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Iodine-mediated cyclization of *ortho*-alkynylarylketones for the synthesis of indenone derivatives

Pennapa Chuangsoongnern,[b] Chareef Surinrach,[b] Jumreang Tummatorn,*[a][b] Charnsak Thongsornkleeb,[a][b] and Somsak Ruchirawat[a][b]

Abstract: A new approach for the synthesis of indenone derivatives using I_2-promoted cyclization of *ortho*-alkynylarylketones has been developed. This method provides a metal-free and convenient route for regioselective synthesis of indenones employing *ortho*-alkynylarylketones with predefined substituents to obtain indenone products in moderate to good yields.

Introduction

Indenone is an important core structure of several natural products[1] and synthetic bioactive compounds (Figure 1).[2] Moreover, indenones are also used as a key intermediate in many syntheses of more complex molecules. Therefore, the development of synthetic strategy to construct indenones is still an active area of research. Several reported methods employ expensive transition metal catalysts to promote intermolecular annulation between alkynes and coupling partners (Scheme 1).[3] However, these methods suffer from the lack of regioselectivity in the annulation process which make them not suitable for the synthesis of unsymmetrical 2,3-disubstituted indenones. With this restriction, the intramolecular cyclization of substrates with predefined substituents is a more trusted strategy in controlling the regioselectivity issue in the ring formation. Surprisingly, not many methods are reported in the literature for this conversion. 2-(1-Alkynyl)benzylic alcohol is one of the substrates employed to synthesize indenone using I_2-mediated intramolecular annulation. In this transformation, the benzylic hydroxyl group was first activated by I_2 to generate carbocation intermediate before further cyclization by the tethered alkyne resulting in the formation of indenone product regioselectively (Scheme 1).[4] Moreover, *ortho*-alkynylarylketone substrates could also be converted to indenone products employing a catalytic amount of $NaAuCl_4.2H_2O$[5] or a stoichiometric amount of Tf_2NH.[6] The reaction mode of these two procedures is in reversal of the previous method; alkyne moiety is initially promoted by such reagents before the cyclization which was triggered by the participation of *ortho*-keto moiety (Scheme 1).

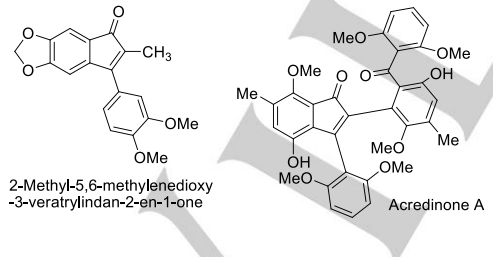
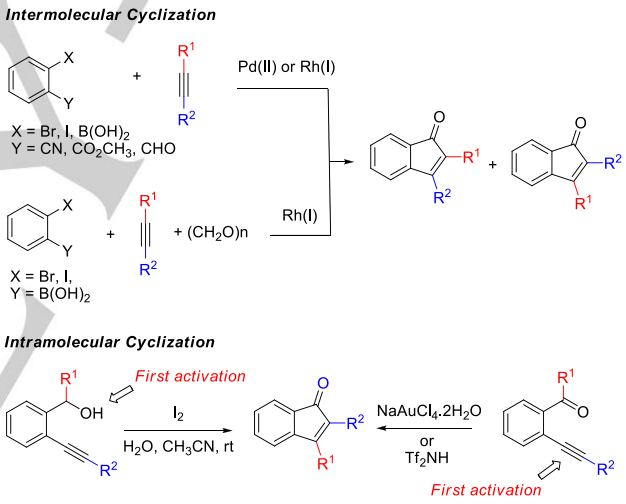
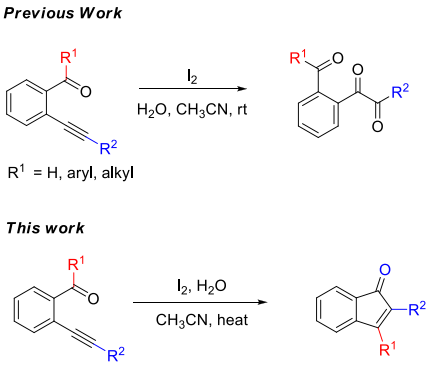


Figure 1. Indenone natural products.



Scheme 1. The synthesis of indenone derivatives



Scheme 2. The utilization of *ortho*-alkynylarylketone substrates.

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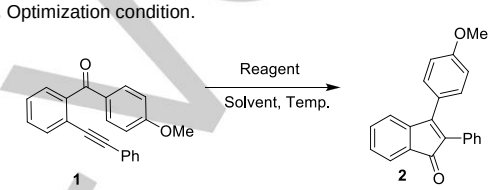
Since our research group has been interested in the utilization of *ortho*-alkynylarylketones to prepare polycyclic compounds,[7] during our study we observed an unexpected result that *ortho*-alkynylarylketones could be activated by molecular iodine to promote the cyclization to provide indedone products. Surprisingly, the previously reported method demonstrated that the same substrates, *ortho*-alkynylarylketones and *ortho*-alkynylarylaldehydes, could be oxidized by I_2 to provide 1,4,5-tricarbonyl compounds when the reaction was carried out in CH_3CN/H_2O at room temperature.[8] These results implied that I_2 could play multiple important roles in the reaction of *ortho*-alkynylarylketones depending on the reaction conditions. As molecular iodine is an environmentally friendly and inexpensive reagent which has been established as a good mediator and reagent in several organic reactions,[9] therefore in this work, we aim to develop a new methodology for the synthesis of indenones using I_2-mediated cyclization of *ortho*-alkynylarylketone substrates.

Results and Discussion

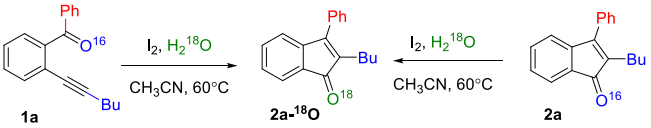
In the optimization of conditions, we used (4-methoxyphenyl)(2-(phenylethynyl)phenyl)methanone (**1**) as our screening substrate (Table 1). Initially, compound **1** was treated with 0.5 eq of I_2 in DCM at 60°C for overnight. Unfortunately, the starting material underwent the decomposition under these reaction conditions providing the desired product in only 3% yields (entry 1). The improvement of yield was achieved when 1.0 eq of I_2 was employed giving indenone **2** in 23% yield (entry 2). However, the excess amount of I_2 adversely affected the reaction in decreasing the yield of the desired product (entry 3). Next, the effect of solvents was investigated in entries 4-10. The reactions were carried out in various AR grade solvents using 1.0 eq of I_2 as a reagent. The results showed that the desired product was obtained in most promising yields when the reactions were carried out in CH_3CN and MeOH. However, the reaction using CH_3CN gave a cleaner reaction product than MeOH. Therefore, CH_3CN was used as the solvent for further optimization. To ensure that water was required for this conversion, the reactions in entries 11 and 12 were then carried out. The results illustrated that when the reaction was treated with 1.0 eq of I_2 and H_2O in dry CH_3CN at 60°C, the desired product was obtained in highest yield (73%, entry 12). Therefore, the condition in entry 12 was selected as the optimal conditions for this transformation. To investigate the reaction mechanism of this transformation, the reaction of compound **1a** was performed using H_2O-^{18}O (97 atom %). The result from high-resolution mass-spectrometry data showed that ^{18}O could incorporate into the molecule of the corresponding indenone product with the relative intensity of $^{18}O/^{16}O$ = 4:1 ratio. However, it is known that $H_2{}^{18}O$ is also able to exchange with oxygen atom of ketone compounds.[10] Therefore, we set up another experiment by treating indenone **2a** (^{16}O) with $H_2{}^{18}O$ under the same optimal conditions as shown in Scheme 3. The result showed that ^{18}O could exchange with ^{16}O of ketone in indenone **2a** providing the relative intensity of $^{18}O/^{16}O$ = 1:2.5 ratio which was lower than the ratio from the conversion of **1a** to indenone **2a**. Therefore, we speculated that ^{18}O might be able to exchange with ^{16}O of starting material ketone **1a** as well. From our study, we learn that H_2O was required in this transformation; therefore, the proposed mechanism of this transformation was illustrated in Scheme 4. Initially, the alkyne moiety was activated by molecular iodine to form iodonium ion intermediate which underwent the cyclization using the lone pair electron of *ortho*-carbonyl group to form a five-membered oxocarbenium ion (**A**).[8,11] Upon hydrolysis, intermediate **A** was then converted to vinyl iodide (**C**) which further reacted in the intramolecular nucleophilic addition of ketone providing alcohol intermediate **D**. After proton transfer, *alpha*-elimination of iodide proceeded and followed by the elimination of water to obtain the final product.

