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Multidirectional Cobalt-Catalyzed Diels–Alder/1,4-Hydrovinylation Sequences

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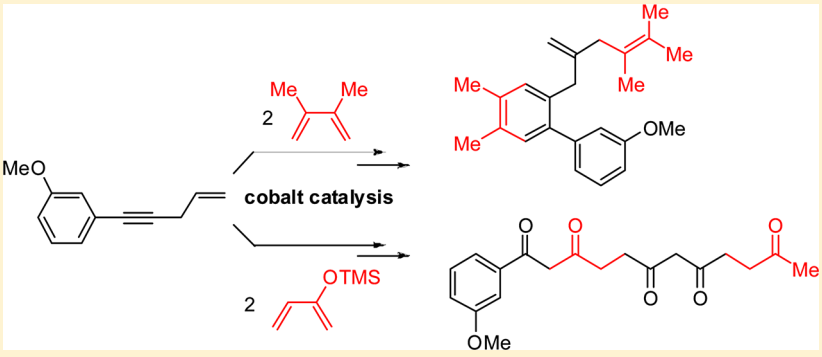
Supporting Information



ABSTRACT: The combination of two powerful cobalt-catalyzed carbon–carbon bond forming transformations, namely, the Diels–Alder and the 1,4-hydrovinylation reaction, in a tandem or a sequential one-pot procedure, opened up a concise and efficient route to polysubstituted aromatic systems and cyclohex-3-enone derivatives. Furthermore, ozonolysis of the latter products led to polycarbonyl compounds with tailored carbonyl group distances which could be characterized via their respective BF_2-borinane complexes. The cobalt catalysts tolerated several functional groups, and a flexible approach to polyfunctionalized compounds in concise fashion was described.

INTRODUCTION

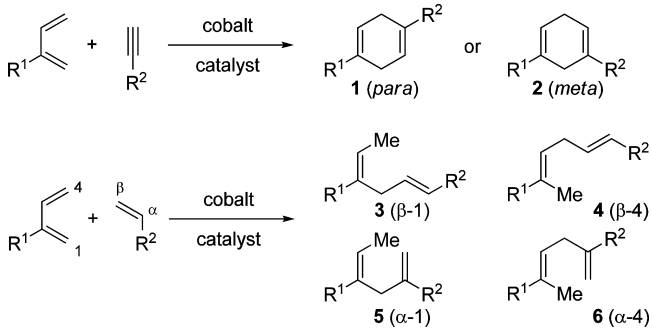
The increasing portfolio of cobalt-catalyzed transformations for the selective formation of carbon–carbon bonds and carbon–heteroatom bonds for the synthesis of increasingly complex structures is a constant driving force for chemists involved in the development of new synthetic methods. Cobalt catalysts have found a number of applications for the construction of cyclic products as well as for the generation of acyclic derivatives via carbon–carbon bond formation processes.[1]

However, a transition-metal-catalyzed method is usually very selective for a specific type of bond formation. In contrast, very few catalysts have been identified that are able to initiate multiple conceptionally different transformations, and an even smaller number of catalysts are able to initiate carbon–carbon bond formations by different types of reactions.[2]

In the past, we reported several types of cycloaddition reactions and formation of acyclic products based on the application of different cobalt catalysts. Alternation of the ligands, the type of starting materials applied, or the solvent led, in some cases, to the formation of alternative regioisomers in cobalt-catalyzed reactions. Among the transformations described thus far, the cobalt-catalyzed regiodiverse cyclotrimerization of alkynes,[3] the regiodiverse Diels–Alder reaction,[4] as well as the regioselective 1,4-hydrovinylation reaction[5] have attracted considerable interest (Scheme 1).

While the cobalt-catalyzed cycloaddition process led to two different regioisomers **1** and **2** (*para*- and *meta*-substitution pattern), the 1,4-hydrovinylation reaction of two unsymmetrical starting materials can generate up to four isomers (**3**–**6**) concerning the site (α or β on the terminal alkene as well as C1 versus C4 on the 1,3-diene) of the carbon–carbon bond formation. Additionally, taking all possible *E*- and *Z*-combinations of the corresponding 1,4-dienes into account, the total number of isomers for the 1,4-hydrovinylation reaction, without even considering the also possible 1,2-hydrovinylation reactions,[6] rises to 12.

Scheme 1



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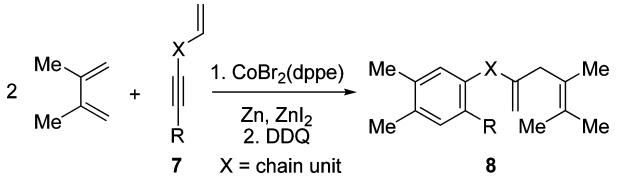
In an effort to combine different types of cobalt-catalyzed carbon−carbon bond formation processes, we initiated a project for the synthesis of more complex structures by applying simple cobalt catalysts in Diels−Alder and 1,4-hydrovinylation reactions in a one-pot reaction sequence. Thereby, multicomponent reactions should be realized and aspects of chemo- and regioselective carbon−carbon bond formations investigated.

RESULTS AND DISCUSSION

We began our studies by exploring the application of internal nonconjugated enynes (**7a−o**; see Experimental Section) with symmetrical 1,3-dienes such as 2,3-dimethyl-1,3-butadiene (DMB) in order to reduce the number of possible regioisomers for both types of reactions. The catalyst system of choice for this initial study comprises $CoBr_2$(dppe),[7] zinc powder, and zinc iodide, which has proven to be an active catalyst system for both transformations. Furthermore, the crude dihydroaromatic intermediate obtained after cobalt catalysis should be directly oxidized to its corresponding aromatic derivative **8** by using DDQ (2,3-dichloro-4,5-dicyano-1,4-benzoquinone). For this purpose, different enynes of type **7** were applied in the cobalt-catalyzed one-pot reaction sequence for the synthesis of products such as **8** in a straightforward fashion (Scheme 2).

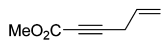
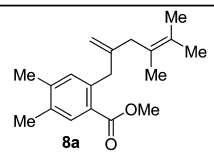
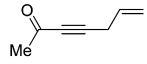
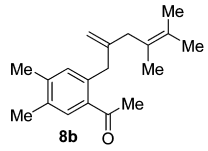
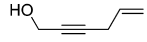
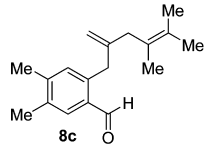
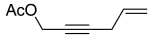
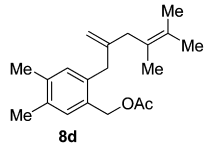
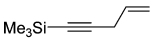
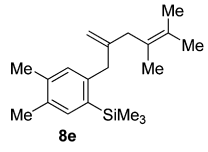
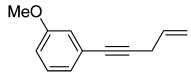
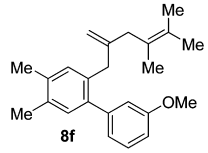
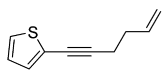
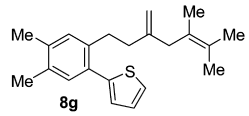
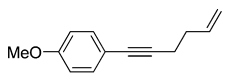
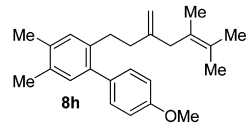
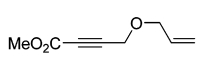
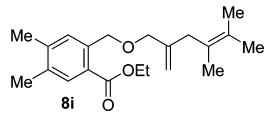
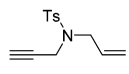
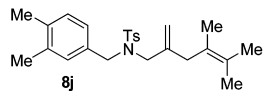
Scheme 2



The results of the cobalt-catalyzed Diels−Alder/1,4-hydrovinylation/oxidation one-pot reaction sequence are summarized in Table 1.

The GC−MS analysis of a reaction around 50% conversion revealed that the cobalt-catalyzed Diels−Alder reaction and the 1,4-hydrovinylation proceeded with similar relative rates. Aromatic enynes proved to be very suitable substrates for this type of one-pot sequence (entries 6−8). The chain unit length of the enyne seems to have no significant influence on the yields obtained after three formal steps. All possible carbon oxidation states could be realized next to the aromatic core using the appropriate enyne. While the enyne ester was converted into **8a** in excellent yield (entry 1), phenone **8b** (entry 2) could be obtained only in a moderate yield. As known from previous reactions, substrates with ketone functionality are more difficult to convert and generally lower yields are obtained. However, an unprotected hydroxyl-functionalized enyne (entry 3) was converted without difficulties, and the benzaldehyde derivative **8c** was obtained directly upon overoxidation with DDQ (entry 3), whereas the acylated enynol could be transformed in the usual manner (entry 4). A trimethylsilyl-functionalized enyne delivered the silylated aromatic compound **8e** in a good yield (entry 5). Furthermore, the reaction sequence was tested upon compatibility with heteroatoms in the enyne chain unit. Therefore, an allyl propargyl ether and a sulfonamide derivative were subjected to the sequence. The sulfonamide generated the corresponding product **8j** in a comparable good yield (entry 10), whereas the product **8i** (entry 9) could only be obtained in a moderate

Table 1. Scope of the Diels−Alder/1,4-Hydrovinylation/Oxidation Strategy

entry	enyne **7**	Product **8**	yield[a]
1		 **8a**	80%
2		 **8b**	47%
3		 **8c**	73%
4		 **8d**	70%
5		 **8e**	67%
6		 **8f**	81%
7		 **8g**	68%
8		 **8h**	99%
9		 **8i**	46%
10		 **8j**	70%

[a]Reaction conditions: Diels−Alder/1,4-hydrovinylation reaction: $CoBr_2$(dppe) (10 mol %), ZnI_2 (20 mol %), Zn powder (20 mol %), alkyne (1 M), DMB (2.4 M) in dichloromethane, room temperature; oxidation: cycloaddition product (0.1 M), DDQ (0.2 M; 0.3 M for compound **8c**) in benzene, room temperature.

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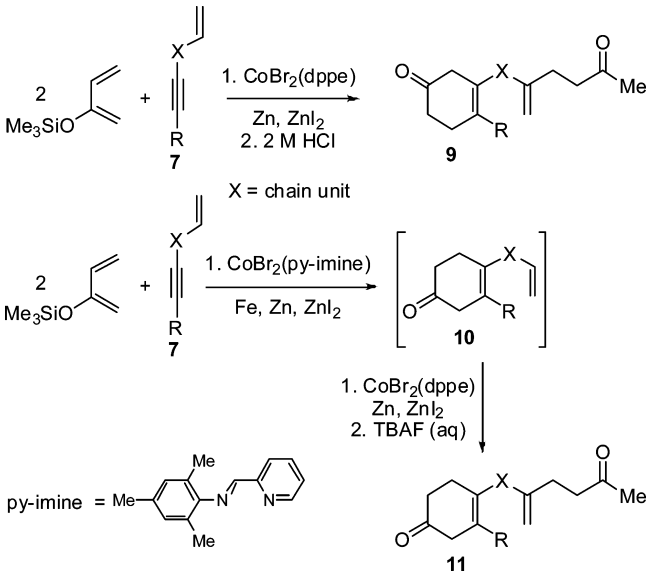
yield, possibly due to partial oxidative cleavage of the benzylic ether with DDQ, as known for electron-rich PMB derivatives.[8]

In the case of unsymmetrical 1,3-dienes, the cobalt catalyst systems investigated by us in the past gave excellent regioselectivities for the cobalt-catalyzed Diels–Alder reactions in favor of the *para*-substituted cycloaddition product **1** (see Scheme 1) with bisphosphine ligands as well as for the *meta*-substituted product **2** when pyridine imine ligands (py-imine) were applied.[4]

When cobalt catalysts are applied in the 1,4-hydrovinylation reaction, the proposed active catalyst [Co(dppe)$^+$] exhibits excellent regioselectivity for the carbon–carbon bond formation at the α-carbon atom of the terminal alkene while a similar cobalt complex utilizing a more complex bidentate phosphine–phosphite ligand (SchmalzPhos) forms the new carbon–carbon bond with high selectivity at the β-carbon.[9]

