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An open-and-shut strategy: preparation of benzo-fused indanes by ring-opening of a vinylogous acyl triflate and metal-catalyzed Asao–Yamamoto benzannulation

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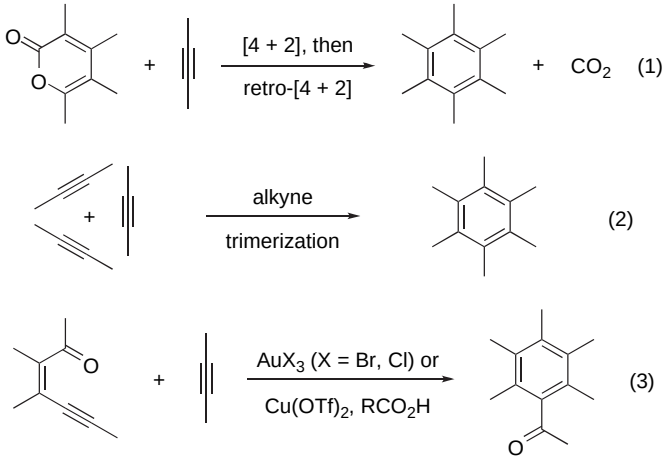
ABSTRACT

A two-step strategy for the synthesis of benzo-fused indanes is outlined herein. The strategy draws on two independent methodologies: the tandem addition/fragmentation of vinylogous acyl triflates (VATs) and the intramolecular benzannulation of *o*-alkynylphenyl ketones. Reduction of this strategy to practice involves the use of aryltriazenes as masked aryl iodides; a synthetic equivalent of 2-iodophenyllithium is featured. Benzo-fused indanes are prepared efficiently and in high yield.

1. Introduction

The practical assembly of highly substituted aromatic rings is one of the long-standing challenges in chemical synthesis.[1] Stepwise aromatic substitution processes will typically deliver the target structures, but regio- and chemoselectivity issues and the problems of cost associated with multi-step sequences ultimately limit the appeal of these strategies. Convergent aromatic annulation methods offer dramatic advantages for the preparation of specific systems; many such methods have been developed over the years (Scheme 1). The classic Alder–Rickert reaction of cyclohexadienes[2] and the Diels–Alder reaction of α-pyrones[3] (Eq. 1) each provide aromatic rings regioselectively by tandem [4+2] and retro-[4+2] pericyclic processes. The Dötz[4] and Danheiser[5] benzannulations feature pericyclic reactions of vinylketenes[6] with alkynes to provide phenols. Alkyne trimerization (Eq. 2) has frequently been exploited for the convergent assembly of substituted arenes,[7] perhaps most notably in the classic Vollhardt synthesis of estrone.[8] Of particular relevance to the present study are the emerging gold- and copper-catalyzed benzannulation reactions of β-alkynyl enones (and *ortho*-alkynylphenyl ketones) described by Asao and Yamamoto (Eq. 3).[9]

The alkyne functionality is the common denominator in the aforementioned convergent benzannulation reactions. Methods for the synthesis of functionalized alkynes therefore enable these processes and find many different applications in the synthesis of complex aromatic systems.



Scheme 1. Selected benzannulation reactions of alkynes.

1.1. Addition/fragmentation of vinylogous acyl triflates

We are developing a strategy for converting symmetric, cyclic 1,3-diones into differentially functionalized, acyclic alkynyl ketones.[10,11] The strategy hinges on the tandem nucleophilic

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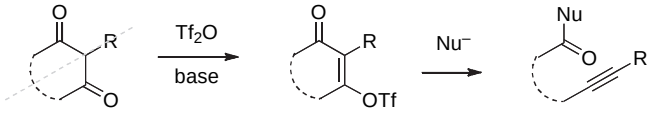
1,2-addition and fragmentation of vinylogous acyl triflates (VATs), which are readily available from cyclic 1,3-diones. Many types of nucleophilic reagents trigger fragmentation of vinylogous acyl triflates, including aryllithiums,[10] alkyl Grignards,[12] lithium amides,[11] enolates,[13] and more, providing convenient access to alkynes tethered to ketones, amides, alcohols,[14] β-keto esters, etc. Applications in synthesis[12,15] and related methodologies[16–18] are beginning to emerge.

We envisioned that our VAT fragmentation methodology (Scheme 2), in conjunction with an intramolecular version of chemistry featured in Eq. 3, could provide a useful entry into highly substituted indane compounds, but such an endeavor would require an extension of the gold- and/or copper-catalyzed benzannulation reactions described previously. We set out to investigate the intramolecular benzannulation reaction in more detail, as outlined below. The goals of this study were (a) to explore new applications for vinylogous acyl triflates in synthesis, (b) to advance the 'top-down' intramolecular version[19] of the Asao–Yamamoto benzannulation, and (c) to merge the two methodologies for the synthesis of benzo-fused indanes from symmetrical cyclic diones.



Scheme 2. Overview of the synthesis and ring-opening fragmentation of vinylogous acyl triflates.

In this article we describe the successful realization of these three goals, and we introduce a new *ortho*-benzene ambiphile, *N*,*N*-diethyl 2-lithiophenyltriazene (**3**). 2-Lithiophenyltriazene **3** serves as a stable and convenient synthetic equivalent for 2-iodophenyllithium (**4**), which itself would undergo rapid decomposition to *ortho*-benzyne[20] (Fig. 1).