Table 1. Optimization condition.

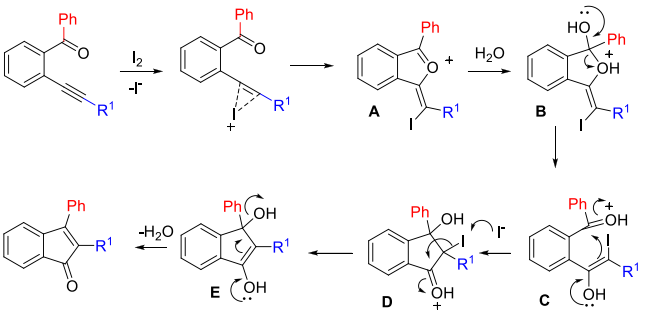


Entry	Reagents	Time (h)	Yield (%)
1	I_2 (0.5 eq), DCM, 60 °C	O/N	3
2	I_2 (1.0 eq), DCM, 60 °C	O/N	23
3	I_2 (3.0 eq), DCM, rt	2	9
4	I_2 (1.0 eq), CH_3CN, 60 °C	1	66
5	I_2 (1.0 eq), Toluene, 60 °C	3.5	13
6	I_2 (1.0 eq), CH_3NO_2, 60 °C	1	50
7	I_2 (1.0 eq.), THF, 60 °C	1.5	55
8	I_2 (1.0 eq), DMF, 60 °C	O/N	12
9	I_2 (1.0 eq), MeOH, 60 °C	1	<68
10	I_2 (1.0 eq), DMSO, 60 °C	1	27
11	I_2 (1.0 eq), CH_3CN (dry) , 60 °C	1.5	54
12	I_2 (1.0 eq), H_2O (1.0 eq), CH_3CN (dry) , 60 °C	6	73

[a]Isolated Yields. [b]O/N = overnight

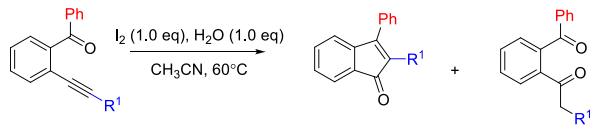


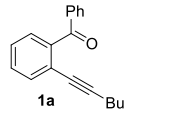
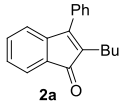
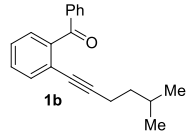
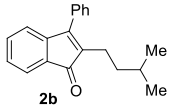
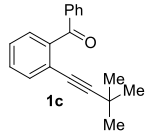
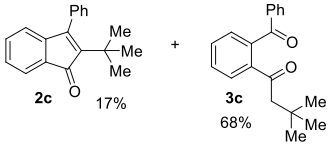
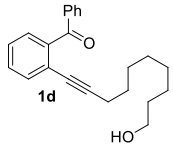
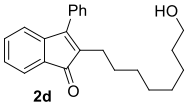
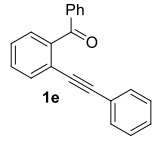
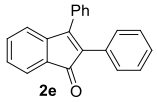
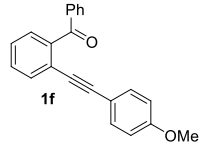
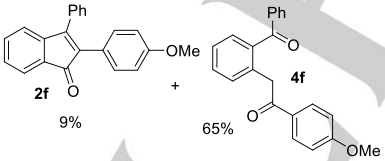
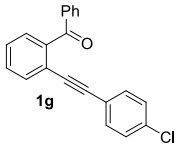
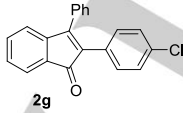
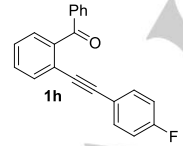
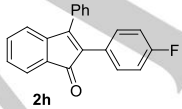
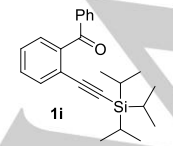
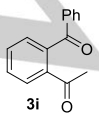
Scheme 3. ^{18}O-labeling experiments



Scheme 4. Proposed reaction mechanism.

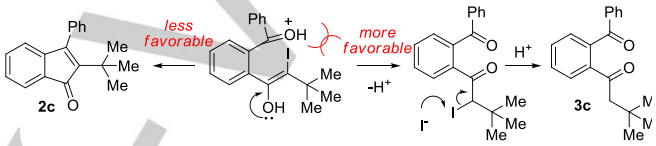
Table 2. Substrate Scope.



Entry	Substrate	Product	Yield (%)
1			79%
2			78%
3			17% (2c), 68% (3c)
4			68%
5			65%
6			9% (2f), 65% (4f)
7			70%
8			71%
9			86%

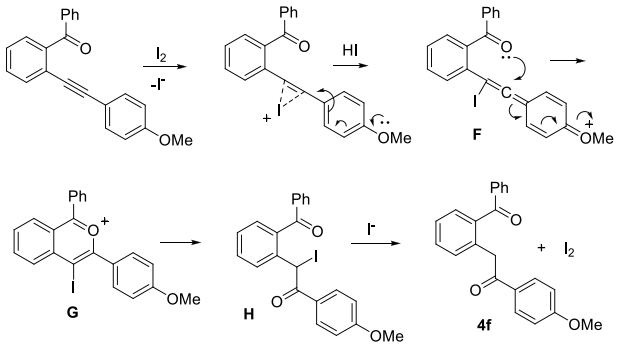
[a]Isolated Yields

With the optimal conditions in hand, a wide variety of substrates were synthesized and subjected to the optimal conditions. Initially, the substituents R^1 of the alkyne of *ortho*-acetylenyl benzophenone derivatives **1** were varied as shown in Table 2. With butyl and isopentyl as substituents, compounds **1a** and **1b** were smoothly converted to the corresponding products **2a** and **2b**, respectively, in good yields. Exploring the influence of steric hindrance of the substituent, compound **1c**, containing *t*-butyl group, was then examined under the optimal conditions. The reaction provided compound **2c** in only 17% yield as the minor product together with compound **3c** as the major product (68%). This result implied that the ability of cyclization process was diminished due to the steric blockade of *t*-butyl group present in the molecule leading to the formation of 1,4-diketone **3c** as the major product. The proposed mechanism for the formation of compound **3c** was illustrated in Scheme 5.



Scheme 5. Proposed reaction mechanism for the formation of **3c**.

Next, the substrate containing free hydroxyl group **1d** was subjected to the optimal conditions. The result revealed that compound **1d** could tolerate under the reaction conditions to afford indenone **2d** in 68% yield (entry 4). In other cases, the substituents on the alkyne were varied using a variety of substituted benzene (entries 5-8). With the electronically neutral benzene as the substituent (**1e**), the reaction proceeded smoothly and gave the corresponding product **2e** in 65% yield. Conversely, the reaction of substrate containing electron-rich substituent **1f** (*para*-methoxybenzene) gave indenone product **2f** in very low yield (9%) along with side product **4f** in 65% yield.[12]

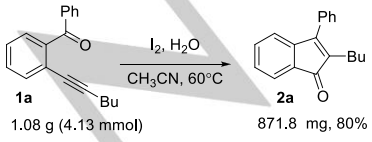


Scheme 6. Proposed mechanism for the formation of 1,5-diketone compound.

The presumable formation of compound **4f** was that the electron delocalization of *para*-methoxyphenyl could faciltate the ring opening of iodonium ion to generate intermediate **F**. Then, the lone pair electron of the *ortho*-carbonyl underwent the cyclization onto iodo-allene to form oxonium ion which was then hydrolyzed to obtain *alpha*-iodoketone **H**, followed by *alpha*-elimination of iodide to form the final product (Scheme 6). Furthermore, other substituents were investigated including *para*-chloro and *para*-fluorobenzene. Both substrates could be converted to the corresponding products in high yields. However, the substrate containing the triisopropylsilyl group on the alkyne **1i** was not compatible with this protocol, proving compound **4i** in 86% yield.

