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Article

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[2+2+2]-Cycloaddition reactions using immobilized alkynes. A proof of concept for an integral use of the outcoming products in solid-phase synthetic methodologies

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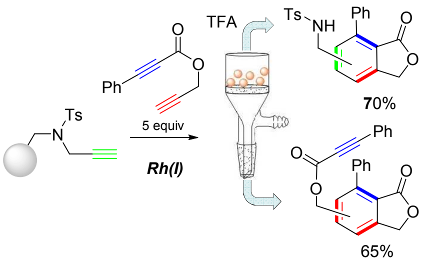


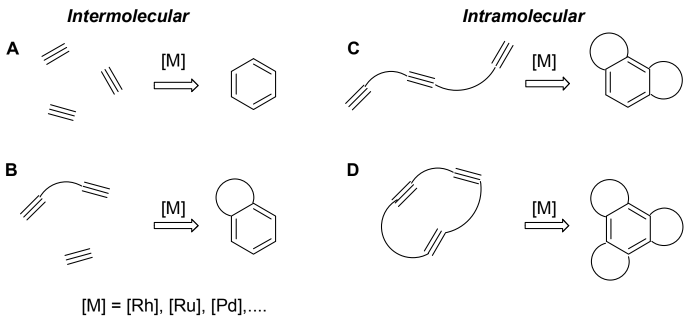
ABSTRACT

The transition-metal-catalyzed [2+2+2]-cycloaddition of alkynes has become a powerful atom-economical strategy for aromatic ring construction. Unfortunately, the control of the stereo-, regio- and chemoselectivity of these processes is usually challenging and these reactions can potentially lead to complex unuseful mixtures. While solid-phase chemistry has proven to be a successful tool for decreasing the number of cycloadducts formed and for facilitating the purification step, an integral use of the outcoming products in this complex reaction is described herein. By using an immobilized monoalkyne, the transition-metal-catalyzed [2+2+2]-cycloaddition with soluble 1,6-diyne-esters led to the

simultaneous preparation of soluble and solid-supported phthalides, showing a new way to benefit from solid-phase synthetic methodologies.

INTRODUCTION

The preparation of highly-substituted aromatic systems has received considerable attention in organic synthesis as these structural motifs dress-up countless essential pharmaceutical ingredients, natural products and important materials. The construction of accurately decorated molecules of this type has mostly relied on performing substitution and coupling reactions on simpler, more rudimentary aromatic precursors. In the last decades, however, great interest has been devoted to the transition-metal-mediated construction of aromatic rings and, in particular, on the [2+2+2]-cycloaddition.[1] This attractive transition-metal catalyzed transformation cleanly merges three alkyne moieties into an aromatic ring. Depending on the combinations of triple bonds, mono, bi, tri and tetracyclic benzene ring-containing scaffolds can be obtained through inter or intramolecular cycloadditions (Scheme 1).



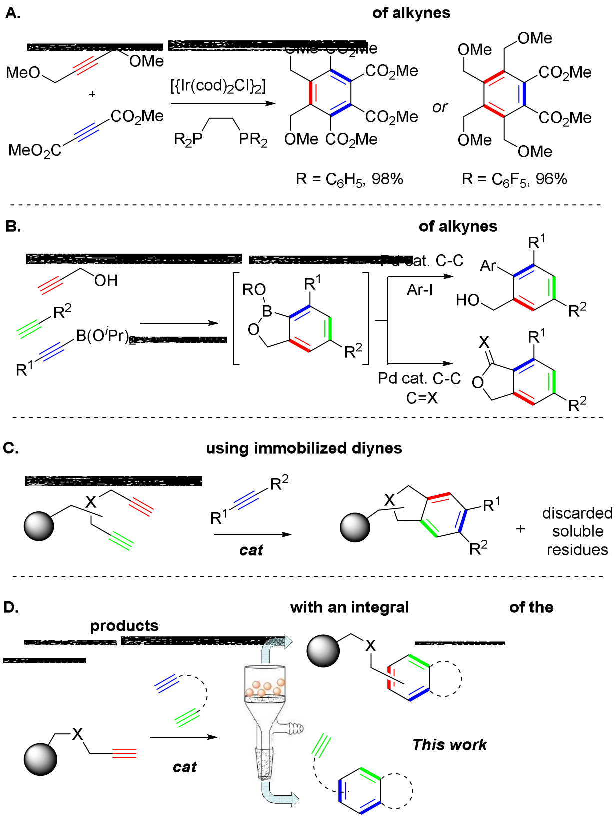
Scheme 1. [2+2+2]-Cycloaddition of alkynes

The continuous development of the field led to the successful application of the process to the total synthesis of natural products,[2] macrocycle construction,[3] the preparation of molecules for materials science such as dendrimers or polyaromatic hydrocarbons,[4] and the asymmetric synthesis of axially chiral compounds,[5] just to name a few.[6] Notwithstanding these advances, it is unarguable that the control of the chemo- and regioselectivity of these processes is a critical issue. Even if side reactions are excluded (*e.g.* linear di- and trimerizations),[7] 38 possible products can be generated from the combination of three different non-symmetrical alkynes! In this context, several strategies have been developed to control and ultimately simplify the outcome of these apparently unwieldy cycloadditions. Within this context, the group of Takeuchi reported highly selective and controllable Ir-catalyzed [2+2+2]-cycloadditions in which changing the phosphine ligand completely switches the product outcome (Scheme 2A, 2:1 *vs*. 1:2).[8] On the other hand, Yamamoto's group reported the formal cyclotrimerization between alkynylboronates, propargyl alcohols and terminal alkynes in which the boron group acts as a tether that controls initial boraruthenacycle construction eventually leading to a single boraphthalide regioisomer that, in turn, can be transformed into diverse attractive aromatic products (Scheme 2B).[9] In a related approach, silicon-based tethered-[2+2+2]-cycloadditions have been reported as well. For improving chemo- and regioselectivity, silyl ethers temporary connect isolated alkyne units in order to transform an intermolecular reaction into an intramolecular one.[10]

The use of immobilized substrates in transition-metal catalyzed processes has been beneficial to overcome selectivity problems.[11] In particular, the usefulness of [2+2+2]-cycloadditions on solid-supports has been independently demonstrated by the groups of Sun,[12] Deiters[13] and Martinez (Scheme 2C).[14] By using solid-supported diynes, these authors got rid of side-products such as those arising from di- or trimerizations of the diyne components. As in any typical solid-phase strategy, these reactions were driven to completion by using an excess of the soluble component, so any non immobilized side-products and unused reagents is removed by a simple filtration during work-up procedures.

Addressing the solid-phase synthesis from a different viewpoint, we envisaged a new approach to improve the outcome of the process. We sought to devise a dual-purpose strategy for fully harnessing the solid-phase methodology. We reasoned that, by using an immobilized alkyne in lieu of a diyne, synthetic and biologically relevant products could be formed both in solution and on resin; a process in which no phase is wasted (Scheme 2D).

Herein we report the application of this conceptually new approach to the generation of isolated, soluble and immobilized, substituted phthalides by means of a "convergent" process integrating solution and solid-phase synthesis.

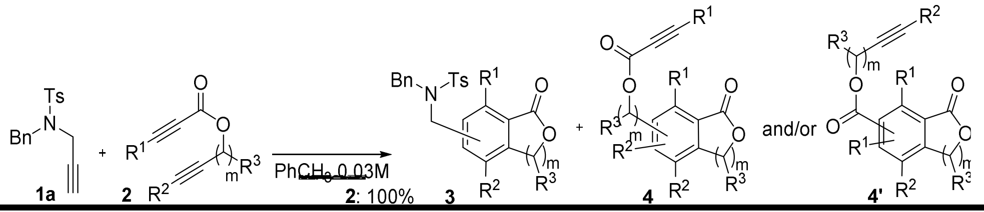


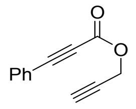
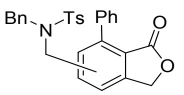
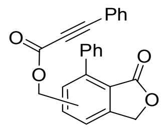
Scheme 2. Facilitated or controlled [2+2+2]-cycloadditions of alkynes

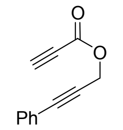
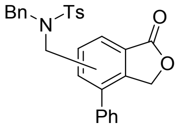
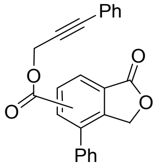
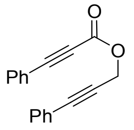
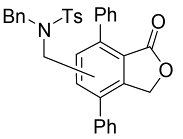
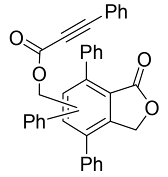
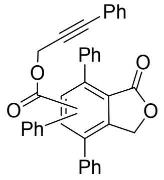
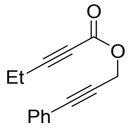
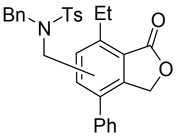
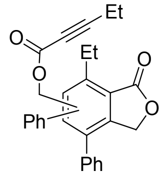
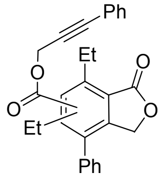
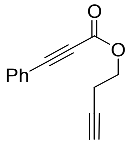
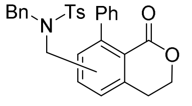
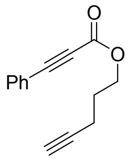
RESULTS AND DISCUSSION

Solution-phase [2+2+2]-Cycloaddition for the Synthesis of Phthalides. In order to establish the basis of the process and to explore the scope of the cycloaddition, our first set of experiments were performed in solution based on a procedure reported by Witulski and Zimmermann which involves the use of Wilkinson's catalyst.[15] As shown in Table 1, ester-type diynes were used as substrate since the cycloadditions would then lead to phthalide-type products which are attractive structures since these benzolactones are frequently found in naturally occurring substances that exhibit a broad spectrum of biological activities.[16-18] The other substrate, *N*-benzyl-*N*-propargyl-*p*-toluenesulfonamide (**1a**), was chosen as the monoyne component for three reasons: the benzyl amine group would be easily translated to solid-phase either through alkylation or substitution strategies,[19] the behaviour of propargylamines has not been extensively explored in cyclotrimerization reactions and, finally, because there has been recent interest in the biological properties of secondary and tertiary sulfonamides.[20]

Table 1. Solution-phase [2+2+2]-cycloaddition for the synthesis of phthalides



Entry	Diyne 2	Conv. 1a	~~T~~	*t*	Products[a,b]	
1	 **2a**	45%	40 °C	66 h	 **3aa**, 38% (2.8:1)	 **4a**, 28% (2.4:1)
2	**2a**	50%	80 °C	4 h	**3aa**, 45% (2.1:1)	**4a**, 28% (1.8:1)
3	**2a**	66%	reflux	1.2 h	**3aa**, 55% (2:1)	**4a**, 24% (1.5:1)

4	-	25%	reflux	2 h	-		
5^{c}	**2a**	<20%	reflux	9 h	**3aa**, traces (3:1)	**4a**, traces (4:1)	
6^{d}	**2a**	82%	reflux	1.3 h	**3aa**, 15% (2.3:1)	-	
7	**2a** (2 equiv)	74%	reflux	2 h	**3aa**, 71% (2.1:1)	**4a**, 50% (1.7:1)	
8	**2a** (5 equiv)	82%	reflux	1.8 h	**3aa**, 76% (2.2:1)	**4a**, 56% (1.7:1)	
9	 **2b** (2 equiv)	57%	reflux	2 h	 **3ab**, 46% (1:1)	 **4'b**, 35% (2:1)	
10	 **2c** (5 equiv)	99%	reflux	2 h	 **3ac**, 64% (1.2:1)	 **4c**, 13% (2:1)	 **4'c**, 18% (3.4:1)
11	 **2d** (5 equiv)	97%	reflux	1.5 h	 **3ad**,^{e} 80% (1.1:1)	 **4d**, 21% (5:1)	 **4'd**, 20% (1.5:1)
12	 **2e**	55%	reflux	10 h	 **3ae**, < 40% (3:1)		
13	 **2f**	86%	reflux	10 h	-^{f}		

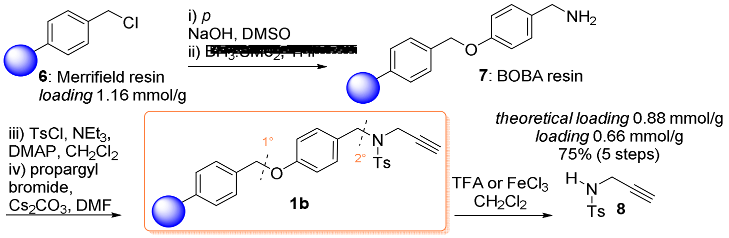
[a]Unless otherwise noted, all reactions were performed with 1 equiv of substrates **2**, using $RhCl(PPh_3)_3$ as catalyst (5 mol%) in toluene (0.03 M). Yields of cross-products **3** refer to the amount of **1a** used. Yields of homodimers **4**/**4’** refer to the amount of substrate **2** employed. [b]Regioisomeric ratio in brackets. [c]Grubbs 1st gen. was used as catalyst (5 mol%). [d]$Pd_2(dba)_3/PPh_3$ was used as catalytic system (2.5/5 mol%). [e]Inseparable from trimers (**5d**) of substrate **2d** (17% yield, see SI). [f]No product could be identified from the complex mixture obtained.

As shown in Table 1, the reaction of substrate **1a** and a variety of unsymmetrical diynes **2** leads to the formation of cross-cycloaddition products **3** and homodimers **4**. In addition, for many substrates, homotrimers arising from a secondary [2+2+2]-cycloaddition event on phthalide products **4** could also be found in the reactions mixtures in yields ranging from 10 to 25% (see SI). The structures of the cycloadducts were determined based on the analyses of the 1D and 2D NMR data, including in some cases NOE experiments (see SI). Regiochemistry of the obtained compounds was determined by analysis of the ^{1}H NMR spectra of the crude mixtures.