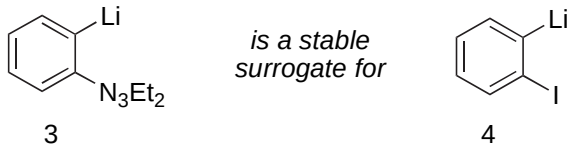
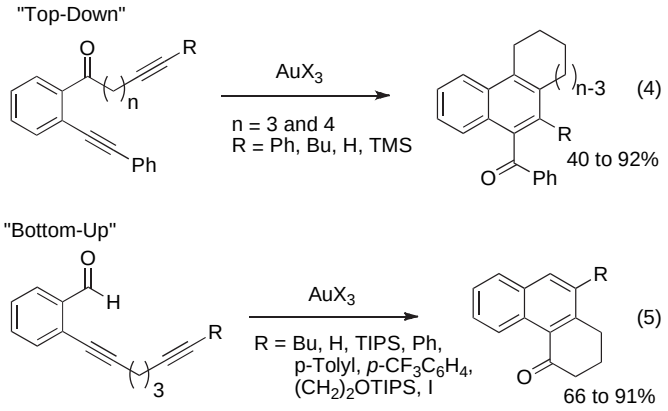


Figure 1. A synthetic equivalent for 2-iodophenyllithium.

1.2. Brief overview of the Asao–Yamamoto 'top-down' benzannulation

As part of on-going efforts into the preparation of highly functionalized arenes (cf. Eq. 3, Scheme 1),[9,19] Asao and Yamamoto reported the synthesis of a series of polycyclic naphthalene derivatives through the use of tethered (intramolecular) alkyne dienophiles (Scheme 3). Two versions of the intramolecular benzannulation were described:[19] the 'top-down' approach, in which the tethered alkyne is linked through the carbonyl group (Eq. 4), and the 'bottom-up approach', in which the tethered alkyne is linked through the aryl-alkyne group (Eq. 5).[21] Gold and copper salts are typically employed as catalysts in the broader methodology, but only gold catalysts were developed for the intramolecular benzannulations.

Combining our vinylogous acyl triflate fragmentation chemistry with the Asao–Yamamoto methodology gives rise to a new approach to the synthesis of benzo-fused indanes from symmetric 1,3-diones. The following section describes new methodology

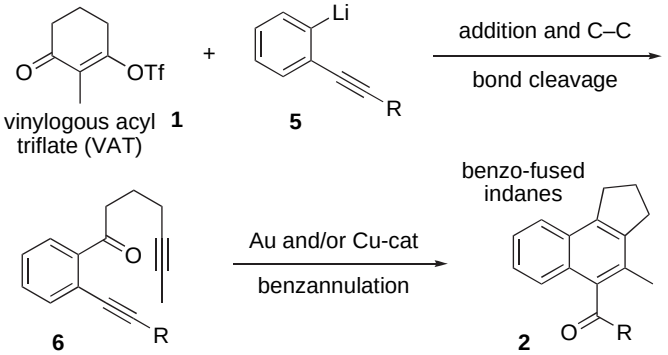


Scheme 3. Overview of intramolecular Asao–Yamamoto benzannulations.

featuring the use of vinylogous acyl triflate fragmentation reactions to provide the needed monocyclic benzannulation precursors.

2. Results and discussion

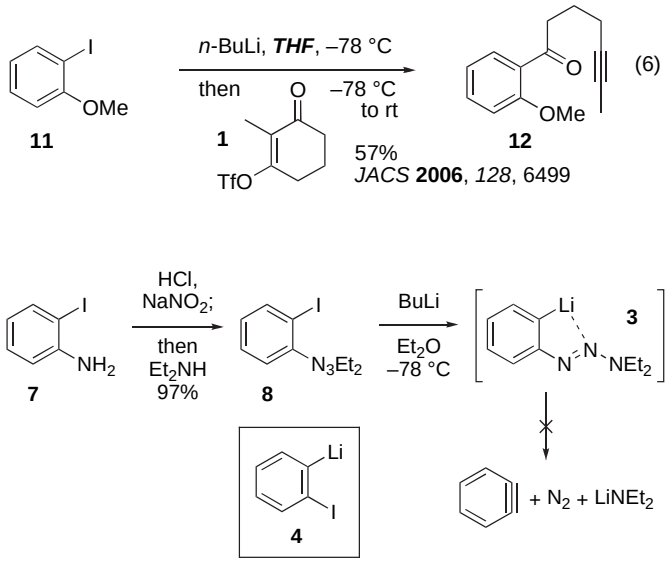
The basic plan for preparing benzo-fused indanes involved the use of *ortho*-alkynylphenyllithium **5** (or equivalent) as a nucleophilic trigger for the addition and fragmentation of vinylogous acyl triflate **1**, followed by benzannulation under conditions to be determined (Scheme 4). However, we specifically wanted to study the role of the *ortho*-alkyne substituent (**6**, R=aryl, alkyl, etc.) on the course of the intramolecular benzannulations. Therefore, it made sense to introduce this substituent later in the sequence using a Sonogashira coupling.[22] *ortho*-Iodophenyl ketone **10** (vide infra) became our initial target, requiring identification of an appropriate surrogate to 2-iodophenyllithium (**4**) that does not break down into benzyne.



Scheme 4. The "open-and-shut" synthesis of benzo-fused indanes.

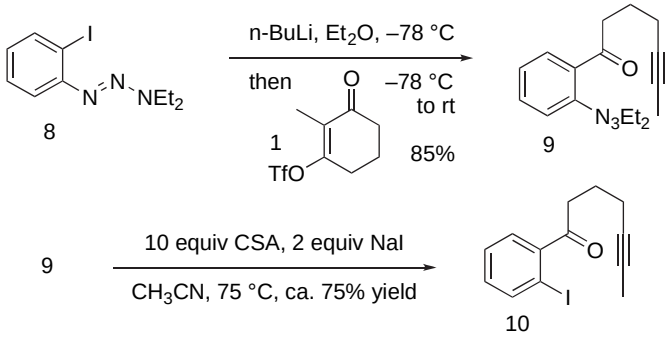
2.1. Vinylogous acyl triflate fragmentation using 2-lithiophenyltriazene 3, a new synthetic equivalent of 2-iodophenyllithium

2-Lithiophenyltriazene **3** serves as a synthetic equivalent to 2-iodophenyllithium (**4**). This new reagent is easily prepared from 2-iodoaniline (**7**, Scheme 5). Diazotization of **7** and trapping with diethylamine provides iodotriazene **8** in nearly quantitative yield.[23] Halogen–metal exchange of **8** with butyllithium at −78 °C gives rise to 2-lithiophenyltriazene **3**, which does not fragment into benzyne, molecular nitrogen, and lithium diethylamide.