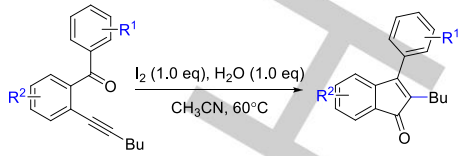
To further illustrate the ability of the current method, the substituents on both sides of ketone (R^1 and R^2) were varied as shown in Table 3. Initially, substrates with a variety of electron densities on aryl ring (R^1) were subjected to the reaction conditions. The results showed that substrates with both electron rich (**1j**) and electron deficient (**1k** and **1l**) substituents could be converted to the corresponding products in very good yields (entries 1-3). In changing from R^1 = aryl group to benzyl group **1m**, the reaction provided a complex mixture and only compound **2m'** was isolable in 39% yield. The result in this case suggested that the reaction possibly generated two enolate intermediates resulting in the formation of side products. In this case, the methylene proton of the benzyl group could compete in the generation of the enolates which underwent the cyclization to give the unexpected indenone product **2m'**. Meanwhile, only compound **2n** was obtained in 23% when the substrate **1n** containing methyl group was subjected to these optimal conditions. In the next investigation, the effect of the substituents R^2 was examined employing both electron-donating and electron-withdrawing groups placed in different positions as presented in entries 6-9. The reaction of compound **1o** having a methoxy group at the *meta*- position with respect to the alkyne provided the desired product **2o** in moderate yield (52%) while compound **1p** having a methoxy group at the *para*-position with respect to the alkyne could provide the desired product in higher yield (72%). These results implied that the efficiency of iodine-activated alkyne might be reduced due to the influence of inductive effect from the *meta*-methoxy group resulting in much lower yield of the desired product **2o**. Similar results were obtained when substrates **1q** and **1r** bearing fluorine atom at the *meta*-position with respect to the alkyne moiety were employed providing the corresponding products in moderate yields.

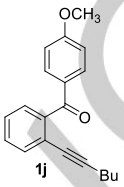
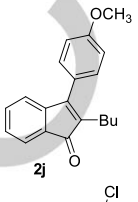
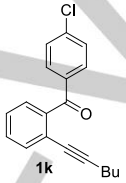
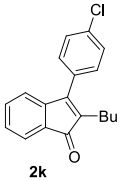
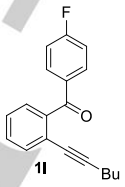
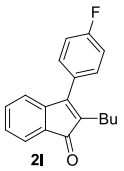
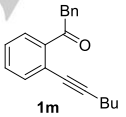
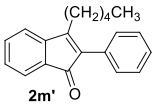
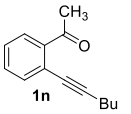
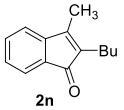
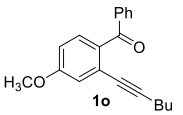
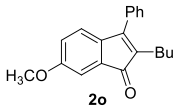
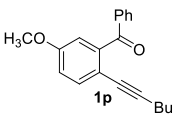
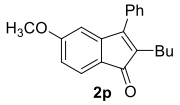
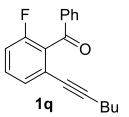
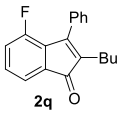
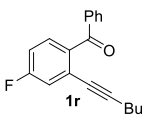
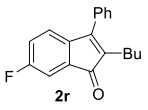
To display the practicality of our method, gram-scale synthesis was conducted as shown in Scheme 7. The reaction of compound **1a** was converted to the corresponding product **2a** in good yield (80%).



Scheme 7. Gram-scale syntheses of compound **2a**

Table 3. Substrate Scope.



Entry	Substrate	Product	Yield (%)
1			79%
2			67%
3			74%
4			39%
5			23%
6			52%
7			72%
8			56%
9			56%

[a]Isolated Yields

Conclusions

In conclusion, we have demonstrated the utility of *ortho*-alkynylarylketones in the synthesis of indenone derivatives using molecular iodine-promoted cyclization. This method provided a convenient and easy control of the regioselectivity in the indenone products. In addition, this protocol could also be applied to a broad range of substrates to give the corresponding indenones in moderate to good yields.

Experimental Section

General procedure for the synthesis of compound 1: (2-iodophenyl)(4-methoxyphenyl)methanone (506.5 mg, 1.4979 mmol, 1.0 equiv) was dissolved in Et_3N (3.5 mL/mmol) in a sealed tube. This mixture was then added CuI (14.2 mg, 0.0749 mmol, 5 mol%), $PdCl_2(PPh_3)_2$ (21.0 mg, 0.0299 mmol, 2 mol%) and PPh_3 (19.7 mg, 0.0749 mmol, 5 mol%) at room temperature and bubbled with argon for 30 min at room temperature before adding phenylacetylene (173 µL, 1.5728 mmol, 1.05 equiv). The reaction was stirred at 85 ºC for overnight and quenched with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the crude product which was purified on silica gel (EtOAc/hexane: 1:9 to yield the corresponding product **1** (463.5 mg, 99%). (Note: For the synthesis of compound **1k**, **1l**, **1m**, **1o**, and **1p** the reactions employed 2-bromobenzophenone derivatives as the starting material. In these cases, the reactions were stirred at 85 ºC for 2 day).

(4-Methoxyphenyl)(2-(phenylethynyl)phenyl)methanone (**1**):[13] yield 463.5 mg (99%, yellow oil); IR (neat) ν_{max} 2940, 1651, 1580, 1412, 1330, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (dt, 2H, *J* = 9.0, 2.7 Hz), 7.62-7.59 (m, 1H), 7.51-7.40 (m, 3H), 7.27-7.17 (m, 3H), 7.12-7.08 (m, 2H), 6.94 (dt, 2H, *J* = 9.0, 2.7 Hz), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.6, 163.7, 142.1, 132.6, 132.4, 131.4, 130.3, 129.9, 128.3, 128.2, 128.11, 128.06, 122.7, 121.6, 113.6, 94.7, 87.5, 55.5; HRMS (ESI-TOF) calcd for $C_{22}H_{16}NaO_2$ $[M+Na]^+$ 335.1043, found 335.1048.

(2-(Hex-1-ynyl)phenyl)(phenyl)methanone (**1a**):[7] yield 250.1 mg (96%, yellow oil); IR (neat) ν_{max} 1667, 1597, 1285, 927, 755, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.80 (m, 2H), 7.58-7.53 (m, 1H), 7.49-7.36 (m, 6H), 2.10 (t, 2H, *J* = 6.9 Hz), 1.21-1.14 (m, 4H), 0.78 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 141.7, 137.3, 132.9, 132.5, 130.1, 129.9, 128.2, 128.0, 127.3, 122.5, 96.6, 78.6, 30.2, 21.7, 18.9, 13.5; HRMS (ESI-TOF) calcd for $C_{19}H_{18}NaO$ $[M+Na]^+$ 285.1250, found 285.1255.

(2-(5-Methylhex-1-ynyl)phenyl)(phenyl)methanone (**1b**) : yield 215.6 mg (82%, yellow oil); IR (neat) ν_{max} 2956, 1667, 1449, 1316, 1288, 927, 754, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.80 (m, 2H), 7.59-7.53 (m, 1H), 7.48-7.33 (m, 6H), 2.10 (t, 2H, *J* = 7.2 Hz), 1.47-1.33 (m, 1H), 1.13-1.05 (m, 2H), 0.75 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 141.8, 137.3, 133.0, 132.5, 130.1, 129.9, 128.2, 128.0, 127.3, 122.5, 96.7, 78.5, 37.0, 26.9, 22.0, 17.3; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NaO$ $[M+Na]^+$ 299.1406, found 299.1411.

(2-(3,3-Dimethylbut-1-ynyl)phenyl)(phenyl)methanone (**1c**):[7] yield 241.8 mg (97%, white solid); mp 59.2-60.0 °C; IR (neat) ν_{max} 2969, 1664,1449, 1284, 753, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.82 (m, 2H), 7.59-7.54 (m, 1H), 7.48-7.36 (m, 6H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 141.8, 137.4, 132.9, 132.2, 130.1, 129.9, 128.2, 128.1, 127.5, 122.3, 104.7, 77.3, 30.2, 27.7; HRMS (ESI-TOF) calcd for $C_{19}H_{18}NaO$ $[M+Na]^+$ 285.1250, found 285.1243.

(2-(10-Hydroxydec-1-ynyl)phenyl)(phenyl)methanone (**1d**): yield 313.9 mg (90%, colorless oil); IR (neat) ν_{max} 3402, 2929, 2856, 1663, 1288, 928, 755, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82-7.80 (m, 2H), 7.56 (tt, 1H, *J* = 7.5, 1.2 Hz), 7.49-7.33 (m, 6H), 3.63 (t, 2H, *J* = 6.6 Hz), 2.11-2.04 (m, 2H), 1.60-1.51 (m, 3H), 1.35-1.18 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 141.7, 137.3, 133.0, 132.5, 130.1, 130.0, 128.2, 128.1, 127.3, 122.5, 96.6, 78.6, 63.0, 32.7, 29.1, 29.0, 28.5, 28.1, 25.6, 19.2; HRMS (ESI-TOF) calcd for $C_{23}H_{26}NaO_2$ $[M+Na]^+$ 357.1825, found 357.1831.

