DOI: 10.1002/ejoc.200900809

Highly Selective Electrophile-Induced Cascade Reactions between *o*-Alkynylbenzaldehydes and Styrene Oxides Leading to the Formation of 1-Naphthyl Ketones

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Keywords: Alkynes / Enols / Cycloaddition / Domino reactions / Ketones

An efficient method for the synthesis of naphthalene derivatives through reaction of *o*-alkynylbenzaldehydes and styrene oxides in the presence of molecular iodine was developed. The reaction involves Meinwald rearrangement of styrene oxides to form the corresponding aryl acetaldehydes. The enol forms of aryl acetaldehydes might undergo [4+2] benzannulation reactions with iodinated benzopyrilium ions, formed in situ from *o*-alkynylbenzaldehydes and iodine, to afford 1-naphthyl ketones. The reaction was found to be highly selective, and of two possible products, only one was formed. Mechanistic aspects are discussed.

Introduction

The electrophilic cyclization of alkynes has proven to be an efficient method for constructing a variety of carbocycles and heterocycles.[1] These reactions are generally considered to proceed through intramolecular attack of protected or naked carbon,[2] nitrogen,[3] oxygen,[4] sulfur,[5] selenium,[6] or Ar-H[7] moieties to electrophile-coordinated alkynes. Recently, the electrophile-induced cascade[8] cyclization has become a highly fascinating area of study, because those reactions offer the opportunity to access highly functionalized final products from simple starting materials. The majority of the reported cascade reactions, trigged by the coordination of alkynes to electrophiles, involve the use of a single starting material containing an alkyne functionality tethered to one more functional group.[9] Upon treatment with electrophiles, coordination to the alkyne initiates a reaction sequence leading to various products. Much more appealing strategies would involve the use of alkynes and nucleophiles/functional groups present in two different substrates.

Recently, Barluenga reported the [4+2] benzannulation between the iodinated isobenzopyrilium ion, generated in situ from alkynal and IPy_2BF_4/HBF_4, with alkenes and alkynes for the synthesis of naphthalenes.[10] The subsequent paper from the same research group applied this strategy for the synthesis of indoles and benzofurans.[11] Pioneering work from the laboratory of Larock revealed that simple molecular iodine can equally be used to synthesize naphthalenes from alkynals and alkenes/alkynes.[12] It should be noted that all these processes are complimentary to the metal-catalyzed process.[13]

As a part of our continued interest in alkyne activation,[14] we considered the process shown in Figure 1 as a potentially useful metal-free approach for the synthesis of naphthalenes. We envisioned that in the presence of iodine, styrene oxides would undergo Meinwald rearrangement[15] to form enols **6**, which after [4+2] cycloaddition[16] with in situ generated **5**, followed by loss of water would produce **7**.[17] Intermediate **7**, thus formed, may either undergo extrusion of iodine or a retro Diels–Alder reaction to produce 1-naphthyl ketones **3** or iodonaphthalenes **4**, respectively.[11a] Notably, the substituted naphthalenes[18] are found in several biologically important compounds[19] and exhibit promising electronic and optical properties.[20]

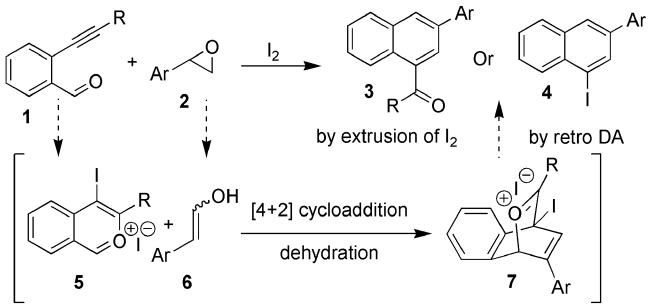

Figure 1. Concept of electrophile-induced [4+2] benzannulation.

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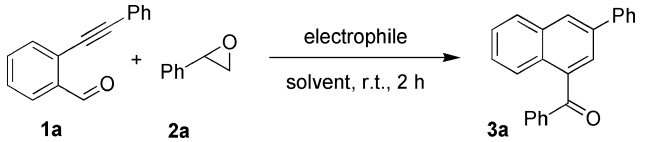
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900809.

Results and Discussion

We first allowed *o*-alkynylbenzaldehyde **1a** to react with styrene oxide (**2a**; 1.2 equiv.) and iodine (1.2 equiv.) in dichloroethane (DCE; Table 1, Entry 1). To our pleasure, 1-naphthyl ketone **3a** was obtained in a 30% yield. When THF was used, the yield increased to 80% (Table 1, Entry 2). When **1a** was treated with **2a** in the presence of iodine (1.5 equiv.), **3a** was obtained in 94% yield (Table 1, Entry 3). The use of 4 Å molecular sieves (MS) as an additive suppressed the formation of product (Table 1, Entry 4). This observation indicated that the presence of water is necessary. A small amount of HI may be generated by the reaction between I_2 and H_2O, which might be responsible for the enolization of phenyl acetaldehyde. The addition of carbonate bases such as $NaHCO_3$, K_2CO_3, and Na_2CO_3 hampers the reaction (Table 1, Entry 5–7). The strong electrophilic reagents ICl and NIS were also examined and proved unsatisfactory (Table 1, Entries 8 and 9). The reaction is very sensitive to solvent, and of the various solvents screened (CH_3CN, toluene, MeOH) THF proved to be the best. It is surprising to note that in all cases only **3a** was obtained and no formation of **4** (Ar = Ph) was detected as judged by ^1H NMR spectroscopic analysis of the crude reaction mixtures. This observation is in marked contrast to previously reported IPy_2BF_4/HBF_4-mediated benzannulation reactions, wherein compounds **4** were obtained exclusively from an intermediate similar to **7**.[11a]