The advantage of the one-pot sequence presented here is exemplified by the variability of the coupling partners. For example, the replacement of DMB with the unsymmetrical 2-(trimethylsilyloxy)buta-1,3-diene (TMSO-diene) led to completely different types of products. After hydrolysis of the silyl enol ether intermediates, cyclic enones were generated[10] while acyclic enones were formed via the 1,4-hydrovinylation process (**9** in Scheme 3). Moreover, when pyridine imine type ligands[11]

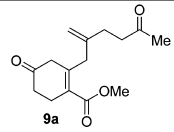
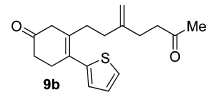
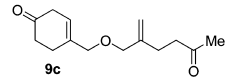
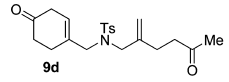
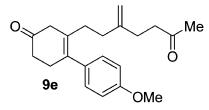
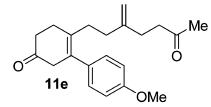
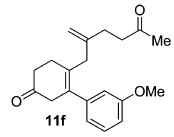
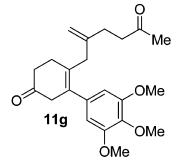
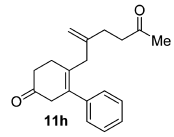
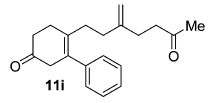
Scheme 3



were applied in the Diels–Alder reactions, the *meta*-substituted regioisomer **10** was formed instead of the *para*-regioisomer.[4c,d] In addition to this remarkable regioselectivity in the Diels–Alder reaction, pyridine imine type cobalt catalysts are unreactive in the 1,4-hydrovinylation reaction. Accordingly, the terminal alkene moiety remains unchanged, and the application of the $CoBr_2$(dppe) catalyst can be used to generate an acyclic enone unit after hydrolysis in product **11**. Therefore, it is possible to form either the *para*-substituted cyclohex-3-enone product **9** via a tandem Diels–Alder/1,4-hydrovinylation reaction or the *meta*-substituted derivative **11** via a sequential Co(py-imine)-catalyzed Diels–Alder and Co(dppe)-catalyzed 1,4-hydrovinylation reaction approach (Scheme 3).

The results of the cobalt-catalyzed Diels–Alder/1,4-hydrovinylation/hydrolysis one-pot reaction sequence are summarized in Table 2.

Table 2. Scope of the Diels–Alder/1,4-Hydrovinylation/Hydrolysis Strategy

entry	reaction conditions [a]	R, X	products **9** and **11**	yield
1	**A**	CO_2Me CH_2	 **9a**	60%
2	**A**	2-thienyl CH_2CH_2	 **9b**	46%
3	**A**	H CH_2OCH_2	 **9c**	47%
4	**A**	H CH_2NTsCH_2	 **9d**	46%
5	**A**	4-$MeOC_6H_4$ CH_2CH_2	 **9e**	66%
6	**B**	4-$MeOC_6H_4$ CH_2CH_2	 **11e**	37%
7	**B**	3-$MeOC_6H_4$ CH_2	 **11f**	70%
8	**B**	3,4,5-$(MeO)_3C_6H_2$ CH_2	 **11g**	82%
9	**B**	C_6H_5 CH_2	 **11h**	68%
10	**B**	C_6H_5 CH_2CH_2	 **11i**	55%

[a] **A**: Diels–Alder/1,4-hydrovinylation reaction: $CoBr_2$(dppe) (10 mol %), ZnI_2 (20 mol %), Zn powder (20 mol %), alkyne (1 M), TMSO-diene (2.4 M) in dichloromethane, room temperature; hydrolysis: substrate (0.125 M), aqueous HCl (2 M) in THF/water, room temperature. **B**: Diels–Alder reaction: $CoBr_2$(py-imine) (10 mol %), ZnI_2 (20 mol %), Zn powder (20 mol %), alkyne (1 M), TMSO-diene (1.5 M) in dichloromethane, room temperature; 1,4-hydrovinylation reaction: $CoBr_2$(dppe) (10 mol %), ZnI_2 (20 mol %), Zn powder (20 mol %), TMSO-diene (1.5 M) in dichloromethane, room temperature; hydrolysis: substrate (0.1 M), TBAB (0.06 M), KF (saturated aqueous solution, buffered to pH = 7) in THF/water/dichloromethane, room temperature.

The yields obtained for the tandem Diels–Alder/1,4-hydrovinylation/hydrolysis sequence range from moderate to

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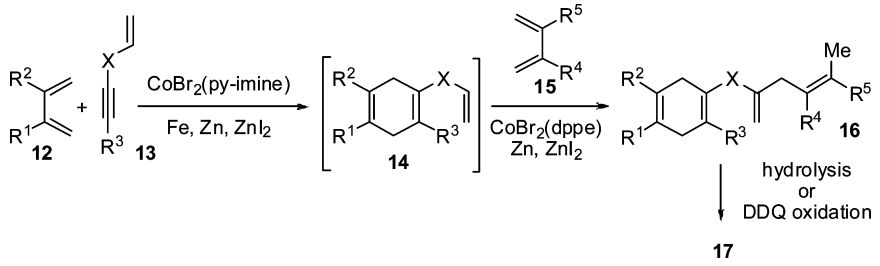
Scheme 4



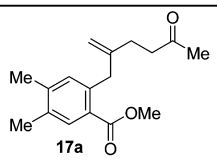
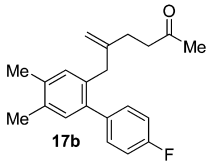
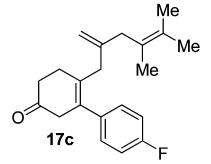
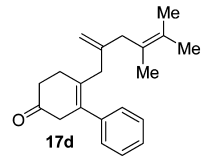
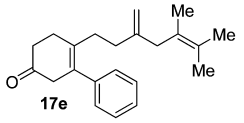
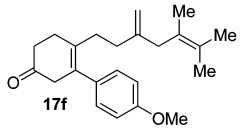
good and are slightly lower compared to the reactions involving DMB (entries 1−5). Nevertheless, different types of enynes were accepted, and unprecedented polyfunctionalized products were obtained. The use of the cobalt pyridine imine catalyst successfully enabled the synthesis of the corresponding cyclohexenone derivatives of type **11** with excellent regiocontrol. The overall yields for the reaction sequence are acceptable to good concerning the formation of three new carbon−carbon bonds and a single workup after hydrolysis of the silyl enol ether intermediates.

The use of a sequential Diels−Alder/1,4-hydrovinylation strategy bears a further advantage. In principal, it should be possible to obtain mixed products using different 1,3-dienes in the cobalt-catalyzed reactions. Therefore, the cobalt pyridine imine catalyst system initiates the Diels−Alder reaction of the first 1,3-diene (**12**) and the alkyne subunit of **13**, leaving the terminal double bond of intermediate **14** untouched (Scheme 4). Then the second 1,3-diene **15** is added, and the cobalt-catalyzed 1,4-hydrovinylation reaction is initiated by the cobalt bisphosphine catalyst system now added to the reaction mixture. The workup of the dihydroaromatic intermediate **16** can either generate the corresponding aromatic products, when **16** is treated with DDQ (compare to Scheme 2), or the hydrolysis strategy is used as before for the production of ketone substructures (compare to Scheme 3). Although the variation of the substituents R^1, R^2 and R^4, R^5 of the dienes **12** and **15** would have allowed the synthesis of a huge variety of different products, we concentrated our attention on the use of DMB (R^1 = R^2 = Me) and TMSO-diene (R^4 = H, R^5 = $OSiMe_3$). Nevertheless, still a wide variety of products **17** became accessible, and the results of these multicomponent one-pot reaction sequences utilizing two different cobalt catalysts are summarized in Table 3.

In two examples (entries 1 and 2), an aromatic and an ester-substituted enyne provided the aromatic products **17a** and **17b** after Diels−Alder reaction with DMB, 1,4-hydrovinylation with TMSO-diene, and subsequent hydrolysis in moderate yields. As a side product of the DDQ oxidation of **17b**, an overoxidized derivative was also observed (~15%), where an additional double bond was introduced between the ketone functionality and the *exo*-chain double bond. Unfortunately, this derivative could not be isolated in pure form, but it clearly indicated that the corresponding intermediate for the generation of **17b** was originally formed in higher yield.

The inversion of the reaction sequence using first TMSO-diene in the regioselective Diels−Alder reaction then DMB in the 1,4-hydrovinylation and subsequent hydrolysis furnished the corresponding products **17c**−**17f** in moderate to excellent yields (entries 3−6). The flexibility of this approach lies in the possibility for variation of the enyne functionality, the chain length, or incorporation of heteroatoms between as well as in the use of different butadiene derivatives. Thereby, it is easily imaginable that a concise approach to complex organic structures can be realized using rather simple building blocks and their proper combination with each other.

Table 3. Results of the Sequential Diels−Alder/1,4-Hydrovinylation Strategy

entry	R^3, X	product **17**	yield[a]
1	CO_2Me, CH_2	 **17a**	51%
2	4-FC_6H_4, CH_2	 **17b**	31%
3	4-FC_6H_4, CH_2	 **17c**	99%
4	Ph, CH_2	 **17d**	74%
5	Ph, CH_2CH_2	 **17e**	64%
6	4-$MeOC_6H_4$, CH_2CH_2	 **17f**	56%

[a]Reaction conditions: Diels−Alder reaction: $CoBr_2$(py-imine) (10 mol %), ZnI_2 (20 mol %), Zn powder (20 mol %), alkyne (1 M), diene (1.2−1.5 M) in dichloromethane, room temperature; 1,4-hydrovinylation reaction: $CoBr_2$(dppe) (10 mol %), ZnI_2 (20 mol %), Zn powder (20 mol %), 1,3-diene (1.2−1.5 M) in dichloromethane, room temperature; hydrolysis: substrate (0.1 M), TBAB (0.06 M), KF (saturated aqueous solution, buffered to pH = 7) in THF/water/dichloromethane, room temperature.

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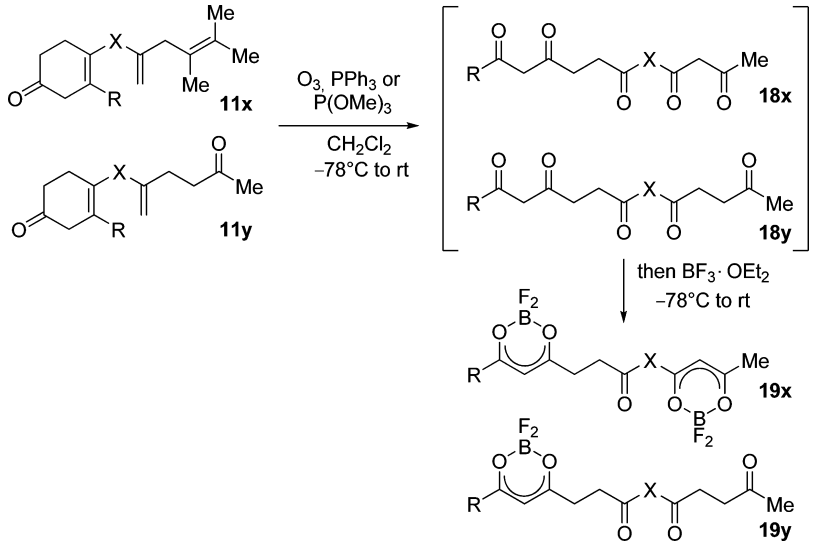
Scheme 5



Finally, we envisaged the possibility to generate polycarbonyl derivatives upon ozonolysis from the cyclohex-3-enone products formed via the regioselective cobalt-catalyzed tandem Diels–Alder/1,4-hydrovinylation/hydrolysis sequence. One valuable aspect in this approach is the flexibility in which the carbonyl group distance within the pentacarbonyl derivatives can be varied. This is made possible first by the control of the Diels–Alder reaction, second by the chain length between alkyne and alkene subunit (X), and third the type of 1,3-diene (e.g., **12** or **15**) used in the 1,4-hydrovinylation reaction.