Phenyl(2-(phenylethynyl)phenyl)methanone (**1e**):[7] yield 541.0 mg (97%, brown oil); IR (neat) ν_{max} 1663, 1287, 928, 753, 701, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90-7.86 (m, 2H), 7.63-7.40 (m, 7H), 7.26-7.16 (m, 3H), 7.06-7.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 141.5, 137.3, 133.1, 132.5, 131.4, 130.3, 130.2, 128.7, 128.4, 128.1, 128.0, 122.6, 121.8, 95.1, 87.4; HRMS (ESI-TOF) calcd for $C_{20}H_{15}O$ $[M+H]^+$ 283.1117, found 283.1122.

(2-((4-Methoxyphenyl)ethynyl)phenyl)(phenyl)methanone (**1f**):[14] yield 186.0 mg (56%, yellow solid); mp 90.8-93.6 °C; IR (neat) ν_{max} 2215, 1664 1511, 1288, 1249, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ δ 7.89-7.87 (m, 2H), 7.60-7.39 (m, 7H), 6.97 (d, 2H, *J* = 8.4 Hz), 6.72 (d, 2H, *J* = 8.7 Hz), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 159.7, 141.2, 137.4, 133.0, 132.9, 132.3, 130.23, 130.17, 128.6, 128.3, 127.8, 122.2, 114.7, 113.7, 95.3, 86.3, 55.2 ; HRMS (ESI-TOF) calcd for $C_{22}H_{16}NaO_2$ $[M+Na]^+$ 335.1043, found 335.1037.

(2-((4-Chlorophenyl)ethynyl)phenyl)(phenyl)methanone (**1g**): yield 174.0 mg (56%, white solid); mp 98.5-99.4°C; IR (neat) ν_{max} 1662, 1595, 1491, 1287, 1089, 927, 826, 753, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ δ 7.88-7.86 (m, 2H), 7.62-7.44 (m, 7H), 7.18 (d, 2H, *J* = 8.4 Hz), 6.97 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 141.5, 137.3, 134.4, 133.1, 132.6, 132.5, 130.3, 130.2, 129.1, 128.7, 128.41,128.37, 121.5, 121.1, 93.9, 88.4; HRMS (ESI-TOF) calcd for $C_{21}H_{13}ClNaO$ (Cl-35) $[M+Na]^+$ 339.0546, found 339.0542.

(2-((4-Fluorophenyl)ethynyl)phenyl)(phenyl)methanone (**1h**): yield 259.0 mg (89%, orange solid); mp 62.2-63.1 °C; IR (neat) ν_{max} 1665, 1596, 1508, 1288, 1232, 1156, 928, 836, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2H), 7.62-7.45 (m, 7H), 7.05-7.00 (m, 2H), 6.93-6.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 162.4 (d, J_{CF} = 248 Hz), 141.3, 137.2, 133.2 (d, J_{CF} = 8 Hz), 133.0, 132.3, 130.2, 130.0, 128.6, 128.3, 128.1, 121.5, 118.6 (d, *J* = 3 Hz), 115.2 (d, *J* = 0.3 Hz), 93.9, 87.1 (d, *J* = 1 Hz); HRMS (ESI-TOF) calcd for $C_{21}H_{13}FNaO$ $[M+Na]^+$ 323.0843, found 323.0836.

Phenyl(2-((triisopropylsilyl)ethynyl)phenyl)methanone (**1i**): yield 310.7 mg (87%, white solid); mp 45.5-46.3 °C; IR (neat) ν_{max} 2941, 2864, 2155, 1659, 1291, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.81 (m, 2H), 7.58-7.51 (m, 2H), 7.46-7.39 (m, 5H), 0.90 (d, 18H, *J* = 3.6 Hz), 0.94-0.85 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 142.4, 136.8, 133.2, 133.1, 130.3, 129.6, 128.33, 128.27, 127.6, 127.5, 104.0, 97.1, 18.4, 11.0; HRMS (ESI-TOF) calcd for $C_{24}H_{31}OSi$ $[M+H]^+$ 363.2139, found 363.2138.

(2-(Hex-1-ynyl)phenyl)(4-methoxyphenyl)methanone (**1j**):[7] yield 216.4 mg (80%, yellow oil); IR (neat) ν_{max} 2957, 2933, 1659, 1595, 1253, 1149, 929, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dt, 2H, *J* = 8.8, 2.0 Hz.), 7.46 (d, 1H, *J* = 7.2 Hz), 7.42-7.35 (m, 3H), 6.92 (dt, 2H, *J* = 8.8, 2.0 Hz),

3.86 (s, 3H), 2.14 (t, 2H, *J* = 6.8 Hz), 1.23-1.11 (m, 4H), 0.78 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 163.6, 142.2, 132.5, 132.4, 130.2, 129.5, 127.6, 127.3, 122.1, 113.4, 96.1, 78.5, 55.4, 30.3, 21.7, 19.0, 13.5 ; HRMS (ESI-TOF) calcd for $C_{20}H_{21}O_2$ $[M+H]^+$ 293.1536, found 293.1533.

(4-Chlorophenyl)(2-(hex-1-ynyl)phenyl)methanone (**1k**): yield 90.3 mg (30%, colorless oil); IR (neat) ν_{max} 2958, 2932, 2232, 1667, 1586, 1288, 1089, 927, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dt, 2H, *J* = 11.1, 2.4 Hz), 7.51-7.34 (m, 6H), 2.14-2.09 (m, 2H), 1.25-1.10 (m, 4H), 0.82-0.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 141.1, 139.3, 135.6, 132.5, 131.4, 130.1, 128.4, 127.9, 127.4, 122.3, 96.9, 78.4, 30.1, 21.6, 18.9, 13.4; HRMS (ESI-TOF) calcd for $C_{19}H_{18Cl}O$ $[M+H]^+$ 297.1041, found 297.1039.

(4-Fluorophenyl)(2-(hex-1-ynyl)phenyl)methanone (**1l**): yield 261.9 mg (84%, brown oil); IR (neat) ν_{max} 2957, 2933, 2871, 1668, 1597, 1287, 1234, 1148, 929, 849, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 -7.81 (m, 2H), 7.49-7.33 (m, 4H), 7.15-7.07 (m, 2H), 2.14-2.12 (m, 2H), 1.26-1.10 (m, 4H), 0.80 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 165.8 (d, J_{CF} = 253.3 Hz), 141.4, 133.5 (d, J_{CF} = 2.9 Hz), 132.8 (d, J_{CF} = 9.3 Hz), 132.6, 130.1, 127.9, 127.5, 122.4, 115.4 (d, J_{CF} = 21.8 Hz), 96.8, 78.5, 30.2, 21.7, 18.9, 13.5; HRMS (ESI-TOF) calcd for $C_{19}H_{18}FO$ $[M+H]^+$ 281.1336, found 281.1337.

1-(2-(Hex-1-ynyl)phenyl)-2-phenylethanone (**1m**): yield 41.4 mg (14%, yellow oil); IR (neat) ν_{max} 2960, 2869, 1723, 1601, 1453, 1276, 1261, 764, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (t, 2H, *J* = 7.8 Hz), 7.38-7.24 (m, 7H), 4.43(s, 2H), 2.45 (t, 2H, *J* = 6.6 Hz), 1.65-1.53 (m, 2H), 1.51-14.3 (m, 2H), 0.93 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 141.3, 134.5, 133.7, 130.6, 129.6, 128.4, 128.1, 127.5, 126.7, 121.9, 96.7, 79.3, 48.6, 30.5, 22.0, 19.3, 13.5; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NaO$ $[M+Na]^+$ 299.1406, found 299.1406.

1-(2-(Hex-1-ynyl)phenyl)ethanone (**1n**):[15] yield 379.4 mg (88%, brown oil); IR (neat) ν_{max} 2958, 2932, 1682, 1356, 1279, 1274, 1257, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, 1H, *J* = 7.5, 0.9 Hz), 7.48 (dd, 1H, *J* = 7.8, 0.9 Hz), 7.37 (td, 1H, *J* = 7.5, 1.5 Hz), 7.32 (td, 1H, *J* = 7.8, 1.5 Hz), 2.73 (s, 3H), 2.46 (t, 2H, *J* = 6.9 Hz),1.66-1.57 (m, 2H), 1.55-1.42 (m, 2H), 0.95 (t, 3H, *J* = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 140.7, 133.6, 130.7, 127.9, 127.2, 122.1, 96.5, 79.3, 30.2, 29.7, 21.7, 19.1, 13.2; HRMS (ESI-TOF) calcd for $C_{14}H_{16}NaO$ $[M+Na]^+$ 223.1093, found 223.1091.