Scheme 5. Preparation of 2-lithiophenyltriazene (**3**) for use as a synthetic equivalent for 2-iodophenyllithium (**4**).

Consistent with our earlier reports,[11] addition of vinylogous acyl triflate **1** to a cold solution of **3** triggers fragmentation upon warming to produce aryltriazene **9** (Scheme 6). Actually, this result compares favorably to the closest precedent from our earlier work (cf. Eq. 6). We originally employed THF as the solvent for the nucleophilic addition and C–C bond cleaving fragmentation process. Subsequently it has been determined that less polar solvents like toluene offered better control over the reactivity of unstabilized organolithium reagents.[24] In this case, ether provided an ideal solvent medium for the sequence of halogen–metal exchange, nucleophilic addition, and fragmentation, which proceeded in excellent overall yield (85% based on VAT **1**). We have also noticed that stabilizing influences on the organolithium reagent are beneficial,[25] and the *ortho*-triazene may provide positive coordinative stabilization of the aryllithium moiety.

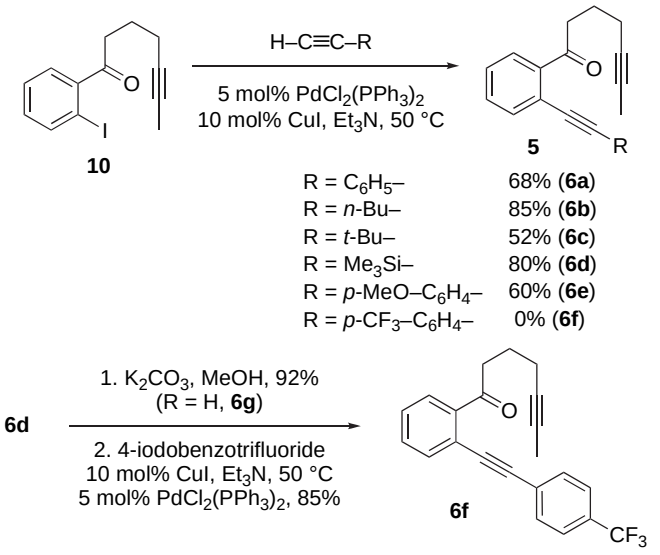


Scheme 6. Synthesis of 2-iodophenyl ketone **10**.

Aryltriazenes (i.e., **8**) have been used extensively in the synthesis of phenylacetylene-based systems.[26] Conversion of aryltriazenes to the corresponding aryl iodides is typically accomplished by heating in sealed tubes with iodomethane at temperatures in excess of 100 °C.[27] In the case of electron-deficient aryltriazenes, decomposition of the triazene in iodomethane requires higher temperatures. The toxicity of iodomethane and the high temperatures and pressures required for the decomposition of aryltriazenes to iodoarenes prompted us to seek alternative methods for this transformation. Electron-deficient aryltriazenes have been reported to undergo decomposition to afford iodoarenes in high yields upon treatment with sodium iodide and sulfonic acid cation exchange resins (H^+ form) in dry acetonitrile at 75 °C; other protic acids also provided aryl iodides in acceptable yields.[28] Likewise, we completed the synthesis of our model benzannulation substrates using camphorsulfonic acid (CSA) in warm acetonitrile to convert aryltriazene **9** into aryl iodide **10** in 75% yield.

2.2. New metal-catalyzed Asao–Yamamoto benzannulation reactions

Aryl iodide **10** marked the divergence point in our synthesis of substrates for the focused benzannulation methodology. Sonogashira coupling with a series of alkyne partners is depicted in Scheme 7. Coupling with phenylacetylene provided **6a** in 68% yield; two alkylacetylenes—one linear (**6b**, 85%) and one tertiary (**6c**, 52%)—and silylacetylene derivative **6d** (80%) were likewise prepared. Sonogashira coupling between **10** and the electron-rich *p*-methoxyphenylacetylene provided **6e** (60%), but our attempt to install an electron-deficient aromatic substituent (R=*p*-trifluoromethylphenyl, **6f**) under similar conditions failed. This problem was overcome by a slight tactical adjustment: desilylation of silylacetylene **6d** with methanolic potassium carbonate provided the terminal alkyne (**6g**), which was coupled with *p*-iodobenzotrifluoride (*p*-I–C_6H_4–CF_3) to provide electron-deficient benzannulation substrate **6f** in good overall yield (Scheme 7).

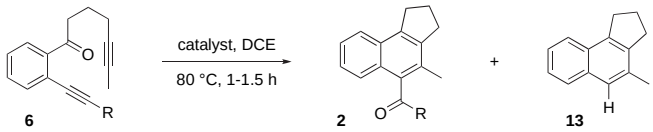


Scheme 7. Preparation of benzannulation substrates.

With a series of appropriate substrates in hand, we began to examine benzannulation reactions using both the $AuCl_3$ and the $Cu(OTf)_2/CF_2HCO_2H$ catalyst systems. Cyclization of substrates similar to phenylacetylene derivative **6a** (R=Ph) using the gold catalyst system has been reported previously.[19] Our goals were to understand better the scope, discern any reactivity trends with respect to the alkyne substituent (R), and identify any advantages of employing the copper catalyst system in the intramolecular benzannulations.