In general, moderate to low regioselectivity was obtained and, although this selectivity was shown to be slightly affected as higher temperatures were reached, this was necessary to guarantee high conversion of substrate **1a** (entries 1-3). Indeed, alkyne **1a** exhibited poor reactivity, probably due to the bulky tertiary sulfonamide group and, in the absence of any diyne substrate **2**, *ca.* 75% of the starting material could be recovered unaltered after 2 h under reflux in the presence of Wilkinson cat. (entry 4). Although the production of cross-cycloadducts **3**, as well as the conversion of substrate **1a**, could be raised by using an excess of diyne substrates **2** (entries 3 *vs* 7 and 8), yields of benzolactone-type products **3** and **4** were in general moderate. It should be noted that the use of other solvents (*e.g.* EtOH, dichloromethane and chloroform), or other standard Pd and Ru catalysts that have been previously used for this type of processes,[21,22] did not provide any improvement (*e.g.* entries 5-6). While it can instinctively be proposed that this outcome could be due to lack of chemoselectivity, the advantages of a solid-phase approach became apparent from the very beginning. The main disadvantage of this methodology lies in the purification of the crude mixtures thus obtained. For instance, after successive chromatography purifications, benzolactones **3aa** could not be efficiently separated from *ortho*-homodimer of **4a**; nor *ortho*-substituted phthalide of **3ab** could be separated from unidentified side-products (entry 9). In addition, whereas products **3ad** were, in turn, inseparable from trimers of the diyne **2d** (entry 11), isochromanones **3ae** obtained using 1,7-diyne **2e** could not be separated from unidentified side-products (entry 12).[23]

Side-by-side Solid- and Solution-phase Synthesis of Phthalides via [2+2+2]-Cycloadditions. In order to face such limitations, we envisaged that, by immobilizing the mono-alkyne component to a solid support, homodimers of type **4** would only form in solution-phase which can be easily separated by simple filtration. Resin-bound cross-cycloadducts, on the other hand, could be then selectively cleaved from the solid support by an appropriate reagent.

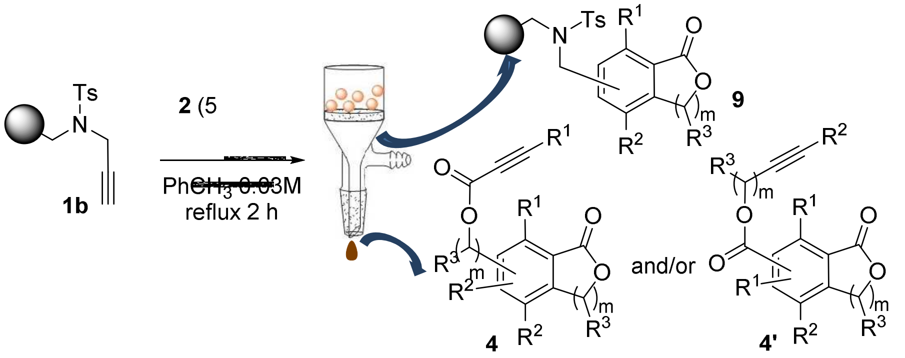
To this aim, resin-bound propargylamine **1b** was prepared in two steps from BOBA resin (**7**), which was in turn obtained from readily available Merrifield resin (**6**) according to the procedure reported by Kobayashi and Aoki (Scheme 3).[24,25] The loading of the resin **1b** was calculated based on the amount of *N*-propargyl-*p*-toluenesulfonamide (**8**) released upon treatment with either iron chloride or trifluoroacetic acid in dichloromethane (75% overall yield).



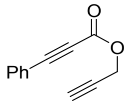
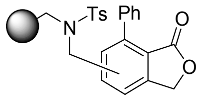
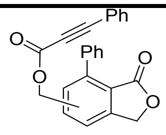
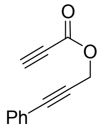
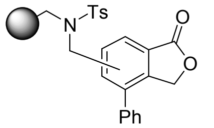
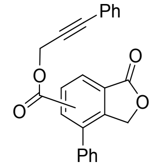
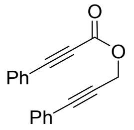
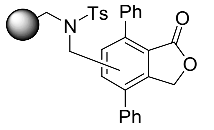
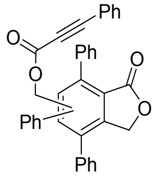
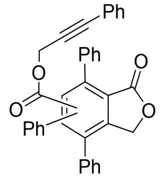
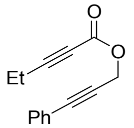
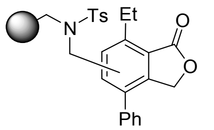
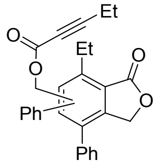
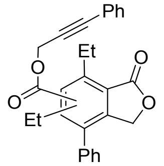
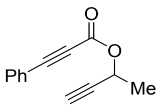
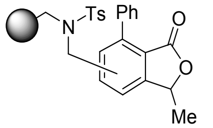
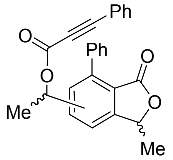
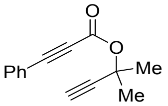
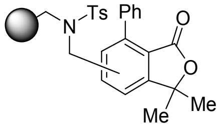
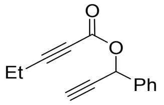
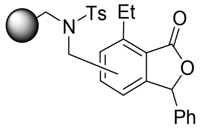
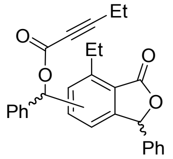
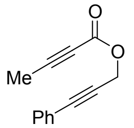
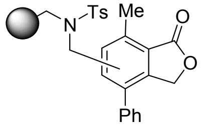
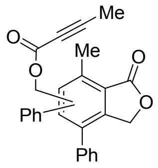
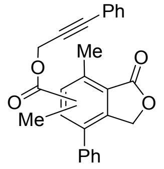
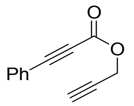
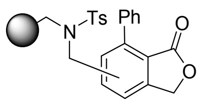
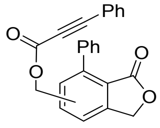
Scheme 3. Preparation of resin **1b** from Merrifield resin.

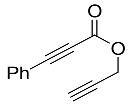
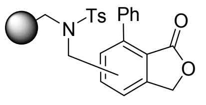
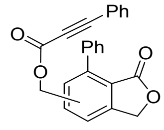
The use of resin **1b** effectively resulted in the simultaneous generation of benzolactones in both solution and solid phase and the results are summarized in Table 2. Using RhCl(PPh$_3$)$_3$ as catalyst (entries 1-8), the yields and selectivities obtained were comparable to those observed in homogeneous media except for the fact that cycloadducts **9** and **4** are naturally easily separated. From the practical point of view, the end of the reaction can be determined by the disappearance of the dyine in the solution phase by TLC, an operation which is not possible in traditional solid-phase synthesis. The release of immobilized products from the resins has been achieved by treatment with trifluoroacetic acid in dichloromethane at room temperature. Thus, released products, derived from immobilized phthalides **9ba-bj**, were obtained in good overall yields (40-70%). Moderate regioselectivity was mostly obtained under conditions used in solution phase experiments, with a preference for the *meta* regioisomer when the dyine was substituted with a phenyl or ethyl group at the electron deficient triple bond (diynes **2a**, **2g**, **2h** and **2i**, entries 1, 5, 6 and 7), regardless of the presence or absence of an internal substituent. Regioselectivity decreased even more when both triple bonds were substituted, such as dyines **2c**, **2d** and **2j** (entries 3, 4 and 8), or when the phenyl substituent was attached to the less electron deficient triple bond (**2b**, entry 2). In general, this pattern of regioselectivity was repeated in the solution-phase products.

Table 2. Side-by-side solid- and solution-phase synthesis of phthalides *via* [2+2+2]-cycloadditions



Entry	Diyne 2	Resin-bound products^a	Solution-phase products^a

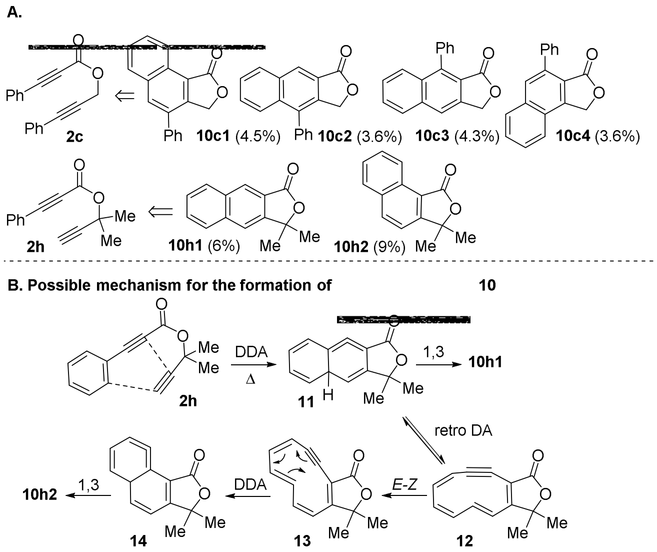
1	 **2a**	 **9ba**, 70% (2.7:1)	 **4a**, 65% (2.2:1)	
2	 **2b**	 **9bb**, 40% (1.3:1)	 **4’b**, 30% (1.3:1)	
3	 **2c**	 **9bc**, 60% (1.2:1)	 **4c**, 9% (1.4:1)	 **4’c**, 17% (3.5:1)
4	 **2d**	 **9bd**, 60% (1.2:1)	 **4d**, 24% (4.6:1)	 **4’d**, 25% (1.7:1)
5	 **2g**	 **9bg**, 70% (2.7:1)	 **4g**, 52% (3.3:1)	
6	 **2h**	 **9bh**, 60% (2.5:1)	–^{b}	
7	 **2i**	 **9bi**, 55% (2.8:1)	 **4i**, 27% (2.3:1)	
8	 **2j**	 **9bj**, 63% (1.5:1)	 **4j**, 13% (2.4:1)	 **4’j**, 15% (1.2:1)
9^{c}	 **2a**	 **9ba**, 50% (14:1)	 **4a**, 37% (13:1)	

10^{d}	 **2a**	 **9ba**, 52% (11:1)	 **4a**, 52% (13:1)

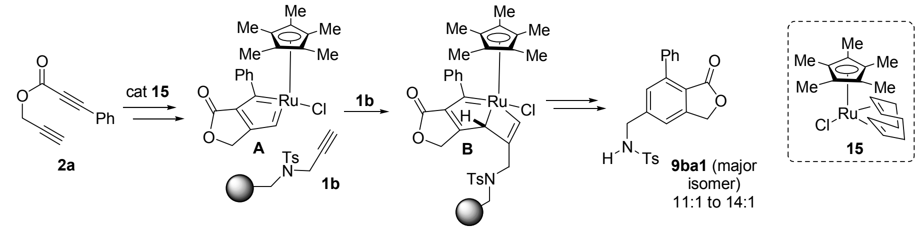
Unless stated, all reactions were performed with 5 equiv of substrates **2**, using $RhCl(PPh_3)_3$ as catalyst (5 mol%) in toluene (0.03 M), at reflux for 2 hours. Yields of cross-products **9** refer to the amount of resin **1b** used. Yields of homodimers **4**/**4’** refer to the amount of substrate **2** employed. Yields of cross-products **9** refer to free phthalides released from resins after TFA treatment (see SI). [a]Regioisomeric ratio in brackets. [b]Only DDA products **10h1-2** could be identified in the complex mixture obtained (see text). [c]Reaction performed with Cp*RuCl(cod) (20 mol%) as catalyst, 4 h at 128 °C. [d]Conditions as entry 9, at 100 °C for 6 h.

Also, under these specific experimental reaction conditions it was possible to elucidate a secondary mode of reactivity for diynes **2c** and **2h**. Naphthofuranones **10c1-4** and **10h1-2** were isolated in the corresponding filtrates in yields ranging from 3.6 to 9% (Scheme 4A).[26] A possible mechanism for the formation of such cycloisomerization products is depicted in Scheme 4B (particularly for the case of diyne **2h**) and involves a thermal dehydro-Diels-Alder (DDA) cycloaddition as key step, a reaction that is witnessing a renewed interest by the chemical community.[27] DDA reaction on substrate **2h** leads to the initial formation of a strained cyclic allene intermediate (**11**). Product **10h1** is then formed after strain release on intermediate **11** *via* hydrogen migration. On the other hand, the formation of **10h2** can be explained *via* a *retro*-Diels-Alder reaction on intermediate **11**. This ring-opening reaction produces intermediate **12** which undergoes a *E-Z* isomerization and, once again, a DDA cycloaddition. Cyclic allene **14** thus formed delivers product **10h2** after a hydrogen migration.

Scheme 4. Unexpected lactones obtained as side-products.