Table 1. Selected screening of the reaction conditions.[a]



1a 2a 3a

Entry	Electrophile (equiv.)	Additives (equiv.)	Solvent	Yield [%][b]
1	I_2 (1.2)	–	DCE	30
2	I_2 (1.2)	–	THF	80
3	I_2 (1.5)	–	THF	94
4	I_2 (1.5)	4 Å MS	THF	10
5	I_2 (1.5)	$NaHCO_3$ (1)	THF	–[c]
6	I_2 (1.5)	K_2CO_3 (1)	THF	–[c]
7	I_2 (1.5)	Na_2CO_3 (1)	THF	30[c]
8	NIS (1.5)	–	THF	–[d]
9	ICl (1.5)	–	THF	–[d,e]

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (1.2 equiv.), electrophiles and additives (wherever specified), r.t., 2 h. [b] Isolated yields. [c] Alkynal **1a** was recovered in 70, 62, and 30% yield for Entries 5, 6, and 7, respectively. [d] Starting material **1a** was consumed; however, the desired product could not be isolated. [e] The reaction was run at –78 °C then brought to r.t. and stirred for 2 h.

As the optimal reaction conditions had become clear, we then investigated the generality of the reaction by using various *o*-alkynylbenzaldehydes with styrene oxides. The results are summarized in Table 2. Treatment of **1a** with 2-(4-methylphenyl)oxirane (**2b**) under the standard conditions gave desired product **3b** in 90% yield (Table 2, Entry 1). The reaction of halo-substituted epoxides **2c**–**e** with **1a** also proceeded smoothly to produce **3c**, **3d**, and **3e** in 70, 65, and 90% yield, respectively (Table 2, Entries 2–4). Styrene oxides **2f**, **2g**, and **2h** bearing electron-donating substituents in the aromatic ring gave products **3f**, **3g**, and **3h** in good yields (Table 2, Entries 5–7). However, styrene oxides, bearing strong electron-donating (cf. **2i**) and strong electron-withdrawing (cf. **2j**) substituents on the aromatic ring proved to be inert (Table 2, Entries 8 and 9). We assumed that in the case of **2i** the presence of the electron-donating $–NMe_2$ substituent may hamper the enolization of the resulting aldehyde, and substrate **2j** containing the electron-withdrawing $–NO_2$ group might be reluctant to undergo Meinwald rearrangement. Treatment of 2-(1-octynyl)benzaldehyde (**1b**) and 2-(1-hexynyl)benzaldehyde (**1c**) with various styrene oxides gave good to acceptable yields of 1-naphthyl ketones **3k**–**n** (Table 2, Entries 10–13). Substrate **1d** also reacted well with epoxides **2a** and **2h** to give the corresponding naphthyl ketones **3o** and **3p**, respectively, in good yields (Table 2, Entries 14 and 15). The reaction is very sensitive to the electronic nature of the R group in the *o*-alkynylbenzaldehydes. Substrates **1e** and **1f** bearing –OH and –OMe groups, respectively, in the *meta* position reacted well with **2a**/**2c** to give desired products **3q**–**s** in high yields (Table 2, Entries 16–18). However, in case of **1g** bearing an –OMe group in the *para* position, pure product **3t** could not isolated (Table 2, Entry 19).

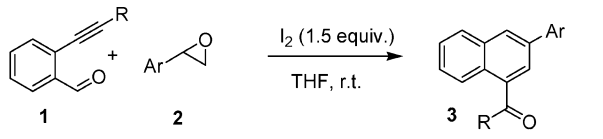
The presence of an electron-withdrawing group had no impact on the yield of the reaction and product **3u** was obtained from **1h** in 59% yield (Table 2, Entry 20). It should be noted that this reaction is limited only to styrene oxides. The epoxide derived from 1-octene did not undergo the present reaction.

A plausible mechanism is depicted in Figure 2. As shown in cycle A, the attack of the aldehydic oxygen to the I^+-coordinated alkyne (cf. **8**) leads to benzopyrilium cation **5**. Benzopyrilium cation **5** would undergo [4+2] cycloaddition with **6**, generated in situ from **2a** (vide infra), to produce intermediate **9**. Intermediate **9** may undergo spontaneous dehydration to produce **7**. The extrusion of I_2 from **7** would give **3a**. It is interesting to note that iodonaphthalenes **4** were not obtained by retro [4+2] cycloaddition in intermediate **7**.[21] The formation of **6** from styrene oxide (**1a**) is explained in cycle B. The coordination of iodine to the oxygen atom of **1a** would lead to the formation of intermediate **10** and then subsequently **11**. The rearrangement as shown in **11**, might produce **6** with the regeneration of iodine. Thus, the whole process can be considered as formally catalytic, although an excess amount of iodine was used.

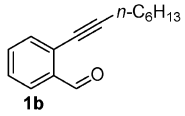
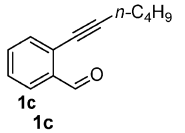
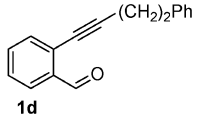
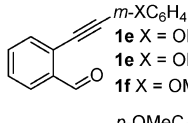
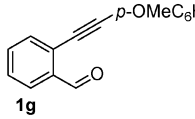
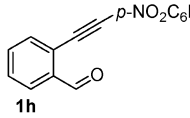
To gain some insight into the mechanism, we treated **1a** with commercially available 1-phenyl acetaldehyde (**6b**) under standard conditions [Equation (1)]. Indeed, product **3a** was isolated in 90% yield.