Under the gold-catalyzed conditions, successful benzannulation reaction was observed with the phenyl-derived substrate (Table 1, entry 1): the target indane was isolated in ca. 80% yield (8 mg, small scale), consistent with the previous reports.[19] Alkylacetylene substrates **6b** (R=*n*-Bu, entry 2) and **6c** (R=*t*-Bu, entry 3) underwent similar cyclizations, as did the electron-deficient arylacetylene **6f** (entry 6, R=*p*-CF_3–C_6H_4–). In contrast, the electron-rich

Table 1
Preliminary screening of benzannulation reactions of substrates **6a–f**[a]



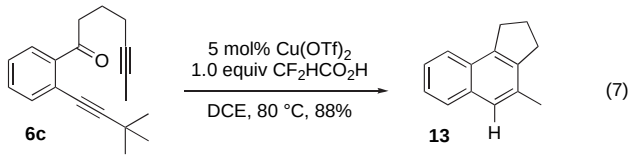
Entry	R	Substrate	$AuCl_3$ Catalyst[b]		$Cu(OTf)_2/CF_2HCO_2H$ System[c]	
			2, Yield[d] (%)	**13**, Yield[d] (%)	**2**, Yield[d] (%)	**13**, Yield[d] (%)
1	Ph	**6a**	**2a**, 80	0	**2a**, 70	20
2	*n*-Bu	**6b**	**2b**, 70	0	**2b**, 10	70
3	*t*-Bu	**6c**	**2c**, 50	0	**2c**, 0	70
4	Me_3Si	**6d**	**2d**, 0	0[e]	**2d**, 0[e]	0[e]
5	*p*-MeO-C_6H_4	**6e**	**2e**, 0	0[e]	**2e**, 0[e]	0[e]
6	*p*-CF_3-C_6H_4	**6f**	**2f**, 80	0	**2f**, 80	0

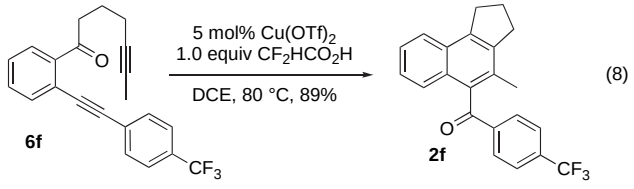
[a] Reactions performed on 10 mg scale for screening purposes.
[b] 5 mol % $AuCl_3$.
[c] 5 mol % $Cu(OTf)_2$, 1.0 equiv CF_2HCO_2H.
[d] Isolated yields.
[e] No reaction was detected by TLC after 15 h, substrates were recovered.

arylacetylene **6e** (entry 5, R=*p*-MeO–C_6H_4–) proved to be inert to the reaction conditions: even after 15 h, only unreacted starting material was recovered. Silylacetylenes also appear to be beyond the current scope (entry 4).

Similar reactivity trends were observed under the alternative copper-catalyzed protocol, but in this series the deacylated indane (**13**) was often produced. The *ortho*-acetylene substrates with phenyl (entry 1), *p*-trifluoromethylphenyl (entry 6), and alkyl substituents (entries 2 and 3) achieved full conversion to indanes, whereas the electron-rich aryl (entry 5) and silyl (entry 4) -substituted ynones were unreactive. Interestingly, the deacylated indane **13** emerged as the major or exclusive product of the alkylacetylene substrates (entries 2 and 3), whereas none of this product was produced in the reaction of the electron-deficient trifluoromethylated substrate (entry 6).

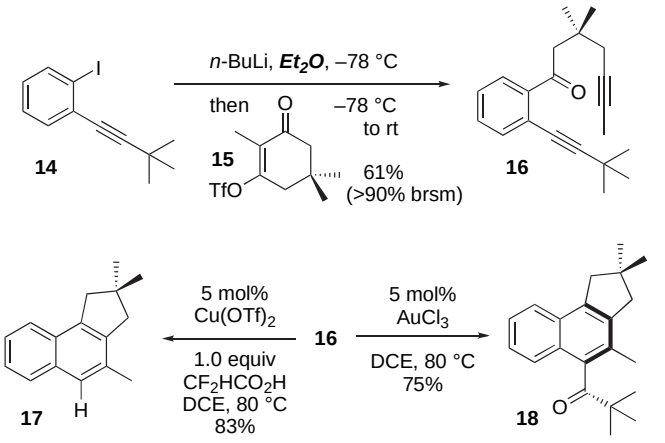
Three specific intriguing entries are highlighted in Table 1. The *t*-butylacetylene substrate (entry 3) undergoes selective conversion to pivaloylindane **2c** under the action of gold(III) chloride, whereas the copper-catalyzed protocol converts the same substrate selectively to deacylated indane **13**. Thus, one can opt for either product based on choice of catalyst system.[29] A similar divergence can be achieved within the copper-catalyzed series: by choosing the appropriate acetylene substituent—electron-deficient aryl vs hindered alkyl—one can gain access to either acylated or deacylated indane product (entries 3 and 6).





To follow up on this initial screening and establish more precise estimation of reaction yields, we reexamined the diverging reactivity of alkyl and aryl substrates **6c** and **6f** under copper-catalysis on a larger scale. Copper(II) triflate in conjunction with difluoroacetic acid efficiently converts *t*-Bu substrate **6c** to deacylated indane **13** in 88% yield (Eq. 7). The same protocol effects the conversion of arylacetylene **6f** to acylindane **2f** in 89% yield (Eq. 8).

The convergent fragmentation/annulation ('open-and-shut') strategy for the synthesis of benzo-fused indanes is concisely illustrated in the synthesis of indanes **17** and **18** (Scheme 8). Coupling of aryl iodide **14**[30] with VAT **15**[31] using our addition/fragmentation reaction provided dialkynyl ketone **16** in 61% yield. Mindful of our observations described above (Table 1), we subjected ketone **16** to the Asao–Yamamoto benzannulation conditions to provide either **17** or **18** (Scheme 8).



Scheme 8. Open-and-shut synthesis of benzo-fused indanes.

3. Conclusion

A two-step strategy for the synthesis of benzo-fused indanes arises from the sequential application of vinylogous acyl triflate fragmentation and metal-catalyzed benzannulation. The new benzannulation reactions described herein contribute to the methodology reported previously made by Yamamoto and Asao and expand the scope of their intramolecular reaction. The ability to obtain either the ketone or decarbonylated benzannulated products selectively through choice of catalyst or by altering the substrate provides synthetic versatility in the synthesis of

substituted indanes, and the addition/fragmentation of vinylogous acyl triflates offers direct access to the benzannulation substrates.