As stated above, a moderate regioselectivity in phthalides **4** and **9** was obtained with Wilkinson's catalyst (Table 2, entries 1-8). To reach an improved regioisomeric ratio, we decided to examine other catalysts. Best results were achieved by using Cp*RuCl(cod) [**15**, Cp* = η^5-$C_5(CH_3)_5$, cod = 1,5-cyclooctadiene] (Scheme 5). Thus, when the [2+2+2]-cycloaddition between resin **1b** and unsymmetrical diyne **2a** was performed in the presence of 20 mol% of Cp*RuCl(cod) in toluene at reflux, both soluble and immobilized phthalides were obtained with very high regioselectivity, in favor of the *meta*-substituted aromatic ring (Scheme 5 and Table 2, entries 9 and 10). The regioselectivity of the process can be reasonably explained taking into account the accepted mechanism of the Cp*RuCl-catalyzed [2+2+2] cycloaddition of alkynes.[18c,28] After initial ruthenabicycle **A** formation between catalyst **15** and diyne substrate **2a**, four modes of approach of the resin **1b** can be conceived for the ensuing [2+2]-cycloaddition step, two ultimately leading to the major product **9ba1** (*meta*-isomer) and two leading to **9ba2** (*ortho*-isomer). The regioselectivity observed can be explained by an initial preferable access of the terminal alkyne to the Ru-C_α bond from the less substituted side. This approach would occur, at the same time, regioselectively with the terminal alkyne pointing its terminus toward the chlorine ligand thus avoiding steric congestion. Ring opening on brand new **B** and eventual reductive elimination would release the catalytically active species Cp*RuCl and major phthalide derivative **9ba1**. On the other hand, comparable regioselectivity and yields were obtained when the reaction was also carried out in a one-gram scale of resin **1b**, proving the reliability of the protocol.



Scheme 5. Regioselective [2+2+2]-cycloaddition of immobilized alkyne **1b**

In summary, a complementary approach to simplify [2+2+2]-cycloadditions was explored involving the use of a polymer-supported alkyne. Polysubstituted phthalides were side-by-side assembled both in solution and on a polymer support pointing to a shift in solid-phase chemistry culture in which the filtrate phase becomes waste once the reaction ends. We believe that this proof-of-concept approach can be extended to other reactions such as enyne-alkyne and diyne-sulfonimine[29] cycloadditions and alkyne-alkyne metathesis, and finds its way into diverse combinatorial strategies.

EXPERIMENTAL SECTION

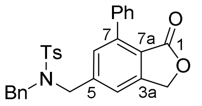
Materials and methods

Unsaturated precursors **1a**[30] and **2** have been previously prepared in the literature.[15,18,31] All other chemical reagents were purchased from commercial suppliers and used without further purification. Solvents were analytical grade or were purified by standard procedures prior to use. Yields were calculated for material judged homogeneous by thin layer chromatography (TLC) and nuclear magnetic resonance (^{1}H NMR). All reactions were monitored by thin layer chromatography performed on silica gel 60 F_{254} pre-coated aluminum sheets, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 4-anisaldehyde. Column flash chromatography was performed using silica gel 60 (230 – 400 mesh). Melting points (M.p.) were taken on an electrothermal melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were acquired at 300 MHz for ^{1}H and 75 MHz for ^{13}C using $CDCl_3$ as solvent. Chemical shifts for proton nuclear magnetic resonance spectra are reported in parts per million relative to the signal of tetramethylsilane (TMS) at 0 ppm (internal standard) and coupling constants (*J*) are reported in hertz (Hz). Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.0 ppm. The following abbreviations are used to indicate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, quint = quintet, h = sextet, br = broad signal. IR spectra were obtained using an FT-IR spectrometer and only partial spectral data are listed. High resolution mass spectra (HRMS) were obtained on a Q-TOF mass spectrometer and detection of the ions was performed in electrospray ionization, positive ion mode. The structure of the products were determined by a combination of spectroscopic methods such as IR, 1D and 2D NMR (including NOE, DEPT, COSY, HSQC and HMBC experiments) and HRMS. NMR signals assignments were based on 2D NMR experiments performed.

Representative procedure for the preparation of phthalides 3 and 4 in solution

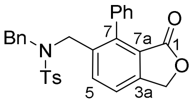
A mixture of *N*-benzyl-*N*-propargyl-*p*-toluenesulfonamide (**1a**, 1 mmol, 299 mg), diyne **2** (5 mmol, 5 equiv), and Wilkinson catalyst [Rh(PPh$_3$)$_3$Cl, 46 mg, 0.05 mmol] in toluene (33.0 mL, 0.03 M) was heated at reflux. After approx. 2 hours, the solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent hexanes/ethyl acetate) to afford the following phthalides **3** and **4**.

Compounds 3aa



3aa1

+

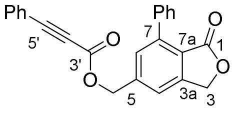


3aa2

Obtained as a pale yellow liquid consisting of an inseparable mixture of **3aa1** and **3aa2** in an approx. ratio 2.2:1 (0.367 g, 0.76 mmol, 76% yield). IR (film) (cm^{-1}): 3084, 3061, 3028, 2926, 1776, 1769, 1454, 1159. ^{1}H NMR (CDCl$_3$, 300 MHz): Major isomer **3aa1**: δ 7.79-7.72 (m, 2H, Ts), 7.49-7.29 (m, 7H, Ar-H, Ts), 7.20-7.11 (overlapping s and m, 3H, Ar-H, 4-H), 7.10-7.03 (m, 2H, Ar-H), 7.00 (s, 1H, 6-H), 6.96-6.88 (s, 1H, Ar-H), 5.15 (s, 2H, 3-H), 4.41 (s, 2H, 5-CH$_2$), 4.36 (s, 2H, Bn), 2.43 (s, 3H, Ts). Minor isomer **3aa2**: δ 7.87 (d, *J* = 8.0, 1H, 5-H), 7.61-7.55 (m, 2H, Ts), 7.49-6.88 (m, 11H, Ar-H, 4-H), 7.26-7.21 (m, 2H, Ts), 5.20 (s, 2H, 3-H), 4.18 (s, 2H, 6-CH$_2$), 4.12 (s, 2H, Bn), 2.41(s, 3H, Ts). ^{13}C NMR (CDCl$_3$, 75 MHz): Major isomer **3aa1**: δ 169.3 (C, C-1), 148.1 (C, C-3a), 143.7 (C, Ts), 143.0 (C, C-5), 142.4 (C, C-7), 136.6 (C, Ts), 135.8 (C, C7-Ph), 135.1 (C, Bn), 130.5 (CH, C-6), 129.8 (2 × CH, Ts), 129.3 (2 × CH, Ar), 128.6 (2 × CH, Ar), 128.3 (3 × CH, Ar), 127.9 (CH, Ar), 127.8 (2 × CH, Ar), 127.1 (2 × CH, Ts), 120.8 (C, C-7a), 120.4 (CH, C-4), 68.1 (CH$_2$, C-3), 52.3 (CH$_2$, Bn), 51.1 (CH$_2$, C5-CH$_2$), 21.4 (CH$_3$, Ts).

Minor isomer **3aa2**: δ 169.2 (C, C-1), 146.2 (C, C-3a), 143.4 (C, Ts), 140.3 (C, C-7), 136.3 (C, Ts), 136.1 (C, C-6), 135.0 (C, Bn), 134.4 (CH, C-5), 133.9 (C, Ar), 129.6 (2 × CH, Ts), 128.9 (2 × CH, Ar), 128.5 (2 × CH, Ar), 128.3 (2 × CH, Ar), 128.0 (CH, Ar), 127.8 (2 × CH, Ar), 127.6 (CH, Ar), 127.0 (2 × CH, Ts), 122.7 (C, C-7a), 121,0 (CH, C-4), 67.9 (CH_2, C-3), 52.4 (CH_2, Bn), 48.0 (CH_2, C6-CH_2), 21.4 (CH_3, Ts). HRMS *m/z* calcd. for $C_{29}H_{26}NO_4S$ $[M + H]^+$ 484.1577, found 484.1573.

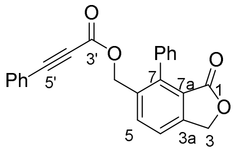
Compound 4a1



4a1

Obtained as a colourless solid (0.322 g, 0.87 mmol, 35% yield). M.p.: 128.0-129.0 °C. IR (film) (cm^{-1}): 3059, 3030, 2936, 2222, 1749, 1724, 1279, 1190, 1171, 1049. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.63-7.52 (m, 4H, Ar-H), 7.52-7.35 (m, 6H, Ar-H), 7.51 (overlapping s, 1H, 4-H), 7.49 (overlapping s, 1H, 6-H), 5.40 (s, 2H, 1'-H), 5.33 (s, 2H, 3-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.1 (C, C-1), 153.4 (C, C-3'), 148.4 (C, C-3a), 143.1 (C, C-7), 141.3 (C, C-5), 135.8 (C, 7-Ph), 132.9 (2 × CH, Ar), 130.8 (CH, Ar), 130.4 (CH, C-6), 129.4 (2 × CH, Ar), 128.52 (2 × CH, Ar), 128.49 (CH, Ar), 127.9 (2 × CH, Ar), 121.8 (C, C-7a), 120.0 (CH, C-4), 119.1 (C, C-6'), 87.5 (C, C-5'), 79.9 (C, C-4'), 68.2 (CH_2, C-3), 66.3 (CH_2, C-1'). HRMS *m/z* calcd. for $C_{24}H_{17}O_4$ $[M + H]^+$ 369.1121, found 369.1129.

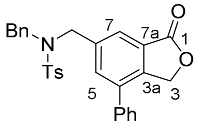
Compound 4a2



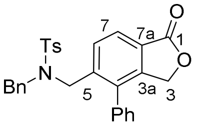
4a2

Obtained as a colourless liquid (0.193 g, 0.52 mmol, 21% yield). IR (film) (cm^{-1}): 2920, 2849, 2218, 1771, 1707, 1281, 1169. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.87 (d, *J* = 7.9 Hz, 1H, 5-H), 7.61-7.55 (m, 2H, Ar), 7.52 (d, *J* = 7.9 Hz, 1H, 4-H), 7.50-7.26 (m, 8H, Ar), 5.29 (s, 2H, 3-H), 5.12 (s, 2H, 1'-H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 169.0 (C, C-1), 153.3 (C, C-3'), 147.4 (C, C-3a), 142.0 (C, C-7), 134.8 (CH, C-5), 134.6 (C, C-6), 133.6 (C, C7-Ph), 132.9 (2 × CH, Ar), 130.7 (CH, Ar), 128.9 (2 × CH, Ar), 128.5 (2 × CH, Ar), 128.3 (CH, Ar), 128.0 (2 × CH, Ar), 123.3 (C, C-7a), 121.3 (CH, C-4), 119.2 (C, C-6'), 87.0 (C, C-5'), 80.0 (C, C-4'), 67.9 (CH$_2$, C-3), 64.2 (CH$_2$, C-1'). HRMS *m/z* calcd. for $C_{24}H_{17}O_4$ [M + H]$^+$ 369.1121, found 369.1124.

Compounds 3ab



3ab1

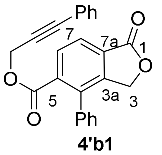


3ab2

Obtained as a pale yellow liquid consisting of a difficult to separable mixture of **3ab1** and **3ab2** in an approx. ratio 1:1 (0.222 g, 0.46 mmol, 46% yield). NMR spectra recorded corresponds to a column chromatography fraction enriched in *meta* isomer **3ab1**. IR (film) (cm^{-1}): 3061, 3028, 2922, 1765, 1339, 1159. ^{1}H NMR (CDCl$_3$, 300 MHz): *meta* isomer **3ab1**: δ 7.79-7.74 (m, 2H, Ts), 7.52-7.38 (m, 5H, Ar, 5-H, 7-H), 7.36-7.30 (m, 2H, Ts), 7.30-7.25 (m, 2H, Ar), 7.22-7.14 (m, 3H, Ar), 7.14-7.06 (m, 2H, Ar), 5.31 (s, 2H, 3-

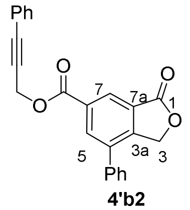
H), 4.43 (s, 2H, 6-CH_2), 4.36 (s, 2H, Bn), 2.44 (s, 3H, Ts). *ortho* Isomer **3ab2**: δ 7.81-7.56 (overlapping signal, 1H, 7-H), 7.66-7.58 (overlapping signals, 3H, Ts, 6-H), 7.52-7.08 (m, 8H, Ar, Ts), 6.94-6.88 (m, 4H, Ar), 4.91 (s, 2H, 3-H), 4.25 (s, 2H, 5-CH_2), 4.19 (s, 2H, Bn), 2.44 (s, 3H, Ts). ^{13}C NMR ($CDCl_3$, 75 MHz): *meta* isomer **3ab1**: δ 170.5 (C, C-1), 143.7 (C, Ts), 143.4 (C, C-3a), 138.5 (C, C-6), 137.0 (C, C-4), 136.9 (C, Ar), 136.8 (C, Ts), 135.2 (C, Ar), 133.9 (CH, C-5), 129.8 (2 × CH, Ts), 129.0 (2 × CH, Ar), 128.5 (3 × CH, Ar), 128.4 (2 × CH, Ar), 127.7 (CH, Ar), 127.5 (2 × CH, Ar), 127.1 (2 × CH, Ts), 126.3 (C, C-7a), 123.9 (CH, C-7), 69.4 (CH_2, C-3), 51.9 (CH_2, Bn), 50.7 (CH_2, C6-CH_2), 21.4 (CH_3, Ts). *ortho* Isomer **3ab2**: δ 170.8 (C, C-1), 145.8 (C-3a), 143.5 (C, Ts), 140.7 (C, C-5), 136.4 (C, Ts), 135.5 (C, C-4), 134.9 (C, Ar), 134.8 (C, Ar), 129.7 (CH, C-6), 128.5 (2 × CH, Ar), 128.3 (2 × CH, Ar), 127.1 (2 × CH, Ts), 124.6 (C, C-7a), 124.5 (CH, C-7), 69.0 (CH_2, C-3), 52.2 (CH_2, Bn), 48.1 (CH_2, C5-CH_2), 21.4 (CH_3, Ts). Unassigned signals: δ 128.9, 128.2, 127.8. HRMS *m/z* calcd. for $C_{29}H_{25}KNO_4S$ $[M + K]^+$ 522.1136, found 522.1135.