We have also explored a metal-catalyzed version of this process. The reaction of **1a** with **2a** in the presence of $Cu(OTf)_2$ (10 mol-%) at 80 °C in either THF or DCE afforded a mixture of **3a** and **13** in variable ratios [Equation (2)].[17]

Table 2. Reaction of *o*-alkynylbenzaldehydes with styrene oxides.[a]



1 2 3

Entry	1	2	3	*T* [h]	Yield[b] [%]
1	**1a** R = Ph	**2b** Ar = *p*-MeC_6H_4	**3b**	2	90
2	**1a** R = Ph	**2c** Ar = *p*-ClC_6H_4	**3c**	2	70
3	**1a** R = Ph	**2d** Ar = *p*-BrC_6H_4	**3d**	2	65
4	**1a** R = Ph	**2e** Ar = *p*-FC_6H_4	**3e**	2	90
5	**1a** R = Ph	**2f** Ar = *p*-$OMeC_6H_4$	**3f**	2	74
6	**1a** R = Ph	**2g** Ar = *m*-$OMeC_6H_4$	**3g**	2	78
7	**1a** R = Ph	**2h** Ar = *m*-$OPhC_6H_4$	**3h**	2	61
8	**1a** R = Ph	**2i** Ar = *p*-$NMe_2C_6H_4$	**3i**	2	–[c]
9	**1a** R = Ph	**2j** Ar = *p*-$NO_2C_6H_4$	**3j**	2	–[c]
10	 **1b**	**2a**	**3k**	3	72
11	**1b**	**2g**	**3l**	3	56
12	 **1c**	**2a**	**3m**	4	78
13	**1c**	**2d**	**3n**	3	50
14	 **1d**	**2a**	**3o**	3	75
15	**1d**	**2h**	**3p**	4	78
16	 **1e** X = OH	**2a**	**3q**	3	80
17	**1e** X = OH	**2c**	**3r**	3	70
18	**1f** X = OMe	**2a**	**3s**	3	92
19	 **1g**	**2a**	**3t**	6	–[d]
20	 **1h**	**2a**	**3u**	3	59

[a] Reaction conditions: **1** (0.24 mmol), **2** (0.29 mmol), iodine (1.5 equiv.), THF (0.1 M), r.t. [b] Isolated yields. [c] Starting material **1a** was consumed; however, the desired product could not be isolated. [d] The desired product could not be isolated in pure form.

Although a variety of iodine-mediated benzannulation reactions between *o*-alkynylbenzaldehydes and electron-rich alkenes and alkynes have been developed previously, our method has useful and unique features: (1) The process avoids the use of the extremely moisture-sensitive $AuBr_3$ catalyst and employs simple molecular iodine and, therefore, may prove complimentary to known processes.[17] (2) The process makes use of styrene oxides in place of aryl

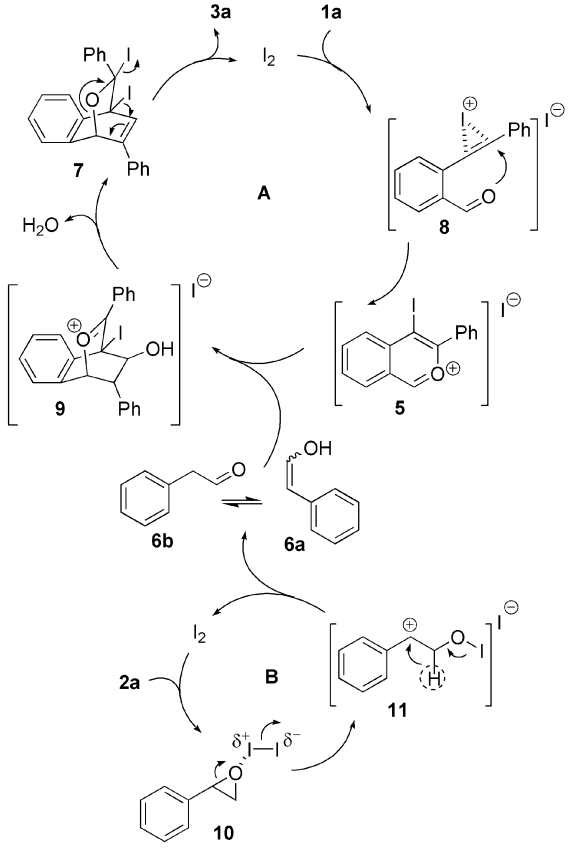
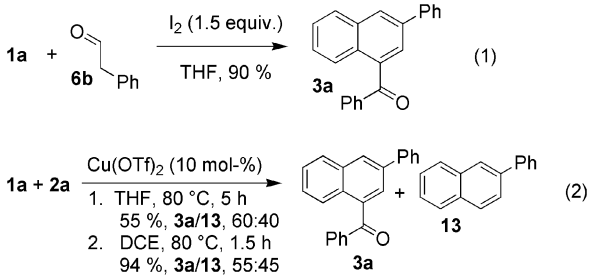


Figure 2. The plausible mechanism.



acetaldehydes, which are rather unstable. (3) The process is completely chemoselective and only 1-naphthyl ketones were obtained; iodonaphthalenes were not obtained.[11a] (4) Electrophile-mediated reactions have been reported to give 1-naphthyl ketones of type **14**;[11–13] however, the present method produces only regioisomers of type **3** (Figure 3).

Figure 3. 1-Naphthyl ketones of types **3** and **14**.

