Article

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Iron Carbonyl-Mediated Parallel Solution-Phase Synthesis of Cyclohexadienoic Acid Amides

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Iron carbonyl-stabilized cations have been employed to develop methodology for carbon−carbon and carbon−heteroatom formation suitable for the preparation of combinatorial libraries. Different nucleophiles were added to tricarbonyl(cyclohexa-1,3-dienylcarboxylic acid 4-nitro-phenyl ester)iron hexafluorophosphate. Aminolysis, followed by decomplexation, yielded substituted cyclohexadienyl amides of high purity. Carbon, oxygen, and sulfur nucleophiles gave good results, while amine nucleophiles gave products of somewhat lower purity.

Introduction

Solution-phase parallel synthesis has become an efficient way of accessing potential drug candidates, mainly due to the number of new polymer-bound reagents and scavengers that have appeared in the past few years.[1] Solution-phase parallel synthesis combines the advantages of solid-phase synthesis and conventional solution-phase synthesis; that is, automation is possible, while the development time is generally shorter as conventional methods for analysis can be used when the intermediates are not polymer-bound.[2] While many methods for carbon−carbon bond formation have been adapted for parallel synthesis both in solution and on solid phase, the majority of these are palladium-catalyzed reactions. Carbocations stabilized by metal carbonyl complexes can be used both for carbon−carbon and carbon−heteroatom formation,[3] yet there are few examples of the application of such methods in parallel synthesis although iron carbonyl-mediated S_NAr reactions on solid phase have been adapted for combinatorial purposes.[4]

We have investigated the solution-phase parallel synthesis of amides **12** and **13** via reaction of cation **7** with different nucleophiles, followed by aminolysis of the ester moiety and subsequent oxidative removal of the iron carbonyl group. The target amides show structural similarity to the neuraminidase inhibitor oseltamivir (Tamiflu),[5] used in the treatment of influenza, but can also be seen as building blocks for more general lead generation libraries, where the diene moiety could be used in cycloaddition reactions, for example. Both the nucleophilic attack on the cation and the aminolysis used polymer-bound reagents and scavengers, making the reaction sequence amenable to automation. Our results from this study are reported herein.

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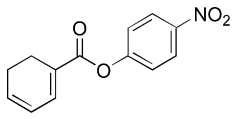
Results and Discussion

Carboxylic acid **4** was prepared via a tandem Michael/Wittig reaction of **2** with acrolein,[6] followed by hydrolysis of the methyl ester formed (Scheme 1).

Conversion to *p*-nitrophenol ester **6** was best effected by iron complexation of carboxylic acid **4** with diiron nonacarbonyl followed by esterification with *p*-nitrophenol. Attempted reversal of the order of these two steps was not successful; reaction of *p*-nitrophenol ester **8** with diiron nonacarbonyl resulted in exothermic decomposition of the reaction mixture, probably involving reduction of the nitro-group by the iron-complex.[7]



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Reaction of esters **6** with triphenylcarbenium hexafluorophosphate yielded the desired stable iron carbonyl cation **7**, which was used as the starting material for the parallel synthesis of the target amides. **7** was treated with different nucleophiles in the presence of polymer-bound *N*,*N*-diisopropylethylamine (PS-DIEA) using two different protocols (Scheme 2). In the first case (method A), an excess of cation was used, enabling a common scavenger, PS-Trisamine, to be employed for all of the reactions independent of the nucleophile. In the second method, 2 equiv of the nucleophile was used, and suitable scavengers for the different nucleophiles were added upon completion of the reaction (method B). When volatile alcohols were used as nucleophiles, no scavenger was added, as unreacted nucleophile could be removed by evaporation. The crude product was taken directly to the next step without any further purification. Aminolysis with diethylamine or morpholine was carried out