Compounds 4'b



4'b1

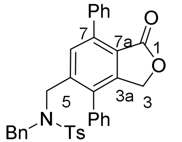
+



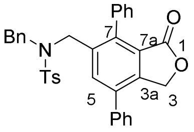
4'b2

Obtained as a yellow liquid consisting of a difficult to separate mixture of **4'b1** and **4'b2** in an approx. ratio 2:1 (0.322 g, 0.87 mmol, 35% yield). IR (film) (cm^{-1}): 3059, 3024, 2232, 1769, 1732, 1217. ^{1}H NMR (CDCl$_3$, 300 MHz): Major isomer **4’b1**: δ 8.10 (d, *J* = 7.9 Hz, 1H, 6-H), 7.98 (d, *J* = 7.9, 1H, 7-H), 7.57-7.24 (m, 10H, Ar-H), 5.14 (s, 2H, 3-H), 4.90 (s, 2H, 3’-H). Minor isomer **4’b2**: δ 8.65 (d, *J* = 1.2 Hz, 1H, 7-H), 8.46 (d, *J* = 1.3, 1H, 5-H), 7.57-7.24 (m, 10H, Ar-H), 5.46 (s, 2H, 3-H), 5.22 (s, 2H, 3’-H). ^{13}C NMR (CDCl$_3$, 75 MHz): Major isomer **4’b1**: δ 170.0 (C, C-1), 166.0 (C, C-1’), 146.2 (C, C-3a), 137.7 (C, C-4), 135.8 (C, Ar), 135.0 (C, C-5), 131.7 (2 × CH, Ar), 131.0 (CH, C-6), 128.74 (2 × CH, Ar), 128.3 (C, C-7a), 128.2 (2 × CH, Ar), 127.62 (2 × CH, Ar), 124.4 (CH, C-7), 121.84 (C, Ar), 86.7 (C, C-5’), 81.9 (C, C-4’), 69.4 (CH$_2$, C-3), 53.6 (CH$_2$, C-3’). Minor isomer **4’b2**: δ 169.8 (C, C-1), 164.4 (C, C-1’), 148.3 (C, C-3a) 137.4 (C, C-4), 136.4 (C, Ar), 134.7 (CH, C-5), 131.8 (2 × CH, Ar), 127.0 (C, C-7a), 126.0 (CH, C-7), 121.79 (C, Ar), 87.0 (C, C-5’), 82.3 (C, C-4’), 69.6 (CH$_2$, C-3), 53.9 (CH$_2$, C-3’). Unassigned signals: δ 129.6, 129.2, 128.82, 128.76, 128.65, 128.4, 127.64, 127.1. HRMS *m/z* calcd. for $C_{24}H_{17}O_4$ [M + H]$^+$ 369.1121, found 369.1122.

Compounds 3ac



3ac1

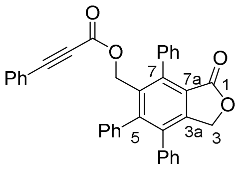


3ac2

Obtained as a pale yellow solid consisting of an inseparable mixture of **3ac1** and **3ac2** in an approx. ratio 1.2:1 (0.358 g, 0.64 mmol, 64% yield). M.p.: 159.6-165.7 °C. IR (film) (cm^{-1}): 3059, 3026, 2924, 1763, 1447, 1340, 1159. ^{1}H NMR (CDCl$_3$, 300 MHz): Major isomer **3ac1**: δ 7.63-6.93 (m, 19 H, Ar-H, Ts), 7.34 (overlapping s, 1H, 6-H), 4.88 (s, 2H, 3-H), 4.28 (s, 2H, 5-CH$_2$), 4.24 (s, 2H, Bn), 2.37 (s, 3H, Ts). Minor isomer **3ac2**: δ

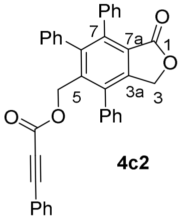
7.70 (s, 1H, 5-H), 7.63-6.93 (m, 19H, Ar-H, Ts), 5.27 (s, 2H, 3-H), 4.23 (s, 2H, 6-CH$_2$), 4.18 (s, 2H, Bn), 2.38 (s, 3H, Ts). ^{13}C NMR (CDCl$_3$, 75 MHz): Major isomer **3ac1**: δ 169.5 (C, C-3), 147.2 (C, C-3a), 140.4 (C, C-5), 134.1 (C, C-4), 130.9 (CH, C-6), 120.5 (C, C-7a), 67.8 (CH$_2$, C-3), 52.3 (CH$_2$, Bn), 48.0 (CH$_2$, C5-CH$_2$), 21.4 (CH$_3$, Ts). Minor isomer **3ac2**: δ 169.2 (C, C-3), 143.7 (C, C-3a), 139.1 (C, C-7), 137.1 (C, Ar), 136.9 (C, C-6), 135.6 (C, C-4), 133.8 (CH, C-5), 123.3 (C, C-7a), 67.9 (CH$_2$, C-3), 52.7 (CH$_2$, Bn), 48.2 (CH$_2$, C6-CH$_2$), 21.4 (CH$_3$, Ts). Unassigned signals: δ 143.5, 143.4, 143.3, 141.4, 136.5, 136.2, 135.8, 135.2, 135.0, 134.7, 129.68, 129.66, 129.4, 129.1, 128.9, 128.6, 128.5, 128.4, 128.32, 128.26, 127.9, 127.82, 127.76, 127.7, 127.6, 127.1, 126.97. HRMS *m/z* calcd. for $C_{35}H_{30}NO_4S$ [M + H]$^+$ 560.1890, found 560.1898.

Compounds 4c and **4’c**



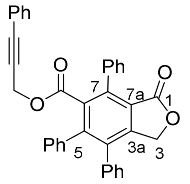
4c1

+



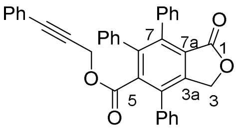
4c2

+



4'c1*

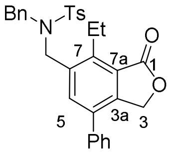
+



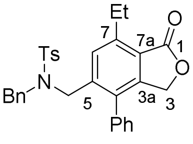
4'c2*

Obtained as a pale yellow liquid consisting of an inseparable mixture of compounds **4c1/4c2** and **4’c1/4’c2** in an approx. ratio 2:1:3.4:1 (0.403 g, 0.77 mmol, 31% yield). IR (film) (cm^{-1}): 3057, 3022, 2218, 1771, 1738, 1711, 1194. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.63-7.01 (m, 80H, Ar-H), 5.17 (s, 2H, 3-H), 5.13 (s, 2H, 3-H), 5.10 (s, 2H, 3-H), 5.08 (s, 2H, 3-H), 4.84 (s, 2H, 1’-H), 4.82 (s, 2H, 1’-H), 4.45 (s, 2H, 3’-H), 4.42 (s, 2H, 3’-H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 169.2, 169.1, 168.90, 168.87, 166.7, 166.6, 152.7, 152.6, 148.7, 147.3, 146.8, 145.6, 145.3, 145.2, 144.1, 143.1, 141.1, 141.0, 140.8, 138.9, 138.7, 137.8, 136.9, 136.8, 136.5, 136.44, 136.40, 136.2, 136.0, 135.7, 135.3, 135.2, 134.8, 134.7, 134.1, 133.9, 133.51, 133.46, 133.1, 132.9, 131.7, 130.7, 130.6, 130.1, 130.00, 129.96, 129.8, 129.7, 129.6, 129.1, 129.0, 128.9, 128.8, 128.7, 128.65, 128.60, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.64, 127.56, 127.53, 127.48, 127.4, 127.3, 127.2, 127.1, 123.7, 123.2, 122.5, 122.0, 121.95, 121.92, 119.4, 119.3, 86.4, 86.3, 82.3, 81.8, 81.6, 80.1, 79.9, 68.1, 68.0, 67.8, 67.7, 62.9, 62.7, 53.13, 53.06. HRMS *m/z* calcd. for $C_{36}H_{25}O_4$ [M + H]$^+$ 521.1747, found 521.1731.

Compounds 3ad



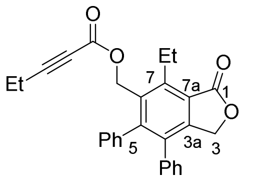
3ad1



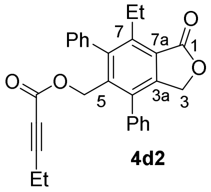
3ad2

Obtained as a pale yellow liquid consisting of an inseparable mixture of **3ad1** and **3ad2** in an approx. ratio 1.1:1 and trimers **5d** (0.409 g, 0.80 mmol, 80% yield). IR (film) (cm^{-1}): 3061, 3028, 2970, 2934, 1759, 1730, 1342, 1159. ^{1}H NMR ($CDCl_3$, 300 MHz): Major isomer **3ad1**: δ 7.81-7.74 (m, 2H, Ts), 7.52-6.86 (m, 13H, Ar, Ts, 5-H), 5.21 (s, 2H, 3-H), 4.50 (s, 2H, 6-CH_2), 4.37 (s, 2H, Bn), 2.96 (q, *J* = 7.4 Hz, 2H, 7-Et), 2.42 (s, 3H, Ts), 1.02 (t, *J* = 7.5 Hz, 3H, 7-Et). Minor isomer **3ad2**: δ 7.66-7.59 (m, 2H, Ts), 7.52-6.86 (m, 13H, Ar, Ts, 6-H), 4.84 (s, 2H, 3-H), 4.23 (s, 2H, 5-CH_2), 4.21 (s, 2H, Bn), 3.01 (q, *J* = 7.5 Hz, 2H, 7-Et), 2.43 (s, 3H, Ts), 1.21 (t, *J* = 7.5 Hz, 3H, 7-Et). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **3ad1**: δ 170.3 (C, C-1), 144.1 (C, C-3a), 143.6 (C, Ts), 143.1 (C, C-7), 137.2 (C, Ph), 136.6 (C, Ts), 135.3 (C, Bn), 135.2 (C, C-6), 134.1 (CH, C-5), 133.8 (C, C-4), 129.8 (2 × CH, Ts), 127.1 (2 × CH, Ts), 123.1 (C, C-7a), 68.0 (CH_2, C-3), 51.9 (CH_2, Bn), 47.4 (CH_2, C6-CH_2), 21.4 (CH_3, Ts), 19.2 (CH_2, C7-Et), 14.8 (CH_3, C7-Et). Minor isomer **3ad2**: δ 170.6 (C, C-1), 146.4 (C-3a), 144.6 (C, C-7), 143.5 (C, Ts), 140.2 (C, C-5), 136.6 (C, Ts), 135.02 (C, Bn), 134.98 (C, Ph), 132.9 (C, C-4), 129.7 (2 × CH, Ts), 129.2 (CH, C-6), 127.0 (2 × CH, Ts), 121.4 (C, C-7a), 68.2 (CH_2, C-3), 52.2 (CH_2, Bn), 48.1 (CH_2, C5-CH_2), 23.8 (CH_2, C7-Et), 21.3 (CH_3, Ts), 14.8 (CH_3, 7-Et). Unassigned signals: δ 128.84, 128.79, 128.3, 128.2, 127.5. HRMS *m/z* calcd. for $C_{31}H_{30}NO_4S$ $[M + H]^+$ 512.1890, found 512.1881.

Compounds 4d



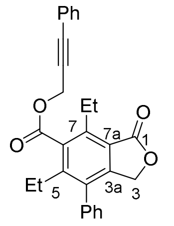
4d1



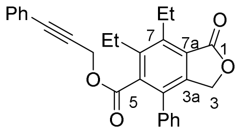
4d2

Obtained as a colourless liquid consisting of an inseparable mixture of **4d1** and **4d2** in an approx. ratio 5:1 (0.222 g, 0.52 mmol, 21% yield). IR (film) (cm^{-1}): 3059, 2980, 2938, 2235, 1759, 1713, 1244. ^{1}H NMR ($CDCl_3$, 300 MHz): Major isomer **4d1**: δ 7.25-7.13 (m, 6H, Ar-H), 7.08-7.00 (m, 2H, Ar-H), 6.99-6.93 (m, 2H, Ar-H), 5.043 (s, 2H, 3-H), 5.039 (s, 2H, 6-CH_2), 3.29 (q, *J* = 7.5 Hz, 2H, 7-Et), 2.34 (q, *J* = 7.5 Hz, 2H, 6'-H), 1.35 (t, *J* = 7.4 Hz, 7-Et), 1.20 (t, *J* = 7.5 Hz, 7'-H). Minor isomer **4d2**: δ 7.50-7.39 (m, 6H, Ar-H), 7.35-7.28 (m, 2H, Ar-H), 7.27-7.19 (m, 2H, Ar-H), 5.03 (s, 2H, 3-H), 4.65 (s, 2H, 1'-H), 2.88 (q, *J* = 7.5 Hz, 2H, 7-Et), 2.32 (q, *J* = 7.5 Hz, 2H, 6'-H), 1.20 (t, *J* = 7.5 Hz, 3H, 7'-H), 1.08 (t, *J* = 7.5 Hz, 3H, 7-Et). ^{13}C NMR (CDCl$_3$, 75 MHz): Major isomer **4d1**: δ 170.4 (C, C-1), 153.0 (C, C-3’), 148.7 (C, C-5), 147.0 (C, C-3a), 146.1 (C, C-7), 137.4 (C, Ar), 136.3 (C, Ar), 134.4 (C, C-4), 132.4 (C, C-6), 129.6 (2 × CH, Ar), 128.9 (2 × CH, Ar), 128.1 (2 × CH, Ar), 127.7 (2 × CH, Ar), 127.4 (CH, Ar), 127.3 (CH, Ar), 122.2 (C, C-7a), 91.1 (C, C-5’), 71.9 (C, C-5’), 68.3 (CH$_2$, C-3), 61.8 (CH$_2$, C-1’), 20.8 (CH$_2$, 7-Et), 15.7 (CH$_3$, 7-Et), 12.4 (CH$_3$, C-7’), 12.3 (CH$_2$, C-6’). Minor isomer **4d2**: δ 170.5 (C, C-1), 152.5 (C, C-3’), 145.8 (C, C-3a), 145.0 (C, C-6), 143.9 (C, C-7), 137.0 (C, Ar), 136.4 (C, C-5), 135.8 (C, C-4), 135.4 (C, Ar), 129.4 (2 × CH, Ar), 128.8 (2 × CH, Ar), 128.5 (2 × CH, Ar), 128.4 (CH, Ar), 128.2 (2 × CH, Ar), 127.8 (CH, Ar), 123.0 (C, C-7a), 90.7 (C, C-5’), 71.8 (C, C-4’), 68.3 (CH$_2$, C-3), 62.4 (CH$_2$, C-1’), 21.6 (CH$_2$, 7-Et), 15.4 (CH$_3$, 7-Et), 12.4 (CH$_3$, C-7’), 12.3 (CH$_2$, C-6’). HRMS *m/z* calcd. for C$_{28}$H$_{25}$O$_4$ [M + H]$^+$ 425.1747, found 425.1753.

