On the Regioselectivity of the Nickel-Catalyzed Insertion of Alkynes into the Carbon–Carbon Bond of Oxetan-3-one

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Abstract: The study of the regioselectivity of insertion of unsymmetrical alkynes into the carbon–carbon bond of oxetan-3-one in the presence of a nickel catalyst has revealed a strong directing effect of a 2- thienyl substituent. This effect is larger than those of 2-vinylbenzene, trimethylsilyl, aryl, or 3-thienyl groups.

Key words: carbon–carbon bond activation, nickel, catalysis, oxetanone, alkynes, regioselectivity, insertion, pyrans

Pyrans are prominent heterocycles found in numerous compounds of biological interest[1] that display various properties such as antibacterial,[2] immunosuppressant,[3] nematocidal,[4] or other inhibitory activity[5] (Figure 1). Recently, we reported the synthesis of 2H-pyran-3(6H)-ones by insertion of alkynes into the carbon–carbon bond of oxetan-3-one in the presence of a nickel catalyst.[6–8] This reaction is a relatively rare example of metal-catalyzed cleavage of a C–C bond[9] in oxetane derivatives,[10] as C–O bond cleavage is much more frequent under a wide array of conditions.[11,12] Significantly, oxetan-3-one is now an essential building block in the synthesis of numerous oxetane derivatives that have recently gained a great interest in medicinal chemistry and pharmaceutical industry,[13] and it is therefore important to understand its reactivity. Herein, we report on the regioselectivity of the insertion of unsymmetrical alkynes into the C–C bond of oxetan-3-one in the presence of a nickel catalyst generated in situ from an air-stable Ni(II) precursor.

In our initial study, we reported only three examples of the nickel-catalyzed cycloaddition of alkynes with oxetan- 3-one using a combination of $Ni(cod)_2$ (cod = cyclooctadiene) and triphenylphosphine as pre-catalyst.[6] Recently, Louie et al. reported that $NiCl_2(PPh_3)_2$ or $NiBr_2(PPh_3)_2$ with zinc powder in MeCN were also competent systems, but the regioselectivity of the insertion of unsymmetrical alkynes into the C–C bond of oxetan-3-one was not examined.[14] Moreover, we observed that using $NiBr_2(PPh_3)_2$ and Zn led to inferior results in the regioselective cycloaddition of azetidin-3-ones and 1,3-enynes when compared to the combination of $Ni(cod)_2$ and PPh_3.[15] Thus, the cycloaddition of N-Ts-azetidin-3-one **1** (Ts = p-toluenesulfonyl) with 2- methylhex-1-en-3-yne led to the isolation of 4 in only 14% yield (Table 1, entry 1). However, the yield was greatly improved by using THF instead of MeCN (entry 2). Moreover, the cycloaddition of N-Boc-azetidin-3-one 2 (Boc = tert-butoxycarbonyl) with methylphenylacetylene led to a superior yield of 5 in i-PrOH as compared to the reaction in THF (entries 3 vs 4). Focusing our attention on oxetan-3-one **3** and its cycloaddition with bis-phenylacetylene into 6 (entries 5–9), we found that using $NiBr_2(PPh_3)_2$ and zinc powder in THF gave the best yield (entry 7) when compared to other combinations of pre-catalyst and solvent, and those conditions were therefore used in the study of the regioselectivity of the reaction with unsymmetrical alkynes **7a–o**[16] (Scheme 1, method A). It is noteworthy that the zinc powder was used without activation.[17]

All the cycloadditions of alkynes substituted with a silyl group at one terminus and an aryl or thienyl group at the other gave only one regioisomer, as determined by NMR spectroscopy. Thus, 2H-pyran-3(6H)-ones **8a–d** were isolated in 55–85% yield according to our optimized method A (Scheme 1). Alkyne **7e** with a trimethylsilyl substituent at one terminus and a linear alkyl chain at the other gave a mixture **8e** and **9e**. It is noteworthy that silylated alkynes do not undergo the same reaction with cyclobutanones,[18] although the strain energies of oxetane, azetidine, and cyclobutane are very similar.[19] Alkynes substituted with an alkyl group at one terminus and an aryl group at the other gave superior yields in the case of an electron-poor aryl group (**8g** vs **8f** and **8h**). However, the regioselectivity was minimally better in the case of an electron-rich aryl group. Substitution of the alkyl chain, even in the homopropargylic position, led to a slight erosion of the regioselectivity (**8i**). Although the origin of this effect is not clear, it is noteworthy that the conditions had to be modified by adding 10 mol% of PPh_3 and by adding a solution of oxetan-3-one **3** and alkyne **7i** to a solution of the nickel catalyst in order to obtain **8i** in good yield (Scheme 1, method B). The same mode of addition was also necessary for this alkyne in our previous protocol based on $Ni(cod)_2$.[6] As was the case with azetidin-3-ones,[15] the reaction of a 1,3-enyne with oxetan- 3-one gave **8j** with good regioselectivity. Strikingly, a much better regioselectivity was observed when the alkyne was substituted with a 2-thienyl group than with the 3-thienyl isomer (**8k** vs **8l**) whereas and the regioselectivity was the same when the 2-thienyl group was replaced with a 2-furyl group, although **8m** was only isolated in low to moderate yields. However, 2-pyridylalkynes **8n** and **8o** did not undergo the desired reaction, the former being recovered intact whereas the latter underwent decomposition.

Moreover, it is noteworthy that using a combination of $NiCl_2(PPh_3)_2$ and Zn in MeCN (Scheme 1, method C) led to a markedly decreased yield in the case of **8m**, when compared with the other methods, whereas regioselectivity in the of case **8g** was slightly inferior when we used this method. On the other hand, the previously reported method relying on $Ni(cod)_2$ and PPh_3 in 1,4-dioxane (Scheme 1, method D)[6] and the method relying on $NiBr_2(PPh_3)_2$ and Zn in THF (Scheme 1, method A) gave very good results both with challenging substrates (e.g., **7c** into **8c**) and with more reactive substrates (e.g., **7g** into **8g**).

The markedly enhanced regioselectivity observed in the conversion of 2-(hex-1-yn-1-yl)thiophene (**7k**) into **8k** when compared to the conversion of 3-(hex-1-yn-1-yl)thiophene (**7l**) into **8l** could be explained by η^1 -coordination of the sulfur atom (Scheme 2),[20] either in oxidative cyclization transition state **I** towards intermediate **II** (pathway *a*) or in transition state **IV** from intermediates **III** to **V** (pathway *b*). Both pathways would converge towards intermediate **V** that would then liberate the catalyst and the major regioisomer of **8k**.

