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Synthesis of 3-substituted 2-cyclohexenones through umpoled functionalization

Harim Lechuga-Eduardo, Eduardo Zarza-Acuña, Moisés Romero-Ortega *

Departamento de Química Orgánica, Facultad de Química, Universidad Autónoma del Estado de México, Paseo Colón/Paseo Tollocan, Toluca Estado de México, Mexico

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ABSTRACT

A new protocol to obtain 3-substituted 2-cyclohexenones, was developed by reversing the chemical reactivity of 2-cyclohexenone. One-pot synthesis of 3-substituted 2-cyclohexenones can be achieved by treatment of 3-phenylthiosilyl enol ether with a mixture of *t*-BuLi/HMPA that allows hydrogen-selective exchange in presence of reactive electrophiles such as aldehydes, ketones and alkyl halides. This affords the corresponding product in moderate overall yield, after silyl enol ether cleavage and concomitant thiophenol elimination initiated with TBAF.

Introduction

The development of new methods for the efficient construction of organic molecules continues to be essential for accessing natural products and their structural analogues. In this context, the concept of *umpolung* or polarity inversion is associated with a temporal masking of a functional group to reverse its polarity and perform secondary reactions that would otherwise not be possible.[1–3] Since retrosynthetic analysis was pioneered by E. J. Corey and co-workers in the early 1970s,[4] the umpolung approaches attracted more attention because it enables the usage of a wider variety of starting materials for building complex natural products. From the perspective of natural product synthesis, little is known about 2-cyclohexenone, a cheap and widely available compound with great synthetic potential. 2-cyclohexenone has been used to synthesize highly valuable molecules, such as antimalarial-drug (+)-artemisinin, via normal reactivity.[5] An example of an umpolung strategy was described in a protocol for insertion of side chains at the 3-position of the 2-cyclohexenone allowed the formation of epoxyquinol analogues.[6] For this reason, 3-substituted 2-cyclohexenones **4** are highlighted as recurrent building blocks for many purposes. They can be accessed through the umpolung reactivity of 2-cyclohexenone by means of its synthetic equivalents such as 1,3-bis(phenylthio)cyclohex-1-ene,[7] 3-cyanocyclohexanone,[8] 1-dioxo lanyl-3-tosylcyclohexane,[9] or (3-(*tert*-butyldimethylsiloxy) cyclohex-2-en-1-yl)triphenylphosphonium triflate.[10–12] These methods required multi-step transformations and overall yields are moderate.

An interesting and practical methodology to achieve the 3-electrophilic substitution of 2-cyclohexenone was reported by Katritzky's group in 1995.[13] It consisted in the reaction between 2-cyclohexenone and trimethylsilylbenzotriazole to generate a 1,4-adduct similar to compound **2b**. Treatment of this non-isolated-intermediate with LDA promoted the formation of an allylic anion which was then trapped by an electrophile. Subsequent addition of aqueous acid obtained the corresponding 3-substituted 2-cyclohexenones **4** (yields 50–75%).

On the other hand, Evans demonstrated in 1977 that (phenylthio)trimethylsilane **1a**[14,15] can be used as a protecting group of aldehydes and α,β-unsaturated carbonyls due to the high affinity between silicon and oxygen atoms. Interestingly, the 1,4-adduct **2a** that arises from the reaction between **1a** and 2-cyclohexenone is also air-labile. Therefore, we thought that a more stable analogue such as (phenylthio)triisopropylsilane **1b** might afford an analogue of **2a** which also would undergo a 3-electrophilic substitution after its treatment with a base. Finally, TBAF would trigger a one-pot transformation of corresponding intermediates **3** into 3-susbtituted 2-cyclohexenones **4** as described in Scheme 1.

Results and discussion

The (phenylthio)silanes **1** were prepared using Davis' protocol.[16] It involves a condensation between thiophenol and corresponding trialkylsilyl chloride in presence of Et_3N. While triisopropyl **1b** and *t*-butyldimethyl **1c** derivatives were isolated

* Corresponding author.
E-mail address: mromeroo@uaemex.mx (M. Romero-Ortega).