Conclusions

An efficient metal-free process for the synthesis of 1-naphthyl ketones was developed by the cascade reaction be-

tween *o*-alkynylbenzaldehydes and styrene oxides in the presence of molecular iodine. Interestingly, the reaction is completely selective and only 1-naphthyl ketones were obtained. The tolerance of halo substituents is particularly noteworthy, because the resulting naphthalenes can be further functionalized using well-known organopalladium chemistry.

Experimental Section

General Methods: All reactions were carried out in oven- or flame-dried vials with magnetic stirring under a nitrogen atmosphere. Dried solvents and liquid reagents were transferred by oven-dried syringes or hypodermic syringe cooled to ambient temperature in a desiccators. All experiments were monitored by analytical thin-layer chromatography (TLC). TLC was performed on precoated plates, Merck 60 F_{254}. After elution, the plates were visualized under UV illumination at 254 nm for UV-active materials. Further visualization was achieved by staining with $KMnO_4$ and charring on a hot plate. Solvents were removed in vacuo under ca. 30 Torr and heated with a water bath at 35 °C. Silica gel finer than 200 mesh was used for flash column chromatography. Columns were packed as slurries of silica gel in hexane and equilibrated with the appropriate solvent/solvent mixture prior to use. The compounds were loaded neat or as a concentrated solution by using the appropriate solvent system. The elution was assisted by applying pressure with an air pump. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Melting points are uncorrected. Infrared spectra were recorded with a Thermo Nicolet Nexus 670 spectrometer. IR spectra were recorded as neat liquids or KBr pellets. NMR spectra were recorded with 300 and 400 MHz spectrometers in appropriate solvents by using TMS as internal standard or the solvent signals as secondary standards. ^{13}C NMR spectra were recorded with a 75 MHz spectrometer. High-resolution mass spectra were obtained by using ESI-QTOF mass spectrometry.

Preparation of 3a as a Representative Example: To a THF (2.0 mL, 0.1 M) solution of **1a** (50 mg, 0.24 mmol) and **2a** (35 mg, 0.29 mmol) in 2.5-mL screw-cap vial was added molecular iodine (92 mg, 1.5 equiv.) under a nitrogen atmosphere. The mixture was stirred at room temperature for 2 h. Then, the reaction mixture was diluted with ethyl acetate (10 mL), and a saturated solution of sodium thiosulfate (10 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash silica gel column chromatography (hexane) to obtain **3a** (70 mg, 94%) as a pure compound.

Phenyl(3-phenyl-1-naphthyl)methanone (3a):[17a] Yield: 70 mg, 94%; yellow oil; R_f = 0.40 (**1a**, R_f = 0.45) (hexane/EtOAc, 95:5). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 8.02 (d, J = 8.8 Hz, 1 H), 7.93–7.90 (m, 2 H), 7.88 (d, J = 1.4 Hz, 1 H), 7.79 (d, J = 1.4 Hz, 1 H), 7.64 (d, J = 8.0 Hz, 2 H), 7.56 (t, J = 7.32 Hz, 1 H), 7.51–7.47 (m, 1 H), 7.46–7.42 (m, 5 H), 7.32 (t, J = 7.35 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.8, 140.1, 138.3, 137.2, 134.1, 133.1, 130.4, 130.2, 129.7, 128.9, 128.6, 128.5, 128.4, 127.6, 127.3, 127.0, 126.9, 126.8, 125.7 ppm. IR (film): $\tilde{\nu}$ = 3057, 1660, 1591, 1497, 1449, 1313, 1253, 1209, 1169, 933, 813, 892, 762, 698 cm^{-1}. HRMS: calcd. for $C_{23}H_{17}O$ $[M + H]^+$ 309.1280; found 309.1269.

[3-(4-Methylphenyl)-1-naphthyl](phenyl)methanone (3b): Yield: 71 mg, 90%; pale-yellow oil; R_f = 0.42 (**1a**, R_f = 0.45) (hexane/EtOAc, 95:5). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, J = 1.5 Hz, 1 H), 7.99 (d, J = 7.3 Hz, 1 H), 7.91 (m, 2 H), 7.88 (d, J = 1.4 Hz, 1 H), 7.77 (d, J = 2.1 Hz, 1 H), 7.58–7.52 (m, 3 H), 7.51–7.48 (m, 1 H), 7.44 (t, J = 8.1 Hz, 3 H), 7.24–7.21 (m, 2 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 138.2, 137.7, 137.2, 137.1, 136.9, 134.2, 133.3, 130.5, 129.9, 129.7, 128.6, 128.5, 128.4, 127.9, 127.2, 127.1, 126.8, 125.5, 21.1 ppm. IR (film): $\tilde{\nu}$ = 3051, 2923, 1661, 1595, 1509, 1448, 1314, 1254, 1113, 1059, 936, 897, 814, 750 cm^{-1}. HRMS: calcd. for $C_{24}H_{19}O$ 323.1435 $[M + H]^+$; found 323.1450.

[3-(4-Chlorophenyl)-1-naphthyl](phenyl)methanone (3c): Yield: 58 mg, 70%; pale-yellow oil; R_f = 0.40 (**1a**, R_f = 0.45) (hexane/EtOAc, 95:5). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, J = 1.5 Hz, 1 H), 8.09 (d, J = 8.1 Hz, 1 H), 7.95–7.87 (m, 2 H), 7.86 (d, J = 1.5 Hz, 1 H), 7.80 (d, J = 8.49 Hz, 1 H), 7.73 (d, J = 1.8 Hz, 1 H), 7.54–7.45 (m, 4 H), 7.42 (t, J = 8.3 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7, 138.5, 138.1, 137.4, 135.9, 134.1, 133.9, 133.4, 130.4, 129.5, 129.2, 128.7, 128.5, 127.4, 127.1, 126.6, 125.6 ppm. IR (film): $\tilde{\nu}$ = 3059, 2926, 1661, 1597, 1495, 1448, 1315, 1254, 1220, 1176, 934, 897, 825, 751, 662 cm^{-1}. HRMS: calcd. for $C_{23}H_{15}ClONa$ $[M + Na]^+$ 365.0711; found 365.0719.

