzofuran-1(3*H*)-one (5ag):[26] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-2-fluorobenzene (264 mg, 2.2 mmol) afforded **5ag** as

a white solid; yield: 299 mg (1.24 mmol, 62%); mp 151–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.33 (m, 1H), 7.94 (m, 1H), 7.82–7.69 (m, 2H), 7.55 (m, 1H), 7.29–7.24 (m, 2H), 7.10 (m, 1H), 6.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8, 160.3 (d, $J_{C,F}$ = 251.0 Hz), 145.6 (d, $J_{C,F}$ = 2.4 Hz), 140.4, 134.6, 131.3 (d, $J_{C,F}$ = 1.9 Hz), 130.1, 129.8 (d, $J_{C,F}$ = 8.6 Hz), 125.5, 124.5 (d, $J_{C,F}$ = 3.6 Hz), 123.4, 121.1 (d, $J_{C,F}$ = 11.2 Hz), 120.1, 115.2 (d, $J_{C,F}$ = 22.0 Hz), 97.9 (d, $J_{C,F}$ = 8.0 Hz).

(*Z*)-3-(4-Fluorobenzylidene)isobenzofuran-1(3*H*)-one (5ah):[19] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-4-fluorobenzene (264 mg, 2.2 mmol) afforded **5ah** and **4ah** in the ratio of 85:15 as a white solid; yield: 350 mg (1.46 mmol, 73%); mp 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (m, 1H), 7.87–7.78 (m, 2H), 7.76–7.66 (m, 2H), 7.60 (m, 1H), 7.19–7.02 (m, 2H), 6.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 142.2 (d, $J_{C,F}$ = 244.2 Hz), 140.1, 138.5, 134.3, 130.2, 130.0, 129.4, 125.3, 125.0, 123.1, 119.6, 107.1, (*peaks for **4ah**:* 162.3, 153.7, 137.6, 134.7, 129.0, 127.7, 125.8, 100.9).

(*Z*)-3-(3-Chlorobenzylidene)isobenzofuran-1(3*H*)-one (5ai):[16c] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynyl-3-chlorobenzene (300 mg, 2.2 mmol) afforded **5ai** and **4ai** in the ratio of 96:4 as a pale yellow solid; yield: 302 mg (1.18 mmol, 59%); mp 147–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (m, 1H), 7.80 (m, 1H), 7.74–7.71 (m, 3H), 7.55 (m, 1H), 7.34-7.26 (m, 2H), 6.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 145.4, 140.2, 134.8, 134.6, 134.6, 130.2, 129.9, 129.7, 128.3, 128.1, 125.7, 123.5, 119.9, 105.4.

(*Z*)-3-Butylideneisobenzofuran-1(3*H*)-one (5aj): 2-Iodobenzoic acid (496 mg, 2.0 mmol) and pent-1-yne (150 mg, 2.2 mmol) afforded **5aj** and **4aj** in the ratio of 4:96 as a pale-yellow oil; yield: 106 mg (0.70 mmol, 35%); only one proton peak was detected due to its low yield and low selectivity. ^{1}H NMR (300 MHz, $CDCl_3$, peak for **5aj**): δ = 5.63 (t, J = 7.8 Hz, 1H).

(*Z*)-3-(Cyclopropylmethylene)isobenzofuran-1(3*H*)-one (5al):[22] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 1-ethynylcyclopropane (145 mg, 2.2 mmol) afforded **5al** and **4al** in the ratio of 58:42 as a pale-yellow oil; yield: 153 mg (0.82 mmol, 41%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (m, 1H), 7.56 (m, 1H), 7.40 (m, 1H), 7.32 (m, 1H), 5.10 (d, J = 10.2 Hz, 1H), 2.10 (m, 1H), 1.04–0.98 (m, 2H), 0.66–0.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 145.1, 139.3, 134.1, 128.9, 125.2, 123.7, 119.1, 114.4, 9.4, 8.4, (*peaks for **4al**:* 162.7, 158.3, 137.9, 134.7, 129.5, 127.1, 124.6, 119.9, 101.3, 13.8, 6.9)