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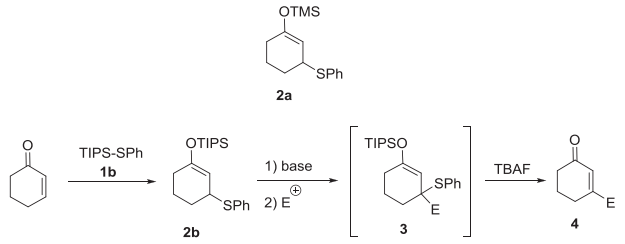


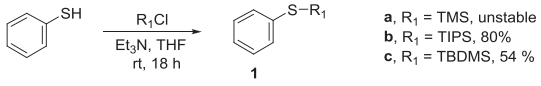
Scheme 1. General procedure to synthesize 3-substituted 2-cyclohexen-1-ones.

in yields of 80% and 54% respectively, the (phenylthio)trimethylsilane **1a** was unstable during the heating process for vacuum distillation (Scheme 2).[16b]

With compounds **1b** and **1c** at hand, we proceeded to find the best reaction conditions for generating 1,4-adducts **2** (Table 1). In the first experiment, a neat equimolar mixture of 2-cyclohexenone and (phenylthio)triisopropylsilane **1b** did not afford any product **2b** after stirring for 2 h even in the presence of potassium cyanide-18-crown-6 complex[17] (0.3% mol) as initiator (Entry 1). These conditions were reported by Evans to produce **2a** using (phenylthio)trimethylsilane **1a**.[14,15] However, an increase in the reaction time to 18 h resulted in the desired compound **2b**, but with a poor yield of 21% (Entry 2). Moreover, when the amount of the anionic initiator was increased by 5 times with a reaction time of 2 h, the yield was slightly improved to 28% (Entry 3). Interestingly, carrying out the reaction in THF, while applying 0.9%-mol of the complex for 18 h, dramatically increased the yield provided **2b** to 60% (entry 4); a higher quantity of the complex, longer stirring time, or even heating, had a worse yield of the 1,4-adduct **2b**. On the other hand, the treatment of 2-cyclohehexenone and (phenylthio)*t*-butyldimethylsilane **1c** under similar conditions (THF, 0.9% mol of the complex, 18 h), provided a moderate yield of compound **2c** (37%, entry 5).

Because of the 1,4-adduct **2b** was obtained with the highest yield, we decided to take it as the synthetic equivalent of 2-cyclohexenone in order to develop our umpolung procedure. A typical experiment consisted in the reaction of a base and **2b** at low temperatures, where the allylic anion could be trapped by an electrophile. Initial screening that employed Ph_2CO, allyl bromide, or PhCHO as electrophiles, demonstrated that bases such as LDA or *n*-BuLi were not sufficiently reactive to carry out the α-lithiation of sulfide-derivative **2b**. In all these experiments only the starting material **2b** was recovered. We believe that the reason for which the acid-base reaction did not happen was due to the short half-life time that *n*-BuLi exhibits in THF at −78 °C.[18,19] Likewise, the proton abstraction by the base on the sulfide **2b** was not accomplished when Et_2O was used instead of THF. Nor was it achieved by employing a much stronger base such as *t*-BuLi at 0 °C. It is known that the presence of TMEDA or HMPA as additives has an important effect on the generation and stabilization of the respective carbanion.[20] Consequently, when experiments were carried out at 0 °C in the presence of TMEDA using benzaldehyde as an electrophile, it was evident that the β-lithiation reaction took place in the thiophenyl ring instead of the α-lithiation reaction of the sulfide-side of **2b** because the alcohol **8** was isolated (Fig 1). It is worth noting that at −78 °C the directed *o*-metalation of **2b** did not occur in THF. The finding that TMEDA readily promotes the β-lithiation increased expectations for positive outcomes by using HMPA. Gratifyingly, when the reaction was carried out in THF/HMPA (2.5 equiv) at −78 °C, the expected anion of sulfide **2b** was consumed by PhCHO, resulting in intermediate **3a**. The crude product **3a** went through a slow one-pot process of deprotection/β-elimination when TBAF was added, and ultimately led to the isolation of 2-cyclohexenone **4a** with a yield of 71% (table 2, entry 1). This umpolung strategy was expanded when derivatives **4b–h** were synthesized using *m*-anisaldehyde, piperonal, acetophenone, chloromethyl pivalate, benzyl bromide, 2-cyclohexenone and paraformaldehyde as electrophiles (Table 2). Hence, the procedure could be applied to ketones (Entry 4), alkyl halides (Entries 5–6) and even α,β-unsaturated compounds such as 2-cyclohexenone (Entry 7). Here it is worth mentioning that this methodology comprises two continuous reactions in a single step, therefore yields are acceptable.