Pathway *a* would be in agreement with recent theoretical studies of the nickel-catalyzed reductive coupling of alkynes and aldehydes,[21] whereby the η^1-coordination of the sulfur atom in **I** and **II** would replace the η^3-coordination proposed to explain the regioselectivity observed for 1,3-enynes.[22] It would also be in agreement with several isolated nickel-dihydrofuran complexes.[23] However, recent theoretical studies by Lin and Li suggest that the rearrangement of **II** into **V** is not kinetically viable under the reaction conditions, and the direct C–C oxidative addition of 3 to the active nickel catalyst would instead be much more feasible and lead to **III**.[24] Nevertheless, the regioselectivity of the insertion of alkyne **7k** into the $C(sp^2)$–Ni bond of **III** to **V** via transition state **IV**[25] would also be controlled by the η^1-coordination of the sulfur atom of the thienyl group. Accordingly, the difference of regioselectivity observed during the formation of 8k and 8l would not be easily explained by invoking a η^2-coordination of the thienyl group in either of the pathways, as both 2-thienyl and 3-thienyl isomers would be equally capable of such coordination in both pathways.

Similarly, neither η^1-coordination nor η^2-coordination of the thienyl group are possible if we postulate an insertion of alkyne **7k** into the C(sp^3)–Ni bond of **III** in the pathway leading to the major regioisomer of **8k**. It would follow that only the cleavage of C(sp^2)–Ni bond in **III** occurs in pathway *b*, as we would otherwise obtain the same level of regioselectivity for **8k** and **8l**.

Moreover, as discussed previously,[6] and on the basis of the NMR data of isolated nickel-alkyne complexes,[26] the electronic density at the alkyne terminus attached to the silyl group is greater than at the other terminus, and insertion of the alkyne into the polarized C(sp^3)(δ–)–Ni(δ+) bond of the metallacycle that results from the oxidative addition of the catalyst into the C–C bond of oxetan-3-one **3** would then match the polarization of the alkyne in the reactions leading to **8a–e**.[24,26] This electronic effect can overcome steric hindrance, as illustrated with the formation of **8e** as major regioisomer. Overall, by comparing the ratios of regioisomers for **8e–h** and **8j–m**, the influence of substituents on the regioselectivity of the alkyne insertion in this reaction decreases in the order 2-thienyl, 2-furyl > 2-vinylbenzene > trimethylsilyl > aryl ~ 3-thienyl.

We also examined the regioselectivity of the ring opening with substituted oxetan-3-one **10** that was prepared by the method reported by Zhang.[27] In stark contrast to the nickel-catalyzed insertion of alkynes in substituted azetidin-3-ones that leads exclusively to the cleavage of the least sterically hindered C–C bond,[6,7b,14,15] we observed that the reaction of **10** with oct-4-yne led to a mixture of regioisomers **11** and **12**, independently of the pre-catalyst, although combining $Ni(cod)_2$ and PPh_3 in 1,4-dioxane gave a much superior yield and better regioselectivity (Scheme 3). This result also contrasts with the closely related nickel-catalyzed cycloadditions of 1,6-diynes with cyclobutanones,[28] of alkynes and 1,3-dienes with benzocyclobutanones,[29] and of 1,3-dienes with azetidin-3-ones.[10b] In all cases, only cleavage of the least sterically hindered C–C bond of the 4-membered ring was observed. The decrease of regioselectivity in the ring cleavage of **10**, as compared to the selectivity observed for similarly substituted azetidin-3-ones with various protective groups on the nitrogen atom,[6,7b,14,15] is likely a result of the decreased steric bulk around the oxygen atom of the oxetane.

In conclusion, we have examined the regioselectivity of the insertion of unsymmetrical alkynes in oxetan-3-one in the presence of a nickel catalyst generated in situ from an air-stable precursor and we have observed that the 2-thienyl group exerts a stronger directing effect than 2-vinylbenzene or trimethylsilyl substituents and approximately twice as strong as the 3-thienyl group or other aryl groups.

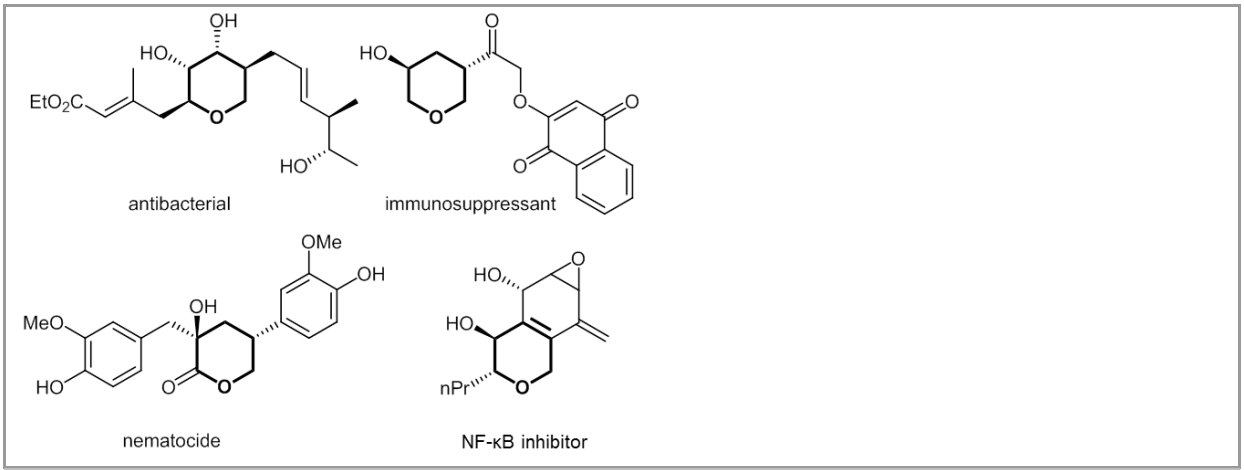
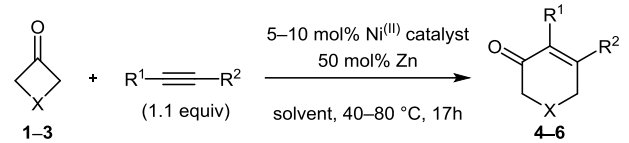
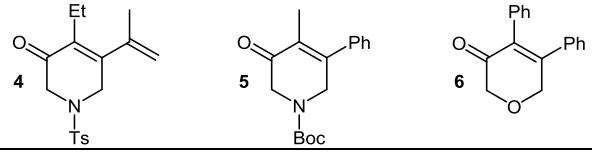


Figure 1 Examples of biologically active compounds containing a pyran motif.