In these studies, we concentrated our attention on the sequentially produced cyclohex-3-enones of type **11**, varying only the enynes and the second introduced 1,3-diene. Accordingly, the hypothetical products such as **11x**, which is accessible with DMB in the cobalt-catalyzed 1,4-hydrovinylation reaction, would lead to a 1,3-dicarbonyl unit in the eastern part of **18x** (Scheme 5). The oxidative cleavage of the cyclohex-3-enone subunit in **11x** would also lead to a 1,3,6-tricarbonyl substructure in the western section of **18x**. The synthesis of a 1,4-dicarbonyl subunit in the eastern section could be realized when hypothetical products such as **11y**, generated from the TMSO-diene in the 1,4-hydrovinylation step, would be submitted to ozonolysis to afford products such as **18y**. Herein, also the 1,3,6-tricarbonyl substructure in the western section of **18y** would be generated by ozonolysis. Accordingly, two pentacarbonyl products **18x** and **18y** would be obtainable with tailored carbonyl distances in the eastern part, and the chain length determined by X is decisive for the carbonyl distances toward the western part with its 1,3,6-tricarbonyl units.

The isolation and characterization of such pentacarbonyl derivatives is nontrivial as we reported earlier.[12] The keto–enol tautomers are relatively polar, and the yields are generally reduced by purification using column chromatography on regular silica gel. Also, the tautomeric forms give rise to multiple sets of signals in NMR analysis, which makes the assignment of signals more complicated. Therefore, we decided to transform the polycarbonyl derivatives in most cases into their corresponding borinane derivatives of type **19** via reaction with BF_3. These BF_2 adducts can be isolated by column chromatography on regular silica gel and are mostly yellowish solids. The tautomeric forms are annihilated in the BF_2 adduct, and the NMR signals can be assigned doubtlessly.

The results of these reaction sequences are summarized in Table 4.

The isolation of the mono- and bis-BF_2-borinane adducts **19a–19c** and **19d** was accomplished in only moderate yields by column chromatography over silica gel. At this point, we were interested to find ways to isolate and characterize the polycarbonyl compounds regardless of the yields. The BF_2-borinane adducts seem to be an appropriate way not only for the isolation of the compounds but also for the determination of the identity of the desired products. In the absence of the tautomeric forms, unambiguous assignment of the NMR signals was possible. The 1,3-dicarbonyl units were all converted into the corresponding BF_2-borinane adducts, while the 1,4-dicarbonyl substructures remained unchanged. Accordingly, the 1,3-dicarbonyl subunits are protected, while the other carbonyl groups are now available for follow-up chemical transformations. In order to prove that the initial yields for the ozonolysis are much higher, we attempted to isolate some of the pentacarbonyl compounds. Product **18c** could be isolated by chromatography on silica gel after reduction by either PPh_3 or $P(OMe)_3$ in acceptable yield (50–59%). Product **18e**, which consists of a 1,3-dicarbonyl and a 1,3,5-tricarbonyl subunit, could also be isolated by chromatography but only in a poor yield of 18%, while aqueous extraction of the phosphate byproduct by using $P(OMe)_3$ as the reducing agent delivered **18e** in good yield. This showed that we were able to generate several pentacarbonyl derivatives from nonconjugated enynes in only two to three steps based on the versatile and regiodiverse application of cobalt catalysts.

CONCLUSION

In conclusion, we have demonstrated that different cobalt-catalyzed transformations as the Diels–Alder and the 1,4-hydrovinylation reaction can be combined in a one-pot procedure. Moreover, the sequences described here allow a very flexible product assembly as there are a lot of possibilities given for substructure variations. We could show that the nature of the product is strongly dependent on the diene(s) used for the cobalt-catalyzed transformations as the reaction with DMB in the Diels–Alder reaction led to aromatic

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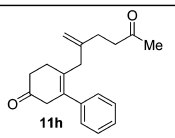
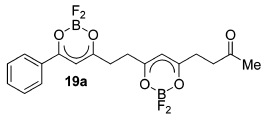
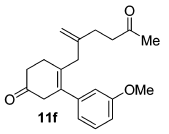
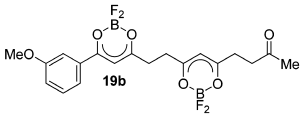
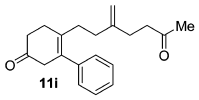
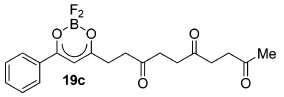
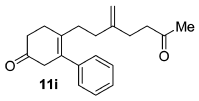
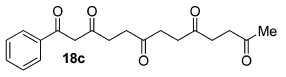
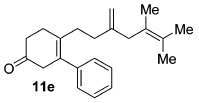
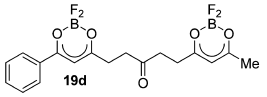
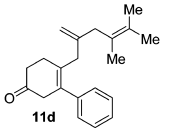
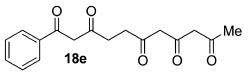
Table 4. Results of the Ozonolysis/Borinane Formation of Polycarbonyl Derivatives

entry	substrate	product of type **18**/**19**	yield
1	 **11h**	 **19a**	23%
2	 **11f**	 **19b**	36%
3	 **11i**	 **19c**	20%[a]
4	 **11i**	 **18c**	59%[b] 50%[c]
5	 **11e**	 **19d**	38%
6	 **11d**	 **18e**	90%[d] 18%[b]

[a]The yield refers to the formation of the BF_2 adduct from the previously isolated 1,3-dicarbonyl compound **18c** with BF_3 etherate in dichloromethane. [b]The reduction of the ozonide was performed using triphenylphosphine. The product was purified by column chromatography. [c]The reduction of the ozonide was performed using trimethyl phosphite. The product was purified by column chromatography. [d]The reduction of the ozonide was performed using trimethyl phosphite. The product was purified by extraction.

compounds, while the TMSO-diene led to the synthesis of cyclohex-3-enones accessible in a regiodivergent fashion, dependent on the cobalt catalyst used. Furthermore, the modular and sequential approach for these three-component reactions enables the formation of pentacarbonyl compounds with tailored functional group distances. The products, which look hardly approachable by other methods, could be isolated and undoubtedly characterized via their respective BF_2 complexes. Our future work will focus on exploring the chemistry of these interesting polycarbonyl compounds.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an argon atmosphere in heat-gun-dried glassware and were stirred magnetically. Unless otherwise noted, all reactions were performed with anhydrous solvents, and ZnI_2 was dried in vacuo at 150 °C prior to use. Commercially available materials were used without further purification. Ozonolysis was conducted using an ozone generator, and O_2/O_3 mixture was dried by a P_4O_5 column. Flash chromatography was performed on silica gel 60 (230−400 mesh), and analytical thin layer chromatography (TLC) was carried out on silica gel 60 F-254 precoated aluminum plates. The TLC plates were analyzed by short-wave UV illumination and by dipping in CAM stain (composed of 40 g of ammonium molybdate, 1.6 g of ceric ammonium molybdate, 80 mL of concentrated sulfuric acid, and 720 mL of water) with subsequent heating by using a heat-gun. ^1H and ^{13}C NMR spectra were obtained using $CDCl_3$ as a solvent and tetramethylsilane as internal standard. Chemical shifts δ are reported in parts per million downfield from tetramethylsilane. Coupling constants are indicated in hertz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet), and m (multiplet). Broad singlets are reported as bs. IR spectra were measured on an FT-IR spectrometer and are reported in wave numbers (cm^{-1}). High-resolution mass spectra were acquired using electron impact ionization (EI) or atmospheric pressure chemical ionization (APCI).

General Procedure for the Preparation of 1,4-Enynes 7a−7i. Following a literature procedure,[13] CuI (10 mol %), Na_2SO_3 (0.5 equiv), and K_2CO_3 (1.0 equiv) were dissolved in the indicated solvent at 50 °C. Then the terminal alkyne (1.0 equiv) was added to form a bright yellow suspension. Upon treatment with allylbromide (1.2 equiv), the color changes to orange. The resulting suspension was stirred overnight at 50 °C. The reaction mixture was then transferred into a 1:1 solution of saturated aqueous NH_4Cl/water and extracted with diethyl ether. The combined organic phases were dried over $MgSO_4$ followed by evaporation of the solvent. The crude product was then purified by flash column chromatography (silica gel) to obtain the products of type 7. For the synthesis of aryl-substituted enynes **7a** and **7b**, dimethylformamide was used as the solvent and 1,8-diazabicyclo[5.4.0]undec-7-ene (10 mol %, DBU) was added to the reaction mixture. The ester-substituted 1,4-diene **7f** was generated in dimethyl sulfoxide, and $KHCO_3$ was used instead of K_2CO_3. The acyl-substituted 1,4-enyne **7g** was obtained via allylation of but-3-yn-2-ol in water and subsequent oxidation with pyridinium chlorochromate (2.0 equiv, PCC) in dichloromethane.[14] The products 1-fluoro-4-(pent-4-en-1-ynyl)benzene (**7c**), pent-4-en-1-ynylbenzene (**7d**), trimethyl-(pent-4-en-1-ynyl)silane (**7e**), hex-5-en-2-yn-1-ol (**7h**), and hex-5-en-2-ynyl acetate (**7i**) are known. The analytical data for these compounds are in accordance with the literature; the analytical data for new enyne compounds are given below.

*1-Methoxy-3-(pent-4-en-1-ynyl)benzene (**7a**):* colorless liquid; 463 mg (2.69 mmol, 85%); eluent, pentane/diethyl ether = 10:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, J = 7.9 Hz, 1H), 7.02 (dt, J = 7.6, 1.1 Hz, 1H), 6.96 (dd, J = 2.5, 1.4 Hz, 1H), 6.85 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 5.90 (ddt, J = 17.0, 10.0, 5.3 Hz, 1H), 5.41 (dq, J = 17.0, 1.7 Hz, 1H), 5.17 (dq, J = 10.0, 1.7 Hz, 1H), 3.80 (s, 3H), 3.20 (dt, J = 5.3, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 132.4, 129.3, 124.7, 124.2, 116.5, 116.3, 114.4, 86.4, 82.8, 55.2, 23.7; MS (EI) m/z (%) 172 (M^+, 100), 157 (12), 141 (12), 128 (29), 115 (8); HRMS (EI, ICP, m/z) calcd for $C_{12}H_{12}O$ 172.0888, found 172.0877; IR (film, cm^{-1}) 3078, 3006, 2940, 2911, 2835, 2236, 1640, 1598, 1576, 1484, 1421, 1317, 1282, 1203, 1167, 1083, 1042, 990, 915, 853, 780, 685, 630, 561, 518, 464.

*1,2,3-Trimethoxy-5-(pent-4-en-1-ynyl)benzene (**7b**):* colorless oil; 470 mg (2.02 mmol, 94%); eluent, pentane/diethyl ether = 4:1; ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 2H), 5.91 (ddt, J = 17.0, 10.0, 5.3 Hz, 1H), 5.39 (dq, J = 17.0, 1.7 Hz, 1H), 5.17 (dq, J = 10.0, 1.7 Hz, 1H), 3.84 (s, 9H), 3.19 (dt, J = 5.3, 1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 138.5, 132.4, 118.7, 116.3, 108.8, 85.6, 82.8, 60.9, 56.1, 23.7; MS (EI) m/z (%) 232 (M^+, 100), 231 (98), 217 (81), 189 (11), 172 (16), 128 (16); HRMS (EI, ICP, m/z) calcd for $C_{14}H_{16}O_3$ 232.1099, found 232.1096; IR (film, cm^{-1}) 2938, 2835, 1574, 1501, 1456, 1408, 1348, 1314, 1284, 1233, 1165, 1122, 999, 917, 831, 769, 737, 626, 560, 526.