Aldehydes showed unusual behavior and exhibited a poor performance (Entries 2 and 3) especially paraformaldehyde (entry 8). We believe that low yields are due to an isomerization/oxidation process that happened, especially for 2-cyclohexenones **4a** and **4h** in a slightly acidic or basic media. For example, when 2-cyclo-



Scheme 2. Synthesis of (phenylthio)trialkylsilanes **1.**

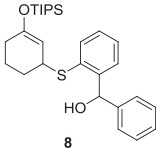
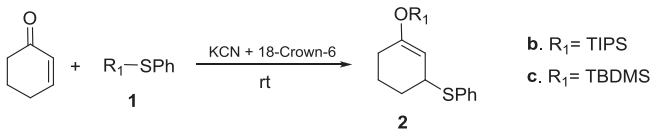


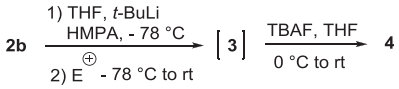
Fig. 1. *o*-Metallation of thiophenyl ring.

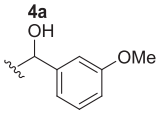
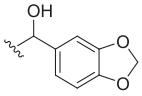
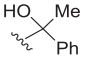
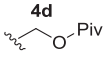
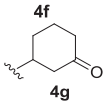
Table 1
Screening of the 2-cyclohexenone activation process.



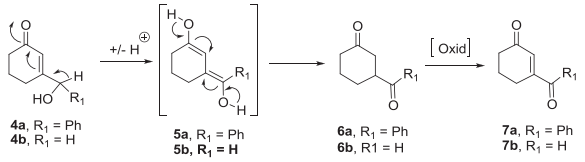
Entry	SM	Complex (%)	Solvent	Time (h)	Product	Yield (%)
1	**1b**	0.3	neat	2	**2b**	0
2	**1b**	0.3	neat	18	**2b**	21
3	**1b**	1.5	neat	2	**2b**	28
4	**1b**	0.9	THF	18	**2b**	60
5	**1c**	0.9	THF	18	**2c**	37

Table 2
Preparation of 3-substituted 2-cyclohexenones **4** by an umpolung electrophilic-substitution procedure.[a]



Entry	E^+	**4** (E=)	Yield (%)
1	Benzaldehyde	**4a** 	71
2	*m*-Anisaldehyde	**4b** 	38
3	Piperonal	**4c** 	27
4	Acetophenone	**4d** 	58
5	Chloromethyl pivalate	**4e** 	60
6	Benzyl bromide	**4f** 	50
7	Cyclohexenone	**4g** 	55
8	Paraformaldehyde	**4h**	12

[a] Reactions were performed by using (phenylthio)silane **2b** (1.0 equiv), HMPA (2.25 equiv), *t*-BuLi (2.25 equiv), 1.5–2.0 equiv of E^+, and TBAF (1.2 equiv).



Scheme 3. Isomerization/oxidation of 2-cyclohexenones **4a** and **4b**.

hexenones **4a** or **4h** remained dissolved in $CDCl_3$ for a long time, the formation of compounds **7a** and **7h** was observed (Scheme 3). Apparently, delocalization of the electron density in the α,β-unsaturated system would allow tautomerization to bis-enol intermediate **5**. Then, the keto-enol equilibrium would stimulate the obtaining of 1,4-dicarbonyl compound **6**, which might be oxidized to the 2-cyclohexenones **7** by air. This mechanism of reaction was proposed because it was possible to isolate and characterize the 2-cyclohexanone **6a** and the 2-cyclohexenone **7a** after the reaction of 2-cyclohexenone **4a** with TFA (1.0 equiv) in DCM at room temperature for 24 h. Additionally, the oxidation of 3-(hydroxymethyl)-2-cyclohexenone **4h** to the 3-carbaldehyde derivative **7h** was also promoted by a base such as K_2CO_3. The observation of this behavior turned out to be relevant since it has not been previously described in the literature.

In summary, we have developed a novel and direct methodology for the preparation of 3-substituted 2-cyclohexenones **4** employing an umpolung strategy. The versatility and potential this methodology possess is revealed by the use of a variety of electrophilic species, notably the cheap and widely available 2-cyclohexenone, to generate in one-pot process 3-substituted 2-cyclohexenones **4** which could serve as useful buildings blocks to synthesize highly valuable molecules. Further investigation in this area is being carried out in our laboratory.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.07.007.