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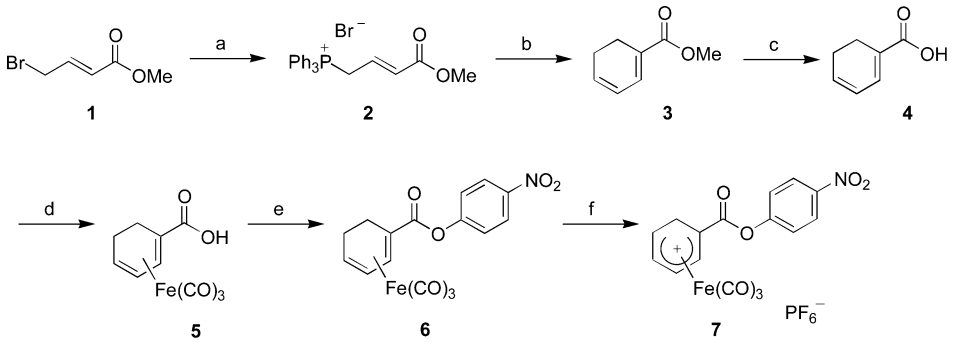
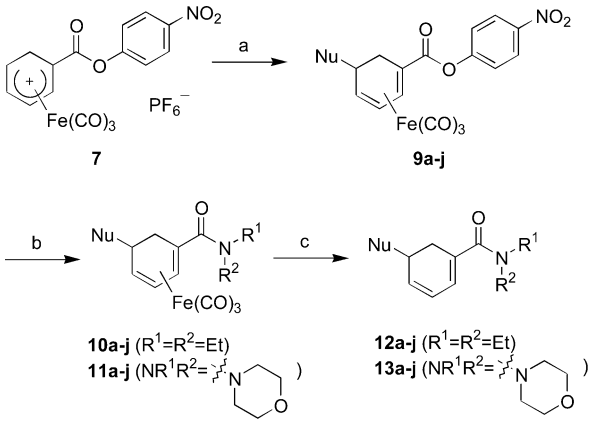
Scheme 1. Preparation of Carbocationic Precursor **7**[a]



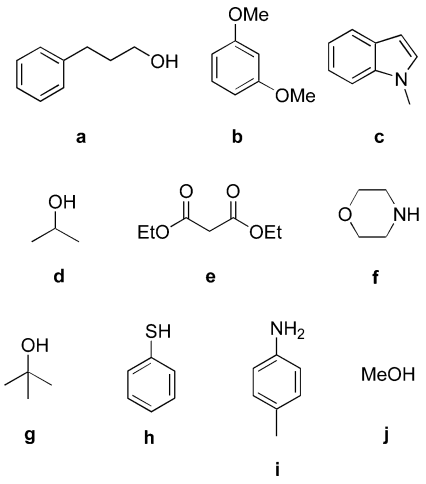
[a] Reagents and conditions: (a) PPh_3, toluene, RT, 48 h, 90%; (b) acrolein, $NaHCO_3$ (aq), CH_2Cl_2, RT, 48 h, 70%; (c) NaOH (aq), MeOH, RT, 3 h, 80%; (d) $Fe_2(CO)_9$, dioxane, 55 °C, 3 h, 80%; (e) *p*-nitrophenol, DIC, DMAP, CH_2Cl_2, RT, 16 h, 99%; (f) Ph_3CPF_6, CH_2Cl_2, RT, 16 h, 70%.

Scheme 2. Parallel Synthesis of Cyclohexadienyl Amides **12** and **13**[a]



[a] Reagents and conditions: (a) method A: (1) nucleophile (0.9 equiv), PS-DIEA, CH_2Cl_2, RT, 12 h; (2) PS-Trisamine, 3 h. Method B: (1) nucleophile (2 equiv), PS-DIEA, CH_2Cl_2, RT, 12 h; (2) scavenger, solvent, 3 h; (b) (1) amine, CH_3CN, 50 °C, 12 h; (2) MP-Carbonate, 4 h; (c) H_2O_2, NaOH, MeOH/H_2O, 0 °C, 5 min.