*Methyl Hex-5-en-2-ynoate (**7f**):* colorless liquid; 1.91 g (15.36 mmol, 77%); eluent, pentane/diethyl ether = 20:1; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83−5.70 (m, 1H), 5.33 (d, J = 17.0 Hz, 1H), 5.17 (d, J = 11.7 Hz, 1H), 3.75 (s, 3H), 3.10 (td, J = 3.6, 1.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.0, 129.7, 117.7, 85.9, 74.7, 52.5, 22.8; MS (EI) m/z (%) 124 (M^+, 23), 109 (1), 93 (100), 79 (11), 65 (58), 53 (13); HRMS (EI, ICP, m/z) calcd for $C_7H_8O_2$ 124.0524, found 124.0526; IR (film, cm^{-1}) 3414, 3089, 3020, 2988, 2956, 2901, 2844, 2243, 1716, 1643, 1507, 1436, 1417, 1324, 1258, 1090, 1074, 1042, 992, 929, 816, 753, 663, 564.

*Hept-6-en-3-yn-2-one (**7g**):* colorless liquid; 533 mg (4.93 mmol, 25%, two steps); eluent, pentane/diethyl ether = 10:1; ^1H NMR (300

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MHz, $CDCl_3$) δ 5.85−5.72 (m, 1H), 5.32 (dd, J = 17.0, 1.1 Hz, 1H), 5.18 (dd, J = 10.2, 1.5 Hz, 1H), 3.13 (td, J = 3.5, 1.7 Hz, 2H), 2.33 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6, 130.0, 117.6, 89.9, 83.0, 32.7, 23.1; MS (EI) m/z (%) 108 (M^+, 6), 93 (100), 77 (4), 65 (52), 62 (5), 53 (6), 50 (4); HRMS (EI, ICP, m/z) calcd for C_7H_8O 108.0575, found 108.0569; IR (film, cm^{-1}) 3336, 3089, 2986, 2920, 2214, 1678, 1643, 1416, 1360, 1321, 1285, 1230, 1107, 1077, 1019, 992, 965, 929, 712, 620, 583, 561.

General Procedure for the Preparation of 1,5-Enynes 7j−7l. Following a literature procedure,[15] pent-4-yn-1-ol (1.0 equiv) and the arylhalide (1.0 equiv) were added to a degassed solution of CuI (4 mol %) and $(PPh_3)_2PdCl_2$ (2 mol %) in triethylamine (0.375 M). The reaction mixture was then heated to 60 °C and stirred overnight. Afterward, the suspension was filtered over a small plug of silica gel and flashed with diethyl ether. After evaporation of the solvent, the crude product was dissolved in anhydrous dichloromethane (0.2 M). The solution was treated with pyridinium chlorochromate (1.5 equiv, PCC) and stirred at room temperature overnight.[16] The resulting suspension was filtered over silica gel, followed by evaporation of the solvent. The crude product was then purified by flash column chromatography. From a known procedure,[9] methyltriphenylphosphonium bromide (2.0 equiv) was dissolved in tetrahydrofuran (0.18 M). To this suspension was added dropwise *n*-butyllithium (2.5 M, 2.0 equiv) at 0 °C and stirred for 30 min at room temperature. The resulting solution was treated with a solution of the pure aldehyde in 5 mL of tetrahydrofuran at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred overnight. After hydrolysis with half-concentrated aqueous NH_4Cl solution and extraction with diethyl ether, the combined organic phases were dried over $MgSO_4$ followed by evaporation of the solvent. The crude product was then purified by flash column chromatography to obtain a colorless liquid.

The products 1-(hex-5-en-1-ynyl)-4-methoxybenzene (**7k**), hex-5-en-1-ynylbenzene (**7l**), and 3-(prop-2-ynyloxy)prop-1-ene (**7n**) are known. The analytical data for these compounds are in accordance with the literature; the analytical data for new enyne compounds are given below.

*2-(Hex-5-en-1-ynyl)thiophene (**7j**):* colorless liquid; 662 mg (4.08 mmol, 41%, three steps); eluent, pentane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, J = 5.3, 1.1 Hz, 1H), 7.12 (dd, J = 3.4, 1.1 Hz, 1H), 6.94 (dd, J = 5.3, 3.8 Hz, 1H), 5.98−5.84 (m, 1H), 5.16−5.03 (m, 2H), 2.54−2.49 (m, 2H), 2.40−2.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 131.0, 126.7, 126.0, 124.0, 115.8, 93.6, 74.1, 32.7, 19.5; MS (EI) m/z (%) 162 (M^+, 22), 147 (7), 134 (7), 128 (3), 121 (100), 115 (2), 108 (2), 93 (2), 87 (1), 77 (21), 69 (6), 63 (6), 51 (5); HRMS (EI, ICP, m/z) calcd for $C_{10}H_{10}S$ 162.0503, found 162.0497; IR (film, cm^{-1}) 3438, 3106, 3077, 2980, 2921, 2844, 2227, 1796, 1642, 1519, 1428, 1355, 1328, 1238, 1191, 1080, 1044, 994, 916, 848, 830, 699.

The 1,5-enyne **7m** was prepared in two steps via Williamson's ether synthesis[17] and subsequent functionalization of the terminal alkyne subunit of **7n** with ethyl carbonochloridate,[18] whereas the sulfonamide **7o** was obtained via tosylation of allylamine and subsequent propargylation following a literature procedure.[19]

*Ethyl 4-(Allyloxy)but-2-ynoate (**7m**):* colorless liquid; 1.20 g (7.14 mmol, 47%, two steps); eluent, pentane/diethyl ether = 10:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94−5.82 (m, 1H), 5.32 (dq, J = 17.2, 1.6 Hz, 1H), 5.26−5.21 (m, 1H), 4.27−4.20 (m, 4H), 4.07 (d, J = 6.0 Hz, 2H), 1.30 (t, J = 6.99 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 133.4, 118.4, 83.1, 78.1, 71.0, 62.1, 56.7, 14.0; MS (EI) m/z (%) 168 (M^+, 2), 139 (4), 122 (4), 111 (30), 95 (30), 84 (45), 66 (100), 55 (67); HRMS (ESI, FT-ICR, m/z) calcd for $C_9H_{12}O_3Na$ 191.0679, found 191.0680; IR (film, cm^{-1}) 3477, 3084, 2985, 2941, 2906, 2860, 2236, 1716, 1649, 1466, 1447, 1384, 1367, 1251, 1157, 1096, 1057, 1019, 931, 863, 751.

General Procedure for the Tandem Diels−Alder/1,4-Hydrovinylation/DDQ Oxidation Sequence with 2,3-Dimethylbuta-1,3-diene. Zinc iodide (20 mol %), zinc powder (20 mol %), and $CoBr_2$(1,2-bis(diphenylphosphino)ethane) (10 mol %) were suspended in dichloromethane (1 mL) under argon atmosphere. Then 2,3-dimethyl-1,3-butadiene (2.4 mmol) and the enyne 7 (1.0 mmol) were added, and the mixture was stirred at room temperature for 16 h. Afterward, the suspension was filtered over a short pad of silica gel, and the solvent was removed under vacuum. The residue was dissolved in benzene (10 mL) and was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.0 mmol, 3.0 mmol for **8c**, DDQ). The mixture was stirred for 1 h at room temperature and was then filtered over a short pad of deactivated silica gel. The solvent was removed in vacuo, and the residue was purified by flash column chromatography.

*Methyl 2-(4,5-Dimethyl-2-methylenehex-4-enyl)-4,5-dimethylbenzoate (**8a**):* colorless oil; 230 mg (0.80 mmol, 80%); eluent, pentane/diethyl ether = 20:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.00 (s, 1H), 4.71 (s, 1H), 4.41 (s, 1H), 3.83 (s, 3H), 3.59 (s, 2H), 2.76 (s, 2H), 2.26 (s, 6H), 1.68 (s, 3H), 1.61−1.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 147.6, 140.7, 138.5, 134.3, 132.8, 131.6, 127.6, 126.1, 125.1, 110.5, 51.6, 41.6, 39.9, 20.5, 20.3, 19.7, 19.1, 18.4; MS (EI) m/z (%) 286 (M^+, 6), 271 (2), 254 (4), 239 (39), 224 (10), 211 (11), 203 (100), 186 (13), 173 (10), 165 (3), 157 (7), 141 (8), 128 (12), 119 (7), 109 (20), 91 (13), 77 (8), 67 (12), 55 (14); HRMS (EI, ICP, m/z) calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1934; IR (film, cm^{-1}) 3077, 2986, 2919, 2861, 1723, 1643, 1616, 1563, 1502, 1434, 1372, 1293, 1267, 1233, 1189, 1138, 1049, 1022, 1002, 955, 892, 833, 792.

*1-(2-(4,5-Dimethyl-2-methylenehex-4-enyl)-4,5-dimethylphenyl)-ethanone (**8b**):* yellow oil; 121 mg (0.45 mmol, 45%); eluent, pentane/diethyl ether = 10:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.00 (s, 1H), 4.71 (s, 1H), 4.40 (s, 1H), 3.50 (s, 2H), 2.75 (s, 2H), 2.51 (s, 3H), 2.28−2.27 (m, 6H), 1.68 (s, 3H), 1.60 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 147.8, 140.2, 136.8, 136.3, 134.1, 133.1, 130.4, 126.2, 125.1, 110.7, 41.7, 39.5, 29.6, 20.6, 20.4, 19.7, 19.3, 18.4; MS (EI) m/z (%) 270 (M^+, 2), 252 (8), 237 (10), 227 (6), 211 (5), 195 (2), 187 (100), 170 (4), 160 (6), 152 (2), 141 (4), 128 (6), 115 (5), 105 (2), 91 (5), 83 (3), 67 (3), 55 (5); HRMS (EI, ICP, m/z) calcd for $C_{19}H_{26}O$ 270.1984, found 270.2001; IR (film, cm^{-1}) 3077, 2983, 2919, 2861, 1685, 1643, 1612, 1557, 1498, 1449, 1385, 1372, 1354, 1291, 1263, 1231, 1199, 1132, 1020, 948, 887, 656, 635.

*2-(4,5-Dimethyl-2-methylenehex-4-enyl)-4,5-dimethylbenzaldehyde (**8c**):* colorless oil; 188 mg (0.73 mmol, 73%); eluent, pentane/diethyl ether = 10:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.63 (s, 1H), 7.01 (s, 1H), 4.80 (s, 1H), 4.41 (s, 1H), 3.59 (s, 2H), 2.80 (s, 2H), 2.30 (s, 6H), 1.69 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 147.7, 143.5, 139.8, 135.2, 132.9, 132.2, 131.0, 126.6, 124.8, 112.1, 41.7, 37.8, 20.6, 20.4, 20.0, 19.2, 18.3; MS (EI) m/z (%) 256 (M^+, 5), 241 (46), 223 (56), 208 (21), 193 (19), 181 (10), 173 (100), 159 (16), 141 (11), 128 (18), 115 (14), 105 (5), 91 (12), 77 (8), 67 (5), 55 (6); HRMS (EI, ICP, m/z) calcd for $C_{18}H_{24}O$ 256.1827, found 256.1816; IR (film, cm^{-1}) 3079, 2983, 2919, 2859, 2755, 1690, 1643, 1611, 1560, 1499, 1450, 1399, 1373, 1295, 1258, 1184, 1070, 1023, 895, 778, 693, 629.