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16. (a) Davis FA, Rizvi SQA, Ardecky R, Gosciniak DJ, Friedman AJ, Yocklovich SG. *J Org Chem*. 1980;45:1650
(b) *Synthesis of phenyl(trialkylsilyl)sulfides **1b** and **1c***. To a solution of thiophenol (1.0 equiv) and the corresponding trialkylsilyl chloride (1.1 equiv) in anhydrous THF [1.95 M], under nitrogen atmosphere, triethylamine (1.2 equiv) dissolved in anhydrous THF [2.37 M] was added dropwise. Immediately the triethylammonium chloride is observed as a white solid. After stirring for 18 h at room temperature, the reaction mixture was filtered through celite, the filter was washed with 10 mL of THF, and the filtrate was washed with 10 mL of an aqueous solution of KOH (10%) in order to eliminate the excess of tiophenol. The organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The crude reaction was then distillated under reduced pressure affording the corresponding phenyl(trialkylsilyl)sulfide **1**.*Compound* **1b**: The general procedure was applied using 1.0 mL of thiophenol (1.073 g, 9.74 mmol), 2.3 mL of TIPSCl (2.072 g, 10.75 mmol) in 5 mL of anhydrous THF. This reaction afforded 2.07 g (80%) of **2b** as a colorless oil. TLC-R_f (Hexanes 100%) 0.62; bp 109 °C (9.0 mmHg); NMR-^{1}H (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 6.5, 3.0 Hz, 2H), 7.24–7.18 (m, 3H), 1.25 (ddd, J = 15.6, 13.0, 7.1 Hz, 3H), 1.09 (d, J = 7.1 Hz, 18H); NMR-^{13}C (75 MHz, $CDCl_3$) δ 135.4, 131.5, 128.5, 126.6, 18.4, 13.1. Mass spectrum *m/z* [M^+] 266, 223(100%).*Compound* **1c**:[16] The general procedure was applied using 1.0 mL of thiophenol (1.073 g, 9.74 mmol), 1.62 g of TBDMSCl (10.75 mmol) in 5 mL of anhydrous THF. This reaction afforded 1.173 g (54%) of **1c** as a colorless oil. TLC-R_f (Hexanes 100%) 0.55; bp 90 °C (9.0 mmHg); NMR-^{1}H (300 MHz, $CDCl_3$) δ 7.26 (dd, J = 6.6, 3.0 Hz, 2H), 7.08–7.01 (m, 3H), 0.80 (s, 9H), −0.00 (s, 6H); NMR-^{13}C (75 MHz, $CDCl_3$) δ 135.6, 131.5, 128.6, 126.8, 26.4, 19.0, −3.3.*Synthesis of 3-phenylthio-1-(trialkylsilyloxy)cyclohex-1-ene* **2:** The KCN/18-crown-6 complex was added to a well-stirred solution of 2-cyclohexenone (1.0 equiv) and the respective phenyl(trialkylsilyl)sulfide (1.0 equiv) in freshly distilled dry THF [1.6 M]. Stirring under nitrogen atmosphere at room temperature was continued for 18 h and the yellow solution was concentrated *in vacuum* and the products were obtained as oils and used in their crude form.*Compound **2b**:* The general procedure was applied using 376 mg of 2-cyclohexenone (3.91 mmol), 1.04 g of **1b** and 12 mg of KCN/18-crown-6 complex (0.04 mmol) in anhydrous THF (2.5 mL). The reaction crude was purified by column chromatography (4.0 × 10.0 cm, silica gel; Hexanes 100%), affording 847 mg (60%) of **2b** as a yellow pallid oil. TLC-R_f