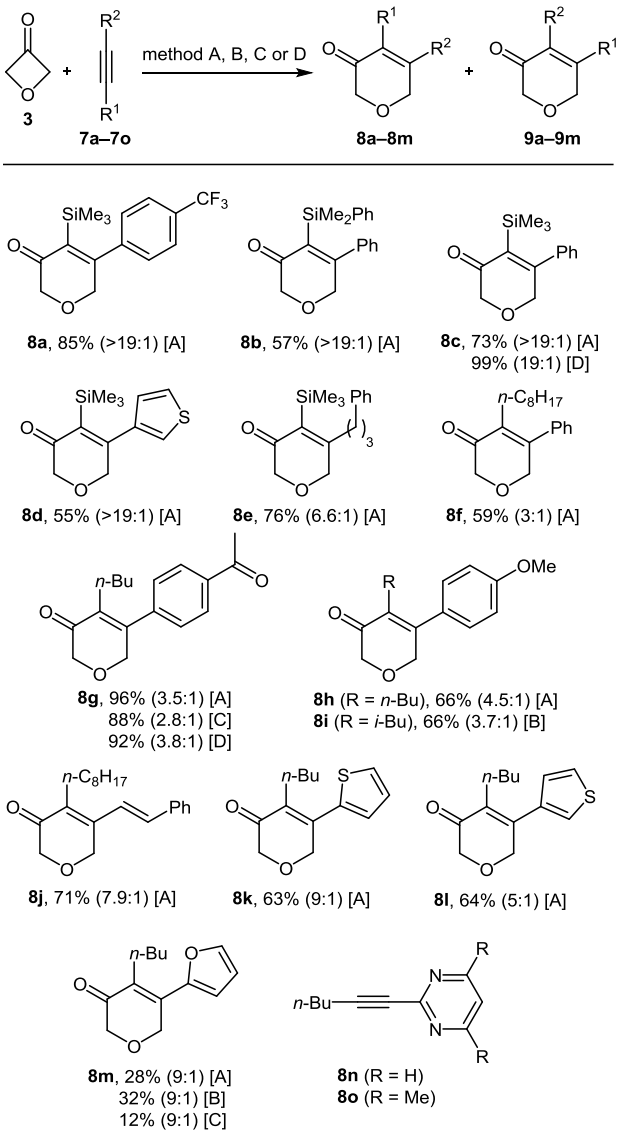
Table 1 Optimisation of general reaction conditions[a]



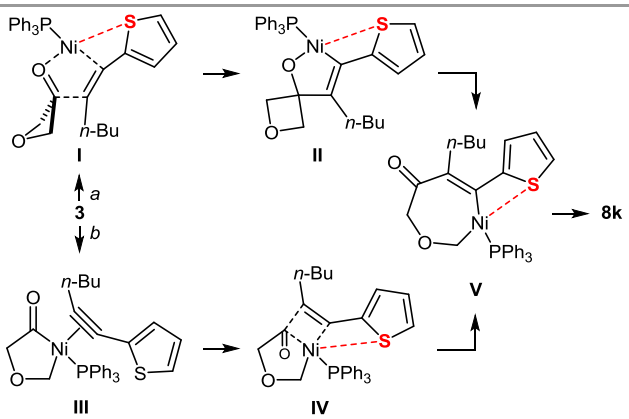


entry	product	$Ni^{(II)}$ catalyst[b]	solvent	t (°C)	yield (%)[c]	r.r.[d]
1	**4**	$NiBr_2(PPh_3)_2$	MeCN	70	14	84:16
2	**4**	$NiBr_2(PPh_3)_2$	THF	70	67	83:17
3	**5**	$NiBr_2(PPh_3)_2$	iPrOH	40	84	89:11
4	**5**	$NiBr_2(PPh_3)_2$	THF	40	60	90:10
5	**6**	$NiBr_2(PPh_3)_2$	iPrOH	70	50	n.a.
6	**6**	$NiBr_2(PPh_3)_2$	MeCN	70	76	n.a.
7	**6**	$NiBr_2(PPh_3)_2$	THF	70	86	n.a.
8	**6**	$NiCl_2(PPh_3)_2$	MeCN	80	77	n.a.
9	**6**	$NiCl_2(PPh_3)_2$	THF	70	13	n.a.

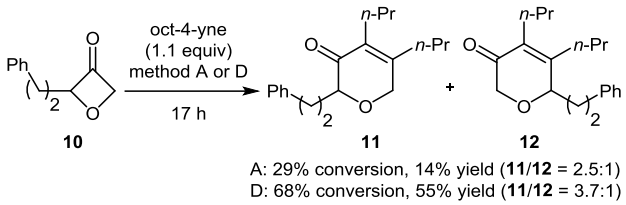
[a] Reaction conditions: **1**–**3** (0.22 mmol), alkyne (0.24 mmol), $Ni^{(II)}$ catalyst (0.022 mmol), Zn powder (0.11 mmol), solvent (0.2 M), 17 h except otherwise noted. [b] 5 mol% of $Ni^{(II)}$ catalyst was used in entries **3** and **4**. [c] Yield of combined regioisomers after isolation. [d] Regioisomers ratio determined by ^1H NMR of the crude mixture.



Scheme 1 Regioselective insertion of unsymmetrical alkynes into the C–C bond of oxetan-3-one. Reaction conditions: [A] as in table 1, entry 7; [B] as [A] but 10 mol% PPh_3 was added whilst oxetan-3-one and the alkyne were added as a THF solution to a solution of the nickel catalyst; [C] as in table 1, entry 8; [D] 10 mol% $Ni(cod)_2$, 30 mol% PPh_3, dioxane, 90 °C.[6] Yields are given for the combined regioisomers after isolation. The ratio of regioisomers (**8**/**9**) is given in parentheses and was determined from purified material except for **8g** (ratio from crude material).



Scheme 2 Possible rationale explaining the enhanced regioselectivity of the insertion of 2-(hex-1-yn-1-yl)thiophene **7k** during the formation of **8k**.



Scheme 3 Regioselective C–C cleavage of substituted oxetan-3-one **10**. Reaction conditions: [A] as in table 1, entry 7; [D] 10 mol% $Ni(cod)_2$, 30 mol% PPh_3, dioxane, 90 °C.