*2-(4,5-Dimethyl-2-methylenehex-4-enyl)-4,5-dimethylbenzyl acetate (**8d**):* yellow oil; 207 mg (0.70 mmol, 70%); eluent, pentane/diethyl ether = 10:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.95 (s, 1H), 5.01 (s, 2H), 4.77 (s, 1H), 4.47 (s, 1H), 3.27 (s, 2H), 2.75 (s, 2H), 2.25−2.23 (m, 6H), 2.06 (s, 3H), 1.70 (s, 3H), 1.62−1.60 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 146.7, 136.8, 135.8, 134.5, 131.9, 131.5, 131.2, 126.4, 125.0, 111.4, 64.3, 41.4, 38.7, 21.0, 20.6, 20.4, 19.4, 19.2, 18.3; MS (EI) m/z (%) 300 (M^+, 1), 240 (92), 225 (100), 210 (16), 197 (38), 183 (61), 170 (77), 157 (47), 141 (31), 128 (20), 115 (19), 105 (12), 91 (18), 77 (8), 67 (5), 55 (10); HRMS (EI, ICP, m/z) calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2097; IR (film, cm^{-1}) 3466, 3077, 2980, 2919, 2861, 2728, 1742, 1643, 1506, 1451, 1376, 1331, 1228, 1119, 1073, 1022, 959, 895, 749, 631, 605.

*(2-(4,5-Dimethyl-2-methylenehex-4-enyl)-4,5-dimethylphenyl)-trimethylsilane (**8e**).* colorless oil; 200 mg (0.67 mmol, 67%); eluent: pentane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (s, 1H), 6.97 (s, 1H), 4.82 (s, 1H), 4.50 (s, 1H), 3.36 (s, 2H), 2.77 (s, 2H), 2.26 (s, 3H), 2.24 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 142.5, 137.4, 135.8, 135.7, 133.2, 131.0, 126.3, 125.1, 111.9, 42.2, 41.7, 20.6, 20.4, 19.6, 19.3, 18.6, 0.4; MS (EI) m/z (%) 300 (M^+, 29), 285 (6), 257 (54), 241 (12), 227 (7), 211 (16), 201 (4), 183 (21), 173 (12), 161 (12), 143 (5), 133 (4), 119

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(10), 107 (11), 93 (2), 83 (18), 73 (100), 55 (14); HRMS (EI, ICP, *m/z*) calcd for $C_{20}H_{32}Si$ 300.2273, found 300.2260; IR (film, cm^{-1}) 3079, 2918, 2861, 2728, 1768, 1643, 1604, 1550, 1489, 1448, 1407, 1379, 1330, 1248, 1179, 1119, 1021, 896, 837, 759, 713, 688, 646.

*2-(4,5-Dimethyl-2-methylenehex-4-enyl)-3′-methoxy-4,5-dimethylbiphenyl (**8f**):* colorless oil; 136 mg (0.41 mmol, 81%); eluent, pentane/diethyl ether = 10:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.23 (m, 1H), 7.04 (d, J = 5.3 Hz, 2H), 6.90–6.85 (m, 3H), 4.76 (s, 1H), 4.51 (s, 1H), 3.81 (s, 3H), 3.17 (s, 2H), 2.64 (s, 2H), 2.29 (s, 6H), 1.64 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 147.9, 143.2, 139.7, 135.4, 134.1, 134.0, 131.6, 131.1, 128.7, 126.1, 125.0, 121.7, 114.8, 112.2, 111.4, 55.2, 41.5, 39.4, 20.5, 20.3, 19.4, 19.3, 18.3; MS (EI) *m/z* (%) 334 (M^+, 65), 319 (23), 304 (1), 291 (48), 276 (22), 263 (18), 250 (100), 236 (45), 223 (39), 210 (16), 195 (16), 178 (16), 165 (18), 152 (9), 141 (2), 128 (3), 107 (9), 91 (4), 79 (4), 67 (4), 55 (6); HRMS (EI, ICP, *m/z*) calcd for $C_{24}H_{30}O$ 334.2297, found 334.2284; IR (film, cm^{-1}) 3442, 2917, 1643, 1600, 1580, 1481, 1452, 1430, 1385, 1315, 1286, 1240, 1212, 1179, 1117, 1051, 1021, 985, 892, 859, 781, 753, 734, 703.

*2-(2-(5,6-Dimethyl-3-methylenehept-5-enyl)-4,5-dimethylphenyl)thiophene (**8g**):* colorless oil; 110 mg (0.34 mmol, 68%); eluent, pentane; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (dd, J = 5.3, 1.1 Hz, 1H), 7.17 (s, 1H), 7.08–7.06 (m, 2H), 7.00 (dd, J = 3.4, 1.1 Hz, 1H), 4.71 (s, 1H), 4.66 (s, 1H), 2.84–2.79 (m, 2H), 2.71 (s, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 2.19–2.14 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 142.9, 138.0, 136.5, 134.0, 132.3, 131.2, 131.0, 126.9, 126.0, 125.9, 125.2, 124.8, 109.5, 41.4, 37.8, 31.9, 20.6, 20.4, 19.4, 19.1, 18.3; MS (EI) *m/z* (%) 324 (M^+, 24), 281 (7), 254 (3), 239 (8), 225 (2), 213 (4), 201 (100), 186 (31), 171 (19), 152 (3), 141 (4), 123 (5), 109 (1), 93 (2), 81 (2), 67 (1), 55 (2); HRMS (EI, ICP, *m/z*) calcd for $C_{22}H_{28}S$ 324.1912, found 324.1924; IR (film, cm^{-1}) 3073, 2919, 2861, 2727, 1785, 1643, 1495, 1451, 1384, 1372, 1264, 1225, 1192, 1151, 1103, 1076, 1021, 886, 847, 830, 734, 694, 659.

*2-(5,6-Dimethyl-3-methylenehept-5-enyl)-4′-methoxy-4,5-dimethylbiphenyl (**8h**):* colorless oil; 173 mg (0.50 mmol, 99%); eluent, pentane/diethyl ether = 20:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.22 (m, 2H), 7.06 (s, 1H), 7.00 (s, 1H), 6.95–6.92 (m, 2H), 4.63 (s, 1H), 4.61 (s, 1H), 3.86 (s, 3H), 2.71–2.67 (m, 2H), 2.64 (s, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 2.12–2.06 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 147.6, 139.0, 137.2, 135.3, 134.3, 133.8, 131.6, 130.6, 130.2, 125.8, 125.2, 113.4, 109.4, 55.3, 41.3, 37.7, 31.6, 20.6, 20.4, 19.4, 19.2, 18.2; MS (EI) *m/z* (%) 348 (M^+, 27), 305 (4), 278 (3), 263 (18), 250 (2), 237 (3), 225 (100), 210 (59), 195 (29), 179 (11), 165 (10), 152 (7), 115 (1), 93 (2), 79 (1), 67 (1), 55 (1); HRMS (EI, ICP, *m/z*) calcd for $C_{25}H_{32}O$ 348.2453, found 348.2446; IR (film, cm^{-1}) 2917, 2862, 1643, 1608, 1570, 1495, 1448, 1378, 1287, 1241, 1175, 1107, 1035, 965, 885, 832, 646, 564, 523, 488, 413.

*Ethyl 2-((4,5-dimethyl-2-methylenehex-4-enyloxy)methyl)-4,5-dimethylbenzoate (**8i**):* colorless oil; 151 mg (0.46 mmol, 46%); eluent, pentane/diethyl ether = 10:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.47 (s, 1H), 5.09 (s, 1H), 4.88 (s, 1H), 4.85 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.98 (s, 2H), 2.82 (s, 2H), 2.31–2.25 (m, 6H), 1.68 (s, 3H), 1.66 (s, 3H), 1.62 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 144.3, 141.4, 138.5, 135.0, 131.5, 128.8, 126.4, 125.6, 124.6, 111.6, 73.5, 69.8, 60.6, 38.4, 20.6, 20.4, 20.0, 19.2, 18.4, 14.3; MS (EI) *m/z* (%) 330 (M^+, 1), 251 (5), 223 (2), 207 (6), 191 (28), 177 (7), 163 (100), 146 (25), 133 (9), 121 (13), 107 (40), 91 (19), 79 (13), 67 (5), 55 (6); HRMS (ESI, FT-ICR, *m/z*) calcd for $C_{21}H_{30}O_3Na$ 353.2087, found 353.2101; IR (film, cm^{-1}) 2981, 2919, 2860, 1713, 1650, 1615, 1565, 1052, 1449, 1385, 1367, 1301, 1267, 1230, 1190, 1137, 1097, 1050, 902, 782, 631.

*N-(4,5-Dimethyl-2-methylenehex-4-enyl)-N-(3,4-dimethylbenzyl)-4-methylbenzene Sulfonamide (**8j**):* colorless oil; 268 mg (0.65 mmol, 70%); eluent, pentane/diethyl ether = 10:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 6.84 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 4.77 (s, 1H), 4.73 (s, 1H), 4.28 (s, 2H), 3.68 (s, 2H), 2.55 (s, 2H), 2.43 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H), 1.64 (s, 3H), 1.49 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 141.4, 137.9, 136.4, 135.9, 133.2, 130.0, 129.5, 129.4, 127.3, 126.7, 126.3, 124.2, 112.8, 52.1, 50.5, 38.6, 21.5, 20.5, 20.3, 19.6, 19.4, 18.4; MS (EI) *m/z* (%) 411 (M^+, 6), 292 (9), 256 (86), 240 (9), 225 (1), 212 (1), 184 (10), 171 (1), 155 (13), 136 (21), 119 (100), 107 (14), 91 (32), 77 (5), 65 (4), 53 (1); HRMS (EI, ICP, *m/z*) calcd for $C_{25}H_{33}NO_2S$ 411.2232, found 411.2232; IR (film, cm^{-1}) 2921, 2860, 1649, 1598, 1505, 1448, 1341, 1305, 1215, 1160, 1119, 1094, 1072, 1020, 909, 815, 778, 752, 735, 708, 693, 656, 600, 547.

General Procedure for the Tandem Diels–Alder/1,4-Hydrovinylation Sequence with 2-(Trimethylsilyloxy)buta-1,3-diene. Zinc iodide (20 mol %), zinc powder (20 mol %), and $CoBr_2$(1,2-bis(diphenylphosphino)ethane) (10 mol %) were suspended in dichloromethane (1 mL) under argon atmosphere. Then 2-(trimethylsilyloxy)buta-1,3-diene (2.4 mmol) and the enyne **7** (1.0 mmol) were added, and the mixture was stirred at room temperature for 16 h. Afterward, the suspension was filtered over a short pad of silica gel, and the solvent was removed under vacuum. The residue was dissolved in tetrahydrofuran (8 mL) and was treated with aqueous HCl (2 mL, 2 M). The mixture was stirred for 1 h at room temperature and was then filtered over a short pad consisting of a silica gel/$MgSO_4$ mixture. The solvent was removed in vacuo, and the residue was purified by flash column chromatography.

*Methyl 2-(2-Methylene-5-oxohexyl)-4-oxocyclohex-1-enecarboxylate (**9a**):* pale yellow oil; 159 mg (0.60 mmol, 60%); eluent, diethyl ether; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.73 (s, 1H), 3.71 (s, 3H), 3.36 (s, 2H), 3.18 (s, 2H), 2.62 (td, J = 7.5, 2.1 Hz, 2H), 2.51 (t, J = 6.4 Hz, 2H), 2.42–2.38 (m, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.15–2.14 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 207.9, 166.7, 148.9, 145.1, 123.4, 111.3, 51.6, 41.7, 41.0, 40.7, 37.5, 30.1, 29.9, 29.6; MS (EI) *m/z* (%) 264 (M^+, 2), 249 (7), 232 (29), 215 (8), 204 (4), 193 (100), 175 (42), 161 (21), 147 (36), 133 (22), 119 (25), 105 (31), 91 (29), 77 (17), 65 (8), 55 (6); HRMS (EI, ICP, *m/z*) calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1366; IR (film, cm^{-1}) 3417, 3079, 2952, 2905, 2844, 1716, 1642, 1435, 1361, 1322, 1233, 1190, 1162, 1095, 1058, 1022, 995, 953, 896, 847, 766, 634, 589.