(Hexanes, 100%) 0.26; NMR-^{1}H (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.1 Hz, 2H), 7.27 (t, J = 7.3 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 4.99 (d, J = 4.4 Hz, 1H), 3.99 (d, J = 4.2 Hz, 1H), 2.14–1.94 (m, 3H), 1.72 (ddtq, J = 27.8, 22.2, 11.6, 5.8, 5.2 Hz, 3H), 1.17–0.98 (m, 21H); NMR-^{13}C (126 MHz, $CDCl_3$) δ 154.4, 136.4, 131.3, 128.7, 126.4, 103.7, 44.9, 29.8, 28.1, 19.2, 18.0, 12.6. MS (EI, 70 eV) m/z [M$^+$] 361, 255 (100%).*t*-butyldimethyl(((3-(phenylthio)cyclohex-1-en-1-yl)oxy)silane **(2c).** The general procedure was applied using 100 mg of cyclohexenone (1.04 mmol), 233 mg of **1c** and 5.0 mg of KCN/18-crown-6 complex (0.02 mmol) in 0.8 mL of anhydrous THF. The product was purified by column chromatography (3.0 × 9.0 cm, silica gel; Hexanes 100%), affording 123 mg (37%) of **2c** as a colorless oil. TLC-R_f (Hexanes, 100%) 0.23; NMR-^{1}H (300 MHz, $CDCl_3$) δ 7.26 (d, J = 6.6 Hz, 2H), 7.10 (dd, J = 16.0, 6.9 Hz, 3H), 4.85 (s, 1H), 3.83 (s, 1H), 1.89 (s, 3H), 1.71–1.43 (m, 3H), 0.78 (s, 9H), 0.00 (s, 6H); NMR-^{13}C (126 MHz, $CDCl_3$) δ 154.2, 136.3, 131.3, 128.8, 126.5, 104.4, 44.8, 29.8, 28.2, 25.6, 19.1, 18.0, −4.4, −4.5.*Synthesis of 2-cyclohexen-1-one-3-sustituted* **4**. A solution of 1.0 equiv of **2b** and HMPA (2.0–2.5 equiv) in anhydrous THF [0.092 M] was cooled at −78 °C (N_2 atmosphere). *t*-BuLi (1.5 M, 2.0–2.5 equiv) was added dropwise over 5 min period. Stirring at −78 °C was continued for 30 min, and then the respective electrophile (1.5–2.0 equiv) was added and then the reaction mixture was stirred for 30 min at −78 °C. The reaction temperature was allowed to rise to room temperature for 2 h and the reaction was quenched with saturated NH_4Cl solution. The product was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The crude reaction was dissolved in anhydrous THF [0.069 M] and was cooled at 0 °C. TBAF (1.0 M, 1.25 equiv) was added and the reaction temperature was allowed to rise the room temperature and stirred for 18 h. At the end of this period of time, the reaction was quenched by adding brine and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuum* and the product was purified by column chromatography on silica gel.*Compound* ***4a***:[13] The general procedure was applied using 105 mg of **2b** (0.28 mmol), 0.10 mL of HMPA (103 mg, 0.58 mmol), *t*-BuLi (0.45 mL, 1.5 M, 0.60 mmol) and 65 μL of benzaldehyde (63 mg, 0.59 mmol) in 3.5 mL of anhydrous THF. For the deprotection 0.36 mL of TBAF (1.0 M, 95 mg, 0.36 mmol) were used in 4 mL anhydrous THF. The reaction crude was purified by column chromatography (2.0 × 8.0 cm, silica gel; 55:45 Hexanes/EtOAc) affording 41 mg (71%) of **4a** as a yellow oil. TLC-R_f (Hexanes/EtOAc 3:2) 0.23; NMR-^{1}H (300 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 6.35 (d, J = 1.4 Hz, 1H), 5.24 (s, 1H), 2.38 (t, J = 6.6 Hz, 2H), 2.27 (s, 1H), 2.15 (t, J = 5.5 Hz, 2H), 1.93 (dq, J = 12.2, 7.0, 6.3 Hz, 2H); NMR-^{13}C (75 MHz, $CDCl_3$) δ 200.0, 165.0, 140.4, 128.9, 128.6, 126.8, 124.0, 76.7 , 37.8, 25.9, 22.6. Mass spectrum m/z [M$^+$] 246, 93(84%).