[3-(4-Bromophenyl)-1-naphthyl](phenyl)methanone (3d): Yield: 62 mg, 65%; pale-yellow oil; R_f = 0.42 (**1a**, R_f = 0.45) (hexane/EtOAc, 95:5). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, J = 1.5 Hz, 1 H), 8.01 (d, J = 8.3 Hz, 1 H), 7.97–7.91 (m, 2 H), 7.85 (d, J = 1.5 Hz, 1 H), 7.71 (d, J = 1.5 Hz, 1 H), 7.58–7.52 (m, 5 H), 7.49–7.40 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 138.9, 137.9, 137.3, 135.9, 133.9, 133.4, 132.1, 130.4, 130.2, 128.8, 128.6, 128.5, 127.4, 127.0, 126.4, 125.5, 122.1 ppm. IR (film): $\tilde{\nu}$ = 3058, 1660, 1596, 1492, 1448, 1314, 1254, 1214, 1176, 934, 896, 856, 750, 709 cm^{-1}. HRMS: calcd. for $C_{23}H_{15}BrONa$ $[M + Na]^+$ 409.0206; found 409.0210.

[3-(4-Fluorophenyl)-1-naphthyl](phenyl)methanone (3e): Yield: 72 mg, 90%; thick oil; R_f = 0.42 (**1a**, R_f = 0.45) (hexane/EtOAc, 95:05). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, J = 1.5, Hz, 1 H), 7.99 (d, J = 8.3 Hz, 1 H), 7.92–7.89 (m, 2 H), 7.85 (d, J = 1.5 Hz, 1 H), 7.72 (d, J = 1.5 Hz, 1 H), 7.63–7.59 (m, 2 H), 7.58–7.41 (m, 5 H), 7.11 (t, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7, 164.3, 138.1, 136.1, 134.1, 133.4, 130.4, 130.1, 128.9, 128.8, 128.6, 128.5, 128.4, 127.2, 126.9, 126.7, 125.5, 115.9, 115.7 ppm. IR (film): $\tilde{\nu}$ = 3059, 1660, 1510, 1447, 1313, 1228, 1159, 1099, 924, 896, 832, 713, 690 cm^{-1}. HRMS: calcd. for $C_{23}H_{16}FO$ $[M + H]^+$ 327.1185; found 327.1189.

[3-(4-Methoxyphenyl)-1-naphthyl](phenyl)methanone (3f): Yield: 61 mg, 74%; thick liquid; R_f = 0.30 (**1a**, R_f = 0.45) (hexane/EtOAc, 95:05). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, J = 1.1 Hz, 1 H), 7.99 (d, J = 8.3 Hz, 1 H), 7.91–7.87 (m, 3 H), 7.75 (d, J = 1.7 Hz, 1 H), 7.60–7.52 (m, 3 H), 7.50–7.39 (m, 4 H), 6.93 (d, J = 8.6 Hz, 2 H), 3.8 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 159.6, 136.8, 134.2, 133.3, 133.2, 132.5, 131.1, 130.4, 130.0, 128.5, 128.4, 128.3, 127.9, 127.4, 126.9, 126.8, 126.0, 125.5, 114.4, 55.3 ppm. IR (film): $\tilde{\nu}$ = 3055, 1660, 1604, 1512, 1449, 1389, 1251, 1178, 1111, 936, 817, 733 cm^{-1}. HRMS: calcd. for $C_{24}H_{19}O_2$ $[M + H]^+$ 339.1385; found 339.1392.

[3-(3-Methoxyphenyl)-1-naphthyl](phenyl)methanone (3g): Yield: 64 mg, 78%; yellow oil; R_f = 0.43 (**1a**, R_f = 0.45) (hexane/EtOAc, 95:05). ^1H NMR (300 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.99 (d, J = 7.9 Hz, 1 H), 7.93–7.89 (m, 2 H), 7.87 (d, J = 1.5 Hz, 1 H), 7.77 (d, J = 1.7 Hz, 1 H), 7.58–7.50 (m, 2 H), 7.46–7.38 (m, 3 H), 7.31 (t, J = 7.7 Hz, 1 H), 7.23–7.14 (m, 2 H), 6.85 (d, J = 8.1 Hz, 1 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.3, 160.1, 133.3, 133.0, 131.3, 130.5, 130.4, 129.9, 129.2, 128.8, 128.5, 128.3,

127.1, 126.8, 126.4, 119.8, 113.2, 113.0, 111.3, 55.0 ppm. IR (film): $\tilde{\nu}$ = 3057, 1660, 1591, 1490, 1451, 1311, 1211, 1172, 1045, 948, 886, 781, 689 cm^{-1}. HRMS: calcd. for $C_{24}H_{19}O_2$ [M + H]$^+$ 339.1385; found 339.1382.