*3-(3-Methylene-6-oxoheptyl)-4-(thiophen-2-yl)cyclohex-3-enone (**9b**):* orange oil; 70 mg (0.23 mmol, 46%); eluent, pentane/diethyl ether = 1:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.24 (m, 1H), 7.02–6.98 (m, 1H), 6.88–6.85 (m, 1H), 4.74–4.66 (m, 2H), 3.20 (s, 1H), 3.01 (s, 1H), 2.80 (t, J = 6.8 Hz, 1H), 2.59–2.49 (m, 5H), 2.45–2.32 (m, 2H), 2.25–2.10 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 209.5, 147.3, 142.9, 136.9, 133.5, 126.8, 125.3, 124.5, 109.8, 46.2, 43.9, 41.7, 38.6, 38.3, 34.7, 32.5, 29.5; MS (EI) *m/z* (%) 302 (M^+, 20), 284 (3), 269 (2), 256 (3), 244 (7), 231 (9), 215 (4), 203 (4), 191 (100), 178 (7), 163 (16), 149 (19), 134 (13), 115 (10), 97 (11), 77 (5), 65 (4), 55 (5); HRMS (EI, ICP, *m/z*) calcd for $C_{18}H_{22}O_2S$ 302.1341, found 302.1349; IR (film, cm^{-1}) 3411, 3076, 2922, 2853, 2253, 1716, 1646, 1625, 1578, 1432, 1359, 1297, 1238, 1196, 1162, 1082, 1050, 964, 895, 842, 702, 588, 525.

*4-((2-Methylene-5-oxohexyloxy)methyl)cyclohex-3-enone (**9c**):* yellow oil; 110 mg (0.47 mmol, 47%); eluent, diethyl ether; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (s, 1H), 5.02 (s, 1H), 4.87 (s, 1H), 3.89 (s, 4H), 2.88 (s, 2H), 2.66–2.59 (m, 2H), 2.52–2.48 (m, 4H), 2.33 (t, J = 7.4 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 207.9, 144.6, 135.6, 121.1, 112.0, 73.2, 73.0, 41.6, 39.3, 38.3, 29.8, 26.9, 26.0; MS (EI) *m/z* (%) 236 (M^+, 1), 178 (1), 160 (1), 125 (10), 111 (100), 97 (32), 79 (62), 53 (25); HRMS (ESI, FT-ICR, *m/z*) calcd for $C_{14}H_{20}O_3Na$ 259.1305, found 259.1308; IR (film, cm^{-1}) 3465, 3080, 2918, 2852, 1716, 1654, 1424, 1359, 1230, 1192, 1161, 1086, 1051, 962, 903, 809, 783, 589.

*4-Methyl-N-(2-methylene-5-oxohexyl)-N-((4-oxocyclohex-1-enyl)methyl)benzene-sulfonamide (**9d**):* colorless oil; 180 mg (0.46 mmol, 46%); eluent, diethyl ether; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 5.56 (s, 1H), 4.86 (s, 1H), 4.84 (s, 1H), 3.70 (s, 4H), 2.82–2.81 (m, 2H), 2.54 (t, J = 7.4 Hz, 2H), 2.42 (s, 3H), 2.41–2.34 (m, 4H), 2.23–2.18 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 207.4, 143.5, 143.1, 136.7, 133.8, 129.7, 127.3, 123.2, 113.9, 53.2, 53.1, 41.3, 39.3, 38.1, 29.8, 26.9, 26.3, 21.5; MS (EI) *m/z* (%) 389 (M^+, 1), 281 (1), 263 (5),

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248 (3), 238 (1), 224 (17), 198 (2), 184 (3), 172 (1), 155 (57), 139 (8), 126 (100), 109 (33), 91 (75), 81 (11), 65 (20), 55 (3); HRMS (ESI, FT-ICR, m/z) calcd for $C_{21}H_{27}NO_4SNa$ 412.1553, found 412.1552; IR (film, cm^{-1}) 3412, 2922, 1716, 1652, 1598, 1495, 1442, 1339, 1036, 1290, 1190, 1160, 1094, 1035, 1019, 987, 911, 817, 770, 710, 657, 586, 549.

*4-(4-Methoxyphenyl)-3-(3-methylene-6-oxoheptyl)cyclohex-3-enone (**9e**):* pale yellow oil; 107 mg (0.33 mmol, 66%); eluent, pentane/diethyl ether = 1:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08−7.02 (m, 2H), 6.90−6.85 (m, 2H), 4.63−4.61 (m, 2H), 3.81 (s, 3H), 2.97 (s, 2H), 2.69 (t, J = 6.6 Hz, 2H), 2.59−2.54 (m, 2H), 2.45−2.40 (m, 2H), 2.14−2.04 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 208.0, 158.4, 147.4, 134.3, 133.7, 130.2, 129.0, 113.7, 109.7, 55.2, 43.3, 41.7, 38.9, 34.7, 32.2, 32.0, 29.8, 29.4; MS (EI) m/z (%) 326 (M^+, 92), 308 (1), 268 (23), 255 (24), 237 (4), 225 (8), 215 (100), 197 (14), 187 (14), 173 (35), 159 (30), 141 (12), 128 (19), 115 (22), 103 (5), 91 (9), 77 (7), 65 (2), 55 (14); HRMS (EI, ICP, m/z) calcd for $C_{21}H_{26}O_3$ 326.1882, found 326.1872; IR (film, cm^{-1}) 2915, 2844, 2359, 1711, 1647, 1606, 1508, 1444, 1357, 1288, 1242, 1175, 1111, 1031, 952, 890, 829, 556, 506.

General Procedure for the Sequential Diels−Alder/1,4-Hydrovinylation Sequence with 2-(Trimethylsilyloxy)buta-1,3-diene. Zinc iodide (20 mol %), zinc powder (20 mol %), and $CoBr_2$(2,4,6-trimethylphenyl-*N*-(pyridin-2-ylmethylene)aniline) (10 mol %) were suspended in dichloromethane (1 mL) under argon atmosphere. Then 2-(trimethylsilyloxy)buta-1,3-diene (1.5 mmol) and the enyne **7** (1 mmol) were added, and the mixture was stirred at room temperature for 16 h. Then the suspension was treated with further zinc iodide (20 mol %), zinc powder (20 mol %), $CoBr_2$(1,2-bis(diphenylphosphino)ethane) (10 mol %), and 2-(trimethylsilyloxy)buta-1,3-diene (1.5 mmol) followed by stirring for 16 h at room temperature. The mixture was taken up in THF/water (5:1, 10 mL) and treated with tetrabutylammonium bromide (200 mg, 0.62 mmol) and a saturated aqueous solution of KF (2 mL; buffered to pH = 7 by addition of 1 M acetic acid). The suspension was stirred for 1 h at room temperature, and the phases were separated. The aqueous phase was extracted twice with diethyl ether (20 mL), and the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo and the residue was purified by flash column chromatography.

*3-(4-Methoxyphenyl)-4-(3-methylene-6-oxoheptyl)cyclohex-3-enone (**11e**):* yellow oil; 121 mg (0.37 mmol, 37%); eluent, pentane/ethyl acetate = 3:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06−6.99 (m, 2H), 6.89−6.82 (m, 2H), 4.66−4.55 (m, 2H), 3.78 (s, 3H), 3.06 (s, 2H), 2.52 (s, 4H), 2.45−2.37 (m, 2H), 2.21−1.98 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 208.0, 158.3, 147.5, 133.6, 130.4, 129.03, 128.96, 113.7, 109.5, 55.1, 45.9, 41.6, 38.5, 34.9, 32.1, 29.7, 29.4, 28.8; MS (EI) m/z (%) 326 (M^+, 14), 295 (7), 253 (8), 215 (100), 197 (8), 171 (21), 159 (13), 115 (11); HRMS (ESI, FT-ICR, m/z) calcd for $C_{21}H_{26}O_3Na$ 349.1774, found 349.1777; IR (film, cm^{-1}) 1712, 1607, 1510, 1442, 1359, 1287, 1245, 1176, 1161, 1034, 891, 834, 733, 702.

*3-(3-Methoxyphenyl)-4-[2-(3-oxobutyl)prop-2-en-1-yl]cyclohex-3-en-1-one (**11f**):* yellow oil; 218 mg (0.70 mmol, 70%); eluent, pentane/ethyl acetate = 3:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.19 (m, 1H), 6.80 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 6.73 (dt, J = 7.6, 1.4 Hz, 1H), 6.69 (dd, J = 2.4, 1.6 Hz, 1H), 4.87−4.73 (m, 2H), 3.78 (s, 3H), 3.15 (s, 2H), 2.77 (s, 2H), 2.58−2.44 (m, 4H), 2.42−2.34 (m, 2H), 2.20−2.12 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 207.8, 159.5, 146.2, 142.4, 132.3, 131.7, 129.4, 120.1, 113.4, 112.5, 111.0, 55.1, 45.6, 41.6, 40.4, 38.6, 29.8, 29.7, 28.5; MS (EI) m/z (%) 312 (M^+, 6), 254 (10), 241 (100), 211 (23), 185 (44), 171 (18), 115 (20), 83 (36); HRMS (EI, ICP, m/z) calcd for $C_{20}H_{24}O_3$ 312.1725, found 312.1728; IR (film, cm^{-1}) 2939, 1716, 1598, 1577, 1485, 1427, 1360, 1286, 1265, 1211, 1163, 1046, 893, 788, 704.

*4-[2-(3-Oxobutyl)prop-2-en-1-yl]-3-(3,4,5-trimethoxyphenyl)-cyclohex-3-en-1-one (**11g**):* yellow oil; 246 mg (0.66 mmol, 82%); eluent, pentane/ethyl acetate = 3:2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (s, 2H), 4.85−4.76 (m, 2H), 3.83 (s, 3H), 3.81 (s, 6H), 3.16 (s, 2H), 2.78 (s, 2H), 2.56−2.37 (m, 6H), 2.21−2.15 (m, 2H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 207.7, 153.1, 146.4, 136.9, 136.6, 132.4, 131.7, 110.8, 104.8, 60.8, 56.1, 45.7, 41.6, 40.7, 38.5, 29.8, 29.6, 28.6; MS (EI) m/z (%) 372 (19, M^+), 301 (58), 270 (22), 140 (16), 97 (51), 83 (75), 43 (100); HRMS (EI, ICP, m/z) calcd for $C_{22}H_{28}O_5$ 372.1937, found 372.1939; IR (film, cm^{-1}) 2939, 1715, 1581, 1506, 1452, 1412, 1363, 1241, 1167, 1127, 1007, 896, 840, 756.

*4-[2-(3-Oxobutyl)prop-2-en-1-yl]-3-phenylcyclohex-3-en-1-one (**11h**):* yellow oil; 192 mg (0.68 mmol, 68%); eluent, pentane/ethyl acetate = 3:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (m, 2H), 7.29−7.22 (m, 1H), 7.18−7.11 (m, 2H), 4.83−4.76 (m, 2H), 3.16 (s, 2H), 2.76 (s, 2H), 2.60−2.45 (m, 4H), 2.39−2.32 (m, 2H), 2.19−2.12 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 207.8, 146.1, 141.0, 132.4, 131.7, 128.4, 127.7, 127.0, 111.0, 45.7, 41.6, 40.3, 38.6, 29.8, 29.7, 28.5; MS (EI) m/z (%) 282 (12, M^+), 264 (8), 249 (8), 224 (16), 211 (100), 193 (34), 181 (52), 167 (80), 155 (80), 141 (41), 128 (44), 115 (34); HRMS (EI, ICP, m/z) calcd for $C_{19}H_{22}O_2$ 282.1620, found 282.1631; IR (film, cm^{-1}) 2915, 1716, 1442, 1361, 1161, 895, 759, 704.