(2-(Hex-1-ynyl)-4-methoxyphenyl)(phenyl)methanone (**1o**):[7] yield 295.2 mg (89%, brown oil); IR (neat) ν_{max} 2958, 2932, 2228, 1658, 1596, 1562, 1447, 1316, 1281, 1207, 1173, 1033, 923, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.77 (m, 2H), 7.56-7.51 (m, 1H), 7.45-7.40 (m, 3H), 6.98 (d, 1H, *J* = 2.7 Hz), 6.89 (dd, 1H, *J* = 8.7, 2.7 Hz), 3.85 (s, 3H), 2.12-2.08 (m, 2H), 1.23-1.19 (m, 4H), 0.82-0.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 161.0, 138.2, 133.9, 132.4, 130.9, 130.0, 128.0, 124.7, 117.4, 113.6, 96.7, 78.8, 55.4, 30.2, 21.8, 18.9, 13.5; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NaO_2$ $[M+Na]^+$ 315.1356, found 315.1348.

(2-(Hex-1-ynyl)-5-methoxyphenyl)(phenyl)methanone (**1p**): yield 302.9 mg (98%, brown oil); IR (neat) ν_{max} 2959, 1670, 1599, 1489, 1294, 1274, 1260, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.81 (m, 2H), 7.53 (tt, 1H, *J* = 7.2, 1.5 Hz), 7.45-7.36 (m, 3H), 6.96-6.93 (m, 2H), 3.80 (s, 3H), 2.08-2.03 (m, 2H), 1.17-1.11 (m, 4H), 0.78-0.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.0, 158.7, 143.0, 137.0, 133.7, 132.9, 130.0, 128.1, 116.1, 114.5, 112.9, 94.6, 78.1, 55.3, 30.2, 21.6, 18.8, 13.4; HRMS (ESI-TOF) calcd for $C_{20}H_{21}O_2$ $[M+H]^+$ 293.1536, found 293.1537.

(2-Fluoro-6-(hex-1-ynyl)phenyl)(phenyl)methanone (**1q**):[7] Yield 242.9 mg (90%, yellow oil); IR (neat): u_{max} 2960, 2931, 2354, 1670, 1598, 1484, 1292, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.59 (tt, 1H, *J* = 7.5, 1.2 Hz), 7.48-7.43 (m, 2H), 7.39-7.32 (m, 1H), 7.27-7.25 (m, 1H), 7.08 (td, 1H, *J* = 9.0, 1.2 Hz), 2.14 (t, 2H, *J* = 6. Hz), 1.27-1.07 (m, 4H), 0.75 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 159.0 (d, J_{CF} = 247 Hz), 136.8, 133.7, 130.5 (d, J_{CF} = 9 Hz), 130.0 (d, J_{CF} = 19 Hz), 129.7, 128.5, 128.0 (d, J_{CF} = 3 Hz), 124.1 (d, J_{CF} = 5 Hz), 115.2 (d, J_{CF} = 21.6 Hz), 96.9, 77.2 (d, J_{CF} = 4 Hz), 30.1, 21.6, 18.9, 13.5; HRMS (ESI-TOF) calcd for $C_{19}H_{17}FNaO$ $[M+Na]^+$ 303.1156 found 303.1165.

(4-Fluoro-2-(hex-1-ynyl)phenyl)(phenyl)methanone (**1r**):[7] yield 274.2 mg (91%, yellow oil); IR (neat) ν_{max} 2959, 2933, 1163, 1279, 748, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.77(m, 2H), 7.55 (t, 1H, *J* = 7.5 Hz), 7.45-7.40 (m, 3H), 7.15 (dd, 1H, *J* = 9.3, 2.4 Hz), 7.05 (td, 1H, *J* = 8.1, 2.7 Hz), 2.08 (t, 2H, *J* = 6.9 Hz), 1.20-1.14 (m, 4H), 0.80-0.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.2, 163.2 (d, J_{CF} = 249.3 Hz), 137.8 (d, J_{CF} = 3 Hz), 137.3, 133.0, 130.5 (d, J_{CF} = 9 Hz), 130.0, 128.2, 125.1 (d, J_{CF} = 10 Hz), 119.3 (d, J_{CF} = 23 Hz), 114.8 (d, J_{CF} = 22 Hz), 98.0, 77.7 (d, J_{CF} = 3 Hz), 30.0, 21.7, 18.9, 13.4; HRMS (ESI-TOF) calcd for $C_{19}H_{18}FO$ $[M+H]^+$ 281.1336, found 281.1333.

General procedure for the synthesis of indenone derivatives; Compound **1** (101.2 mg, 0.3240 mmol) was dissolved with dry CH_3CN (6 mL/mmol) in sealed tube and then a mixture was added H_2O (6 µL, 0.3240 mmol) and I_2 (82.2 mg, 0.3240 mmol) at room temperature. The reaction mixture was then heated to 65° C and stirred for 1 hr. The reaction was quenched with sat. $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the crude product which was purified on silica gel (EtOAc/hexane: 1:9) to yield the corresponding product **2** (73.8 mg, 73%).

3-(4-Methoxyphenyl)-2-phenyl-1*H*-inden-1-one (**2**):[3h] yield 73.8 mg (73%, red solid); mp 119.5-120.0 °C; IR (neat) ν_{max} 1704, 1605,1250, 1176, 1028, 753, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47(d, 1H, *J* = 6.6 Hz), 7.27-7.23(m, 9H), 7.20-7.09(m, 1H), 6.82(d, 2H, *J* = 8.7 Hz), 3.74 (s, 3H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 160.4, 155.2, 145.1, 133.2, 131.6, 131.1, 131.0, 130.2, 130.0, 128.9, 128.0, 127.5, 124.8, 122.7, 121.2, 114.1, 55.2; HRMS (ESI-TOF) calcd for $C_{22}H_{17}O$ $[M+H]^+$ 313.1223, found 313.1236.

2-Butyl-3-phenyl-1*H*-inden-1-one (***2a***):[6] yield 83.7 mg (79%, yellow oil); IR (neat) ν_{max} 1703, 1608, 1456,934, 775, 720, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.42 (m, 6H), 7.31-7.26 (m, 1H), 7.21-7.16 (m, 1H), 6.99 (d, 1H, *J* = 6.9 Hz), 2.34 (t, 2H, *J* = 7.5 Hz), 1.52-1.42 (m, 2H), 1.35-1.23 (m, 2H), 0.84 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 154.9, 145.8, 135.5, 133.1, 132.8, 130.9, 129.0, 128.7, 128.1, 127.7, 122.3, 120.4, 31.3, 23.0, 22.7, 13.7; HRMS (ESI-TOF) calcd for $C_{19}H_{18}NaO$ $[M+Na]^+$ 285.1250, found 285.1255.

2-Isopentyl-3-phenyl-1*H*-inden-1-one (***2b***): yield 76.2 mg (78%, yellow oil); IR (neat) ν_{max} 2955, 1705, 1609, 1456, 1364, 775, 721, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53-7.41 (m, 6H), 7.29-7.24 (m, 1H), 7.19-7.14 (m, 1H), 6.98 (d, 1H, *J* = 7.2 Hz.), 2.36-2.31 (m, 2H), 1.59-1.46 (m, 1H), 1.41-1.33 (m, 2H), 0.83 (d, 6H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 154.7, 145.8, 135.1, 133.1, 132.8, 131.0, 129.0, 128.7, 128.0, 127.7, 122.3, 120.4, 38.2, 28.1, 22.2, 21.2; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NaO$ $[M+Na]^+$ 299.1406, found 299.1415.

2-*tert*-Butyl-3-phenyl-1*H*-inden-1-one (***2c***):[6] yield 11.9 mg (17%, yellow solid); mp 108.4-109.2 °C; IR (neat) ν_{max} 2955, 1701, 1607, 1595, 1482, 1456,1325, 770, 756, 733, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-

7.36 (m, 3H), 7.27-7.12 (m, 5H), 6.50-6.47 (m, 1H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 154.1, 147.8, 141.6, 135.5, 133.4, 130.0, 128.2, 128.1,127.9, 121.8, 120.4, 33.7. 30.7, 29.7; HRMS (ESI-TOF) calcd for $C_{19}H_{19}O$ $[M+H]^+$ 263.1430, found 263.1427.