This approach to benzo-fused indanes incorporates the use of aryltriazenes for the synthesis of useful intermediates and the fragmentation of vinylogous acyl triflates. In addition to demonstrating the utility of aryltriazene nucleophiles in our tandem addition and C–C bond cleavage reactions, in this study we have taken the opportunity to highlight the use of *ortho*-lithiated phenyltriazene **3** as a synthetic equivalent of 2-iodophenyllithium.

The detailed benzannulation studies presented above provide a firm foundation for future synthetic efforts. We demonstrate the use of the $Cu(OTf)_2/CF_2HCO_2H$ catalyst system to promote intramolecular benzannulation reactions and document the advantage of employing the alternative gold and copper protocols to control product distribution. The application of the fragmentation/benzannulation strategy to target-oriented chemical synthesis will be reported in due course.

4. Experimental section

4.1. General information

^1H NMR and ^{13}C NMR spectra were recorded on a Varian 300 (300 MHz), Bruker 400 (400 MHz), or Bruker 600 (600 MHz) spectrometer, using $CDCl_3$ as the deuterated solvent. The chemical shifts (δ) are reported in parts per million (ppm) relative to the residual chloroform peak (7.26 ppm for ^1H NMR and 77.00 for ^{13}C NMR). Coupling constants (J) are reported in Hertz (Hz). IR spectra were recorded on a Perkin-Elmer FTIR spectrometer with diamond ATR accessory as thin film. Mass spectra were recorded on a JEOL JMS600H spectrometer. Yields refer to isolated material judged to be >95% pure by ^1H NMR spectroscopy following silica gel chromatography (F-254 silica, 230–499 mesh particle size). All chemicals were used as received unless otherwise noted. Acetonitrile (CH_3CN) was distilled from calcium hydride (CaH_2) and stored over molecular sieves. Diethyl ether (Et_2O) was dried through a solvent purification system packed with alumina and molecular sieves under an Ar atmosphere. Triethylamine and diethylamine were distilled from CaH_2 and stored over KOH pellets. The *n*-butyllithium (*n*-BuLi) solutions were titrated with a known amount of menthol, using 1,10-phenanthroline as an indicator, in a solution of ether. All reactions were carried out under an inert argon atmosphere unless otherwise stated.

4.2. General procedure for the addition and fragmentation of vinylogous acyl triflates 1 and 15

To a solution of iodotriazene **8** (2.0 g, 6.6 mmol) in diethyl ether (180 mL) at −78 °C was added *n*-BuLi (4.13 mL, 6.6 mmol, 1.6 M solution in hexane) dropwise. The mixture was stirred at −78 °C for 30 min. To the solution was added triflate **1** (1.87 g, 7.26 mmol) in dry ether (50 mL), dropwise. The solution was stirred at −78 °C for 15 min, 0 °C for 15 min, and at rt for 30 min. The reaction was then quenched with $^1/_2$ satd NH_4Cl, extracted two times with Et_2O, washed with H_2O and brine, and dried with $MgSO_4$. The concentrated solution provided a crude oil, which was purified by flash column chromatography using 1% EtOAc/Hex. The product (**9**) was isolated as a yellowish-brown oil in 85% yield (1.59 g).

*4.2.1. 1-(2-(3,3-Diethyl-1-triazo)phenyl)-1-oxo-5-heptyne (**9**).* ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, J=8.2, 1.0 Hz, 1H), 7.43 (dd, J=7.6, 1.3 Hz, 1H), 7.37 (ddd, J=8.2, 7.6, 1.5, 1H), 7.14 (dt, J=7.6, 1.0 Hz, 1H), 3.77 (q, J=7.0 Hz, 4H), 3.06 (t, J=7.4 Hz, 2H), 2.19 (tq, J=7.0, 2.5 Hz, 2H), 1.93–1.77 (app. quintet, J=7.2 Hz, 2H), 1.74 (t, J=2.5 Hz, 3H), 1.40–1.14 (broad multiplet, 6H); ^{13}C NMR (100 MHz, CDCl3) δ 206.4, 148.9, 135.1, 131.1, 128.0, 124.9, 118.1, 78.6, 76.0, 49.0, 43.5, 41.5, 23.8, 18.4, 14.5, 11.3, 3.5; IR (neat) 1674, 1592, 1403, 1328, 1092, 757 cm^{-1}; HRMS (ESI^+) Calcd for $C_{17}H_{24}N_3O$ ($[M+H]^+$) 286.1919. Found 286.1915.

*4.2.2. 1-(2-(2-tert-Butylethynyl)phenyl)-3,3-dimethyl-5-heptyn-1-one (**16**).* ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, J=7.4, 1.5 Hz, 1H), 7.43 (dd, J=7.4, 1.5 Hz, 1H), 7.34 (dt, J=7.4, 1.5 Hz, 1H), 7.29 (dt, J=7.4, 1.5 Hz, 1H), 3.13 (s, 2H), 2.21 (q, J=2.5 Hz, 2H), 1.75 (t, J=2.5 Hz, 3H), 1.32 (s, 9H), 1.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 143.6, 133.4, 130.2, 127.4, 121.4, 103.7, 79.0, 77.5, 76.8, 76.5, 51.4, 34.6, 32.4, 30.6, 28.2, 27.1, 3.5; IR (neat) 2359, 1684, 1472, 1362, 758 cm^{-1}; HRMS (EI+) Calcd for $C_{21}H_{26}O$ (M^+) 294.1984. Found 294.1984.

4.3. Aryltriazene to aryl iodide conversion (9→10)

To a solution of camphor-10-sulfonic acid (2.44 g, 10.5 mmol) and NaI (0.315 g, 2.1 mmol) in acetonitrile (25 mL) at 75 °C was added a solution of triazene **9** (300 mg, 1.05 mmol in 5 mL of acetonitrile) dropwise. The evolution of nitrogen was complete after 5 min of stirring at 75 °C. The mixture was cooled to rt and diluted with 25 mL of hexane. The product was extracted five times with hexane. The combined hexane layers were then dried with Na_2SO_4 and concentrated to provide a reddish oil. The crude material was then purified by flash column chromatography using hexane. The resulting red-brown oil (**10**) was used in the next step without further purification (ca. 75% yield, >85% pure).