Chart 1. Nucleophiles Used in the Reaction with Cation **7**



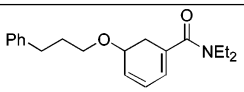
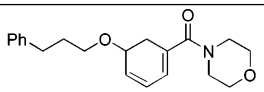
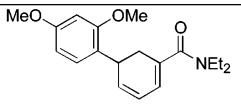
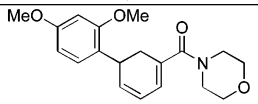
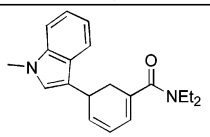
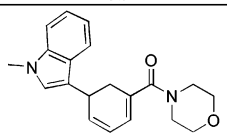
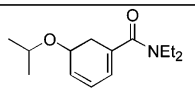
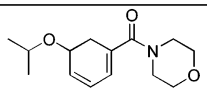
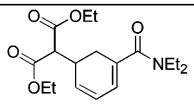
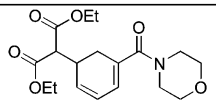
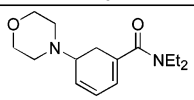
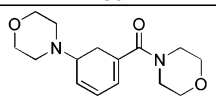
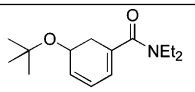
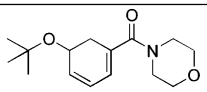
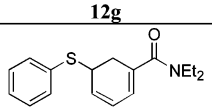
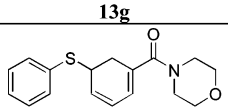
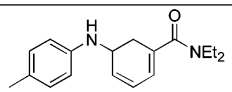
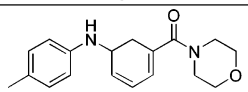
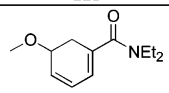
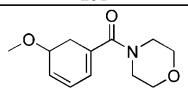
by heating iron carbonyl ester **9** in acetonitrile containing an excess of amine, yielding iron carbonyl complexed amides **10** and **11**.

Several methods were tested for the decomplexation step, using the corresponding methyl ester as a model compound. Copper (II) chloride in dichloromethane[8] was found to be too acidic, causing elimination in the case of alkoxide substituents. Trimethylamine oxide was also tried on the underivatized iron diene complex,[9] but resulted in partial oxidation to benzoic acid methyl ester. Treatment with basic aqueous hydrogen peroxide,[10] however, resulted in the decomplexation of iron complexes **10** and **11** in a clean and rapid manner, yielding the desired amides **12** and **13** in high purities. To investigate the scope and limitations of the method for combinatorial purposes, different carbon, sulfur, oxygen, and nitrogen nucleophiles were tried in the reaction sequence (Chart 1). The results are reported in Table 1.

Primary alcohols in general gave products of high purity, with overall yields for the three-step sequence in the range of 39−57% (entries 1, 10, 11, and 20). Somewhat surprisingly, the more hindered alcohols 2-propanol (entries 4 and 14) and *tert*-butyl alcohol (entries 7 and 17) performed as well as or even better than methanol, although in this case the diethylamide products were of somewhat lower purity. Thiophenol (entries 8 and 18) gave excellent results, that is, pure products in all four cases and yields in the range of 43−49%. In this case, one can envisage both the sulfur moiety and the aromatic ring as potential nucleophiles, but it is known for anilines that the reaction generally takes place on the heteroatom at room temperature,[11] and this was found to be the case also for thiophenol. Amines, disappointingly, gave impure products, although in the case of the doubly morpholine-substituted substrate (entry 16), pure product was formed but in low yields. One complication when using amines as nucleophiles could be oxidation of the amino-groups to the corresponding *N*-oxides during the oxidative deprotection step. Carbon nucleophiles are the most interesting nucleophiles in this reaction sequence, as this would open up an alternative method for carbon−carbon bond formation in combinatorial chemistry. Three different carbon nucleophiles were tried, dimethoxybenzene, *N*-methylindole, and diethylmalonate. These all performed well, and the aromatic nucleophiles (entries 2, 3, 12, and13) gave higher yields than those obtained with hetero-nucleophiles. Method B gave markedly better results in this case; apparently an excess of nucleophile is important to drive the reaction to completion. Diethylmalonate gave somewhat lower yields but pure product in all four runs (entries 5 and 15).