[3-(3-Phenoxyphenyl)-1-naphthyl](phenyl)methanone (3h): Yield: 60 mg, 61%; yellow oil; R_f = 0.30 (**1a**, R_f = 0.45) (hexane/EtOAc, 95:05). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, J = 1.4 Hz, 1 H), 8.02 (d, J = 8.1 Hz, 1 H), 7.90 (m, 2 H), 7.89 (d, J = 1.4 Hz, 1 H), 7.78 (d, J = 2.2 Hz, 1 H), 7.61–7.50 (m, 3 H), 7.47–7.44 (m, 2 H), 7.41–7.39 (m, 2 H), 7.37–7.31 (m, 3 H), 7.11–7.03 (m, 3 H), 6.99–6.96 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.2, 157.8, 141.9, 138.1, 137.1, 136.4, 133.3, 130.4, 130.2, 129.8, 128.8, 128.7, 128.5, 127.5, 127.3, 126.9, 126.8, 125.5, 123.4, 122.2, 118.9, 117.9, 117.8 ppm. IR (film): $\tilde{\nu}$ = 3060, 1661, 1584, 1448, 1409, 1313, 1250, 1220, 1168, 959, 908, 846, 753, 694 cm^{-1}. HRMS: calcd. for $C_{29}H_{21}O_2$ [M + H]$^+$ 401.1542; found 401.1554.

1-(3-Phenyl-1-naphthyl)heptan-1-one (3k):[13d] Yield: 54 mg, 72%; yellow oil; R_f = 0.48 (**1b**, R_f = 0.52) (hexane/EtOAc, 95:05). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, J = 8.7 Hz, 1 H), 8.09 (s, 1 H), 8.01 (d, J = 1.4 Hz, 1 H), 7.87 (dd, J = 7.3, 2.2 Hz, 1 H), 7.66 (dd, J = 7.3, 1.4 Hz, 2 H), 7.59–7.49 (m, 2 H), 7.46 (t, J = 7.3 Hz, 2 H), 7.37 (t, J = 7.3 Hz, 1 H), 3.07 (t, J = 7.2 Hz, 2 H), 1.80 (pent., J = 7.3 Hz, 2 H), 1.44–1.38 (m, 2 H), 1.37–1.30 (m, 4 H), 0.89 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.7, 140.43, 137.3, 134.4, 129.7, 129.5, 129.0, 128.6, 127.7, 127.6, 127.4, 126.8, 126.7, 125.9, 42.3, 31.8, 29.7, 24.7, 22.6, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3056, 2954, 2926, 2855, 1681, 1598, 1498, 1456, 1311, 1237, 1166, 1088, 948, 889, 762, 667 cm^{-1}. HRMS: calcd. for $C_{23}H_{25}O$ [M + H]$^+$ 317.1906; found 317.1912.

1-[3-(3-Methoxyphenyl)-1-naphthyl]heptan-1-one (3l): Yield: 46 mg, 56%; yellow oil; R_f = 0.40 (**1b**, R_f = 0.52) (hexane/EtOAc, 95:05). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (dd, J = 7.5, 1.5 Hz, 1 H), 8.06 (s, 1 H), 7.97 (d, J = 1.8 Hz, 1 H), 7.86 (dd, J = 7.3, 2.0 Hz, 1 H), 7.57–7.46 (m, 2 H), 7.35 (t, J = 7.9 Hz, 1 H), 7.24–7.14 (m, 2 H), 6.88 (dd, J = 7.5, 1.8 Hz, 1 H), 3.87 (s, 3 H), 3.05 (t, J = 7.4 Hz, 2 H), 1.79 (pent., J = 7.4 Hz, 2 H), 1.44–1.25 (m, 6 H), 0.89 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.1, 160.1, 141.6, 137.2, 137.0, 134.2, 130.0, 129.7, 129.2, 128.6, 127.7, 126.6, 125.7, 125.6, 119.7, 113.2, 112.8, 55.3, 42.4, 31.6, 28.9, 24.6, 22.4, 14.0 ppm. IR (film): $\tilde{\nu}$ = 3052, 2961, 2927, 2865, 1680, 1597, 1485, 1436, 1355, 1220, 1174, 1098, 960, 892, 760, 668 cm^{-1}. HRMS: calcd. for $C_{24}H_{27}O_2$ [M + H]$^+$ 347.2012; found 347.2019.

1-(3-Phenyl-1-naphthyl)pentan-1-one (3m): Yield: 61 mg, 78%; yellow oil; R_f = 0.49 (**1c**, R_f = 0.54) (hexane/EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (d, J = 7.5 Hz, 1 H), 8.09 (s, 1 H), 8.01 (d, J = 1.8 Hz, 1 H), 7.87 (dd, J = 7.3, 2.2 Hz, 1 H), 7.67 (d, J = 7.1 Hz, 2 H), 7.57–7.44 (m, 4 H), 7.37 (t, J = 7.3 Hz, 1 H), 3.08 (t, J = 7.3 Hz, 2 H), 1.79 (pent., J = 7.5 Hz, 2 H), 1.45 (sext., J = 7.5 Hz, 2 H), 0.98 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.0, 140.1, 137.3, 137.2, 134.3, 130.3, 129.6, 128.9, 128.6, 127.7, 127.6, 127.3, 126.7, 126.6, 125.5, 42.1, 26.7, 22.4, 13.9 ppm. IR (film): $\tilde{\nu}$ = 3056, 2957, 2929, 2867, 1681, 1598, 1498, 1455, 1340, 1244, 1126, 948, 888, 856, 763, 698 cm^{-1}. HRMS: calcd. for $C_{21}H_{20}ONa$ [M + Na]$^+$ 311.1420; found 311.1411.