(*Z*)-3-(2-Methoxyethylidene)isobenzofuran-1(3*H*)-one (5am): 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 3-methoxyprop-1-yne (154 mg, 2.2 mmol) afforded **5am** and **4am** in the ratio of 83:17 as a pale yellow oil; yield: 121 mg (0.64 mmol, 32%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (m, 1H), 7.74–7.64 (m, 1H), 7.61(m, 1H), 5.75 (t, J = 7.0 Hz, 1H), 4.39 (d, J = 7.0 Hz, 2H), 3.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 147.0, 139.0, 134.5, 130.3, 128.3, 125.5, 124.7, 104.5, 66.2, 58.4, (*peaks for **4am**:* 136.8, 134.9, 129.7, 127.6, 125.7, 124.5, 120.2, 103.8, 70.5, 59.0); HR-MS (APCI): m/z = 191.0708, calcd. for $C_{11}H_{12}O_3$ $[M+H]^+$: 191.0708.

(*Z*)-3-(2-Phenylethylidene)isobenzofuran-1(3*H*)-one (5an): 2-Iodobenzoic acid (496 mg, 2.0 mmol) and benzylacetylene (255 mg, 2.2 mmol) afforded **5an** as an off-white solid; yield: 373 mg (1.58 mmol, 79%); mp 68–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (m, 1H), 7.61 (m, 1H), 7.45–7.39 (m, 2H), 7.35–7.23 (m, 5H), 6.14 (s, 1H), 3.81 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 156.8, 137.2, 135.5, 134.6, 129.27, 129.1, 128.6, 127.7, 127.0, 125.1, 119.9, 103.7, 39.3; HR-MS (APCI): m/z = 237.0917, calcd. for $C_{16}H_{13}O_2$ $[M+H]^+$: 237.0916.

(*Z*)-3-Benzylidene-5-chloroisobenzofuran-1(3*H*)-one (5da): 4-Chloro-2-iodobenzoic acid (450 mg, 1.61 mmol) and phenylacetylene (180 mg, 1.76 mmol) afforded the product **5da**; yield: 210 mg (0.73 mmol, 57%); mp 118–120 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.83 (m, 2H), 7.76 (m, 1H), 7.50–7.46 (m, 2H), 7.41-7.38 (m,, 2H), 7.34 (m, 1H), 6.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 143.3, 142.1, 141.3, 132.6, 131.3, 130.3, 128.9, 126.8, 125.4, 121.7, 119.9, 108.3; HR-MS (APCI): m/z = 257.0368, calcd. for $C_{15}H_{10}ClO_2$ $[M+H]^+$: 257.0369.

General Procedure for Synthesis of Phthalides from Trimethylsilylacetylenes

2-Iodobenzoic acid derivative (2.0 mmol), CsF (304 mg, 2.0 mmol) and Cs_2CO_3 (1.30 g, 4.0 mmol) were added to a vial containing anhydrous DMSO (8 mL), followed by addition of the appropriate trimethylsilylacetylene derivative (2.2 mmol) and CuI (38 mg, 0.2 mmol). The suspension was stirred for 12 h at 25 °C. After completion of the reaction, the mixture was poured into the EtOAc (50 mL) and washed with water (2 × 25 mL), brine (2 × 25 mL), then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography (hexane: EtOAc = 20:1) or re-crystallized from hexane to afford the final product.

(*Z*)-3-Benzylideneisobenzofuran-1(3*H*)-one(5aa):[19] 2-Iodobenzoic acid (496 mg, 2.0 mmol) and trimethyl(phenylethynyl)silane (384 mg, 2.2 mmol) afforded **5aa** and **4aa** in the ratio of 91:9 as a pale yellow solid; yield: 154 mg (0.69 mmol, 35%).

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2012R1A1B3000871).

References

[1] a) J. Cossy, *Pure Appl. Chem.* **1992**, *64*, 1883–1888; b) S. Iimura, L. E. Overman, R. Paulini, A. Zakarian, *J. Am. Chem. Soc.* **2006**, *128*, 13095–13101; c) A. R. Van Dyke, T. F. Jaminson, *Angew. Chem.* **2009**, *121*, 4494–4496; *Angew. Chem. Int. Ed.* **2009**, *48*, 4430–4432; d) I. N. Lykakis, C. Efe, C. Gryparis, M. Stratakis, *Eur. J. Org. Chem.* **2011**, 2334–2338.