1-(2-Benzoylphenyl)-3,3-dimethylbutan-1-one (**3c**):[16] yield 52.2 mg (68%, yellow oil) ; IR (neat) ν_{max} 2954, 1668, 1314, 1262, 930, 755, 714, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.82 (m, 1H,), 7.74-7.73 (d, 2H, J = 7.2 Hz), 7.61-7.51 (m, 3H), 7.41 (t, 3H, J = 6.0 Hz), 2.75 (s, 2H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 197.8, 140.8, 139.8, 137.4, 132.8, 131.5, 129.6, 129.4, 128.8, 128.5, 128.3, 51.4, 31.5, 29.8; HRMS (ESI-TOF) calcd for $C_{19}H_{21}O_2$ $[M+H]^+$ 281.1536, found 281.1532.

2-(6-Hydroxyhexyl)-3-phenyl-1*H*-inden-1-one (**2d**): yield 70.0 mg (68%, yellow oil); IR (neat) ν_{max} 3392, 2928, 1703, 1456, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.42 (m, 6H), 7.28 (td, 1H, J = 7.8, 1.2 Hz), 7.18 (td, 1H, J = 7.4, 0.9 Hz), 6.99 (d, 1H, J = 7.2 Hz), 3.61 (t, 2H, J = 6.6 Hz), 2.33 (t, 2H, J = 7.5 Hz), 1.57-1.45 (m, 5H), 1.31-1.25 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 155.0, 145.9, 135.5, 133.1, 132.9, 131.0, 129.0, 128.7, 128.1, 127.8, 122.4, 120.5, 63.0, 32.7, 29.5, 29.2, 29.12, 29.10, 25.6, 23.2; HRMS (ESI-TOF) calcd for $C_{23}H_{27}O_2$ $[M+H]^+$ 335.2006, found 335.2011.

2,3-Diphenyl-1*H*-inden-1-one (**2e**):[3i] yield 61.2 mg (65%, red solid); mp 149.8-150.3 °C ; IR (neat) ν_{max} 1706, 1606, 1348, 752, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, 1H, J = 6.9 Hz), 7.40-7.31 (m, 6H), 7.28-7.22 (m, 6H), 7.11 (d, 1H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 155.3, 145.2, 133.4, 132.7, 132.3, 130.7, 129.9, 129.2, 128.9,128.7, 128.4, 128.0, 127.7, 122.9, 121.2; HRMS (ESI-TOF) calcd for $C_{21}H_{15}O$ $[M+H]^+$ 282.3353, found 283.1116.

2-(4-Methoxyphenyl)-3-phenyl-1*H*-inden-1-one (**2f**):[3h] yield 7.1 mg (9%, red solid); mp 132.2-125.9 °C; IR (neat) ν_{max} 2931, 1709, 1606, 1510, 1250, 1177 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, J = 6.8 Hz), 7.41-7.37 (m, 4H), 7.35 (dd, 1H, J = 7.2, 0.8 Hz), 7.28-7.22 (m, 4H), 7.11 (d, 1H, J = 7.2 Hz), 6.80 (d, 2H, J = 9.2 Hz), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0,159.2,153.8, 145.5, 133.4, 131.5, 133.0, 131.2, 130.7, 129.1, 128.8, 128.6, 128.5, 123.0, 122.9, 120.9, 113.6, 55.2; HRMS (ESI-TOF) calcd for $C_{22}H_{16}NaO_2$ $[M+Na]^+$ 335.1040, found 335.1038.

2-(2-Benzoylphenyl)-1-(4-methoxyphenyl)ethanone (4f):[12] yield 56.4 mg (65%, yellow solid); mp 91.0-98.8 °C ; IR (neat) ν_{max} 1658, 1598, 1260, 1168, 710, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, 4H, J = 8.7 Hz), 7.59-7.25 (m, 7H), 6.86 (d, 2H, J = 8.7 Hz), 4.54 (s, 2H), 3.81(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 195.6, 163.4, 138.4, 137.9, 134.9, 132.7, 131.9, 130.8, 130.5, 130.3, 130.0, 129.8, 128.2, 126.1, 113.6, 55.4, 42.6; HRMS (ESI-TOF) calcd for $C_{22}H_{19}O_3$ $[M+H]^+$ 331.1329, found 331.1329.

2-(4-Chlorophenyl)-3-phenyl-1*H*-inden-1-one (**2g**):[17] yield 50.6 mg (70%, red solid); mp 145.6-146.5 °C; IR (neat) ν_{max} 1709, 1607, 1487,1343, 1092, 775, 775, 728, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.55 (m, 1H), 7.44-7.40 (m, 3H), 7.38-7.33 (m, 3H), 7.30-7.27 (m, 1H), 7.25-7.21 (m, 4H), 7.13 (d, 1H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.1, 155.7, 145.0, 133.7, 133.5, 132.4, 131.2, 131.1, 130.6, 129.5, 129.2, 129.1, 128.9, 128.3, 123.0, 121.4; HRMS (ESI-TOF) calcd for $C_{21}H_{14}ClO$ (Cl-35) $[M+H]^+$ 317.0728, found 317.0724.

2-(4-Fluorophenyl)-3-phenyl-1*H*-inden-1-one (**2h**):[18] yield 68.5 mg (71%, orange solid); mp 115.8-116.5 °C; IR (neat) ν_{max} 1705, 1604, 1592, 1508, 1492,1343, 1225, 1159, 853, 7742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.58 (d, 1H, J = 6.6 Hz), 7.44-7.35 (m, 6H), 7.31-7.21 (m, 3H), 7.13 (d, 1H, J = 6.9 Hz), 6.99-6.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4, 162.3 (d, J_{CF} = 247 Hz), 155.3, 145.1, 133.5, 132.6, 131.7 (d, J_{CF} = 8 Hz), 131.3, 130.6, 129.4, 129.0, 128.9, 128.4, 126.7 (d, J_{CF} = 3.5 Hz), 123.0, 121.3, 115.2 (d, J_{CF} = 21 Hz); HRMS (ESI-TOF) calcd for $C_{21}H_{14}FO$ $[M+H]^+$ 301.1023, found 301.1026.

1-(2-Benzoylphenyl)ethanone (**3i**):[19] yield 52.4 mg (86%, white solid); mp 97.6-98.1 °C; IR (neat) ν_{max} 1666, 1596, 1264, 929, 760, 707, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.88 (m, 1H), 7.76-7.73 (m, 2H), 7.64-7.51 (m, 3H), 7.44-7.39 (m, 3H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.3, 197.6, 140.7, 137.4, 137.1, 132.8, 132.1, 129.6, 129.2, 129.1, 128.3, 128.1, 27.3; HRMS (ESI-TOF) calcd for $C_{15}H_{13}O_2$ $[M+H]^+$ 225.0910, found 225.0911.

2-Butyl-3-(4-methoxyphenyl)-1*H*-inden-1-one (**2j**):[4] yield 66.3 mg (78% yellow solid); mp 55.9-58.7 °C; IR (neat) ν_{max} 2956, 2927, 1702, 1607, 1509, 1250, 1176, 1031 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.46-7.39 (m, 3H), 7.29 (t, 1H, J = 7.8 Hz), 7.19 (t, 1H, J = 6.9 Hz), 7.06-7.02 (m, 3H), 3.89 (s, 3H), 2.35 (t, 2H, J = 7.5 Hz), 1.59-1.43 (m, 2H), 1.37-1.25 (m, 2H), 0.86 (t, 3H, J = 7.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 160.2, 154.8, 145.9, 134.8, 133.0, 131.3, 129.3, 128.0, 125.2, 122.2, 120.4, 114.2, 55.3, 31.4, 23.1, 22.8, 13.8; HRMS (ESI-TOF) calcd for $C_{20}H_{21}O_2$ $[M+H]^+$ 293.1536, found 293.1536.