1-[3-(4-Bromophenyl)-1-naphthyl]pentan-1-one (3n): Yield: 50 mg, 50%; yellow oil; R_f = 0.50 (**1c**, R_f = 0.54) (hexane/EtOAc, 95:05). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 8.12 (d, J = 8.3 Hz, 1 H), 7.61 (d, J = 1.5 Hz, 1 H), 7.76–7.68 (m, 1 H), 7.46–7.42 (m, 2 H), 7.36–7.32 (m, 4 H), 3.07 (t, J = 6.8 Hz, 2 H), 1.79 (pent., J = 7.5 Hz, 2 H), 1.45 (sext., J = 7.5 Hz, 2 H), 0.97 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.9, 137.6, 136.5, 134.2, 132.1, 129.4, 128.8, 128.6, 127.8, 126.9, 125.9, 125.5, 112.2, 42.2, 29.6, 26.5, 13.9 ppm. IR (film): $\tilde{\nu}$ = 3058, 2951, 2927, 2869, 1680, 1590, 1496, 1435, 1339, 1241, 1110, 952, 890, 860, 765, 692 cm^{-1}. HRMS: calcd. for $C_{21}H_{20}BrO$ [M + H]$^+$ 368.0698; found 368.0689.

3-Phenyl-1-(3-phenyl-1-naphthyl)propan-1-one (3o): Yield: 54 mg, 75%; liquid; R_f = 0.42 (**1d**, R_f = 0.48) (hexane/EtOAc, 95:05). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, J = 8.0 Hz, 1 H), 8.09 (s, 1 H), 7.94 (s, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 2 H), 7.56–7.47 (m, 2 H), 7.43 (t, J = 7.2 Hz, 2 H), 7.36 (t, J = 8.0 Hz, 1 H), 7.20–7.24 (m, 4 H), 7.17–7.12 (m, 1 H), 3.39 (t, J = 7.2 Hz, 2 H), 3.13 (t, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.6, 157.8, 136.8, 136.5, 134.2, 130.3, 129.9, 128.6, 128.4, 128.1, 126.9, 126.8, 126.3, 125.5, 123.5, 122.2, 118.9, 118.1, 117.8, 44.1, 29.7 ppm. IR (film): $\tilde{\nu}$ = 3057, 3028, 2927, 1681, 1599, 1497, 1452, 1404, 1310, 1237, 1143, 949, 888, 857, 763, 698 cm^{-1}. HRMS: calcd. for $C_{25}H_{21}O$ [M + H]$^+$ 337.1593; found 337.1598.

1-[3-(3-Phenoxyphenyl)-1-naphthyl]-3-phenylpropan-1-one (3p): Yield: 72 mg, 78%; orange solid; m.p. 96–98 °C; R_f = 0.40 (**1d**, R_f = 0.48) (hexane/EtOAc, 95:05). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.44–8.40 (m, 1 H), 8.27 (s, 1 H), 8.17 (s, 1 H), 8.02–7.98 (m, 1 H), 7.78 (d, J = 8.4 Hz, 2 H), 7.59–7.54 (m, 3 H), 7.50 (t, J = 7.3 Hz, 3 H), 7.41 (t, J = 7.3 Hz, 2 H), 7.32–7.26 (m, 5 H), 7.18 (t, J = 6.3 Hz, 1 H), 3.51 (t, J = 7.2 Hz, 2 H), 3.12 (t, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 203.3, 141.3, 139.7, 137.0, 136.9, 134.4, 130.1, 129.7, 129.2, 129.1, 129.0, 128.7, 128.5, 128.0, 127.7, 127.4, 127.0, 126.9, 126.2, 125.7, 118.8, 43.6, 30.5 ppm. IR (KBr): $\tilde{\nu}$ = 3058, 3038, 2827, 1682, 1589, 1496, 1462, 1404, 1310, 1238, 1143, 958, 886, 857, 763, 696 cm^{-1}. HRMS: calcd. for $C_{31}H_{25}O_2$ 429.1855 [M + H]$^+$; found 429.1864.

(3-Hydroxyphenyl)(3-phenyl-1-naphthyl)methanone (3q): Yield: 70 mg, 80%; yellow oil; R_f = 0.40 (**1e**, R_f = 0.40) (hexane/EtOAc, 80:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 8.01 (d, J = 8.1 Hz, 1 H), 7.92 (d, J = 8.1 Hz, 1 H), 7.80 (d, J = 1.4 Hz, 1 H), 7.64 (d, J = 8.1 Hz, 2 H), 7.48–7.39 (m, 3 H), 7.32–7.21 (m, 5 H), 7.06 (dt, J = 8.0, 1.4 Hz, 1 H), 6.83 (br. s, 1 H, D_2O exchangeable) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.4, 156.3, 139.3, 137.1, 136.8, 134.1, 129.9, 129.8, 129.0, 128.9, 128.8, 127.8, 127.4, 126.9, 125.3, 123.2, 121.9, 121.1, 116.5 ppm. IR (film): $\tilde{\nu}$ = 3377, 3058, 1651, 1590, 1497, 1449, 1311, 1276, 1233, 1134, 1075, 959, 888, 759, 695 cm^{-1}. HRMS: calcd. for $C_{23}H_{17}O_2$ [M + H]$^+$ 325.1229; found 325.1234.