Compounds 4’d



4'd1

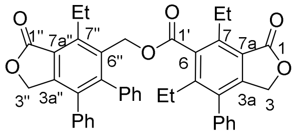


4'd2

Obtained as a pale yellow liquid consisting of an inseparable mixture of **4’d1** and **4’d2** in an approx. ratio 1.5:1 (0.212 g, 0.50 mmol, 20% yield). IR (film) (cm^{-1}): 2972, 2936, 1761, 1738, 1198, 1028. ^{1}H NMR (CDCl$_3$, 300 MHz): Major isomer **4’d1**: δ 7.52-7.20 (m, 10H, Ar-H), 5.21 (s, 2H, 3’-H), 4.89 (s, 2H, 3-H), 3.13 (q, *J* = 7.5 Hz, 2H, 7-Et), 2.61 (q, *J* = 7.5 Hz, 2H, 5-Et), 1.33 (t, *J* = 7.5 Hz, 3H, 7-Et), 1.02 (t, *J* = 7.5 Hz, 3H, 5-Et).

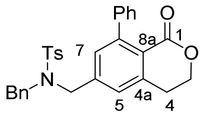
Minor isomer **4’d2**: δ 7.52-7.20 (m, 10H, Ar-H), 5.04 (s, 2H, 3-H), 4.81 (s, 2H, 3’-H), 3.23 (q, *J* = 7.5 Hz, 2H, 7-Et), 2.81 (q, *J* = 7.5 Hz, 2H, 6-Et), 1.27 (t, *J* = 7.5 Hz, 3H, 7-Et), 1.26 (t, *J* = 7.5 Hz, 3H, 6-Et). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **4’d1**: δ 170.1 (C, C-1), 168.2 (C, C-1’), 147.9 (C, C-3a), 145.4 (C, C-5), 142.1 (C, C-7), 135.3 (C, Ar), 134.5 (C, C-4), 131.6 (2 × CH, Ar), 128.9 (2 × CH, Ar), 128.7 (2 × CH, Ar), 128.4 (CH, Ar), 128.2 (2 × CH, Ar), 121.8 (C, C-6’), 120.5 (C, C-7a), 87.0 (C, C-5’), 82.0 (C, C-4’), 68.3 (CH_2, C-3), 53.5 (CH_2, C-3’), 24.3 (CH_2, C5-Et), 22.3 (CH_2, C7-Et), 15.6 (CH_3, C7-Et), 15.3 (CH_3, C5-Et). Minor isomer **4’d2**: δ 170.3 (C, C-1), 167.8 (C, C-1’), 143.9 (C, C-7), 143.8 (C, C-3a), 140.6 (C, C-6), 138.4 (C, C-5), 135.3 (C, Ar), 132.0 (C, C-4), 131.7 (2 × CH, Ar), 128.8 (CH, Ar), 128.7 (CH, Ar), 128.5 (2 × CH, Ar), 128.25 (2 × CH, Ar), 128.20 (2 × CH, Ar), 123.7 (C, C-7a), 121.9 (C, C-6’), 86.7 (C, C-5’), 81.8 (C, C-4’), 67.9 (CH_2, C-3), 53.2 (CH_2, C-3’), 23.0 (CH_2, C6-Et), 19.9 (CH_2, C7-Et), 15.8 (CH_3, C6-Et), 15.5 (CH_3, C7-Et). HRMS *m/z* calcd. for $C_{28}H_{25}O_4$ $[M + H]^+$ 425.1747, found 425.1747.

Compounds 5d

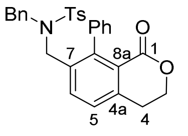


Obtained as a pale yellow liquid consisting of an inseparable mixture of trimers **5d** in an approx. ratio 2:1 (0.178 g, 0.28 mmol, 17% yield). IR (film) (cm^{-1}): 3022, 2972, 2936, 2876, 1759, 1728, 1028. ^{1}H NMR ($CDCl_3$, 300 MHz): Only major isomer could be analysed, δ 7.53-6.85 (m, 15H, Ar-H), 5.32 (s, 2H, 3’-H), 5.04 (s, 2H, 3’’-H), 4.87 (s, 2H, 3-H), 3.34 (q, *J* = 7.4 Hz, 2H, 7’’-Et), 2.95 (q, *J* = 7.5 Hz, 2H, 7-Et), 2.48 (q, *J* = 7.5 Hz, 2H, 5-Et), 1.36 (t, *J* = 7.3 Hz, 3H, 7’’-H), 1.19 (t, *J* = 7.4 Hz, 3H, 7’-H), 0.88 (t, *J* = 7.6 Hz, 3H, 5-H). ^{13}C NMR (CDCl$_3$, 75 MHz): Signals for phenyl groups have not been assigned, δ 170.3 (C, C-1’’), 170.1 (C, C-1), 168.5 (C, C-1’), 148.8 (C, C-6’’), 147.7 (C, C-3a), 147.2 (C, C-3a’’), 146.0 (C, C-7’’), 145.1 (C, C-5), 141.8 (C, C-7), 135.6 (C, C-6), 134.6 (C, C-4), 134.5 (C, C-4’’), 132.1 (C, C-5’’), 122.3 (C, C-7a’’), 120.5 (C, C-7a), 68.3 (2 × CH$_2$, C-3, C-3’’), 61.9 (CH$_2$, C-3’), 24.6 (CH$_2$, C5-Et), 22.6 (CH$_2$, C7-Et), 20.9 (CH$_2$, C7’’-Et), 15.9 (CH$_3$, C7’’-Et), 15.6 (CH$_3$, C7-Et), 15.5 (CH$_3$, C5-Et). HRMS *m/z* calcd. for C$_{42}$H$_{37}$O$_6$ [M + H]$^+$ 637.2585, found 637.2574.

Compounds 3ae



3ae1



3ae2

Obtained as a pale yellow liquid consisting of an inseparable mixture of **3ae1** and **3ae2** in an approx. ratio 3:1 (0.199 g, 0.40 mmol, <40% yield, contaminated with inseparable unidentified side-products). IR (film) (cm^{-1}): 3028, 2920, 2903, 1728, 1339, 1159, 1094. ^{1}H NMR (CDCl$_3$, 300 MHz): Major isomer **3ae1**: δ 7.78-7.71 (m, 2H, Ts), 7.46-7.02 (m, 12H, Ar-H, Ts), 6.96 (s, 1H, 5-H), 6.83 (s, 1H, 7-H), 4.44 (t, *J* = 5.8, 2H, 3-H), 4.34 (s, 2H, Bn), 4.33 (s, 2H, 6-CH$_2$), 2.90 (t, *J* = 5.7, 2H, 4-H), 2.43 (s, 3H, Ts). Minor isomer **3ae2**: δ 7.69 (d, *J* = 8.1 Hz, 1H, 6-H), 7.59-7.52 (m, 2H, Ts), 7.46-6.78 (m, 13H, Ar-H, Ts, 5-H), 4.41 (t, *J* = 5.7, 2H, 3-H), 4.11 (s, 2H, Bn), 4.03 (s, 2H, 7-CH$_2$), 3.01 (t, *J* = 5.7, 2H, 4-H), 2.40 (s, 3H, Ts). RMN de ^{13}C (CDCl$_3$, 300 MHz): Major isomer **3ae1**: δ

163.1 (C, C-1), 145.7 (C, C-8), 143.5 (C, Ts), 141.1 (C, C-4a), 140.7 (C, C-6), 140.6 (C, Ar), 136.8 (C, Ts), 135.3 (C, Bn), 130.3 (CH, C-7), 129.7 (2 × CH, Ar), 128.6 (2 × CH, Ar), 128.2 (2 × CH, Ar), 128.1 (2 × CH, Ar), 127.8 (2 × CH, Ar), 127.0 (2 × CH, Ar), 126.0 (CH, C-5), 122.5 (C, C-8a), 66.5 (CH_2, C-3), 52.0 (CH_2, Bn), 50.8 (CH_2, 6-CH_2), 29.0 (CH_2, C-4), 21.4 (CH_3, Ts). Minor isomer **3ae2**: δ 162.9 (C, C-1), 143.32 (C, Ts), 143.28 (C, C-8), 139.5 (C, C-4a), 138.4 (C, Ar), 136.5 (C, Ar), 135.3 (C, C-7) 135.1 (C, Bn), 132.9 (2 × CH, Ts), 132.7 (CH, C-6), 129.5 (2 × CH, Ar), 128.5 (2 × CH, Ar), 128.1 (2 × CH, Ar), 127.9 (2 × CH, Ar), 127.6 (CH, Ar), 127.0 (2 × CH, Ts), 126.5 (CH, C-5), 123.9 (C, C-8a), 66.5 (CH_2, C-3), 52.2 (CH_2, Bn), 48.7 (CH_2, C7-CH_2), 28.9 (CH_2, C-4), 21.4 (CH_3, Ts). HRMS *m/z* calcd. for $C_{30}H_{28}NO_4S$ $[M + H]^+$ 498.1734, found 498.1731.

Preparation of resin 1b

To 1.0 g of BOBA resin prepared according to Kobayashi and Aoki (**7**, approximate loading: 1.00 mmol/g) suspended in dichloromethane (9 mL) was added p-toluenesulfonyl chloride (0.593 g, 3.10 mmol) and triethylamine (0.65 mL, 1.57 mmol). The reaction mixture was stirred at room temperature for 18 hours and then filtered. The remaining resin was then washed with dichloromethane (7 × 10 mL) and dried under reduced pressure. To this resin in DMF (18 mL) was added cesium carbonate (1.77 g, 5.4 mmol) and propargyl bromide (80% in toluene, 1.2 mL, 10.8 mmol). The reaction mixture was stirred at room temperature for 24 hours and then filtered. The remaining solid was washed with DMF (2 × 10 mL), DMF:H_2O (2 × 10 mL), H_2O (2 × 10 mL), DMF (3 × 10 mL), DCM and MeOH (alternated 5 × 10 mL each) and DCM (3 × 10 mL). The final resin was dried under reduced pressure to afford resin **1b** (approx. 1.18 g). The loading of resin **1b** was calculated based on the amount of compound **8** released upon treatment with TFA in DCM (1 mL TFA/3 mL DCM for 100 mg of resin **1b**, 18 h, room temperature). The crude mixture thus obtained was purified by flash column chromatography on silica gel (eluent hexanes/ethyl acetate) to afford known compound **8** (initial loading resin **6**: 1.16 mmol/g; theoretical loading **1b**: 0.88 mmol/g, isolated amount **8**: 13.8 mg, 0.066 mmol, calculated loading **1b**: 0.66 mmol/g, 75% yield after five steps from resin **6**).

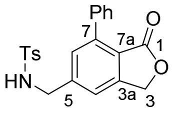
Compound 8[32]

Colourless solid. M.p.: 74.0-75.0 ºC. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.83-7.73 (m, 2H), 7.36-7.28 (m, 2H), 4.76 (t, *J* = 5.5 Hz, 1H), 3.83 (dd, *J* = 6.0 Hz, *J* = 2.5 Hz, 2H), 2.43 (s, 3H), 2.10 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 143.7, 136.4, 129.6, 127.3, 77.8, 72.9, 32.7, 21.4.

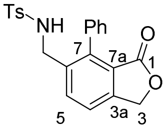
Representative procedure for the solid-phase synthesis of phthalides 9 and 4

A mixture of resin **1b** (200 mg, 0.66 mmol/g, 0.13 mmol), diyne **2** (0.66 mmol, 5 equiv), and Wilkinson catalyst [Rh(PPh$_3$)$_3$Cl, 6 mg, 0.0065 mmol] in toluene (4.5 mL, 0.03 M) was heated at reflux. After approx. 2 hours, the reaction was filtered and the filtrate was evaporated under reduced pressure. This residue was purified by flash column chromatography on silica gel (eluent hexanes/ethyl acetate) to afford the following phthalides **4**. The remaining resin was treated overnight with TFA in DCM (1 mL TFA/3 mL DCM for 100 mg of resin, room temperature). After that time, the solvent was evaporated and the residue purified by flash column chromatography on silica gel (eluent hexanes/ethyl acetate or DCM/methanol) to afford the following phthalides **9**.