4.4. General procedure for Sonogashira couplings (10→6)

To a solution of aryl iodide **10** (32 mg, 0.1 mmol) in triethylamine (1 mL) was added dichlorobis(triphenylphosphine)palladium (4 mg, 5 μmol) and copper(I) iodide (2 mg, 10 μmol). The heterogeneous solution was degassed using the freeze-pump-thaw method (five cycles) and warmed to room temperature. Hexyne (30 μL, 0.22 mmol) was then added to the reaction mixture in one shot. The solution was warmed to 50 °C and stirred for 3 h. The mixture was cooled to rt, diluted with ether, and filtered through Celite™. The filter cake was washed three times with ether and the combined filtrates were concentrated. The crude product was then purified by flash column chromatography using pure hexanes up to 1% EtOAc/Hex, providing **6b** as a pale yellow oil in 85% yield (22 mg).

*4.4.1. 1-(2-(2-Phenylethynyl)phenyl)-5-heptyn-1-one (**6a**).* ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J=7.5, 1.6 Hz, 1H), 7.63 (dd, J=7.5, 1.5 Hz, 1H), 7.59–7.53 (m, 2H), 7.47 (dt, J=7.5, 1.6 Hz, 1H), 7.40 (dt, J=7.5, 1.5 Hz, 1H), 7.37–7.34 (m, 3H), 3.30 (t, J=7.0 Hz), 2.26 (tq, J=7.0, 2.5 Hz, 2H), 1.94 (quintet, J=7.0, 2H), 1.69 (t, J=2.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 141.0, 133.7, 131.5, 130.9, 128.6, 128.4, 128.2, 122.8, 121.2, 94.6, 88.2, 78.3, 76.4, 41.0, 23.6, 18.3, 3.3; IR (neat) 2215, 1678, 1493, 1217, 753, 689 cm^{-1}; HRMS (EI+) Calcd for $C_{21}H_{18}O$ (M^+) 286.1358. Found 286.1353.

*4.4.2. 1-(2-(2-n-Butylethynyl)phenyl)-5-heptyn-1-one (**6b**).* ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J=7.6, 1.6 Hz, 1H), 7.47 (dd, J=7.6, 1.5 Hz, 1H), 7.38, (dt, J=7.6, 1.6 Hz, 1H), 7.32 (dt, J=7.6, 1.5 Hz, 1H), 3.20 (t, J=7.3 Hz, 2H), 2.46 (t, J=7.0, 2H), 2.31–2.16 (m, 2H), 1.89 (quintet, J=7.3 Hz, 2H), 1.76 (t, J=2.5 Hz, 3H), 1.67–1.55 (m, 2H), 1.54 (m, 2H), 0.95 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 141.4, 133.8, 127.8, 127.5, 121.9, 96.3, 79.4, 78.4, 76.1, 41.1, 30.5, 22.1, 18.3, 13.6, 3.4; IR (neat) 2228, 1679, 1440, 758 cm^{-1}; HRMS (EI+) Calcd for $C_{19}H_{22}O$ (M^+) 266.1671. Found 266.1669.

*4.4.3. 1-(2-(2-tert-Butylethynyl)phenyl)-5-heptyn-1-one (**6c**).* ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, J=7.5, 1.5 Hz, 1H), 7.46 (dd, J=7.5,

1.5 Hz), 7.38 (dt, *J*=7.5, 1.5 Hz, 1H), 7.31 (dt, *J*=7.5, 1.5 Hz, 1H), 3.24 (t, *J*=7.2 Hz, 2H), 2.24 (tq, *J*=6.0, 2.5 Hz, 2H), 1.89 (quintet, *J*=7.2 Hz, 2H), 1.76 (t, *J*=2.5 Hz, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 141.3, 133.6, 127.8, 127.5, 104.1, 78.4, 78.2, 76.1, 41.4, 30.6, 28.2, 23.6, 18.3, 3.4; IR (neat) 2235, 1679, 1362, 1273, 757 cm^{-1}; HRMS (EI+) Calcd for $C_{19}H_{22}O$ (M^+) 266.1671. Found 266.1669.

*4.4.4. 1-(2-(2-(p-Methoxyphenyl)ethynyl)phenyl)-5-heptyn-1-one (**6d**).* ^{1}H NMR (300 MHz, CDCl3) δ 7.69 (dd, *J*=7.5, 1.2 Hz, 1H), 7.59 (dd, *J*=7.5, 1.1 Hz, 1H), 7.50 (d, *J*=8.7 Hz, 2H), 7.44 (dt, *J*=7.5, 1.2 Hz, 1H), 7.36 (dt, *J*=7.5, 1.1 Hz, 1H), 6.88 (d, *J*=8.7 Hz, 2H), 3.82 (s, 3H), 3.29 (t, *J*=7.3 Hz, 2H), 2.32–2.18 (m, 2H), 1.93 (app. quintet, *J*=7.0 Hz, 2H), 1.69 (t, *J*=2.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 203.0, 159.9, 140.8, 133.6, 133.0, 130.9, 128.2, 127.8, 121.6, 115.0, 114.0, 94.8, 87.1, 78.4, 76.4, 55.3, 41.0, 23.7, 18.3, 3.4; IR (neat) 2212, 1678, 1605, 151, 1247, 1028, 831, 758 cm^{-1}; HRMS (EI+) Calcd for $C_{22}H_{20}O_2$ (M^+) 316.1463. Found 316.1462.