[3-(4-Chlorophenyl)-1-naphthyl](3-hydroxyphenyl)methanone (3r): Yield: 68 mg, 70%; white solid; m.p. 158–160 °C; R_f = 0.40 (**1e**, R_f = 0.40) (hexane/EtOAc, 80:20). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 9.51 (br. s, 1 H, D_2O exchangeable), 8.22 (s, 1 H), 8.01 (d, J = 8.1 Hz, 1 H), 7.93 (d, J = 8.1 Hz, 1 H), 7.75 (d, J = 1.7 Hz, 1 H), 7.70 (d, J = 8.4 Hz, 2 H), 7.61–7.42 (m, 4 H), 7.35–7.18 (m, 3 H), 7.09–7.01 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 196.7, 157.1, 138.4, 137.7, 136.9, 135.0, 133.2, 133.0, 129.3, 128.8, 128.4, 127.9, 127.8, 127.5, 126.5, 126.2, 125.4, 124.8, 120.9, 120.4, 115.9 ppm. IR (KBr): $\tilde{\nu}$ = 3357, 3056, 1641, 1590, 1496, 1459, 1321, 1279, 1243, 1234, 1075, 959, 898, 756, 696 cm^{-1}. HRMS: calcd. for $C_{23}H_{16}ClO_2$ [M + H]$^+$ 359.0840; found 359.0846.

(3-Methoxyphenyl)(3-phenyl-1-naphthyl)methanone (3s): Yield: 66 mg, 92%; yellow oil; R_f = 0.32 (**1f**, R_f = 0.37) (hexane/EtOAc, 95:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 8.01 (d, J = 8.3 Hz, 1 H), 7.91 (d, J = 8.3 Hz, 1 H), 7.78 (d, J = 2.2 Hz, 1 H), 7.65 (dd, J = 8.3, 1.5 Hz, 2 H), 7.54–7.36 (m, 5 H), 7.35–7.23 (m, 3 H), 7.09 (dt, J = 7.5, 1.5 Hz, 1 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 159.7, 139.9, 139.4, 137.0, 134.0, 129.4, 128.9, 128.7, 128.6, 127.6, 127.3, 127.1, 127.0, 126.8, 125.5,

123.6, 120.0, 113.9, 55.4 ppm. IR (film): $\tilde{\nu}$ = 3056, 1658, 1591, 1490, 1451, 1310, 1201, 1172, 1045, 958, 886, 786, 680 cm^{-1}. HRMS: calcd. for $C_{24}H_{19}O_2$ $[M + H]^+$ 339.1385; found 339.1387.

(4-Nitrophenyl)(3-phenyl-1-naphthyl)methanone (3u): Yield: 42 mg, 59%; yellow oil; R_f = 0.30 (**1h**, R_f = 0.41) (hexane/EtOAc, 90:10). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (dd, J = 8.8, 3.6 Hz, 2 H), 8.20 (s, 1 H), 8.08 (d, J = 8.1 Hz, 1 H), 8.03 (dd, J = 8.8, 2.2 Hz, 2 H), 7.96 (d, J = 8.1 Hz, 1 H), 7.78 (s, 1 H), 7.62 (d, J = 8.1, 2.0 Hz, 2 H), 7.58–7.48 (m, 2 H), 7.44 (t, J = 7.3 Hz, 2 H), 7.35 (t, J = 7.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.8, 150.3, 143.2, 139.6, 137.2, 135.4, 134.2, 131.1, 129.9, 129.8, 129.1, 128.8, 128.2, 127.9, 127.7, 127.2, 125.2, 123.7 ppm. IR (film): $\tilde{\nu}$ = 3060, 1660, 1591, 1496, 1441, 1350, 1301, 1211, 1172, 1045, 948, 886, 781, 689 cm^{-1}. HRMS: calcd. for $C_{23}H_{16}NO_3$ $[M + H]^+$ 354.1131; found 354.1125.

Synthesis of 3a by I_2-Mediated Reaction between 1a and 6b: To a THF (2.0 mL, 0.1 M) solution of **1a** (50 mg, 0.2427 mmol) and **6b** (58 mg, 0.4854 mmol) in a 2.5-mL screw-cap vial was added molecular iodine (92 mg, 1.5 equiv.). The mixture was stirred at room temperature for 3 h. Then, the reaction mixture was diluted with ethyl acetate (10 mL), and a saturated solution of sodium thiosulfate (10 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue thus obtained was purified by flash silica gel column chromatography (hexane) to obtain **3a** (67 mg, 90%) as a pure compound.

Synthesis of 3a and 13 by $Cu(OTf)_2$-Mediated Reaction between 1a and 6b: To a DCE/THF (2.0 mL, 0.1 M) solution of **1a** (50 mg, 0.2427 mmol) and **2a** (35 mg, 0.2912 mmol) in a 2.5-mL screw-cap vial was added $Cu(OTf)_2$ (9 mg, 10 mol-%) under a nitrogen atmosphere. The mixture was stirred at 80 °C for the time specified in Equation (2). Then, the reaction mixture was cooled and passed through a short pad of silica gel (ethyl acetate). The combined filtrate was evaporated under reduced pressure. The residue thus obtained was purified by flash silica gel column chromatography (hexane) to obtain a mixture of compounds **3a** and **13**[22] in variable yields and ratios as shown in Equation (2).

Supporting Information (see footnote on the first page of this article): Synthesis of starting materials, experimental procedures, characterization data, ^1H and ^{13}C NMR spectra.

Acknowledgments

We gratefully acknowledge financial support by the Council of Scientific and Industrial Research, India. N.T.P. is grateful to Dr. J. S. Yadav, Director, IICT, and Dr. T. K. Chakraborty, Director, C.D.R.I., for their support and encouragement.

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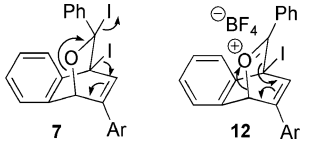

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Received: July 18, 2009
Published Online: September 15, 2009