Compounds 9ba



9ba1

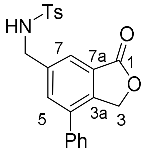


9ba2

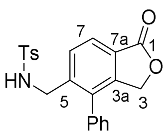
Obtained as a pale yellow liquid consisting of an inseparable mixture of **9ba1** and **9ba2** in an approx. ratio 2.7:1 (0.036 g, 0.09 mmol, 70% yield). IR (film) (cm^{-1}): 3059, 3026, 2924, 1755, 1327, 1159. ^1H NMR ($CDCl_3$, 300 MHz): Major isomer **9ba1**: δ 7.76-7.70 (m, 2H, Ts), 7.48-7.38 (m, 5H, Ar-H), 7.35 (s, 1H, 4-H), 7.30-7.25 (m, 2H, Ts), 7.23 (s, 1H, 6-H), 5.37 (t, J = 6.5 Hz, 1H, N-H), 5.19 (s, 2H, 3-H), 4.27 (d, J = 6.5 Hz, 2H, 5-CH_2), 2.41 (s, 3H, Ts). Minor isomer **9ba2**: δ 7.80 (d, J = 7.9 Hz, 1H, 5-H), 7.57-7.51 (m, 2H, Ts), 7.47-7.36 (m, 3H, Ar, 4-H), 7.29-7.17 (m, 3H, Ar-H), 7.14-7.09 (m, 2H, Ts), 5.24 (s, 2H, 3-H), 4.71 (t, J = 6.3 Hz, 1H, N-H), 4.00 (d, J = 6.3 Hz, 2H, 6-CH_2), 2.41 (s, 3H, Ts). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **9ba1**: δ 169.3 (C, C-1), 148.5 (C, C-3a), 143.7 (C, Ts), 143.2 (C, C-5), 142.7 (C, C-7), 136.7 (C, Ts), 135.7 (C, Ar), 130.1 (CH, C-6), 129.6 (2 × CH, Ts), 129.3 (2 × CH, Ar), 128.4 (CH, Ar), 127.8 (2 × CH, Ar), 126.9 (2 × CH, Ts), 121.0 (C, C-7a), 119.8 (CH, C-4), 68.1 (CH_2, C-3), 46.6 (CH_2, C5-CH_2), 21.4 (CH_3, Ts). Minor isomer **9ba2**: δ 169.1 (C, C-1), 146.8 (C, C-3a), 143.4 (C, Ts), 141.1 (C, C-7), 136.2 (C, Ts), 136.1 (C, C-6), 135.0 (CH, C-5), 133.8 (C, Ar), 129.5 (2 × CH, Ts), 128.6 (2 × CH, Ar), 128.2 (2 × CH, Ar), 128.1 (CH, Ar), 126.8 (2 × CH, Ts), 123.2 (C, C-

7a), 121.4 (CH, C-4), 68.0 (CH_2, C-3), 43.9 (CH_2, C6-CH_2), 21.4 (CH_3, Ts). HRMS *m/z* calcd. for $C_{22}H_{20}NO_4S$ $[M + H]^+$ 394.1108, found 394.1092.

Compounds 9bb



9bb1

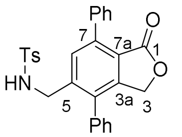


9bb2

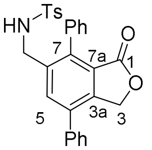
Obtained as a pale yellow liquid consisting of an inseparable mixture of **9bb1** and **9bb2** in an approx. ratio 1.3:1 (0.020 g, 0.052 mmol, 40% yield). IR (film) (cm^{-1}): 3026, 2922, 1751, 1327, 1159. ^1H NMR ($CDCl_3$, 300 MHz): Major isomer **9bb1**: δ 7.79-7.72 (m, 2H, Ts), 7.66 (s, 1H, 7-H), 7.64 (s, 1H, 5-H), 7.53-7.40 (m, 3H, Ar-H), 7.40-7.34 (m, 2H, Ar-H), 7.33-7.27 (m, 2H, Ts), 5.36 (s, 2H, 3-H), 4.97 (t, *J* = 6.5 Hz, 1H, N-H), 4.30 (d, *J* = 6.3 Hz, 2H, 6-CH_2), 2.42 (s, 3H, Ts). Minor isomer **9bb2**: δ 7.84 (d, *J* = 8.1 Hz, 1H, 7-H), 7.60 (d, *J* = 8.0 Hz, 1H, 6-H), 7.60-7.55 (m, 2H, Ts), 7.53-7.28 (m, 3H, Ar-H), 7.24-7.18 (m, 2H, Ts), 7.17-7.11 (m, 2H, Ar-H), 4.99 (s, 2H, 3-H), 4.60 (t, *J* = 6.2 Hz, 1H, N-H), 4.10 (d, *J* = 6.3 Hz, 2H, 5-CH_2), 2.42 (s, 3H, Ts). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **9bb1**: δ 170.5 (C, C-1), 143.8 (C, Ts), 143.7 (C, C-3a), 138.9 (C, C-6), 137.4 (C, C-4), 136.9 (C, Ar), 136.7 (C, Ts), 133.4 (CH, C-5), 129.7 (2 × CH, Ts), 129.1 (2 × CH, Ar), 128.6 (CH, Ar), 127.5 (2 × CH, Ar), 127.0 (2 × CH, Ts), 126.8 (C, C-7a), 123.4 (CH, C-7), 69.5 (CH_2, C-3), 46.6 (CH_2, C6-CH_2), 21.4 (CH_3, Ts). Minor isomer **9bb2**: δ 170.6 (C, C-1), 146.1 (C, C-3a), 143.6 (C, Ts), 140.4 (C, C-5), 136.4 (C, Ts), 136.2 (C, C-4), 134.8 (C, Ar), 130.3 (CH, C-6), 129.6 (2 × CH, Ts), 129.2 (2 × CH, Ar), 128.6 (CH, Ar), 128.1 (2 ×

CH, Ar), 126.9 (2 × CH, Ts), 125.3 (C, C-7a), 124.9 (CH, C-7), 69.1 (CH_2, C-3), 44.3 (CH_2, C5-CH_2), 21.4 (CH_3, Ts). HRMS *m/z* calcd. for $C_{22}H_{20}NO_4S$ $[M + H]^+$ 394.1108, found 394.1101.

Compounds 9bc



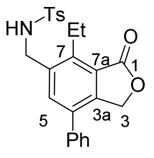
9bc1



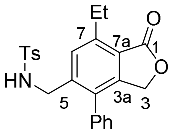
9bc2

Obtained as a colorless to pale yellow solid consisting of an inseparable mixture of **9bc1** and **9bc2** in an approx. ratio 1.2:1 (0.037 g, 0.078 mmol, 60% yield). M.p.: 91.8-96.8 ºC. IR (film) (cm^{-1}): 3059, 3026, 2920, 1755, 1327, 1159. ^{1}H NMR ($CDCl_3$, 300 MHz): Major isomer **9bc1**: δ 7.60-7.13 (m, 15H, Ar-H, Ts, 6-H), 4.96 (s, 2H, 3-H), 4.62 (t, *J* = 6.4 Hz, 1H, N-H), 4.14 (d, *J* = 6.4 Hz, 2H, 5-CH_2), 2.37 (s, 3H, Ts). Minor isomer **9bc2**: δ 7.74 (s, 1H, 5-H), 7.60-7.13 (m, 14H, Ar-H, Ts), 5.32 (s, 2H, 3-H), 4.51 (t, *J* = 6.5 Hz, 1H, N-H), 4.08 (d, *J* = 6.4 Hz, 2H, 6-CH_2), 2.38 (s, 3H, Ts). ^{13}C NMR ($CDCl_3$, 75 MHz): Only signals attributed to the phthalide core are listed, major isomer **9bc1**: δ 169.3 (C, C-1), 147.5 (C, C-3a), 140.1 (C, C-5), 134.7 (C, C-4), 131.6 (CH, C-6), 121.2 (C, C-7a), 67.9 (CH_2, C-3), 44.3 (CH_2, C5-CH_2). Minor isomer **9bc2**: δ 169.0 (C, C-1), 144.3 (C, C-3a), 139.9 (C, C-7), 136.8 (C, C-6), 136.2 (C, C-4), 134.6 (CH, C-5), 123.9 (C, C-7a), 68.0 (CH_2, C-3), 44.2 (CH_2, C6-CH_2). HRMS *m/z* calcd. for $C_{28}H_{24}NO_4S$ $[M + H]^+$ 470.1421, found 470.1417.

Compounds 9bd



9bd1

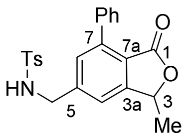


9bd2

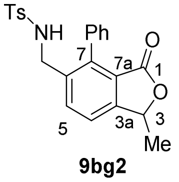
Obtained as a pale yellow liquid consisting of an inseparable mixture of **9bd1** and **9bd2** in an approx. ratio 1.2:1 (0.033 g, 0.078 mmol, 60% yield). IR (film) (cm^{-1}): 3026, 2968, 2930, 2874, 1747, 1329, 1159. ^{1}H NMR (CDCl$_3$, 300 MHz): Major isomer **9bd1**: δ 7.78-7.72 (m, 2H, Ts), 7.52 (s, 1H, 5-H), 7.49-7.36 (m, 3H, Ar-H), 7.34-7.24 (m, 4H, Ts, Ar-H), 5.24 (s, 2H, 3-H), 5.13 (t, *J* = 6.0 Hz, 1H, N-H), 4.27 (d, *J* = 6.1 Hz, 2H, 6-CH$_2$), 3.07 (q, *J* = 7.5 Hz, 2H, 7-Et), 2.40 (s, 3H, Ts), 1.14 (t, *J* = 7.5 Hz, 3H, 7-Et). Minor isomer **9bd2**: δ 7.60-7.54 (m, 2H, Ts), 7.49-7.35 (m, 3H, Ar-H), 7.34-7.24 (overlapping signal, 1H, 6-H), 7.23-7.16 (m, 2H, Ts), 7.14-7.07 (m, 2H, Ar-H), 4.89 (s, 2H, 3-H), 4.88 (t, *J* = 6.3 Hz, 1H, N-H), 4.05 (d, *J* = 6.3 Hz, 2H, 5-CH$_2$), 3.05 (q, *J* = 7.6 Hz, 2H, 7-Et), 2.40 (s, 3H, Ts), 1.24 (t, *J* = 7.6 Hz, 3H, 7-Et). ^{13}C NMR (CDCl$_3$, 75 MHz): Major isomer **9bd1**: δ 170.3 (C, C-1), 144.6 (C, C-3a), 143.6 (C, Ts), 143.3 (C, C-7), 137.1 (C, Ar), 136.5 (C, Ar), 135.7 (C, C-6), 134.7 (CH, C-5), 134.3 (C, C-4), 129.6 (2 × CH, Ts), 128.9 (2 × CH, Ar), 128.2 (CH, Ar), 127.5 (2 × CH, Ar), 127.0 (2 × CH, Ts), 123.5 (C, C-7a), 68.1 (CH$_2$, C-3), 43.4 (CH$_2$, C6-CH$_2$), 21.4 (CH$_3$, Ts), 19.5 (CH$_2$, C7-Et), 15.2 (CH$_3$, C7-Et). Minor isomer **9bd2**: δ 170.5 (C, C-1), 146.7 (C, C-3a), 145.2 (C, C-7), 143.5 (C, Ts), 140.0 (C, C-5), 136.5 (C, Ts), 134.8 (C, Ar), 133.4 (C, C-4), 129.9 (CH, C-6), 129.6 (2 × CH, Ts), 129.1 (2 × CH, Ar), 128.3 (CH, Ar), 128.2 (2 × CH, Ar), 126.8 (2 × CH, Ts), 122.0 (C, C-7a), 68.3

(CH_2, C-3), 44.2 (CH_2, C5-CH_2), 23.8 (CH_2, C7-Et), 21.3 (CH_3, Ts), 14.8 (CH_3, C7-Et). HRMS *m/z* calcd. for $C_{24}H_{24}NO_4S$ $[M + H]^+$ 422.1421, found 422.1433.

Compounds 9bg



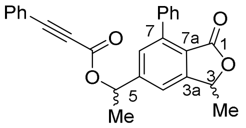
9bg1



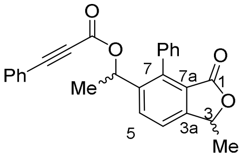
9bg2

Obtained as a pale yellow solid consisting of an inseparable mixture of **9bg1** and **9bg2** in an approx. ratio 2.7:1 (0.037 g, 0.091 mmol, 70% yield). M.p.: 174.9-178.9 °C. IR (film) (cm^{-1}): 3024, 2980, 2926, 1751, 1329, 1159, 1051. ^1H NMR ($CDCl_3$, 300 MHz): Major isomer **9bg1**: δ 7.75-7.69 (m, 2H, Ts), 7.47-7.33 (m, 5H, Ar-H), 7.30-7.23 (m, 2H, Ts), 7.28 (s, 1H, 4-H), 7.21 (s, 1H, 6-H), 5.42 (q, J = 6.5 Hz, 1H, 3-H), 5.22 (t, J = 5.6 Hz, 1H, N-H), 4.28 (d, J = 6.1 Hz, 2H, 5-CH_2), 2.40 (s, 3H, Ts), 1.58 (d, J = 6.6 Hz, 3H, 3-CH_3). Minor isomer **9bg2**: δ 7.77 (d, J = 7.9 Hz, 1H, 5-H), 7.55-7.49 (m, 2H, Ts), 7.47-7.33 (m, 4H, Ar-H, 4-H), 7.22-7.16 (m, 2H, Ts), 7.14-7.06 (m, 2H, Ar-H), 5.47 (q, J = 6.5 Hz, 1H, 3-H), 4.59 (t, J = 6.5 Hz, 1H, N-H), 4.00 (d, J = 6.3 Hz, 2H, 6-CH_2), 2.40 (s, 3H, Ts), 1.62 (d, J = 6.7 Hz, 3H, 3-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **9bg1**: δ 168.6 (C, C-1), 153.1 (C, C-3a), 143.7 (C, Ts), 143.2 (C, C-5), 142.8 (C, C-7), 136.7 (C, Ts), 135.8 (C, Ar), 130.1 (CH, C-6), 129.7 (2 × CH, Ts), 129.3 (2 × CH, Ar), 128.4 (CH, Ar), 127.8 (2 × CH, Ar), 127.0 (2 × CH, Ts), 121.1 (C, C-7a), 119.3 (CH, C-4), 75.9 (CH, C-3), 46.7 (CH_2, C5-CH_2), 21.4 (CH_3, Ts), 20.3 (CH_3, C3-CH_3). Minor isomer **9bg2**: δ 168.4 (C, C-1), 151.4 (C, C-3a), 143.4 (C, Ts), 141.0 (C, C-7), 136.3 (C, Ts), 136.0 (C, C-6), 135.1 (CH, C-5), 133.9 (C, Ar), 129.5 (2 × CH, Ts), 128.7 (CH, Ar), 128.5 (2 × CH, Ar), 128.2 (2 × CH, Ar), 126.8 (2 × CH, Ts), 123.2 (C, C-7a), 120.9 (CH, C-4), 75.8 (CH, C-3), 44.0 (CH_2, C6-CH_2), 21.4 (CH_3, Ts), 20.3 (CH_3, C3-CH_3). HRMS *m/z* calcd. for $C_{23}H_{22}NO_4S$ [M + H]$^+$ 408.1264, found 408.1269.