*4.4.5. 1-(2-(2-Trimethylsilylethynyl)phenyl)-5-heptyn-1-one (**6e**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.59 (m, 1H), 7.57–7.52 (m, 1H), 7.41 (dt, *J*=7.4, 1.9 Hz, 1H), 7.37 (dt, *J*=7.4, 1.7 Hz, 1H), 3.23 (t, *J*=7.3 Hz, 2H), 2.42 (tq, *J*=7.1, 2.5 Hz, 2H), 1.90 (quintet, *J*=7.1 Hz, 2H), 1.76 (t, *J*=2.5 Hz, 3H), 0.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 141.8, 134.0, 130.6, 128.5, 127.9, 120.8, 103.5, 100.4, 78.3, 76.1, 41.2, 23.7, 18.3, 3.4, 0.4; IR (neat) 2157, 1682, 1249, 863, 840, 758 cm^{-1}; HRMS (ESI$^+$) Calcd for $C_{18}H_{22}OSiNa$ ($[M+Na]^+$) 305.1338. Found 305.1333.

4.5. Synthesis of 1-(2-(2-(*p*-trifluoromethylphenyl)-ethynyl)phenyl)-5-heptyn-1-one (6d→6f)

To a methanolic solution (2 mL) of trimethylsilylacetylene (**2d**) (136 mg, 0.48 mmol) was added potassium carbonate (100 mg, 0.72 mmol) at room temperature. The reaction mixture was stirred at room temperature until the starting material was no longer detected by TLC (ca. 30 min). The mixture was diluted with ether and water. The reaction was quenched with 1 N HCl and stirred until CO_2 evolution was no longer observed. The product was extracted twice with EtOAc. The combine organics were washed with water and brine, dried with Na_2SO_4, filtered, and concentrated. The resulting crude oil was purified by flash column chromatography using gradient elution of 0–1% EtOAc/Hex, providing **6g** as a clear oil in 94% yield (94 mg). A Sonogashira reaction was then carried out between **6g** and 4-iodobenzotrifluoride following the general procedure outlined in Section 4.4 to provide 135 mg of **6f** as a pale yellow oil (85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, *J*=7.4, 1.5 Hz, 1H), 7.67 (d, *J*=8.3 Hz, 2H), 7.65–7.58 (m, 3H), 7.50 (dt, *J*=7.4, 1.6 Hz, 1H), 7.44 (dt, *J*=7.4, 1.5 Hz, 1H), 3.24 (t, *J*=7.3 Hz, 2H), 2.26 (tq, *J*=7.0, 2.5 Hz, 2H), 1.94 (quintet, *J*=7.0 Hz, 2H), 1.70 (t, *J*=2.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.2, 141.1, 134.8, 131.0, 130.3 (q, 32.7 Hz), 128.8, 125.3 (q, 3.9 Hz), 123.9 (q, 270.9 Hz), 120.6, 92.7, 90.6, 78.3, 76.5, 40.8, 23.6, 18.3, 3.5; IR (neat) 1683, 1614, 1320, 1126, 1065, 824 cm^{-1}; HRMS (EI+) Calcd for $C_{22}H_{17}OF_3$ (M^+) 354.1232. Found 354.1230.

4.6. General procedure for gold-catalyzed benzannulations (6→2)

To a solution of $AuCl_3$ (0.6 mg, 1.8 μmol) in 100 μL dichloroethane (DCE), obtained from a stock solution (6 mg/mL), was added an additional 200 μL of DCE and diyne **6b** (10 mg, 37 μmol, in 200 μL of DCE). The solution was then heated to 80 °C for 1.5 h. The mixture was cooled to rt and filtered through a plug of silica gel. The filtrate was concentrated and purified by flash column chromatography using 1% EtOAc/Hex, providing naphthyl ketone **2b** in 70% yield (7 mg) as a clear oil.

*4.6.1. (4-Methyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-5-yl)-phenyl-methanone (**2a**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2H), 7.61–7.53 (m, 1H), 7.50–7.38 (m, 3H), 7.34–7.26 (m, 1H), 3.35 (t, *J*=7.5 Hz, 2H), 3.08 (t, *J*=7.5 Hz, 2H), 2.30 (quintet, *J*=7.5 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 141.0, 140.4, 138.0, 134.7, 133.6, 130.3, 129.8, 129.6, 128.7, 125.5, 125.4, 125.3, 124.5; 32.6, 31.6, 23.9, 17.2; IR (neat) 1664, 1448, 1219, 884, 756, 717 cm^{-1}; HRMS (EI+) Calcd for $C_{21}H_{18}O$ (M^+) 286.1358. Found 286.1353.

*4.6.2. n-Butyl-(4-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-5-yl)-methanone (**2b**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dd, *J*=7.8, 1.8 Hz, 1H), 7.55 (dd, *J*=7.2, 1.8 Hz, 1H), 7.43–7.37 (m, 2H), 3.29 (t, *J*=7.2 Hz, 2H), 3.04 (t, *J*=7.8 Hz, 2H), 2.87 (t, *J*=7.8 Hz, 2H), 2.31 (s, 3H), 2.26 (quintet, *J*=7.8 Hz, 2H), 1.78 (quintet, *J*=7.8 Hz), 1.44 (app. sextet, *J*=7.6 Hz, 2H), 0.953 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.2, 141.0, 140.0, 137.8, 128.9, 128.9, 127.5, 125.6, 125.3, 124.7, 124.6, 45.6, 32.6, 31.6, 25.8, 23.9, 22.5, 16.9, 13.9; IR (neat) 1697, 1130, 751 cm^{-1}; HRMS (EI+) Calcd for $C_{19}H_{22}O$ (M^+) 266.1671. Found 266.1670.

*4.6.3. tert-Butyl-(4-methyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-5-yl)-methanone (**2c**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J*=7.6, 1.1 Hz, 1H), 7.53–7.33 (m, 3H), 3.29 (app. triplet, *J*=7.8 Hz, 2H), 3.13–2.94 (m, 2H), 2.29 (s, 3H), 2.26 (app. quintet, *J*=7.8 Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 219.1, 141.0, 139.4, 137.1, 129.3, 128.8, 127.5, 125.7, 129.2, 125.1, 124.7, 45.7, 32.7, 31.5, 28.1, 23.8, 18.3; IR (neat) 1688, 1276, 1261, 764, 749 cm^{-1}; HRMS (EI+) Calcd for $C_{19}H_{22}O$ (M^+) 266.1671. Found 266.1668.