Unless otherwise noted, all reactions were carried out in flame-dried glassware under dry N2 atmosphere. THF was purified with the solvent purification system Pure Solv MD-6 from innovative Technology. MeCN and 1,4-dioxane were purchased as anhydrous solvent on MS 4Å. Merck silica gel 60 (230–00 mesh) was used for chromatography. NMR: Spectra were recorded on a Bruker DRX 500 in CDCl3; chemical shifts (δ) are given in ppm. The solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl3: δC = 77.0; residual CHCl3 in CDCl3: δH = 7.26); apparent splitting patterns are designated using the standard abbreviations. In 13C NMR, an APT sequence was used to separate methylene groups and quaternary carbons (e, even) from methine and methyl groups (o, odd). The regiochemistry of 8a–m, 11, and 12 was established by either HMBC or NOE experiments. IR: PerkinElmer Spectrum 100 FT-IR spectrophotometer. The intensity of the peaks is indicated by w (weak), m (medium), and s (strong). High-resolution mass spectra (HRMS) were determined at the University of Liverpool on micromass LCT mass spectrometer (ESI) and Trio-1000 or Agilent QTOF 7200 mass spectrometers (CI). Melting points: Griffin melting point apparatus (not corrected). Elemental analyses: University of Liverpool. Compounds 1, 6 2, 6 4–6, 6 7a, 30 7b, 31 7e, 32 7f, 33 7g, 6 7h, 34 7i, 6 7j, 15 7k, 19 7l, 19 7m, 35 7n, 36 8c, 6 8g, 6 and 1027 were described previously. Compounds 3, 7c, and 7d are commercially available. All commercially available reagents were used as received.

2-(Hex-1-yn-1-yl)-4,6-dimethylpyrimidine (7o) CuI (12 mg, 0.06 mmol, 0.02 equiv), PdCl2(PPh3)2 (42 mg, 0.06 mmol, 0.02 equiv), PPh3 (30 mg, 0.12 mmol, 0.04 equiv), anhyd i-Pr2NEt (12 mL), anhyd Et3N (3 mL), 2-chloro-4,6-dimethylpyrimidine (426 mg, 3 mmol, 1 equiv), and hex-1-yne (0.52 mL, 4.5 mmol, 1.5 equiv) were added under N2 to a flame-dried two neck round bottom flask. The mixture was stirred at 100 °C for 68 h. The crystalline precipitate was filtered off and all volatiles were removed under vacuum. Purification of the oily residue by flash chromatography (PE/EtOAc, 85:15) gave 7o as a yellow oil; yield: 171 mg (30%); Rf = 0.3. FT-IR (neat): 2959 (w), 2933 (w), 2242 (m), 1583 (s), 1536 (m), 1459 (w), 1440 (m), 1369 (s), 1343 (w), 957 (s), 908 (w), 856 (m), 725 cm–1 (vs). 1H NMR (CDCl3, 500 MHz): δ = 6.89 (s, 1 H), 2.48–2.37 (m, 8 H), 1.59 (quint, J = 7.3 Hz, 2 H), 1.43 (sext, J = 7.4 Hz, 2 H), 0.88 (t, J = 7.5 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 166.9 (e, 2 C), 152.5 (e), 118.6 (o), 89.5 (e), 79.9 (e), 30.0 (e), 23.8 (o, 2 C), 22.0 (e), 18.9 (e), 13.5 (o). MS (CI): m/z (%) = 189 (10) [M + H]+. HRMS (CI): m/z [M + H]+ calcd for C12H17N2: 189.1386; found: 189.1393.

Nickel-Catalyzed Cycloadditions of Alkynes with Oxetan-3-one

General Procedures

Method A: A J-Young Teflon-screw flame-dried Schlenk tube equipped with a small stirrer bar was charged with NiBr2(PPh3)2 (16 mg, 0.022 mmol, 0.1 equiv), Zn (7 mg, 0.111 mmol, 0.5 equiv), and degassed THF (0.4 mL) under N2. Then, 3 (14 µL, 0.22 mmol, 1.0 equiv) and the alkyne (0.244 mmol, 1.1 equiv) were added, followed by THF (0.6 mL). The tube was sealed and the mixture was stirred at 70 °C (oil bath temperature) for 17 h before being filtered through a small plug of silica gel. After evaporation of all volatiles under reduced pressure, the relevant 2H-pyran-3(6H)-one was obtained after purification by flash chromatography as specified.

Method B: This method was identical to method A except that the alkyne (0.244 mmol, 1.1 equiv) was dissolved in THF (0.6 mL) and that this solution was added to a mixture made of NiBr2(PPh3)2, Zn, and PPh3 (5.8 mg, 0.022 mmol, 0.1 equiv) in THF (0.4 mL), before sealing the Schlenk tube.

Method C: This method was identical to method A except that the reaction temperature of the oil bath was set at 80 °C and that NiCl2(PPh3)2 (14 mg, 0.022 mmol, 0.1 equiv) and MeCN (1 mL) were used instead of NiBr2(PPh3)2 and THF, respectively.

5-[4-(Trifluoromethyl)phenyl]-4-(trimethylsilyl)-2H-pyran- 3(6H)-one (8a). This compound was obtained from 7a (59 mg, 0.244 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 9:1) afforded 8a as a white amorphous solid; yield: 59 mg (85%); Rf = 0.3. FT-IR (neat): 2962 (w), 1662 (s), 1570 (m), 1435 (m), 1407 (w), 1323 (vs), 1242 (s), 1164 (s), 1128 (vs), 1109 (vs), 1069 (vs), 1028 (m), 1014 (m), 977 (w), 934 (m), 828 (vs), 759 (m), 688 cm–1 (w). 1H NMR (CDCl3, 500 MHz): δ = 7.68 (d, J = 8.2 Hz, 2 H), 7.37 (d, J = 8.2 Hz, 2 H), 4.41 (s, 2 H), 4.18 (s, 2 H), –0.10 (s, 9 H). 13C NMR (CDCl3, 125 MHz): δ = 197.7 (e), 166.9 (e), 141.4 (e), 137.4 (e), 131.5 (e, q, J = 33.1 Hz), 128.3 (o, 2 C), 125.5 (o, q, J = 4.0 Hz, 2 C), 123.7 (e, q, J = 272.6 Hz), 71.5 (e), 70.1 (e), 0.2 (o, 3 C). Anal. Calcd for C15H17F3O2Si: C, 57.31; H, 5.45. Found: C, 57.11; H, 5.44.

4-[Dimethyl(phenyl)silyl]-5-phenyl-2H-pyran-3(6H)-one (8b). This compound was obtained from 7b (58 mg, 0.244 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 9:1) afforded 8b as a white amorphous solid; yield: 39 mg (57%); Rf = 0.3. FT-IR (neat): 3050 (w), 2951 (w), 1656 (vs), 1600 (w), 1560 (s), 1488 (m), 1424 (m), 1376 (m), 1291 (s), 1277 (s), 1254 (s), 1138 (s), 1114 (s), 1079 (w), 1052 (w), 969 (m), 938 (s), 837 (vs), 809 (vs), 775 (m), 760 (s), 698 cm–1 (vs). 1H NMR (CDCl3, 500 MHz): δ = 7.52–7.45 (m, 2 H), 7.36 (tt, J = 6.4, 1.3 Hz, 1 H), 7.32–7.25 (m, 6 H), 7.15–7.10 (m, 2 H), 4.45 (s, 2 H), 4.18 (s, 2 H), 0.09 (s, 6 H). 13C NMR (CDCl3, 125 MHz): δ = 197.9 (e), 170.2 (e), 138.7 (e), 137.5 (e), 135.0 (e), 133.9 (o, 2 C), 129.6 (o), 128.7 (o), 128.4 (o, 2 C), 128.0 (o, 2 C), 127.5 (o, 2 C), 71.5 (e), 70.3 (e), –1.2 (o, 2 C). MS (ESI): m/z (%) = 331 (100) [M + Na]+. HRMS (ESI): m/z [M + Na]+ calcd for C19H20O2SiNa: 331.1130; found: 331.1125.