*4-[3-(3-Oxobutyl)but-3-en-1-yl]-3-phenylcyclohex-3-en-1-one (**11i**):* yellow oil; 186 mg (0.63 mmol, 55%); eluent, pentane/ethyl acetate = 3:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.29 (m, 2H), 7.29−7.20 (m, 1H), 7.15−7.08 (m, 2H), 4.67−4.56 (m, 2H), 3.10 (s, 2H), 2.56 (s, 4H), 2.46−2.37 (m, 2H), 2.21−2.01 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 208.0, 147.5, 141.3, 133.8, 131.0, 128.4, 128.0, 126.8, 109.6, 45.8, 41.6, 38.6, 34.9, 32.1, 29.8, 29.4, 28.9; MS (EI) m/z (%) 296 (12, M^+), 278 (20), 238 (22), 225 (20), 185 (68), 167 (43), 141 (46), 128 (74), 115 (43), 55 (100); HRMS (EI, ICP, m/z) calcd for $C_{20}H_{24}O_2$ 296.1776, found 296.1785; IR (film, cm^{-1}) 2918, 1710, 1439, 1358, 1160, 890, 757, 702.

General Procedure for the Sequential Diels−Alder/1,4-Hydrovinylation Sequence with 2,3-Dimethylbuta-1,3-diene and 2-(Trimethylsilyloxy)buta-1,3-diene. Zinc iodide (20 mol %), zinc powder (20 mol %), iron powder (20 mol %), and $CoBr_2$(2,4,6-trimethylphenyl-*N*-(pyridin-2-ylmethylene)aniline) (10 mol %) were suspended in dichloromethane (1 mL) under argon atmosphere. Then 2,3-dimethylbuta-1,3-diene or 2-(trimethylsilyloxy)buta-1,3-diene (1.2−1.5 mmol) and the enyne **7** (1.0 mmol) were added, and the mixture was stirred at room temperature for 16 h. Then the suspension was further treated with zinc iodide (20 mol %), zinc powder (20 mol %), $CoBr_2$(1,2-bis(diphenylphosphino)ethane) (10 mol %), and the other 1,3-diene (1.2−1.5 mmol) followed by stirring for 16 h at room temperature. Afterward, the suspension was filtered over a short pad of silica gel, and the solvent was removed under vacuum. If 2,3-dimethylbuta-1,3-diene was used in the first case, the residue was oxidized by DDQ as described in the appropriate general procedure above. In the other case, hydrolysis was performed utilizing a buffered KF solution as described in the general procedure above.

*Methyl 4,5-Dimethyl-2-(2-methylene-5-oxohexyl)benzoate (**17a**):* yellow oil; 140 mg (0.51 mmol, 51%); eluent, pentane/diethyl ether = 1:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 6.99 (s, 1H), 4.73 (s, 1H), 4.44 (s, 1H), 3.83 (s, 3H), 3.66 (s, 2H), 2.64−2.59 (m, 2H), 2.34−2.29 (m, 2H), 2.26−2.25 (m, 6H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 168.0, 148.3, 141.0, 138.2, 134.5, 132.9, 131.8, 127.3, 110.5, 51.7, 41.9, 39.9, 30.2, 29.8, 19.7, 19.1; MS (EI) m/z (%) 274 (M^+, 1), 256 (19), 242 (14), 224 (36), 199 (100), 185 (34), 171 (32), 156 (26), 141 (20), 115 (13), 91 (10), 77 (6), 59 (3); HRMS (EI, ICP, m/z) calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1577; IR (film, cm^{-1}) 3415, 2949, 1719, 1672, 1647, 1615, 1596, 1563, 1503, 1435, 1359, 1295, 1268, 1237, 1190, 1140, 1047, 1003, 955, 893, 834, 792.

*5-((4′-Fluoro-4,5-dimethylbiphenyl-2-yl)methyl)hex-5-en-2-one (**17b**):* yellow oil; 48 mg (0.16 mmol, 31%); eluent, pentane/diethyl ether = 5:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.41 (m, 2H), 7.30−7.23 (m, 2H), 7.21 (s, 1H), 7.20 (s, 1H), 4.97 (s, 1H), 4.74 (s, 1H), 3.40 (s, 2H), 2.62−2.57 (m, 2H), 2.49 (s, 3H), 2.47 (s, 3H), 2.38−2.33 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 161.9 (d, J_{CF} = 243.8 Hz), 148.2, 138.7, 137.6 (d, J_{CF} = 3.8 Hz), 135.7, 134.5, 133.6, 131.6, 131.3, 130.7 (d, J_{CF} = 7.5 Hz), 114.7 (d, J_{CF} = 20.3 Hz), 111.5, 41.7, 39.4, 29.8, 29.7, 19.3, 19.2; MS (EI) m/z (%) 310 (M^+, 40), 295 (3), 277 (4), 267 (3), 252 (19), 239 (100), 225 (27), 211 (49), 196 (22), 183 (31), 170 (4), 157 (2), 146 (1), 133 (2),

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109 (2), 97 (2), 77 (1), 65 (1), 53 (1); HRMS (EI, ICP, *m/z*) calcd for $C_{21}H_{23}FO$ 310.1733, found 310.1720; IR (film, cm^{-1}) 3077, 2920, 1714, 1646, 1601, 1493, 1443, 1357, 1295, 1221, 1157, 1092, 1017, 971, 889, 839, 754, 650, 620, 562, 530, 419.

*4-(4,5-Dimethyl-2-methylenehex-4-enyl)-3-(4-fluorophenyl)-cyclohex-3-enone (**17c**):* yellow oil; 155 mg (0.50 mmol, 99%); eluent, pentane/diethyl ether = 5:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16−7.12 (m, 2H), 7.04−6.97 (m, 2H), 4.81 (s, 1H), 4.76 (s, 1H), 3.16 (s, 2H), 2.66 (s, 2H), 2.63 (s, 2H), 2.58−2.49 (m, 4H), 1.64 (s, 3H), 1.57 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 161.8 (d, J_{CF} = 244.5 Hz), 145.7, 136.9 (d, J_{CF} = 3.0 Hz), 132.8, 131.0, 129.2 (d, J_{CF} = 8.3 Hz), 126.5, 124.6, 115.2 (d, J_{CF} = 21.0 Hz), 110.5, 45.6, 41.7, 40.3, 38.6, 28.9, 20.5, 20.4, 18.3; MS (EI) *m/z* (%) 312 (M^+, 57), 297 (20), 283 (4), 269 (100), 255 (33), 242 (33), 227 (39), 213 (32), 199 (57), 185 (79), 172 (40), 159 (72), 146 (72), 133 (59), 121 (24), 109 (77), 91 (24), 77 (14), 67 (16), 55 (17); HRMS (EI, ICP, *m/z*) calcd for $C_{21}H_{25}FO$ 312.1889, found 312.1908; IR (film, cm^{-1}) 3072, 2981, 2911, 2859, 1716, 1642, 1599, 1506, 1435, 1364, 1296, 1223, 1156, 1103, 1018, 969, 894, 836, 730, 650, 559, 497.

*4-(4,5-Dimethyl-2-methylenehex-4-en-1-yl)-3-phenylcyclohex-3-en-1-one (**17d**):* yellow oil; 442 mg (1.50 mmol, 74%); eluent, pentane/diethyl ether = 4:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.29 (m, 2H), 7.29−7.22 (m, 1H), 7.22−7.14 (m, 2H), 4.88−4.71 (m, 2H), 3.20 (s, 2H), 2.70 (s, 2H), 2.64 (s, 2H), 2.60−2.43 (m, 4H), 1.64 (s, 3H), 1.57 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6, 145.7, 141.0, 132.3, 131.9, 128.3, 127.6, 126.9, 126.4, 124.7, 110.5, 45.6, 41.6, 40.3, 38.7, 28.9, 20.5, 20.4, 18.3; MS (EI) *m/z* (%) 294 (19, M^+), 251 (34), 224 (30), 181 (24), 167 (31), 155 (100), 128 (60), 115 (63); HRMS (EI, ICP, *m/z*) calcd for $C_{21}H_{26}O$ 294.1984, found 294.1981; IR (film, cm^{-1}) 2916, 1718, 1680, 1443, 1372, 1195, 894, 761, 702.

*4-(5,6-Dimethyl-3-methylenehept-5-en-1-yl)-3-phenylcyclohex-3-en-1-one (**17e**):* yellow oil; 197 mg (0.64 mmol, 64%); eluent, pentane/diethyl ether = 5:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.30 (m, 2H), 7.29−7.22 (m, 1H), 7.16−7.09 (m, 2H), 4.70−4.54 (m, 2H), 3.12 (s, 2H), 2.66−2.49 (m, 6H), 2.24−2.13 (m, 2H), 2.08−1.97 (m, 2H), 1.65 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.5, 147.2, 141.4, 134.2, 130.7, 128.4, 128.1, 126.8, 126.0, 125.0, 109.9, 45.9, 41.0, 38.6, 34.4, 32.4, 28.8, 20.6, 20.4, 18.2; MS (EI) *m/z* (%) 308 (15, M^+), 265 (20), 224 (40), 183 (100), 165 (36), 141 (48), 129 (38); HRMS (EI, ICP, *m/z*) calcd for $C_{22}H_{28}O$ 308.2140, found 308.2123; IR (film, cm^{-1}) 2922, 1715, 1671, 1443, 1266, 892, 761, 702.

*4-(5,6-Dimethyl-3-methylenehept-5-enyl)-3-(4-methoxyphenyl)-cyclohex-3-enone (**17f**):* yellow oil; 94 mg (0.28 mmol, 56%); eluent, pentane/diethyl ether = 4:1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07−7.04 (m, 2H), 6.89−6.86 (m, 2H), 4.62−4.61 (m, 2H), 3.81 (s, 3H), 3.09 (s, 2H), 2.60 (s, 2H), 2.54 (s, 4H), 2.22−2.17 (m, 2H), 2.05−1.99 (m, 2H), 1.65 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 158.4, 147.2, 134.0, 133.7, 130.1, 129.2, 126.0, 125.0, 113.8, 109.9, 55.2, 46.1, 41.0, 38.6, 34.4, 32.4, 28.8, 20.6, 20.4, 18.2; MS (EI) *m/z* (%) 338 (M^+, 38), 323 (1), 307 (2), 295 (28), 280 (5), 268 (6), 254 (25), 240 (4), 227 (6), 215 (100), 202 (23), 187 (7), 171 (27), 159 (16), 145 (8), 128 (12), 115 (13), 103 (2), 91 (8), 77 (6), 55 (21); HRMS (EI, ICP, *m/z*) calcd for $C_{23}H_{30}O_2$ 338.2246, found 338.2262; IR (film, cm^{-1}) 3328, 2912, 2851, 1713, 1668, 1605, 1508, 1447, 1366, 1289, 1244, 1177, 1111, 1033, 889, 833, 563, 512, 414.

General Procedure for the Ozonolysis Reaction and BF_2 Complexation. The polyene was dissolved in dichloromethane (0.1 M), and the solution was cooled to −78 °C. A mixture of oxygen and ozone was bubbled through the solution until a blue color appeared. The mixture was purged with oxygen for 5−10 min to obtain a colorless or slightly yellowish solution, which was directly treated with triphenyl phosphine (1.1 equiv per double bond) and allowed to warm to room temperature. After 30 min of stirring, the mixture was purged with argon for 5−10 min and cooled to −78 °C. BF_3 etherate (3 equiv per 1,3-dicarbonyl unit) and triethylamine (1 equiv per 1,3-dicarbonyl unit) were added, and the mixture was stirred for 30 min to form a colorless precipitate. The mixture was allowed to warm slowly to room temperature and was stirred for additional 3−15 h after which it was directly subjected to column chromatography for isolation of the respective BF_2 complex.