*4.6.4. (4-Methyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-5-yl)-p-trifluoromethylphenyl-methanone (**2f**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J*=8.1 Hz, 2H), 7.84 (d, *J*=8.1 Hz, 1H), 7.69 (d, *J*=8.1 Hz, 2H), 7.52–7.39 (m, 2H), 7.36–7.28 (m, 1H), 3.37 (t, *J*=7.5 Hz, 2H), 3.10 (t, *J*=7.5 Hz, 2H), 2.32 (quintet, *J*=7.5 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 141.0, 140.5, 134.7 (q, *J*=32.5 Hz), 133.8, 130.1, 130.0, 129.8, 128.8, 125.8 (q, *J*=3.7 Hz), 125.7, 125.2, 124.7, 123.6 (q, *J*=272.9 Hz), 32.6, 31.7, 23.8, 17.3; IR (neat) 1673, 1409, 1322, 1168, 1128, 1069 cm^{-1}; HRMS (ESI$^+$) Calcd for $C_{22}H_{17}F_3ONa$ ($[M+Na]^+$) 377.1129. Found 377.1135.

*4.6.5. tert-Butyl-(3,3,4-trimethyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-5-yl)-methanone (**18**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, *J*=7.8, 1.4 Hz, 1H), 7.47 (dd, *J*=7.8, 1.3 Hz, 1H), 7.42 (dt, *J*=7.8, 1.4 Hz, 1H), 7.36 (dt, *J*=7.8, 1.4 Hz), 3.09 (s, 2H), 2.89 (d, *J*=16.0 Hz, 1H), 2.80 (d, *J*=16 Hz, 1H), 2.25 (s, 2H), 1.29 (s, 3H), 1.27 (s, 9H), 1.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 219.2, 140.1, 128.6, 137.1, 129.3, 129.1, 127.7, 125.7, 125.1, 125.0, 124.5, 47.7, 46.4, 45.7, 39.2, 29.8, 29.8, 28.1, 18.2; IR (neat) 1685, 1463, 1102, 903, 738 cm^{-1}; HRMS (EI+) Calcd for $C_{21}H_{26}O$ (M^+) 294.1984. Found 294.1984.

4.7. General procedure for copper-catalyzed benzannulations (6→13)

To a solution of $Cu(OTf)_2$ (4 mg, 11 μmol) and difluoroacetic acid (14 μL, 0.22 mmol) in DCE, was added a solution of diyne **6c** (58 mg, 0.22 mmol in 1 mL of DCE). The solution was heated to 80 °C and stirred for 40 min. The reaction mixture was cooled to rt and filtered through silica gel. The filtrate was concentrated; the resulting oil was purified by flash column chromatography using hexanes, providing naphthalene derivative **13** in 88% yield (35 mg).

*4.7.1. 4-Methyl-2,3-dihydro-1H-cyclopenta[a]naphthalene (**13**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J*=7.3 Hz, 1H), 7.75 (d, *J*=7.3 Hz, 1H), 7.47 (s, 1H), 7.46–7.35 (m, 2H), 3.28 (t, *J*=7.5 Hz, 2H), 3.04 (t, *J*=7.5 Hz, 2H), 2.43 (s, 3H), 2.26 (quintet, *J*=7.5 Hz, 2H); ^{13}C NMR

(150 MHz, $CDCl_3$) δ 199.80, 141.03, 140.47, 134.73 (q, J=32.5 Hz), 133.8, 130.1, 130.0, 129.8, 128.8, 125.8 (q, J=3.7 Hz), 125.7, 125.2, 124.7, 123.6 (q, J=272.9 Hz), 32.6, 31.7, 23.8, 17.3. 141.3, 139.1, 133.2, 132.9, 129.0, 127.6, 125.6, 124.9, 124.7, 124.2, 32.4, 31.3, 24.1, 19.8; IR (neat) 1595, 1382, 1020, 872, 766, 743 cm^{-1}; HRMS (ESI^+) Calcd for $C_{14}H_{14}$ (M^+) 182.1096. Found 182.1094.

*4.7.2. 3,3,4-Trimethyl-2,3-dihydro-1H-cyclopenta[a]naphthalene (**17**).* ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, J=6.8, 2.5 Hz, 1H), 7.70 (dd, J=6.6, 2.5 Hz, 1H), 7.46 (s, 1H), 7.44–7.34 (m, 2H), 3.08 (s, 2H), 2.86 (s, 2H), 1.26 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 142.5, 137.5, 137.4, 133.6, 132.0, 130.0, 129.1, 128.9, 128.4, 51.8, 50.6, 43.6, 34.2, 24.0; IR (neat) 1364, 872, 843, 743 cm^{-1}; HRMS (EI+) Calcd for $C_{16}H_{18}$ (M^+) 210.1408. Found 210.1404.

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24. It is our current hypothesis that the higher aggregation of organolithium reagents in less polar solvents leads to better selectivity for the desired 1,2-addition reaction by attenuating their reactivity in electron-transfer reduction processes, which promote decomposition of the VAT substrates.
25. For example, the addition/fragmentation reaction of VAT **1** with TMS–methyllithium provides a higher yield of the corresponding methyl ketone (after hydrolysis of the TMS group) than does direct addition of methyllithium, which is a more reactive nucleophile. See Ref. 11.
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29. A similar phenomenon was documented in the intermolecular benzannulation reactions; see Ref. 9.
30. Prepared in two steps from iodotriazene **8**: Sonogashira coupling and triazene→iodide conversion using NaI and CSA (cf. **9**→**10**, Scheme 6).
31. Prepared by triflation of 2-methyldimedone according to our standard conditions (Ref. 11). For the synthesis of 2-methyldimedone, see Lertpibulpanya, D.; Marsden, S. P. *Org. Biomol. Chem.* **2006**, *4*, 3498–3504.