5-Phenyl-4-(trimethylsilyl)-2H-pyran-3(6H)-one (8c). This compound was obtained from 7c (43 mg, 0.244 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 9:1) afforded 8c as a colorless oil; yield: 40 mg (73%); Rf = 0.3. The analytical data obtained were in agreement with that previously published.[6]

5-(Thiophen-3-yl)-4-(trimethylsilyl)-2H-pyran-3(6H)-one (8d). This compound was obtained from 7d (44 mg, 0.244 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 95:5) afforded 8d as a pale pink amorphous solid; yield: 31 mg (55%); Rf = 0.25. FT-IR (neat): 3106 (w), 2964 (w), 2898 (w), 2866 (w), 2820 (w), 1753 (m), 1654 (vs), 1567 (s), 1431 (m), 1420 (w), 1409 (w), 1359 (w), 1273 (s), 1240 (s), 1182 (m), 1130 (s), 1065 (w), 1051 (w), 1032 (w), 966 (m), 940 (m), 926 (m), 834 (vs), 784 (s), 697 cm–1 (m). 1H NMR (CDCl3, 500 MHz): δ = 7.39 (dd, J = 3.0, 2.1 Hz, 1 H), 7.27 (d, J = 1.3 Hz, 1 H), 7.05 (dd, J = 3.6, 1.3 Hz, 1 H), 4.42 (s, 2 H), 4.14 (s, 2 H), – 0.02 (s, 9 H). 13C NMR (CDCl3, 125 MHz): δ = 198.3 (e), 163.6 (e), 138.4 (e), 136.7 (e), 127.5 (o), 126.6 (o), 125.5 (o), 71.6 (e), 70.0 (e), 0.1 (o, 3 C). MS (CI): m/z (%) = 253 (8) [M + H]+. HRMS (CI): m/z [M + H]+ calcd for C12H17O2SSi: 253.0640; found: 253.0722. Anal. Calcd for C12H16O2SSi: C, 57.10; H, 6.39; S, 12.70. Found: C, 56.39; H, 6.29; S, 12.59.

5-(3-Phenylpropyl)-4-(trimethylsilyl)-2H-pyran-3(6H)-one (8e). This compound was obtained from 7e (106 mg, 0.448 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 95:5) afforded the major regioisomer **8e** [pale yellow oil; yield: 84 mg (66%); Rf = 0.25] besides the minor regioisomer **9e** [pale yellow oil; yield: 13 mg (10%); Rf = 0.3].

Major Regioisomer **8e** FT-IR (neat): 3062 (w), 3026 (w), 2945 (w), 2857 (w), 2812 (w), 1663 (s), 1583 (m), 1496 (w), 1453 (w), 1436 (w), 1378 (w), 1279 (m), 1246 (m), 1187 (w), 1139 (w), 1115 (m), 1082 (w), 1055 (w), 1029 (w), 964 (w), 936 (w), 841 (s), 765 (m), 750 (m), 699 (m), 641 (w), 624 cm–1 (w). 1H NMR (CDCl3, 500 MHz): δ = 7.35–7.29 (m, 2 H), 7.23–7.19 (m, 1 H), 7.18–7.15 (m, 2 H), 4.18 (s, 2 H), 4.01 (s, 2 H), 2.70–2.62 (m, 2 H), 2.35–2.28 (m, 2 H), 1.85–1.75 (m, 2 H), 0.2 (s, 9 H). 13C NMR (CDCl3, 125 MHz): δ = 197.9 (e), 171.0 (e), 141.0 (e), 134.4 (e), 128.6 (o, 2 C), 128.4 (o, 2 C), 126.2 (o), 71.5 (e), 68.6 (e), 36.0 (e), 33.7 (e), 31.0 (e), 1.1 (o, 3 C). MS (ESI): m/z (%) = 311 (100) [M + Na]+.

HRMS (ESI): m/z [M + Na]+ calcd for C17H24O2SiNa: 311.1443; found: 311.1437. Anal. Calcd for C17H24O2Si: C, 70.78; H, 8.39. Found: C, 70.59; H, 8.49.

Minor Regioisomer **9e** 1H NMR (CDCl3, 500 MHz): δ = 7.30–7.25 (m, 2 H), 7.20–7.15 (m, 3 H), 4.35 (s, 2 H), 4.10 (s, 2 H), 2.66 (t, J = 7.7 Hz, 2 H), 2.40–2.33 (m, 2 H), 1.75–1.70 (m, 2 H), 0.15 (s, 9 H). 13C NMR (CDCl3, 125 MHz): δ = 193.6 (e), 156.7 (e), 144.6 (e), 142.0 (e), 128.5 (o, 2 C), 128.3 (o, 2C), 125.8 (o), 72.1 (e), 68.8 (e), 36.2 (e), 31.6 (e), 29.1 (e), –0.84 (o, 3 C).

4-Octyl-5-phenyl-2H-pyran-3(6H)-one (8f). This compound was obtained from 7f (52 mg, 0.244 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 9:1) afforded the major regioisomer **8f** [yellow oil; yield: 28 mg (45%); Rf = 0.3] besides the minor regioisomer **9f** [yellow oil; yield: 9 mg (14%); Rf = 0.25].

Major Regioisomer **8f**: FT-IR (neat): 2955 (m), 2924 (s), 2854 (m), 2815 (w), 1680 (vs), 1625 (w), 1491 (w), 1442 (m), 1379 (m), 1335 (m), 1245 (m), 1146 (s), 1119 (s), 1074 (w), 964 (m), 758 (s), 700 cm–1 (vs). 1H NMR (CDCl3, 500 MHz): δ = 7.46–7.36 (m, 3 H), 7.24–7.20 (m, 2 H), 4.52 (s, 2 H), 4.23 (s, 2 H), 2.24–2.18 (m, 2 H), 1.37–1.09 (m, 12 H), 0.85 (t, J = 7.1 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 194.8 (e), 154.7 (e), 135.9 (e), 134.6 (e), 128.73 (o), 128.67 (o, 2 C), 127.3 (o, 2 C), 72.0 (e), 69.7 (e), 31.8 (e), 29.5 (e), 29.13 (e), 29.10 (e, 2 C), 25.1 (e) 22.6 (e), 14.1 (o). MS (CI): m/z (%) = 287 (100) [M + H]+. HRMS (CI): m/z [M + H]+ calcd for C19H27O2: 287.2006; found: 287.2016.