*Compound* ***4b***: The general procedure was applied using 100 mg of **2b** (0.28 mmol), 0.12 mL of HMPA (124 mg, 0.69 mmol), *t*-BuLi (0.45 mL, 1.5 M, 0.60 mmol) and 70 μL of m-anisaldehyde (75 mg, 0.55 mmol) in 3.0 mL of anhydrous THF. For the deprotection 0.33 mL of TBAF (1.0 M, 86 mg, 0.33 mmol) were used in 4 mL anhydrous THF. The product was purified by column chromatography (2.0 × 10.0 cm, silica gel; 55:45 Hexanes/EtOAc) affording 24 mg (38%) of **4b** as a yellow pallid oil. TLC-R_f (Hexanes/EtOAc 55:45) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, J = 7.6 Hz, 3H), 6.87–6.78 (m, 3H), 6.27 (s, 1H), 5.14 (s, 1H), 3.74 (s, 3H), 2.34–2.28 (m, 2H), 2.13–2.07 (m, 2H), 1.86 (d, J = 6.3 Hz, 3H), 1.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.09, 165.00, 159.99, 142.07, 129.90, 124.05, 119.07, 113.92, 55.29, 37.79, 25.82, 22.60.Mass spectrum m/z [M$^+$] 232, 232 (100%).*Compound* ***4c***: The general procedure was applied using 100 mg of **2b** (0.28 mmol), 0.12 mL of HMPA (124 mg, 0.69 mmol), *t*-BuLi (0,45 mL, 1.5 M, 0.60 mmol) and 83 mg of piperonal (dissolved in 1 mL of THF, 0.55 mmol) in 3.0 mL of anhydrous THF. For the deprotection 0.33 mL of TBAF (1.0 M, 86 mg, 0.33 mmol) were used in 4 mL anhydrous THF. The reaction crude was purified by column chromatography (2.0 × 8.0 cm, silica gel; 55:45 Hexanes/EtOAc) affording 18 mg (27%) of **4c** as a yellow pallid oil. TLC-R_f (Hexanes/EtOAc 55:45) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, J = 5.3 Hz, 3H), 6.34 (d, J = 1.5 Hz, 1H), 5.98 (s, 2H), 5.15 (s, 1H), 2.44–2.35 (m, 3H), 2.15 (d, J = J = 6.0 Hz, 2H), 2.00–1.88 (m, 2H), 1.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.06, 165.19, 148.13, 147.79, 134.42, 123.80, 120.60, 108.35, 107.06, 101.25, 37.79, 25.99, 22.60. Mass spectrum m/z [M$^+$] 246.*Compound* ***4d***: The general procedure was applied using 100 mg of **2b** (0.28 mmol), 0.12 mL of HMPA (124 mg, 0.69 mmol), *t*-BuLi (0.45 mL, 1.5 M, 0.675 mmol) and 70 μL of acetophenone (72 mg, 0.60 mmol) in 3.0 mL of anhydrous THF. For the deprotection 0.33 mL of TBAF (1.0 M, 86 mg, 0.33 mmol) were used in 4 mL anhydrous THF. The reaction crude was purified by column chromatography (2.0 × 10.0 cm, silica gel; 65:35 Hexanes/EtOAc) affording 35 mg (58%) of **4d** as a yellow oil. TLC-R_f (Hexanes/EtOAc 67:33) 0.28; NMR-^{1}H (300 MHz, $CDCl_3$) δ 7.44–7.28 (m, 5H), 6.35 (s, 1H), 2.37 (t, J = 6.6, 6.2 Hz, 2H), 2.22–2.11 (m, 2H), 2.06 (s, 1H), 1.87 (p, J = 6.1, 5.6 Hz, 2H), 1.76 (s, 3H); NMR-^{13}C (75 MHz, $CDCl_3$) δ 200.5, 168.6, 144.2, 128.6, 127.7, 125.3, 123.6, 76.4, 37.6, 27.5, 25.9, 23.0. Mass spectrum m/z [M$^+$] 217, 173 (100%).