Compounds 4g



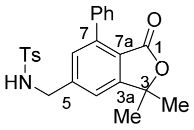
4g1



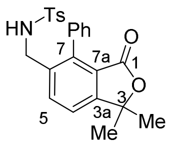
4g2

Obtained as a pale yellow liquid consisting of an inseparable mixture of **4g1** and **4g2** in an approx. ratio 3.3:1 (0.068 g, 0.171 mmol, 52% yield). IR (film) (cm^{-1}): 3022, 2982, 2932, 2212, 1761, 1707, 1283, 1188, 1171. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.910 (d, *J* = 8.1 Hz, 1H, 5-H*), 7.909 (d, *J* = 8.0 Hz, 1H, 5-H*), 7.64-7.10 (overlapping signals, 46H, Ar-H), 6.11 (q, *J* = 6.7 Hz, 2H), 5.93-5.81 (overlapping signals, 2H), 5.61-5.43 (overlapping signals, 4H), 1.73-1.60 (overlapping signals, 18H), 1.51-1.43 (overlapping signals, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.6, 168.4, 153.11, 153.09, 153.02, 152.98, 152.73, 152.72, 151.3, 147.3, 147.1, 143.01, 142.99, 141.1, 139.93, 139.90, 136.0, 133.9, 132.9, 132.8, 131.1, 130.7, 130.6, 129.4, 129.0, 128.8, 128.64, 128.62, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 123.1, 121.6, 121.5, 121.2, 119.3, 119.2, 117.9, 117.6, 87.1, 86.4, 80.4, 80.3, 76.0, 75.7, 73.40, 73.36, 70.83, 70.79, 22.3, 22.2, 22.1, 20.4, 20.32, 20.27. HRMS *m/z* calcd. for $C_{26}H_{20}NaO_4$ [M + Na]$^+$ 419.1254, found 419.1252.

Compounds 9bh



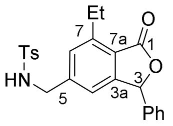
9bh1



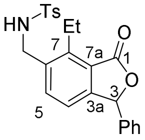
9bh2

Obtained as a pale yellow liquid consisting of an inseparable mixture of **9bh1** and **9bh2** in an approx. ratio 2.5:1 (0.033 g, 0.078 mmol, 60% yield). IR (film) (cm^{-1}): 3026, 2978, 2928, 1751, 1329, 1159, 1092. ^{1}H NMR ($CDCl_3$, 300 MHz): Major isomer **9bh1**: δ 7.76-7.71 (m, 2H, Ts), 7.49-7.30 (m, 5H, Ar-H), 7.30-7.25 (m, 2H, Ts), 7.24 (s, 1H, 4-H), 7.19 (s, 1H, 6-H), 5.16 (t, J = 6.5 Hz, 1H, N-H), 4.29 (d, J = 6.5 Hz, 2H, 5-CH_2), 2.40 (s, 3H, Ts), 1.61 (s, 6H, 3-CH_3). Minor isomer **9bh2**: δ 7.76 (d, J = 8.0 Hz, 1H, 5-H), 7.55-7.48 (m, 2H, Ts), 7.48-7.30 (m, 3H, Ar-H), 7.33 (d, J = 8.0 Hz, 1H, 4-H), 7.22-7.16 (m, 2H, Ts), 7.14-7.09 (m, 2H, Ar-H), 4.53 (t, J = 6.2 Hz, 1H, N-H), 4.01 (d, J = 6.4 Hz, 2H, 6-CH_2), 2.41 (s, 3H, Ts), 1.64 (s, 6H, 3-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **9bh1**: δ 167.9 (C, C-1), 157.0 (C, C-3a), 143.8 (C, Ts), 143.1 (C, C-5), 142.9 (C, C-7), 136.7 (C, Ts), 135.9 (C, Ar), 129.9 (CH, C-6), 129.7 (2 × CH, Ts), 129.3 (2 × CH, Ar), 128.2 (CH, Ar), 127.8 (2 × CH, Ar), 127.0 (2 × CH, Ts), 120.6 (C, C-7a), 118.4 (CH, C-4), 83.3 (C, C-3), 46.7 (CH_2, C5-CH_2), 27.4 (2 × CH_3, C3-CH_3), 21.4 (CH_3, Ts). Minor isomer **9bh2**: δ 167.8 (C, C-1), 155.3 (C, C-3a), 143.4 (C, Ts), 141.1 (C, C-7), 136.4 (C, Ts), 135.8 (C, C-6), 135.1 (CH, C-5), 134.0 (C, Ar), 129.5 (2 × CH, Ts), 129.4 (2 × CH, Ar), 128.5 (2 × CH, Ar), 128.2 (CH, Ar), 126.8 (2 × CH, Ts), 122.7 (C, C-7a), 120.0 (CH, C-4), 83.2 (C, C-3), 44.1 (CH_2, C6-CH_2), 27.3 (2 × CH_3, C3-CH_3), 21.4 (CH_3, Ts). HRMS *m/z* calcd. for $C_{24}H_{24}NO_4S$ $[M + H]^+$ 422.1421, found 422.1404.

Compounds 9bi



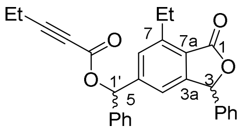
9bi1



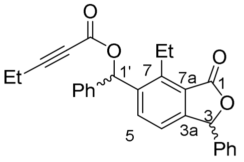
9bi2

Obtained as a pale yellow liquid consisting of an inseparable mixture of **9bi1** and **9bi2** in an approx. ratio 2.8:1 (0.030 g, 0.071 mmol, 55% yield). IR (film) (cm^{-1}): 3030, 2970, 2928, 2872, 1747, 1329, 1159. ^1H NMR ($CDCl_3$, 300 MHz): Major isomer **9bi1**: δ 7.72-7.65 (m, 2H, Ts), 7.39-7.33 (m, 3H, Ar-H), 7.27-7.19 (m, 4H, Ar-H, Ts), 7.12 (s, 1H, 6-H), 6.98 (s, 1H, 4-H), 6.21 (s, 1H, 3-H), 4.97 (t, *J* = 6.5 Hz, 1H, N-H), 4.16 (d, *J* = 6.5 Hz, 2H, 5-CH_2), 3.17-2.97 (m, 2H, 7-Et), 2.41 (s, 3H, Ts), 1.24 (t, *J* = 7.5 Hz, 3H, 7-Et). Minor isomer **9bi2**: δ 7.78-7.72 (m, 2H, Ts), 7.50 (d, *J* = 8.0 Hz, 1H, 5-H), 7.32-7.27 (m, 2H, Ts), 7.25-7.20 (m, 5H, Ar-H), 7.05 (d, *J* = 7.9 Hz, 1H, 4-H), 6.25 (s, 1H, 3-H), 4.79 (t, *J* = 6.0 Hz, 1H, N-H), 4.22 (d, *J* = 6.1 Hz, 2H, 6-CH_2), 3.12-2.97 (q, *J* = 7.4 Hz, 2H, 7-Et), 2.43 (s, 3H, Ts), 1.16 (t, *J* = 7.5 Hz, 3H, 7-Et). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **9bi1**: δ 169.7 (C, C-1), 151.0 (C, C-3a), 146.2 (C, C-7), 143.7 (C, Ts), 143.4 (C, C-5), 136.6 (C, Ts), 136.4 (C, Ar), 129.6 (2 × CH, Ts), 128.8 (2 × CH, Ar), 128.6 (CH, C-6), 127.0 (2 × CH, Ts), 126.7 (2 × CH, Ar), 121.7 (C, C-7a), 119.1 (CH, C-4), 81.5 (CH, C-3), 46.8 (CH_2, C5-CH_2), 24.0 (CH_2, C7-Et), 21.4 (CH_3, Ts), 14.8 (CH_3, C7-Et). Minor isomer **9bi2**: δ 169.7 (C, C-1), 150.4 (C, C-3a), 144.5 (C, C-7), 143.7 (C, Ts), 136.6 (2 × C, Ar, Ts), 135.3 (C, CH, C-6, C-5), 129.7 (2 × CH, Ts), 129.1 (2 × CH, Ar), 127.0 (2 × CH, Ts), 126.8 (2 × CH, Ar), 122.8 (C, C-7a), 120.4 (CH, C-4), 81.1 (CH, C-3), 43.4 (CH_2, C6-CH_2), 21.4 (CH_3, Ts), 19.9 (CH_2, C7-Et), 15.3 (CH_3, C7-Et). HRMS *m/z* calcd. for $C_{24}H_{24}NO_4S$ $[M + H]^+$ 422.1421, found 422.1403.

Compounds 4i



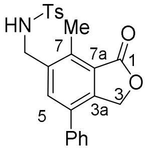
4i1



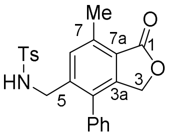
4i2

Obtained as a pale yellow liquid consisting of an inseparable mixture of **4i1** and **4i2** in an approx. ratio 2.3:1 (0.038 g, 0.089 mmol, 27% yield). IR (film) (cm^{-1}): 3032, 2978, 2938, 2876, 2235, 1759, 1713, 1454, 1242. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.71 (d, *J* = 8.0 Hz, 1H, 5-H), 7.69 (d, *J* = 8.0 Hz, 1H, 5-H), 7.45-7.22 (overlapping signals, 42H, Ar-H), 7.18 (s, 1H, 4-H), 7.17 (d, *J* = 8.0 Hz, 2H, 4-H, 4-H), 7.10 (s, 1H, 4-H), 6.90 (s, 2H, 1'-H, 1'-H), 6.89 (s, 2H, 1'-H, 1'-H), 6.31 (s, 2H, 3-H, 3-H), 6.29 (s, 2H, 3-H, 3-H), 3.41-2.99 (overlapping signals, 8H, 7-Et), 2.42-2.28 (overlapping signals, 8H, 6'-H), 1.35-1.14 (overlapping signals, 24H, 7-Et, 7'-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.6, 152.6, 152.50, 152.45, 150.7, 150.50, 150.47, 146.3, 146.2, 146.1, 146.0, 144.05, 143.97, 138.42, 138.40, 138.37, 138.2, 136.41, 136.37, 136.34, 133.69, 133.67, 129.4, 129.13, 129.07, 129.0, 128.8, 128.65, 128.60, 128.55, 128.52, 128.4, 128.30, 128.28, 128.0, 127.4, 127.3, 127.2, 127.02, 126.96, 126.9, 126.8, 126.7, 122.8, 122.2, 122.1, 120.42, 120.38, 120.3, 118.8, 118.3, 92.1, 92.0, 91.9, 81.6, 81.3, 81.1, 81.0, 77.5, 77.4, 74.0, 73.8, 72.05, 71.98, 66.5, 24.2, 24.1, 20.3, 14.85, 14.81, 12.34, 12.26. HRMS *m/z* calcd. for $C_{28}H_{25}O_4$ $[M + H]^+$ 425.1747, found 425.1745.