Minor Regioisomer **9f**: 1H NMR (CDCl3, 500 MHz): δ = 7.42–7.36 (m, 2 H), 7.36–7.31 (m, 1 H), 7.14–7.07 (m, 2 H), 4.48 (s, 2 H), 4.26 (s, 2 H), 2.17–2.09 (m, 2 H), 1.44–1.35 (m, 2 H), 1.30–1.09 (m, 10 H), 0.86 (t, J = 7.0 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 193.2 (e), 159.0 (e), 135.3 (e), 133.0 (e), 129.8 (o, 2 C), 128.2 (o, 2 C), 127.7 (o), 72.2 (o), 68.2 (o), 31.73 (e), 31.65 (e), 29.5 (e), 29.03 (e), 28.97 (e), 27.9 (e), 22.6 (e), 14.1 (o).

5-(4-Acetylphenyl)-4-butyl-2H-pyran-3(6H)-one (8g). This compound was obtained from 7g (98 mg, 0.488 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 9:1) afforded the major regioisomer **8g** [colorless oil; yield: 79 mg (65%); Rf = 0.3] as well as a mixture of 8g and 9g (1:3.9) [colorless oil; yield: 41 mg (31%)]. The analytical data obtained were in agreement with that previously published.[6]

4-Butyl-5-(4-methoxyphenyl)-2H-pyran-3(6H)-one (8h). This compound was obtained from 7h (46 mg, 0.244 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 9:1) afforded the major regioisomer **8h** [yellow oil; yield: 31 mg (54%); Rf = 0.3] besides **9h** [yellow oil; yield: 7 mg (12%); Rf = 0.2].

Major Regioisomer **8h**: FT-IR (neat): 2957 (m), 2930 (m), 2859 (m), 1675 (vs), 1606 (s), 1573 (w), 1510 (s), 1462 (m), 1441 (m), 1379 (m), 1336 (m), 1289 (s), 1250 (vs), 1177 (s), 1150 (vs), 1116 (s), 1075 (w), 1039 (m), 1026 (s), 966 (m), 921 (m), 831 (s), 723 cm–1 (m). 1H NMR (CDCl3, 500 MHz): δ = 7.20–7.15 (m, 2 H), 6.97–6.93 (m, 2 H), 4.50 (s, 2 H), 4.21 (s, 2 H), 3.84 (s, 3 H), 2.26 (dd, J = 9.2, 7.3 Hz, 2 H), 1.36–1.29 (m, 2 H), 1.23–1.16 (m, 2 H), 0.78 (t, J = 7.3 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 194.9 (e), 160.0 (e), 154.5 (e), 134.3 (e), 129.0 (o, 2 C), 128.1 (e), 114.1 (o, 2 C), 72.0 (e), 69.8 (e), 55.3 (o), 31.4 (e), 25.0 (e), 22.6 (e), 13.8 (o). MS (CI): m/z (%) = 261 (100) [M + H]+. HRMS (CI): m/z [M + H]+ calcd for C16H21O3: 261.1485; found: 261.1489.

Minor Regioisomer **9h**: 1H NMR (CDCl3, 500 MHz): δ = 7.03 (d, J = 8.7 Hz, 2 H), 6.92 (d, J = 8.6 Hz, 2 H), 4.46 (s, 2 H), 4.25 (s, 2 H), 3.82 (s, 3 H), 2.18–2.13 (m, 2 H), 1.43–1.35 (m, 2 H), 1.27–1.19 (m, 2 H), 0.81 (t, J = 7.3 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 193.5 (e), 159.1 (e), 158.9 (e), 134.8 (e), 130.9 (o, 2 C), 125.1 (e), 113.7 (o, 2 C), 72.2 (e), 68.3 (e), 55.2 (o), 31.5 (e), 30.1 (e), 22.7 (e), 13.7 (o).

4-Isobutyl-5-(4-methoxyphenyl)-2H-pyran-3(6H)-one (8i): This compound was obtained from 7i (46 mg, 0.244 mmol, 1.1 equiv) according to method B. Flash chromatography (PE/EtOAc, 9:1) afforded the major regioisomer **8i** [yellow oil; yield: 30 mg (52%); Rf = 0.4] besides **9i** [yellow oil; yield: 8 mg (14%); Rf = 0.2].

Major Regioisomer **8i**: FT-IR (neat): 2956 (m), 2868 (w), 1727 (w), 1675 (s), 1605 (s), 1510 (s), 1463 (m), 1440 (w), 1382 (m), 1326 (m), 1291 (m), 1247 (vs), 1177 (m), 1153 (s), 1116 (m), 1025 (m), 1007 (m), 968 (m), 896 (w), 833 cm–1 (s). 1H NMR (CDCl3, 500 MHz): δ = 7.16 (d, J = 8.9 Hz, 2 H), 6.94 (d, J = 8.8 Hz, 2 H), 4.50 (s, 2 H), 4.22 (s, 2 H), 3.84 (s, 3 H), 2.21 (d, J = 7.2 Hz, 2 H), 1.68 (sept, J = 6.9 Hz, 1 H), 0.71 (d, J = 6.5 Hz, 6 H). 13C NMR (CDCl3, 125 MHz): δ = 195.1 (e), 159.9 (e), 155.7 (e), 133.5 (e), 129.3 (o, 2C), 128.1 (e), 114.1 (o, 2C), 72.0 (e), 70.1 (e), 55.3 (o), 33.4 (e), 27.8 (o), 22.4 (o). MS (CI): m/z (%) = 261 (100) [M + H]+. HRMS (CI): m/z [M + H]+ calcd for C16H21O3: 261.1485; found: 261.1494.

Minor Regioisomer **9i**: 1H NMR (CDCl3, 500 MHz): δ = 7.01 (d, J = 8.8 Hz, 2 H), 6.92 (d, J = 8.7 Hz, 2 H), 4.44 (s, 2 H), 4.26 (s, 2 H), 3.83 (s, 3 H), 2.10 (d, J = 7.6 Hz, 2 H), 1.72 (sept, J = 6.9 Hz, 1 H), 0.82 (d, J = 6.6 Hz, 6 H). 13C NMR (CDCl3, 125 MHz): δ = 193.6 (e), 159.0 (e), 157.9 (e), 135.8 (e) 131.1 (o, 2 C), 125.2 (e), 113.7 (o, 2 C), 72.3 (e), 68.6 (e), 55.2 (o), 40.8 (e), 27.1 (o), 22.6 (o).