*1-Phenyldodecane-1,3,6,8,11-pentone BF_2 Complex (**19a**):* yellow solid; 45 mg (0.11 mmol, 23%); eluent, ethyl acetate/pentane = 2:1; mp = 106 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.11−8.03 (m, 2H), 7.75−7.63 (m, 1H), 7.58−7.48 (m, 2H), 6.65 (s, 1H), 6.11 (s, 1H), 3.09−2.94 (m, 4H), 2.91−2.83 (m, 2H), 2.81−2.73 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 196.1, 190.9, 190.7, 184.3, 135.9, 131.0, 129.4, 129.3, 101.5, 97.4, 38.0, 32.7, 32.4, 31.3, 29.4; ^{11}B NMR (128 MHz, $CDCl_3$) δ 0.6, 0.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −138.7, −139.2; HRMS (ESI, FT-ICR, *m/z*) calcd for $C_{18}H_{18}B_2F_4O_5Na$ 435.1170, found 435.1172; IR (KBr, cm^{-1}) 3156, 2921, 1713, 1542, 1493, 1416, 1396, 1377, 1162, 1045, 986, 823, 785.

*1-(4-Methoxyphenyl)-dodecane-1,3,6,8,11-pentone BF_2 Complex (**19b**):* yellow solid; 78 mg (0.18 mmol, 36%); eluent, ethyl acetate/pentane = 2:1; mp = 118−119 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 1H), 7.57−7.52 (m, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.24−7.19 (m, 1H), 6.63 (s, 1H), 6.11 (s, 1H), 3.86 (s, 3H), 3.08−2.94 (m, 4H), 2.91−2.84 (m, 2H), 2.80−2.74 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 196.1, 190.9, 190.8, 184.1, 160.1, 132.3, 130.2, 122.8, 122.0, 113.1, 101.5, 97.6, 55.6, 38.0, 32.6, 32.4, 31.3, 29.4; ^{11}B NMR (128 MHz, $CDCl_3$) δ 0.8, 0.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −138.6, −139.1; HRMS (ESI, FT-ICR, *m/z*) calcd for $C_{19}H_{20}B_2F_4O_6Na$ 465.1281, found 465.1276; IR (KBr, cm^{-1}) 3151, 2919, 1719, 1542, 1495, 1469, 1436, 1388, 1255, 1055, 983, 817, 739.

*1-Phenyltridecane-1,3,6,9,12-pentaone BF_2 Complex (**19c**).* brown oil; 9 mg (0.024 mmol, 20%); eluent, ethyl acetate/pentane = 2:1; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12−8.02 (m, 2H), 7.73−7.64 (m, 1H), 7.58−7.49 (m, 2H), 6.63 (s, 1H), 3.04−2.96 (m, 2H), 2.95−2.87 (m, 2H), 2.84−2.76 (m, 2H), 2.76−2.68 (m, 6H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 207.0, 206.6, 194.1, 182.9, 135.4, 131.3, 129.13, 129.09, 97.1, 37.6, 37.0, 36.3, 35.9, 35.8, 31.6, 29.8; ^{11}B NMR (128 MHz, $CDCl_3$) δ 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −139.1; HRMS (ESI, FT-ICR, *m/z*) calcd for $C_{19}H_{21}BF_2O_5Na$ 401.1346, found 401.1342; IR (film, cm^{-1}) 2922, 2855, 1709, 1594, 1535, 1494, 1453, 1368, 1313, 1172, 1086, 1052, 997, 784, 714, 689.

*1-Phenyltridecane-1,3,6,9,12-pentaone (**18c**):* colorless solid; 79 mg (0.24 mmol, 59%); eluent, pentane/ethyl acetate = 1:1; mp = 77−78 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 15.77 (bs, 0.7H), 8.00−7.81 (m, 2H), 7.62−7.38 (m, 3H), 6.18 (s, 0.7H), 4.13 (s, 0.2H), 3.34−3.27 (m, 0.2H), 2.99−2.58 (m, 11.6H), 2.22−2.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 207.6, 207.0, 197.7, 180.0, 134.2, 132.1, 128.5, 126.8, 96.3, 37.0, 36.9, 36.1, 36.04, 35.98, 33.4, 29.8 (enol form only); HRMS (ESI, FT-ICR, *m/z*) calcd for $C_{19}H_{22}O_5Na$ 353.1359, found 353.1369; IR (film, cm^{-1}) 2910, 1696, 1626, 1576, 1458, 1408, 1357, 1327, 1276, 1094, 1074, 759, 688.

*1-Phenyldodecane-1,3,6,9,11-pentone BF_2 Complex (**19d**):* orange solid; 101 mg (0.25 mmol, 38%); eluent, ethyl acetate/pentane = 2:1; mp = 108−109 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.3 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 2H), 7.55−7.47 (m, 2H), 6.66 (s, 1H), 6.02 (s, 1H), 3.02−2.88 (m, 6H), 2.79 (t, *J* = 6.4 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 193.8, 193.5, 192.8, 182.9, 135.5, 131.1, 129.2, 129.0, 101.4, 97.2, 37.0, 36.8, 31.5, 30.9, 24.1; ^{11}B NMR (128 MHz, $CDCl_3$) δ 0.8, 0.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −138.1, −138.7; HRMS (ESI, FT-ICR, *m/z*) calcd for $C_{18}H_{18}B_2F_4O_5Na$ 435.1170, found 435.1167; IR (KBr, cm^{-1}) 3156, 2917, 1717, 1558, 1494, 1391, 1181, 1051, 822, 792, 709, 681.

*1-Phenylundecane-1,3,6,8,10-pentaone (**18e**):* pale yellow solid; 26 mg (0.086 mmol, 18%); eluent, pentane/ethyl acetate/methanol = 66:32:1; mp = 51−53 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 15.99−15.62 (m, 0.7H), 15.37−14.89 (m, 0.6H), 14.34−14.07 (m, 0.3H), 7.99−7.79 (m, 2H), 7.65−7.39 (m, 3H), 6.24−6.16 (m, 0.8H), 5.65−5.54 (m, 0.7H), 5.30−5.13 (m, 0.4H), 4.18−4.12 (m, 0.2H), 3.81−3.67 (m, 0.3H), 3.53−3.33 (m, 1.5H), 2.99−2.53 (m, 4.1H), 2.29−1.93 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 197.5, 196.5, 195.6, 194.9, 193.8, 190.8, 187.0, 183.4, 182.0, 180.9, 179.8, 179.4, 178.9, 134.1, 133.8, 132.33, 132.29, 132.2, 128.8, 128.6, 126.94, 126.88, 126.8, 101.1, 100.8, 98.8, 98.3, 96.3, 96.2, 57.5, 57.2, 53.7, 53.6, 53.1, 52.9, 37.8, 37.6, 36.9, 36.8, 35.6, 34.3, 33.6, 33.5, 30.9, 30.3, 24.5,

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21.8 (resolved signals of all possible tautomers); HRMS (ESI, FT-ICR, m/z) calcd for $C_{17}H_{18}O_5Na$ 325.1046, found 325.1046; IR (film, cm^{-1}) 2913, 1721, 1595, 1392, 1298, 1134, 754, 688.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) For recent reviews, see: (a) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (b) Jeganmohan, M.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 10876. (c) Omae, I. *Appl. Organomet. Chem.* **2007**, *21*, 318. (d) Laschat, S.; Becheanu, A.; Bell, T.; Baro, A. *Synlett* **2005**, 2547. (e) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (f) Malacria, M.; Aubert, C.; Renaud, J. L. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Lautens, M., Trost, B. M., Eds.; Thieme: Stuttgart, 2001; Vol. *1*, p 439. (g) Welker, M. E. *Curr. Org. Chem.* **2001**, *5*, 785. (h) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (i) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (j) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.

(2) For selected recent reviews, see: (a) Zhou, J. *Chem. Asian J.* **2010**, *5*, 422. (b) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365. (c) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (d) Mayer, S. F.; Kroutil, W.; Faber, K. *Chem. Soc. Rev.* **2001**, *30*, 332. For recent reviews on transition-metal- and organo-catalyzed multicomponent reactions, see: (e) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *J. Organomet. Chem.* **2005**, *690*, 539. (f) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857. For an example of a multicomponent reaction initiated by cobalt catalysis, see: (g) Hilt, G.; Lüers, S.; Smolko, K. I. *Org. Lett.* **2005**, *7*, 251. (h) Erver, F.; Hilt, G. *Org. Lett.* **2012**, *14*, 1884.

(3) (a) Hilt, G.; Hengst, C.; Hess, W. *Eur. J. Org. Chem.* **2008**, 2293. (b) Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F. *Chem. Commun.* **2005**, 1474.

(4) (a) Danz, M.; Hilt, G. *Adv. Synth. Catal.* **2011**, *353*, 303. (b) Auvinet, A.-L.; Harrity, J. P. A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 3893. (c) Hilt, G.; Janikowski, J. *Org. Lett.* **2009**, *11*, 773. (d) Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G. *J. Am. Chem. Soc.* **2008**, *130*, 8952. (e) Hilt, G.; Danz, M. *Synthesis* **2008**, 2257. (f) Hilt, G.; Janikowski, J.; Hess, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 5204.

(5) (a) Hilt, G. *Synlett* **2011**, 1654. (b) Kersten, L.; Hilt, G. *Adv. Synth. Catal.* **2012**, *354*, 863. (c) Erver, F.; Hilt, G. *Org. Lett.* **2011**, *13*, 5700. (d) Hilt, G.; Roesner, S. *Synthesis* **2011**, 662. (e) Arndt, M.; Reinhold, A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 5203. (f) Hilt, G.; Arndt, M.; Weske, D. F. *Synthesis* **2010**, 1321.

(6) (a) Wei, C.-H.; Mannathan, S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 6942. (b) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295. (c) Mannathan, S.; Cheng, C.-H. *Chem. Commun.* **2010**, 1923. (d) Lassauque, N.; Franciò, G.; Leitner, W. *Adv. Synth. Catal.* **2009**, *351*, 3133. (e) Lassauque, N.; Franciò, G.; Leitner, W. *Eur. J. Org. Chem.* **2009**, 3199. (f) Saha, B.; Smith, C. R.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2008**, *130*, 9000. (g) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (h) Saha, B.; RajanBabu, T. V. *J. Org. Chem.* **2007**, *72*, 2357. (i) Chang, H.-T.; Jayanth, T. T.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 4166. (j) Chang, H.-T.; Jayanth, T. T.; Wang, C.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12032. (k) Grutters, M. M. P.; Müller, C.; Vogt, D. *J. Am. Chem. Soc.* **2006**, *128*, 7414. (l) Wang, C.-C.; Lin, T.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 9696.

(7) dppe = 1,2-bis(diphenylphosphino)ethane.

(8) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885. (b) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(9) Arndt, M.; Dindaroğlu, M.; Schmalz, H.-G.; Hilt, G. *Org. Lett.* **2011**, *13*, 6236.

(10) Kuttner, J. R.; Warratz, S.; Hilt, G. *Synthesis* **2012**, *44*, 1293.

(11) py-imine = 2,4,6-trimethylphenyl-*N*-(pyridin-2-ylmethylene) aniline.

(12) Kersten, L.; Hilt, G. *Adv. Synth. Catal.* **2012**, *354*, 863.

(13) Bieber, L. W.; da Silva, M. F. *Tetrahedron Lett.* **2007**, *48*, 7088.

(14) Snider, B. B.; Zhou, J. *Org. Lett.* **2006**, *8*, 1283.

(15) Pereira, R.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **2001**, *57*, 7871.

(16) Horino, Y.; Nakashima, Y.; Hashimoto, K.; Kuroda, S. *Synlett* **2010**, 2879.

(17) Pandey, G.; Sekhar, B. B. V. S. *Tetrahedron* **1995**, *51*, 1483.

(18) Zhao, L.; Lu, X.; Xu, W. *J. Org. Chem.* **2005**, *70*, 4059.

(19) Patel, M. C.; Livinghouse, T.; Pagenkopf, B. L. *Org. Synth.* **2003**, *80*, 93.