2-Butyl-3-(4-chlorophenyl)-1*H*-inden-1-one (**2k**):[4] yield 38.8 mg (67%, yellow oil); IR (neat) ν_{max} 2957, 2929, 1705, 1606, 1490, 1457, 1091, 727 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)δ 7.51-7.45 (m, 3H), 7.40-7.37 (m, 2H), 7.32-7.17 (m, 2H), 6.94 (d, 1H, J = 7.2 Hz), 2.32 (t, 2H, J = 7.5 Hz), 1.48-1.40 (m, 2H), 1.35-1.23 (m, 2H), 0.84 (t, 3H, J = 7.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 153.6, 145.5, 135.9, 135.0, 133.2, 131.3, 131.0, 129.2, 129.1, 128.3, 122.6, 120.2, 31.3, 23.0, 22.8, 13.7; HRMS (ESI-TOF) calcd for $C_{19}H_{17}NaO$ (Cl-35) $[M+Na]^+$ 319.0860, found 319.0853.

2-Butyl-3-(4-fluorophenyl)-1*H*-inden-1-one (**2l**): yield 72.2 mg (74%, yellow oil); IR (neat) ν_{max} 2957, 2926, 2860, 1705, 1601, 1508, 1456, 1225, 1157,853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.37-7.30 (m, 3H), 7.19 (td, 1H, J = 7.8, 1.2 Hz), 7.15-7.07 (m, 3H), 6.86 (d, 1H, J = 7.2 Hz), 2.23 (t, 2H, J = 7.5 Hz), 1.42-1.32 (m, 2H), 1.26-1.13 (m, 2H), 0.75 (t, 3H, J = 7.2);^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 162.9 (d, J_{CF} = 248 Hz), 153.9, 145.7, 135.6, 133.1, 130.8, 129.7 (d, J_{CF} = 8 Hz), 128.7 (d, J_{CF} = 3.4 Hz), 128.2, 122.4, 120.2, 115.9 (d, J_{CF} = 21 Hz), 31.3, 22.9, 22.7, 13.7; HRMS (ESI-TOF) calcd for $C_{19}H_{18}FO$ $[M+H]^+$281.1336, found 281.1334.

3-Pentyl-2-phenyl-1*H*-inden-1-one (**2m'**): yield 32.3 mg (39%, orange oil); IR (neat) ν_{max} 2956, 2930, 2865, 1710, 1602, 1457, 756, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.49 (d, 1H, J = 6.9 Hz), 7.45-7.31 (m, 6H), 7.27-7.22 (m, 1H), 7.17 (d, 1H, J = 7.2 Hz), 2.72-2.66 (m, 2H), 1.74-1.61 (m, 2H), 1.44-1.28 (m, 4H), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 158.9, 145.2, 133.5, 133.31, 131.34, 130.8, 129.3, 128.7, 128.3, 127.7, 122.3, 119.9, 32.0, 27.8, 26.7, 22.3, 13.9; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NaO$ $[M+Na]^+$ 299.1406, found 299.1413.

2-Butyl-3-methyl-1*H*-inden-1-one (**2n**): yield 24.3 mg (23%, yellow oil); IR (neat) ν_{max} 2960, 2940, 2869, 2333, 1715, 1671, 1598, 1316, 1294, 1239, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ δ 7.37-7.29 (m, 2H), 7.18-7.13 (m, 1H), 7.00 (d, 1H, J = 7.2 Hz), 2.27 (t, 2H, J = 7.2 Hz), 2.11 (s, 3H), 1.49-1.25 (m, 4H), 0.93-0.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 153.7, 135.2, 146.3, 133.2, 130.9, 128.0, 121.5, 118.5, 31.2, 22.6, 22.4, 13.9, 11.4; HRMS (ESI-TOF) calcd for $C_{14}H_{17}O$ $[M+H]^+$ 201.1274, found 201.1270.

2-Butyl-6-methoxy-3-phenyl-1*H*-inden-1-one (**2o**): yield 51.4 mg (49%, yellow oil); IR (neat) ν_{max} 2956, 2932, 2859, 1702, 1478, 1430, 1279, 1221, 1024; cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 5H), 7.08 (d, 1H, *J* = 2.4 Hz), 6.88 (d, 1H, *J* = 7.8 Hz), 6.71 (dd, 1H, *J* = 8.1, 2.4 Hz), 3.81 (s, 3H), 2.30 (t, 2H, *J* = 7.5 Hz), 1.51-1.41 (m, 2H), 1.35-1.22 (m, 2H), 0.84 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 160.4, 155.9, 137.6, 134.3, 133.1, 129.0, 128.7, 127.7, 121.2, 115.7, 110.4, 55.7, 31.4, 23.0, 22.7, 13.7; HRMS (ESI-TOF) calcd for $C_{20}H_{21}O_2$ $[M+H]^+$ 293.1536, found 293.1529.

2-Butyl-5-methoxy-3-phenyl-1*H*-inden-1-one (**2p**): yield 69.4 mg (72%, orange solid); mp 56.6-61.4 °C; IR (neat) ν_{max} 2957, 2861, 1700, 1594, 1473, 1366, 1219, 1099, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52-7.40 (m, 6H), 6.58-6.55 (m, 2H), 3.79 (s, 3H), 2.33 (t, 2H, *J* =7.8 Hz), 1.52-1.41 (m, 2H), 1.34-1.22 (m, 2H, *J* = 7.2 Hz), 0.83 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 164.2, 152.7, 148.6, 137.2, 132.8, 128.8, 128.7, 127.8, 124.2, 123.7, 109.8, 109.3, 55.6, 31.3, 22.7, 23.1, 13.7; HRMS (ESI-TOF) calcd for $C_{20}H_{20}NaO_2$ $[M+Na]^+$ 315.1356, found 315.1354.

2-Butyl-4-fluoro-3-phenyl-1*H*-inden-1-one (**2q**): yield 56.8 mg (56%, yellow oil)); IR (neat) ν_{max} 2957, 2927, 2858, 1709, 1607, 1469, 1238, 1008, 759, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-7.41 (m, 5H), 7.32-7.26 (m, 1H), 7.22-7.15 (m, 1H), 7.03-6.96 (m,1H), 2.27 (t, 2H, *J* = 7.8 Hz), 1.49-1.39 (m, 2H), 1.33-1.21 (m, 2H), 0.82 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8 (d, J_{CF} = 2 Hz) 155.5 (d, J_{CF} = 254 Hz), 153.8 (d, J_{CF} = 3 Hz), 136.7 (d, J_{CF} = 3 Hz), 133.7 (d, J_{CF} = 3 Hz), 133.6, 130.5 (d, J_{CF} = 7 Hz), 128.9, 128.3, 128.1, 127.6 (d, J_{CF} = 2 Hz), 123.0 (d, J_{CF} = 23 Hz), 118.5 (d, J_{CF} = 3 Hz), 31.3, 22.8 , 22.7, 13.7; HRMS (ESI-TOF) calcd for $C_{19}H_{18}FO$ $[M+H]^+$ 281.1336, found 281.1340.

2-Butyl-6-fluoro-3-phenyl-1*H*-inden-1-one one (**2r**): yield 64.1mg (56%, orange oil); IR (neat) ν_{max} 2930, 1708, 1473, 109, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.41 (m, 5H), 7.18-7.16 (m, 1H), 6.94-6.91 (m, 2H), 2.35-2.29 (t, 2H, *J* = 7.5 Hz), 1.51 (m, 2H), 1.35-1.23 (m, 2H), 0.86-0.81 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 163.2 (d, J_{CF} = 248 Hz), 155.1 (d, J_{CF} = 2 Hz), 141.2 (d, J_{CF} = 4 Hz), 135.7 (d, J_{CF} = 5 Hz), 133.3 (d, J_{CF} = 7 Hz), 132.6, 129.3, 128.8, 127.6, 121.4 (d, J_{CF} = 8 Hz), 118.1 (d, J_{CF} = 23 Hz), 111.1 (d, J_{CF} = 25 Hz), 31.3, 23.1, 22.7, 13.7; HRMS (ESI-TOF) calcd for $C_{19}H_{18}FO$ $[M+H]^+$ 281.1336, found 281.133 9.

Labeling experiment with $H_2{}^{18}O$ for the synthesis of compound 2a-^{18}O: Compound **2a** (83.0 mg, 0.3163 mmol) was dissolved with dry CH_3CN (6 mL/mmol) in sealed tube and then a mixture was added $H_2{}^{18}O$ (6 µL, 0. 0.3163 mmol) and I_2 (80.3 mg, 0.3163 mmol) at room temperature. The reaction mixture was then heated to 65° C and stirred for 1 hr. The reaction was quenched with sat. $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the crude product. This crude product submitted for HRMS measurement. Ratio of Compound **2a**:**2a-^{18}O**: = 1:2.5.