(E)-4-Octyl-5-styryl-2H-pyran-3(6H)-one (8j). This compound was obtained from 7j (59 mg, 0.244 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 9:1) afforded 8j as a yellow amorphous solid; yield: 98 mg (71%); and a mixture of regioisomers 8j/9j (7.9:1); Rf = 0.3; only the major regioisomer is described below. FT-IR (neat): 3061 (w), 2917 (m), 2850 (m), 1665 (s), 1614 (m), 1585 (w), 1494 (w), 1466 (w), 1444 (w), 1419 (w), 1343 (m), 1325 (m), 1306 (w), 1288 (w), 1244 (m), 1131 (m), 1121 (m), 956 (s), 723(s), 689 (m), 668 cm–1 (s). 1H NMR (CDCl3, 500 MHz): δ = 7.52–7.47 (m, 2 H), 7.42–7.37 (m, 3 H), 7.18 (d, J = 16.5 Hz, 1 H), 6.80 (d, J = 16.5 Hz, 1 H), 4.69 (s, 2 H, major), 4.19 (s, 2 H), 2.57–2.50 (m, 2 H), 1.47–1.22 (m, 12 H), 0.91–0.83 (m, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 194.4 (e), 147.4 (e), 136.1 (e), 134.9 (e), 134.8 (o), 129.3 (o), 128.9 (o, 2 C), 127.2 (o, 2 C), 122.5 (o), 72.0 (e), 65.4 (e), 31.9 (e), 29.8 (e), 29.6 (e), 29.4 (e), 29.2 (e), 23.5 (e), 22.6 (e), 14.1 (o). MS (CI): m/z (%) = 313 (100) [M + H]+. HRMS (CI): m/z [M + H]+ calcd for C21H29O2: 313.2162; found: 313.2174.

4-Butyl-5-(thiophen-2-yl)-2H-pyran-3(6H)-one (8k). This compound was obtained from 7k (80 mg, 0.488 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 95:5) afforded the major regioisomer **8k** [amorphous brown solid; yield: 65 mg (63%); Rf = 0.3] as well as a mixture of 8k and 9k (1:6.5) [amorphous brown solid; yield: 10 mg (9%)].

Major Regioisomer **8k**: FT-IR (neat): 3120 (w), 3075 (w), 2958 (w), 2922 (w), 2858 (w), 1661 (s), 1590 (s), 1511 (w), 1467 (w), 1454 (w), 1435 (m), 1416 (m), 1387 (w), 1337 (m), 1319 (s), 1280 (s), 1227 (m), 1184 (m), 964 (s), 860 (m), 730 (s), 714 cm–1 (s). 1H NMR (CDCl3, 500 MHz): δ = 7.53 (dd, J = 5.0, 1.0 Hz, 1 H), 7.22 (dd, J = 3.8, 1.0 Hz, 1 H), 7.14 (dd, J = 5.0, 3.8 Hz, 1 H), 4.68 (s, 2 H), 4.21 (s, 2 H), 2.59 (m, 2 H), 1.48–1.34 (m, 4 H), 0.91 (t, J = 7.2 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 194.3 (e), 145.1 (e), 136.8 (e), 133.9 (e), 128.7 (o), 128.4 (o), 127.7 (o), 71.9 (e), 69.2 (e), 30.9 (e), 25.4 (e), 22.9 (e), 13.9 (o). MS (CI): m/z (%) = 237 (100) [M + H]+. HRMS (CI): m/z [M + H]+ calcd for C13H17O2S: 237.0944; found: 237.0950. Anal. Calcd for C13H16O2S: C, 66.07; H, 6.82; S, 13.57. Found: C, 66.90; H, 7.17; S, 13.25.

Minor Regioisomer **9k**: 1H NMR (CDCl3, 500 MHz): δ = 7.40 (dd, J = 5.0, 1.2 Hz, 1 H), 7.07 (dd, J = 5.00, 3.5 Hz, 1 H), 6.94 (dd, J = 3.5, 1.2 Hz, 1 H), 4.48 (s, 2 H), 4.27 (s, 2 H), 2.35–2.29 (m, 2 H), 1.52–1.43 (m, 2 H), 1.35–1.22 (m, 2 H), 0.87 (t, J = 7.3 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 192.5 (e),

161.3 (e), 132.3 (e), 128.5 (e), 128.3 (o), 126.7 (o), 126.6 (o), 72.2 (e), 68.6 (e), 31.8 (e), 30.4 (e), 22.8 (e), 13.7 (o).

4-Butyl-5-(thiophen-3-yl)-2H-pyran-3(6H)-one (8l). This compound was obtained from 7l (40 mg, 0.244 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 95:5) afforded the major regioisomer **8l** [pale yellow oil; yield: 28 mg (53%); Rf = 0.3] besides **9l** [colorless oil; yield: 6 mg (11%); Rf = 0.2].

Major Regioisomer **8l**: FT-IR (neat): 3102 (w), 2956 (m), 2928 (m), 2858 (w), 2814 (w), 1670 (s), 1612 (m), 1439 (w), 1409 (w), 1378 (w), 1360 (w), 1329 (m), 1283 (m), 1227 (w), 1191 (w), 1145 (s), 1118 (m), 945 (w), 900 (m), 869 (w), 839 (m), 783 (s), 720 (m), 701 cm–1 (m). 1H NMR (CDCl3, 500 MHz): δ = 7.42 (dd, J = 5.0, 2.9 Hz, 1 H), 7.33 (dd, J = 2.9, 1.4 Hz, 1 H), 7.09 (dd, J = 5.0, 1.4 Hz, 1 H), 4.56 (s, 2 H), 4.21 (s, 2 H), 2.37 (m, 2 H), 1.42–1.36 (m, 2 H), 1.28 (m, 2 H), 0.84 (t, J = 7.3 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 194.7 (e), 148.7 (e), 136.1 (e), 134.6 (e), 127.1 (o), 126.5 (o), 124.8 (o), 72.0 (e), 69.3 (e), 31.4 (e), 25.2 (e), 22.8 (e), 13.8 (o). MS (CI): m/z (%) = 237 (100) [M + H]+. HRMS (CI): m/z [M + H]+ calcd for C13H17O2S: 237.0944; found: 237.0947. Anal. Calcd for C13H16O2S: C, 66.07; H, 6.82; S, 13.57. Found: C, 65.59; H, 6.95; S, 12.90.