Compounds 9bj



9bj1

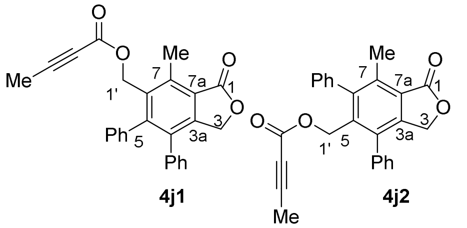


9bj2

Obtained as a colorless liquid consisting of an inseparable mixture of **9bj1** and **9bj2** in an approx. ratio 1.5:1 (0.033 g, 0.082 mmol, 63% yield). IR (film) (cm^{-1}): 3061, 3026, 2924, 1738, 1327, 1159, 1028. ^1H NMR ($CDCl_3$, 300 MHz): Major isomer **9bj1**: δ 7.77-7.70 (m, 2H, Ts), 7.51 (s, 1H, 5-H), 7.49-7.36 (m, 3H, Ar-H), 7.35-7.29 (m, 2H, Ar-H), 7.29-7.23 (m, 2H, Ts), 5.24 (s, 2H, 3-H), 5.04 (t, *J* = 6.0 Hz, 1H, N-H), 4.26 (d, *J* = 6.0 Hz, 2H, 6-CH_2), 2.60 (s, 3H, 7-CH_3), 2.40 (s, 3H, Ts). Minor isomer **9bj2**: δ 7.59-7.53 (m, 2H, Ts), 7.49-7.36 (m, 2H, Ar-H), 7.29-7.23 (overlapping signal, 1H, Ar-H, 1H, 6-H), 7.23-7.16 (m, 2H, Ts), 7.14-7.07 (m, 2H, Ar-H), 4.90 (s, 2H, 3-H), 4.77 (t, *J* = 6.2 Hz, 1H, N-H), 4.04 (d, *J* = 6.3 Hz, 2H, 5-CH_2), 2.61 (s, 3H, 7-CH_3), 2.40 (s, 3H, Ts). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **9bj1**: δ 170.8 (C, C-1), 144.1 (C, C-3a), 143.6 (C, Ts), 137.14 (C, C-7), 137.08 (C, Ar), 136.53 (C, Ts), 136.50 (C, C-6), 134.1 (CH, C-5), 134.0 (C, C-4), 129.6 (2 × CH, Ts), 129.0 (2 × CH, Ar), 128.2 (CH, Ar), 127.5 (2 × CH, Ar), 127.0 (2 × CH, Ts), 124.1 (C, C-7a), 68.1 (CH_2, C-3), 44.2 (CH_2, C6-CH_2), 21.4 (CH_3, Ts), 12.2 (CH_3, C7-CH_3). Minor isomer **9bj2**: δ 170.8 (C, C-1), 146.5 (C, C-3a), 143.5 (C, Ts), 139.8 (C, C-5), 138.8 (C, C-7), 136.5 (C, Ts), 134.8 (C, Ar), 133.4 (C, C-4), 131.6 (CH, C-6), 129.5 (2 ×

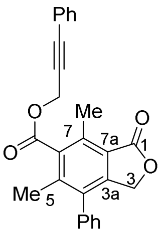
CH, Ts), 129.1 (2 × CH, Ar), 128.4 (CH, Ar), 128.3 (2 × CH, Ar), 126.9 (2 × CH, Ts), 122.7 (C, C-7a), 68.3 (CH_2, C-3), 44.2 (CH_2, C5-CH_2), 21.4 (CH_3, Ts), 16.9 (CH_3, C7-CH_3). HRMS *m/z* calcd. for $C_{23}H_{21}NNaO_4S$ $[M + Na]^+$ 430.1083, found 430.1075.

Compounds 4j

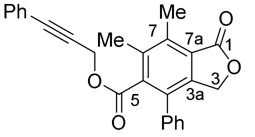


Obtained as a colorless liquid consisting of an inseparable mixture of **4j1** and **4j2** in an approx. ratio 2.4:1 (0.017 g, 0.043 mmol, 13% yield). IR (film) (cm^{-1}): 3022, 2961, 2920, 2239, 1763, 1707, 1252. ^1H NMR ($CDCl_3$, 300 MHz): Major isomer **4j1**: δ 7.52-6.92 (m, 10H, Ar-H), 5.05 (s, 2H, 1'-H), 5.04 (s, 2H, 3-H), 2.85 (s, 3H, 7-CH_3), 1.98 (s, 3H, 6'-H). Minor isomer **4j2**: δ 7.52-6.92 (m, 10H, Ar-H), 5.03 (s, 2H, 3-H), 4.67 (s, 2H, 1'-H), 2.43 (s, 3H, 7-CH_3), 1.96 (s, 3H, 6'-H). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **4j1**: δ 170.9 (C, C-1), 153.0 (C, C-3'), 148.2 (C, C-5), 146.5 (C, C-3a), 140.0 (C, C-6), 134.3 (C, C-7), 122.8 (C, C-7a), 86.1 (C, C-5'), 71.8 (C, C-4'), 68.2 (CH_2, C-3), 62.4 (CH_2, C-1'), 13.1 (CH_3, 7-CH_3), 3.7 (CH_3, C-6'). Minor isomer **4j2**: δ 171.0 (C, C-1), 152.3 (C, C-3'), 145.8 (C, C-6), 145.3 (C, C-3a), 137.8 (C, C-7), 136.1 (C, C-5), 123.6 (C, C-7a), 85.6 (C, C-5'), 71.8 (C, C-4'), 68.2 (CH_2, C-3), 62.5 (CH_2, C-1'), 14.9 (CH_3, 7-CH_3), 3.7 (CH_3, C-6'). Unassigned signals: δ 137.4, 137.3, 136.3, 135.8, 135.4, 133.3, 129.7, 129.1, 128.93, 128.88, 128.6, 128.5, 128.4, 128.2, 127.8, 127.7, 127.5, 127.3. HRMS *m/z* calcd. for $C_{26}H_{21}O_4$ $[M + H]^+$ 397.1434, found 397.1428.

Compounds 4’j



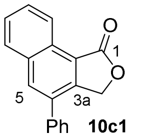
4’j1



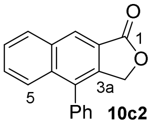
4’j2

Obtained as a pale yellow liquid consisting of an inseparable mixture of **4’j1** and **4’j2** in an approx. ratio 1.2:1 (0.020 g, 0.049 mmol, 15% yield). IR (film) (cm^{-1}): 3057, 3022, 2926, 2228, 1759, 1736, 1443, 1300, 1207, 1159, 1026. ^1H NMR ($CDCl_3$, 300 MHz): Major isomer **4’j1**: δ 7.52-7.15 (m, 10H, Ar-H), 5.21 (s, 2H, 3’-H), 4.95 (s, 2H, 3-H), 2.74 (s, 3H, 7-CH_3), 2.23 (s, 3H, 5-CH_3). Minor isomer **4’j2**: δ 7.52-7.15 (m, 10H, Ar-H), 5.04 (s, 2H, 3-H), 4.84 (s, 2H, 3’-H), 2.72 (s, 3H, 7-CH_3), 2.40 (s, 3H, 6-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **4’j1**: δ 170.7 (C, C-1), 168.3 (C, C-1’), 147.1 (C, C-3a), 139.1 (C, C-5), 136.2 (C, C-6), 135.3 (C, C-7), 134.7 (C, C-4), 131.7 (2 × CH, C-7’), 121.7 (C, C-6’), 121.1 (C, C-7a), 87.2 (C, C-5’), 82.1 (C, C-4’), 68.2 (CH_2, C-3), 53.7 (CH_2, C-3’), 17.5 (CH_3, C5-CH_3), 14.0 (CH_3, C7-CH_3). Minor isomer **4’j2**: δ 170.9 (C, C-1), 167.9 (C, C-1’), 143.2 (C, C-3a), 138.2 (C, C-6), 138.1 (C, C-7), 135.8 (C, C-4), 135.5 (C, C-5), 131.8 (2 × CH, C-7’), 123.8 (C, C-7a), 121.9 (C, C-6’), 86.8 (C, C-5’), 81.8 (C, C-4’), 67.8 (CH_2, C-3), 53.4 (CH_2, C-3’), 16.2 (CH_3, C6-CH_3), 13.1 (CH_3, C7-CH_3). Unassigned signals: δ 131.6, 129.0, 128.83, 128.77, 128.74, 128.4, 128.3, 128.24, 128.19. HRMS *m/z* calcd. for $C_{26}H_{20}NaO_4$ $[M + Na]^+$ 419.1254, found 419.1247.

Compounds 10c1/c2[33]



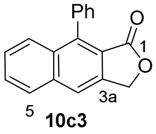
10c1



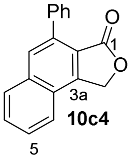
10c2

Obtained as a pale yellow solid consisting of an inseparable mixture of **10c1** and **10c2** in an approx. ratio 1.25:1 (0.013 g, 0.05 mmol, 8% yield). M.p.: 101.8-108.3 °C. IR (film) (cm^{-1}): 3057, 3028, 2930, 1755, 1026. ^{1}H NMR ($CDCl_3$, 300 MHz): Major isomer **10c1**: δ 9.05 (d, *J* = 8.3 Hz, 1H, 9-H), 8.12 (s, 1H, 5-H), 8.00 (d, *J* = 8.1 Hz, 1H, 6-H), 7.72 (ddd, *J* = 8.2 Hz, *J* = 7.0 Hz, *J* = 1.3 Hz, 1H, 8-H), 7.65 (ddd, *J* = 8.2 Hz, *J* = 7.2 Hz, *J* = 1.3 Hz, 1H, 7-H), 7.61-7.36 (m, 5H, Ar-H), 5.43 (s, 2H, 3-H). Minor isomer **10c2**: δ 8.51 (s, 1H, 9-H), 8.11-8.05 (m, 1H, Ar-H), 7.84-7.78 (m, 1H, 8-H), 7.61-7.36 (m, 7H, Ar-H), 5.26 (s, 2H, 3-H). ^{13}C NMR ($CDCl_3$, 75 MHz): Major isomer **10c1** (C-9a signal missing): δ 171.3 (C, C-1), 146.9 (C, C-3a), 137.6 (C, Ph), 134.0 (CH, C-5), 133.8 (C, C-4), 133.7 (C, C-5a), 128.9 (CH, C-8), 128.4 (3 × CH, C-6, Ph), 128.3 (2 × CH, Ph), 127.5 (CH, C-7), 123.2 (CH, C-9), 120.5 (C, C-9b), 69.1 (CH_2, C-3). Minor isomer **10c2**: δ 171.1 (C, C-1), 138.3 (C, C-3a), 134.7 (C, C-4a), 126.3 (CH, C-9), 125.8 (CH, C-8), 122.9 (C, C-9a), 69.4 (CH_2, C-3). Unassigned signals: δ 135.7, 133.6, 130.0, 129.2, 129.1, 128.9, 128.7, 127.8, 126.6.

Compounds 10c3/c4[34]



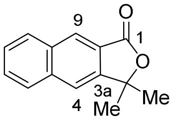
10c3



10c4

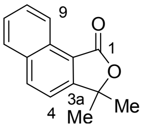
Obtained as a pale yellow solid consisting of an inseparable mixture of **10c3** and **10c4** in an approx. ratio 1.2:1 (0.013 g, 0.05 mmol, 8% yield). M.p.: 130.4-137.7 °C. IR (film) (cm^{-1}): 3057, 3022, 2928, 1763, 1045, 1028. ^1H NMR ($CDCl_3$, 300 MHz): **10c3**: δ 7.96 (d, *J* = 8.2 Hz, 1H, 5-H), 7.90 (s, 1H, 4-H), 7.81 (d, *J* = 8.6 Hz, 1H, 8-H), 7.69-7.34 (m, 7H, Ar-H, 6-H, 7-H), 5.44 (bs, 2H, 3-H). **10c4**: δ 8.01 (d, *J* = 8.0 Hz, 1H, 7-H), 7.86 (s, 1H, 8-H), 7.85 (d, *J* = 7.6 Hz, 1H, 4-H), 7.72 (td, *J* = 6.8 Hz, *J* = 1.0 Hz, 1H, 6-H), 7.69-7.34 (m, 6H, Ar-H, 5-H), 5.64 (s, 2H, 3-H). ^{13}C NMR ($CDCl_3$, 75 MHz): **10c3**: δ 169.5 (C, C-1), 142.1 (C, C-9), 140.0 (C, C-3a), 136.1 (C, C-4a), 132.7 (C, C-8a), 126.6 (CH, C-7), 120.2 (CH, C-4), 68.0 (CH_2, C-3). **10c4**: δ 170.2 (C, C-1), 148.4 (C, C-3a), 136.5 (C, C-9), 135.6 (C, C-7a), 130.5 (CH, C-8), 129.6 (CH, C-6), 128.9 (CH, C-7), 127.5 (CH, C-5), 125.9 (C, C-3b), 123.0 (CH, C-4), 120.1 (C, C-9a), 67.7 (CH_2, C-3). Unassigned signals: δ 137.3, 134.3, 129.9, 128.5, 128.2, 128.0, 127.9, 127.8, 127.5, 119.8.

Compound 10h1[35]



Obtained as a yellow liquid consisting of a difficult to separate mixture of **10h1** and **10h2** in a ratio 1.5:1 (0.008 g, 0.04 mmol, 6% yield). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.44 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.81 (s, 1H), 7.68-7.59 (overlapping signal, 1H), 7.57 (ddd, *J* = 8.2 Hz, *J* = 7.0 Hz, *J* = 1.0 Hz, 1H), 1.76 (s, 6H).

Compound 10h2



Obtained as a pale yellow liquid (0.013 g, 0.06 mmol, 9% yield). IR (film) (cm^{-1}): 3057, 2978, 2928, 1747, 1518, 1306, 1082. ^{1}H NMR (CDCl$_3$, 300 MHz): δ 9.02 (d, *J* = 8.4 Hz, 1H, 9-H), 8.14 (d, *J* = 8.4 Hz, 1H, 5-H), 7.96 (d, *J* = 8.4 Hz, 1H, 6-H), 7.73 (ddd, *J* = 8.2 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz, 1H, 8-H), 7.62 (ddd, *J* = 8.1 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz, 1H, 7-H), 7.45 (d, *J* = 8.5 Hz, 1H, 4-H), 1.72 (s, 6H, 3-CH$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz): δ 170.0 (C, C-1), 156.4 (C, C-3a), 135.5 (CH, C-5), 133.1 (C, C-5a), 129.2 (C, C-9a), 129.0 (CH, C-8), 128.3 (CH, C-6), 127.0 (CH, C-7), 123.6 (CH, C-9), 119.0 (C, C-9b), 117.5 (CH, C-4), 84.1 (C, C-3), 26.9 (2 × CH$_3$, C3-CH$_3$). HRMS *m/z* calcd. for $C_{14}H_{13}O_2$ [M + H]$^+$ 213.0910, found 213.0916.

AUTHOR CONTRIBUTIONS

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript./ †M.J.R. and C.M.D. contributed equally to this work.

NOTES

The authors declare no competing financial interest.

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H, ^{13}C and 2D NMR spectra for all new compounds (PDF).

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