Compound **1** (149.7 mg, 0.5638 mmol) was dissolved with dry CH_3CN (6 mL/mmol) in sealed tube and then a mixture was added $H_2{}^{18}O$ (11 µL, 0. 0.5638 mmol) and I_2 (143.0 mg, 0.5638 mmol) at room temperature. The reaction mixture was then heated to 65° C and stirred for 1 hr. The reaction was quenched with sat. $Na_2S_2O_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide the crude product which was purified on silica gel (EtOAc/hexane: 1:9) to yield the corresponding product **2a-^{18}O** as a yellow oil (104.6 mg, 70%). IR (neat) ν_{max} 2956, 1675, 1456, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.42 (m, 6H), 7.31-7.26 (m, 1H), 7.21-7.16 (m, 1H), 6.99 (d, 1H, *J* = 6.9 Hz), 2.34 (t, 2H, *J* = 7.5 Hz), 1.52-1.42 (m, 2H), 1.35-1.23 (m, 2H), 0.84 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 154.9, 145.8, 135.5, 133.1, 132.8, 130.9, 129.0, 128.7, 128.1, 127.7, 122.3, 120.4, 31.3, 23.0, 22.7, 13.7; HRMS (ESI-TOF) calcd for $C_{19}H_{19}O$ $[M+H]^+$ (O-18) 265.1473, found 26.1471.

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Keywords: indenone • iodine • *ortho*-alkynylarylketones • cyclization• metal-free

[1] a) H. Kim, I. Yang, S.-Y. Ryu, D. H. Won, A. G. Giri, W. Wang, H. Choi, J. Chin, D. Hahn, E. Kim, C. Han, J. Lee, S.-J. Nam, W.-K. Ho and H. Kang, *J. Nat. Prod.* **2015**, *78*, 363-367; b) L. M. X. Lopes, M. Yoshida and O. R. Gottlieb, *Phytochemistry* **1984**, *23*, 2021-2024.

[2] a) J. H. Ahn, M. S. Shin, S. H. Jung, S. K. Kang, K. R. Kim, S. D. Rhee, W. H. Jung, S. D. Yang, S. J. Kim, J. R. Woo, J. H. Lee, H. G. Cheon and S. S. Kim, *J. Med. Chem.* **2006**, *49*, 4781-4784; b) A. Morrell, M. Placzek, S. Parmley, B. Grella, S. Antony, Y. Pommier and M. Cushman, *J. Med. Chem.* **2007**, *50*, 4388-4404.

[3] a) R. C. Larock and M. J. Doty, *J. Org. Chem.* **1993**, *58*, 4579-4583; b) H Tsukamoto and Y. Kondo, *Org. Lett.* **2007**, *9*, 4227-4230. c) Y. Harada, J. Nakanishi, H. Fujihara, M. Tobisu, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 5766-5771; d) T. Morimoto, K. Yamasaki, A. Hirano, K. Tsutsumi, N. Kagawa, K. Kakiuchi, Y. Harada, Y. Fukumoto, N. Chatani and T. Nishioka, *Org. Lett.* **2009**, *11*, 1777-1780; e) T. Miura and M. Murakami, *Org. Lett.* **2005**, *7*, 3339-3341; f) J. Zhang, F. Yang and Y. Wu, *Appl. Organometal. Chem*, **2011**, *25*, 675-679. g) L. Kong, X. Yang, X. Zhou, S. Yu and X. Li, *Org. Chem. Front.* **2016**, *3*, 813-816. h) M. Ueda, T. Ueno, Y. Suyama and I. Ryu, *Chem. Commun.* **2016**, *52*, 13237-13240. i) X. Yan, S. Zou, P. Zhaoa and C. XiY, *Chem. Commun.* **2014**, *50*, 2775-2777. j) B.-J. Li, H.-Y. Wang, Q.-L. Zhu and Z.-J. Shi, *Angew. Chem. Int. Ed.* **2012**, *51*, 3948–3952.

[4] C. Wang, J. Yang, X. Cheng, E. Li, Y. Li, *Tetrahedron Lett.* **2012**, *53*, 4402-4404.

[5] M. E. Domaradzki, Y. Long, Z. She, X. Liu, G. Zhang and Y. Chen, *J. Org. Chem.* **2014**, *79*, 4799-4808.

[6] N. Nagahora, T. Wasano, K. Nozaki, T. Ogawa, S. Nishijima, D. Motomatsu, K. Shioji and K. Okuma, *Eur. J. Org. Chem.* **2014**, 1423-1430.

[7] B. Akkachairin, J. Tummatorn, N. Supantanapong, P. Nimnual, C. Thongsornkleeb and S. Ruchirawat, *J. Org. Chem.* **2017**, *82*, 3727-3740.

[8] a) K. Sakthivel and K. Srinivasan, *Eur. J. Org. Chem.* **2011**, 2781-2784; b) K. Sakthivel and K. Srinivasan, *Eur. J. Org. Chem.* **2013**, 3386-3396.

[9] a) Y.-M. Ren, C. Cai and R.-C. Yang, *RSC. Adv.* **2013**, *3*, 7182-7204; b) M. S. Yusubova and V. V. Zhdankin, *Resource-Efficient Technologies*, **2015**, *1*, 49-67. c) H. Togo and S. Iida, *Synlett* **2006**, 2159-2175. d) S. U. Tekale, S. S. Kauthale, S. A. Dake, S. R. Sarda and R. P. Pawar, *Curr. Org. Chem.*, **2012**, *16*, 1485-1501. e) A. K. Banerjee, W. Vera, H. Mora, M. S. Laya, L. Bedoya and E. V. Cabrera, *J. Sci. Ind. Res.* **2006**, *65*, 299-308.

[10] a) M. Byrn and M. Calvin, *J. Am. Chem. Soc.* **1966**, *88*, 1916-1922. b) Y. Hayashi, T. Mukaiyama, M. Benohoud, N. R. Gupta, T. Ono and S. Toda. *Chem. Eur. J.* **2016**, *22*, 5868-5872.

[11] a) J. Jeong, D. Ray and C. H. Oh, *Synlett* **2012**, *23*, 897-902. b) Z. Cao, H. Zhu, X. Meng, L. Tian, G. Chen, X. Sun and J. You, *J. Org. Chem.* **2016**, *81*, 12401-12407. c) A. Das, H.-K. Chang, C.-H. Yang and R.-S. Liu, *Org. Lett.* **2008**, *10*, 4061-4064. d) A. Das, H.-H. Liao and R.-S. Liu, *J. Org. Chem.* **2007**, *72*, 9214-9218.
[12] S. Perveen, Z. Zhao, G. Zhang, J. Liu, M. Anwar and X. Fang, *Org. Lett.* **2017**, *19*, 2470-2473.
[13] M. Terada, F. Li and Y. Toda, *Angew. Chem. Int. Ed.* **2014**, *53*, 235-239.
[14] M. E. Domaradzki, Y. Long, Z. She, X. Liu, G. Zhang and Y. Chen, *J. Org. Chem.* **2015**, *80*, 11360-11368.
[15] T. Miao, Z.-Y. Tian, Y.-M. He, F. Chen, Y. Chen, Z.-X. Yu and Q.-H. Fan, *Angew. Chem. Int. Ed.* **2017**, *56*, 4135-4139.
[16] K. Gaoa and N. Yoshikai, *Chem. Commun*. **201**2, *48*, 4305-4307.
[17] J. Feng, G. Lu, M. Lv and C. Cai, *J. Org. Chem.,* **2014**, 79, 10561-10567
[18] X. Yu, Y. Duan, W. Guo, T. Wang, Q. Xie, S. Wu, C. Jiang, Z. Fan, J. Wang and G. Liu, *Organometallics*, **2017**, *36*, 1027-1034.
[19] P.-Y. Lee, P. Liang and W.-Y. Yu, *Org. Lett.* **2017**, *19*, 2082-2085.

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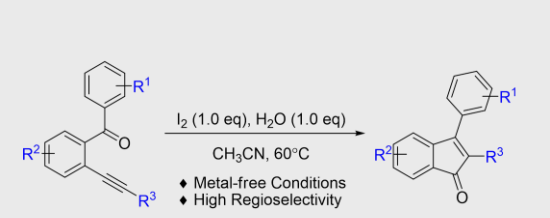
FULL PAPER

The utility of *ortho*-alkynylarylketones in the synthesis of indenone derivatives using molecular iodine-promoted cyclization has been demonstrated. This strategy provided a convenient and easy control of the regioselectivity to obtain indenone products with a broad range of substituents in moderate to good yields.



Iodine-promoted cyclization

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Iodine-mediated cyclization of *ortho*-alkynylarylketones for the synthesis of indenone derivatives