Minor Regioisomer **9l**: 1H NMR (CDCl3, 500 MHz): δ = 7.35 (dd, J = 5.0, 3.0 Hz, 1 H), 7.15 (dd, J = 3.0, 1.3 Hz, 1 H), 6.95 (dd, J = 5.0, 1.3 Hz, 1 H), 4.46 (s, 2 H), 4.25 (s, 2 H), 2.24 (m, 2 H), 1.43 (m, 2 H), 1.28 (m, 2 H), 0.84 (t, J = 7.4 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 193.0 (e), 159.7 (e), 132.4 (e), 130.3 (e), 129.0 (o), 124.9 (o), 124.7 (o), 72.2 (e), 68.4 (e), 31.6 (e), 30.3 (e), 22.8 (e), 13.7 (o).

4-Butyl-5-(furan-2-yl)-2H-pyran-3(6H)-one (8m). This compound was obtained from 7m (36 mg, 0.244 mmol, 1.1 equiv) according to method A. Flash chromatography (PE/EtOAc, 95:5) afforded 8m as a brown oil; yield: 14 mg (28% yield); and a mixture of regioisomers 8m/9m (9:1); Rf = 0.4; only the major regioisomer is described below. FT-IR (neat): 2957 (m), 2930 (m), 2860 (m), 2821 (m), 1667 (vs), 1601 (m), 1468 (m), 1443, (w) 1401 (w), 1378 (w), 1336 (s), 1287 (m), 1260 (m), 1228 (m), 1203 (m), 1148 (s), 1121 (w), 1089 (vw), 1045 (m), 1018 (m), 967 (m), 940 (m), 905 (m), 885 (m), 816 (m), 746 cm–1 (s). 1H NMR (CDCl3, 500 MHz): δ = 7.60 (dd, J = 1.8, 0.6 Hz, 1 H), 6.73 (dd, J = 3.6, 0.5 Hz, 1 H), 6.56 (dd, J = 3.6, 1.8 Hz, 1 H, major), 4.72 (s, 2 H), 4.20 (s, 2 H), 2.70–2.60 (m, 2 H), 1.46–1.38 (m, 4 H), 0.94 (t, J = 7.3 Hz. 3 H). 13C NMR (CDCl3, 125 MHz): δ = 194.5 (e), 149.3 (e), 144.7 (o), 139.6 (e), 131.8 (e), 114.4 (o), 112.3 (o), 72.1 (e), 66.0 (e), 30.6 (e), 25.1 (e), 23.1 (e), 13.9 (o). MS (CI): m/z (%) = 221 (100) [M + H]+. HRMS (CI): m/z [M + H]+ calcd for C13H17O3: 221.1099; found: 221.1181.

Nickel-Catalyzed Cycloaddition of Oct-4-yne with Oxetanone 10. Inside a glovebox, J-Young Teflon-screw flame-dried Schlenk tube equipped with a small stirrer bar was charged with Ni(cod)2 (6 mg, 0.022 mmol, 0.1 equiv) and taken out of the glovebox. Under N2, PPh3 (18 mg, 0.066 mmol, 0.3 equiv) and 1,4-dioxane (1.3 mL) were added. The suspension was stirred for 5 min and then oxetanone 10 (39 mg, 0.22 mmol, 1 equiv) was added as solid in one portion. After stirring for 5 more min, oct-4-yne (36 µL, 0.224 mmol, 1.1 equiv) was added and the flask was sealed and immersed into an oil bath pre-heated at 90 °C. After stirring for 17 h at that temperature, the mixture was allowed to cool and filtered through a silica plug before evaporation of all volatiles. Purification by flash chromatography (PE/EtOAc, 95:5) afforded **11** as a colorless oil; yield: 24 mg (38%) and 1:5 mixture of **11** and **12** as a colorless oil; yield: 8 mg (13%).

2-Phenethyl-4,5-dipropyl-2H-pyran-3(6H)-one (11): FT-IR (neat): 2956 (m), 2930 (m), 1671 (vs), 1634 (m), 1603 (w), 1496 (w), 1454 (m), 1383 (w), 1175 (m), 1126 (s), 1084 (w), 1031 (w), 745 (s), 699 cm–1 (s). 1H NMR (CDCl3, 500 MHz): δ = 7.32–7.26 (m, 2 H), 7.25–7.14 (m, 3 H), 4.36 (d, J = 17.0 Hz, 1 H),

4.28 (d, J = 17.0 Hz, 1 H), 3.88–3.80 (m, 1 H), 2.85–2.67 (m, 2 H), 2.33–2.11 (m, 5 H), 2.05–1.92 (m, 1 H), 1.50 (sext, J = 7.7 Hz, 2 H), 1.36 (sext, J = 7.8 Hz, 2 H), 0.99 (t, J = 7.3 Hz, 3 H), 0.91 (t, J = 7.3 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 196.0 (e), 155.8 (e), 141.6 (e), 133.3 (e), 128.6 (o, 2 C), 128.3 (o, 2 C), 125.8 (o), 79.0 (o), 66.9 (e), 32.6 (e), 31.7 (e), 31.3 (e), 26.3 (e), 22.5 (e), 21.4 (e), 14.3 (o), 14.2 (o). MS (ESI): m/z (%) = 309 (100) [M + Na]+. HRMS (ESI): m/z [M + Na]+ calcd for C19H26O2Na: 309.1831; found: 309.1837.

6-Phenethyl-4,5-dipropyl-2H-pyran-3(6H)-one (12): 1H NMR (CDCl3, 500 MHz): δ = 7.33–7.28 (m, 2 H), 7.24–7.18 (m, 3 H), 4.27 (d, J = 16.8 Hz, 1 H), 4.23 (dd, J = 10.1, 2.7 Hz, 1 H), 4.07 (d, J = 16.9 Hz, 1 H), 2.92–2.83 (m, 1 H), 2.79–2.70 (m, 1 H), 2.37–2.29 (m, 1 H), 2.28–2.20 (m, 2 H), 2.11–1.88 (m, 3 H), 1.53–1.45 (m, 1 H), 1.42–1.32 (m, 3 H), 0.95 (t, J = 7.4 Hz, 3 H), 0.92 (t, J = 7.4 Hz, 3 H). 13C NMR (CDCl3, 125 MHz): δ = 194.5 (e), 159.6 (e), 141.4 (e), 133.6 (e), 128.50 (o, 2 C), 128.46 (o, 2 C), 126.1 (o), 74.6 (o), 67.8 (e), 32.7 (e), 32.5 (e), 32.3 (e), 26.4 (e), 22.6 (e), 21.8 (e), 14.4 (o), 14.2 (o).

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Supporting Information

Supporting information for this article is available online at https://doi.org /10.1055/s-0036-1589052.

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(17) Zinc powder AnalaR® from BDH was used in these experiments. The specifications of the powder were not provided by the supplier. However, scanning electron microscopy showed flakes and scales of 1–2 μm in length on the surface of the irregularly shaped zinc particles of various sizes. Images of the SEM analysis are included in the Supporting Information.

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