[2] a) K. Nozawa, M. Yamada, Y. Tsuda, K. Kawai, S. Nakajima, *Chem. Pharm. Bull.* **1981**, *29*, 2689–2691; b) D. Engelmeier, F. Hadacek, O. Hofer, G. Lutz-Kutschera,

M. Ngl, G. Wurz, H. Greger, *J. Nat. Prod.* **2004**, *67*, 19–25.
[3] M. T. Hussain, N. H. Rama, A. Malik, *Indian J. Chem. Sect. B* **2001**, *40*, 372–376.
[4] M. E. Riveiro, A. Moglioni, R. Vazquez, N. Gomez, G. Facorro, L. Piehl, E. R. De Celis, C. Shayo, C. Davio, *Bioorg. Med. Chem.* **2008**, *16*, 2665–2675.
[5] Y. Shikishima, Y. Takaishi, G. Honda, M. Ito, Y. Takeda, O. K. Kodzhimatov, O. Ashurmetov, K. H. Lee, *Chem. Pharm. Bull.* **2001**, *49*, 877–880.
[6] J. J. Heynekamp, L. A. Hunsaker, T. A. Vander Jagt, R. E. Royer, L. M. Deck, D. L. Vander Jagt, *Bioorg. Med. Chem.* **2008**, *16*, 5285–5294.
[7] F. Bellina, D. Ciucci, P. Vergamini, R. Rossi, *Tetrahedron* **2000**, *56*, 2533–2545.
[8] H. G. Culter, R. H. Cox, F. G. Crumley, P. O. Cole, *Agric. Biol. Chem.* **1986**, *50*, 2943–2945.
[9] M. Miyazawa, T. Tsukamoto, J. Anzai, Y. Ishikawa, *J. Agric. Food Chem.* **2004**, *52*, 4401–4405.
[10] a) J. Rigaudy, P. Derible, *Bull. Soc. Chim. Fr.* **1965**, 3047–3054; b) S. Gabriel, *Chem. Ber.* **1986**, *19*, 838.
[11] a) S. L. Shapiro, K. Geiger, J. Youlus, L. Freedman, *J. Org. Chem.* **1961**, *26*, 3580–3582; b) H. Zimmer, R. D. Barry, *J. Org. Chem.* **1962**, *27*, 3710–3711.
[12] a) D. E. Korte, L. S. Hegedus, R. K. Wirth, *J. Org. Chem.* **1977**, *42*, 1329–1336; b) R. C. Larcok, S. Varaprath, H. H. Lau, C. A. Fellows, *J. Am. Chem. Soc.* **1984**, *106*, 5274–5284; c) E. Napolitano, *Org. Prep. Proced. Int.* **1997**, *29*, 631–664; d) R. C. Larock, M. J. Doty, X. Han, *J. Org. Chem.* **1999**, *64*, 8770–8779; e) M. Hellal, J.-J. Bourguignon, F. J.-J. Bihel, *Tetrahedron Lett.* **2008**, *49*, 62–65.
[13] a) T. Yao, R. C. Larock, *J. Org. Chem.* **2003**, *68*, 5936–5942; b) R. Rossi, A. Carpita, F. Bellina, P. Stabile, L. Mannina, *Tetrahedron* **2003**, *59*, 2067–2081; c) A.-Y. Peng, Y.-X. Ding, *Org. Lett.* **2004**, *6*, 1119–1121.
[14] a) K. E. Nash, P. J. Toscano, *J. Am. Chem. Soc.* **1993**, *115*, 10444–10445; b) L. Bleicher, N. D. P. Cosford, *Synlett* **1995**, 1115–1116; c) L. S. Bleicher, N. D. P. Cosford, A. Herbaut, J. S. McCallum, I. A. McDonald, *J. Org. Chem.* **1998**, *63*, 1109–1118; d) F.-X. Felpin, G. Vo-Thanh, J. Villiéras, J. Lebreton, *Tetrahedron: Asymmetry* **2001**, *12*, 1121–1124; e) R. W. Bates, J. Boonsombat, *J. Chem. Soc. Perkin Trans. 