*Compound* ***4e***: [21] The general procedure was applied using 100 mg of **2b** (0.28 mmol), 0.12 mL of HMPA (124 mg, 0.69 mmol), 0.45 mL of *t*-BuLi (0.45 mL, 1.5 M, 0.675 mmol) and 90 μL of chloromethyl pivalate (94 mg, 0.62 mmol) in 3.0 mL of anhydrous THF. For the deprotection 0.33 mL of TBAF (1.0 M, 86 mg, 0.33 mmol) were used in 4 mL anhydrous THF. The reaction crude was purified by column chromatography (2.0 × 10.0 cm, silica gel; 4:1 Hexanes/EtOAc) affording 35 mg (60%) of **4e** as a yellow pallid oil. TLC-R_f (Hexanes/EtOAc 4:1) 0.28; NMR-^{1}H (300 MHz, $CDCl_3$) δ 6.02 (s, 1H), 4.67 (s, 2H), 2.43 (t, J = 6.0, 5.5 Hz, 2H), 2.28 (t, J = 6.5, 5.5 Hz, 2H), 2.05 (q, J = 10.5, 5.1 Hz, 2H), 1.25 (s, 9H); NMR-^{13}C (75 MHz, $CDCl_3$) δ 199.0, 177.7, 158.7, 124.3, 64.8, 38.9, 37.6, 27.2, 26.3, 22.3.*Compound* ***4f***:[22] The general procedure was applied using 100 mg of **2b** (0.28 mmol), 0.12 mL of HMPA (124 mg, 0.69 mmol), *t*-BuLi (0.45 mL, 1.5 M, 0.675 mmol) and 66 μL of benzyl bromide (96 mg, 0.55 mmol) in 3.0 mL of anhydrous THF. For the deprotection 0.33 mL of TBAF (1.0 M, 86 mg, 0.33 mmol) were used in 4 mL anhydrous THF. The reaction crude was purified by column chromatography (2.0 × 10.0 cm, silica gel; 3:2 Hexanes/EtOAc) affording 23.1 mg (45%) of **4f** as a yellow pallid oil. TLC-R_f (Hexanes/EtOAc 3:2) 0.29; NMR-^{1}H (300 MHz, $CDCl_3$) δ 7.39–7.31 (m, 5H), 6.35 (d, J = 1.3 Hz, 1H), 5.30 (s, 1H), 5.24 (s, 1H), 2.38 (t, J = 6.4 Hz, 2H), 2.16 (t, J = J = 5.9 Hz, 2H), 1.94 (p, J = 12.6, 6.1 Hz, 2H); NMR-^{13}C (126 MHz, $CDCl_3$) δ 200.1, 165.2, 140.4, 128.8, 128.5, 126.8, 124.0, 76.7, 37.8, 25.9, 22.6.*Compound* ***4g***: The general procedure was applied using 100 mg of **2b** (0.28 mmol), 0.12 mL of HMPA (124 mg, 0.69 mmol), *t*-BuLi (0.45 mL, 1.5 M, 0.675 mmol) and 50 μL of 2-cyclohexen-1-one (50 mg, 0.52 mmol) in 3.0 mL of anhydrous THF. For the deprotection 0.33 mL of TBAF (1.0 M, 86 mg, 0.33 mmol) were used in 4 mL anhydrous THF. The reaction crude was purified by column chromatography (2.0 × 8.0 cm, silica gel; 55:45 Hexanes/EtOAc) affording 29 mg (55%) of **4g** as a white solid. TLC-R_f (Hexanes/EtOAc 1:1) 0.36; m.p.: 46–48 °C; NMR-^{1}H (500 MHz, $CDCl_3$) δ 5.89 (d, J = 1.1 Hz, 1H), 2.58–2.37 (m, 5H), 2.36–2.28 (m, 4H), 2.16 (ddt, J = 13.0, 6.5, 3.2 Hz, 1H), 2.02 (dt, J = 12.6, 6.1 Hz, 3H), 1.75–1.63 (m, 2H); NMR- ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.55, 199.70, 166.30, 124.81, 45.87, 45.47, 41.07, 37.48, 29.40, 28.18, 25.13, 22.77.Mass spectrum m/z [M$^+$] 192, 95 (100%).*3-(hydroxymethyl)-cyclohex-2-en-1-one* **(4h):**[21] The general procedure was applied using 100 mg of 147b (0.28 mmol), 0.12 mL of HMPA (124 mg, 0.69 mmol), *t*-BuLi (0.45 mL, 1.5 M, 0.675 mmol) and 35 mg of paraformaldehyde (1.2 mmol) in 3.0 mL of anhydrous THF. For the deprotection 0.33 mL of TBAF (1.0 M, 86 mg, 0.33 mmol) were used in 4 mL anhydrous THF. The reaction crude was purified by column chromatography (2.0 × 8.0 cm, silica gel; 3:7 Hexanes/EtOAc) affording 4 mg (12%) of **4h** as a yellow pallid oil. TLC-R_f (Hexanes/EtOAc 3:7) 0.27; NMR-^{1}H (500 MHz, $CDCl_3$) δ 6.15 (s, 1H), 4.27 (s, 2H), 2.42 (t, J = 6.5 Hz, 2H), 2.27 (t, J = 5.7 Hz, 2H), 2.04 (p, J = 14.9, 6.9, 6.2 Hz, 2H); NMR-^{13}C (126 MHz, $CDCl_3$) δ 199.2, 166.9, 123.3, 65.0, 37.8, 26.1, 22.5.

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