1* **2001**, 654–657; f) R. G. Heidenreich, K. Köhler, J. G. E. Krauter, J. Pietsch, *Synlett* **2002**, 1118–1122; g) Z. Novak, A. Szabo, J. Repasi, A. Kotschy, *J. Org. Chem.* **2003**, *68*, 3327–3329; h) Y. Mori, M. Seki, *J. Org. Chem.* **2003**, *68*, 1571–1574; i) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362–5367; j) S. A. Shahzad, C. Venin, T. Wirth, *Eur. J. Org. Chem.* **2010**, 3465–3472; k) Z.-Y. Ge, X.-D. Fei, T. Tang, Y.-M. Zhu, J.-K. Shen, *J. Org. Chem.* **2012**, *77*, 5736–5743; l) S. Cai, F. Wang, C. Xi, *Synthesis* **2012**, *44*, 1892–1897; m) V. Kavala, C.-C. Wang, D. K. Barange, C.-W. Kuo, P.-M. Lei, C.-F. Yao, *J. Org. Chem.* **2012**, *77*, 5022–5029.
[15] a) H. Sashida, A. Kawamukai, *Synthesis* **1999**, 1145–1148; b) X. Li, A. R. Chianese, T. Vogel, R. H. Crabtree, *Org. Lett.* **2005**, *7*, 5437–5440; c) M. Uchiyama, H. Ozawa, K. Takuma, Y. Matsumoto, M. Yonehara, K. Hiroya, T. Sakamoto, *Org. Lett.* **2006**, *8*, 5517–5520; d) E. Marchal, P. Uriac, B. Legouin, L. Toupet, P. Van de Weghe, *Tetrahedron* **2007**, *63*, 9979–9990; e) C. Kanazawa, M. Terada, *Tetrahedron Lett.* **2007**, *48*, 933–935.
[16] a) N. G. Kundu, M. Pal, *J. Chem. Soc. Chem. Commun.* **1993**, 86–88; b) H.-Y. Liao, C.-H. Cheng, *J. Org. Chem.* **1995**, *60*, 3711–3716; c) N. G. Kundu, M. Pal, B. Nandi, *J. Chem. Soc. Perkin Trans. 1* **1998**, 561–568; d) V. Subramanian, V. R. Batchu, D. Barange, M. Pal, *J. Org. Chem.* **2005**, *70*, 4778–4783; e) L. Zhou, H.-F. Jiang, *Tetrahedron Lett.* **2007**, *48*, 8449–8452; f) S. Inack-Ngi, R. Rahmani, L. Commeiras, G. Chouraqui, J. Thibonnet, A. Duchêne, M. Abarbri, J.-L. Parrain, *Adv. Synth. Catal.* **2009**, *351*, 779–788.
[17] J. H. Park, S. V. Bhilare, S. W. Youn, *Org. Lett.* **2011**, *13*, 2228–2231.
[18] T. Ponpandian, S. Muthusubramanian, *Tetrahedron Lett.* **2012**, *53*, 4248–4252.
[19] X. D. Fei, Z. Y. Ge, T. Tang, Y. M. Zhu, S. J. Ji, *J. Org. Chem.* **2012**, *77*, 10321–10328.
[20] A. Sperança, B. Godoi, S. Pinton, D. F. Back, P. H. Menezes, G. Zeni, *J. Org. Chem.* **2011**, *76*, 6789–6797.
[21] S. Roy, S. Roy, B. Neuenswander, D. Hill, R. C. Larock, *J. Comb. Chem.* **2009**, *11*, 1128–1135.
[22] P. Zhao, D. Chen, G. Song, K. Han, X. Li, *J. Org. Chem.* **2012**, *77*, 1579–1584.
[23] C. N. Lewis, P. L. Spargo, J. Staunton, *Synthesis* **1986**, 944–946.
[24] J. Langer, M. Gartner, H. Gorls, D. Walther, *Synthesis* **2006**, 2697–2706.
[25] T. F. Mikhailovskaya, S. F. Vasilevsky, *Russ. Chem. B.* **2010**, *59*, 632–636.
[26] R. K. Howe, *J. Org. Chem.* **1973**, *38*, 4164–4167.