In comparing the two different methods used, that is, using an excess of cation rather than nucleophile, with PS-Trisamine[12] to scavenge the cation (method A), or using 2 equiv of nucleophile with a suitable scavenger to remove the excess after completion of the reaction (evaporation in the case of volatile nucleophiles), we had expected to obtain

Table 1. Results from the Reaction of **7** with Nucleophiles, Followed by Aminolysis and Decomplexation

entry	product	yield (purity)[a] method A	yield (purity)[a] method B	entry	product	yield (purity)[a] method A	yield (purity)[a] method B
1	 **12a**	57 (99)	43 (99)	11	 **13a**	39 (99)	40 (99)
2	 **12b**	74 (83)	84 (93)	12	 **13b**	76 (78)	74 (99)
3	 **12c**	64 (90)	90 (97)	13	 **13c**	52 (99)	76 (99)
4	 **12d**	66 (74)		14	 **13d**	55 (99)	
5	 **12e**	46 (99)	41 (99)	15	 **13e**	36 (99)	36 (99)
6	 **12f**	63 (78)	53 (74)	16	 **13f**	15 (99)	18 (99)
7	 **12g**	46 (88)		17	 **13g**	39 (99)	
8	 **12h**	48 (99)	39 (99)	18	 **13h**	49 (99)	43 (99)
9	 **12i**	47 (69)	48 (73)	19	 **13i**	46 (73)	43 (74)
10	 **12j**	44 (99)		20	 **13j**	41 (84)	

[a] Purity determined by HPLC. Yield and purity in %.

products of higher purity using method A but better yields with method B. This was not the case, however. Method A in several cases gave comparable or higher yields than method B (see entries 1 and 11, 6 and 16, for example), while the latter in general gave more pure products. One explanation could be that the excess cation used in method A reacts with impurities before the treatment with PS-Trisamine, resulting in byproducts that are difficult to separate from the desired products. In many cases, however, product of high purity was obtained also with method A, and only in the case of carbon nucleophiles was there a significant difference between the two methods.

In conclusion, a new methodology for the parallel synthesis of cyclohexadienoic acid amides has been developed, exploiting the potential of iron carbonyl-stabilized cations of reacting with both carbon and hetereoatom nucleophiles, thus enabling the formation of a wide variety of different compounds with diverse properties in the same library. A more focused study concerning carbon nucleophiles, as well as development of the described methodology for solid-phase synthesis, is currently being carried out. Results from these studies will be reported shortly.

Experimental Section

Materials. All solvents and reagents were obtained commercially and used as received unless noted otherwise. Polymer-bound reagents (PS-Trisamine, PS-DIEA, MP-Isocyanate, PS-TsCl, MP-Carbonate) were purchased from Argonaut Technologies (PS = polystyrene, MP = macroporous polystyrene). NMR spectra were recorded on a Varian

400 MHz UNITY-VXR 5000 spectrometer. Chemical shifts are reported with the appropriate deuterated solvent as reference. HPLC/MS data were recorded on an Agilent 1100 series module with a Waters ZQ 2000 mass spectrometer with pos/neg switch using ELS as primary detector and DAD as secondary detector. Column: ACT ACE C8 3 × 50 mm 3 μm. Eluent: 5 mM formic acid and 5 mM ammonium formiate in a CH_3CN/water gradient.

Preparation of (3-Methoxycarbonylallyl)-triphenylphosphonium Bromide (2).[13] Triphenylphosphine (32 g, 0.12 mol) was dissolved in toluene (200 mL), and 4-bromobut-2-enoic acid methyl ester (26 g, 0.12 mol, 85%) was added dropwise. The reaction mixture was stirred at ambient temperature for 2 days. The precipitate was removed by filtration, washed with toluene and ether, and dried under vacuum, affording white crystals (56.5 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88−7.65 (m, 15H), 6.72 (m, 1H), 6.46 (dd, J = 15.4, 5.0 Hz, 1H), 5.23 (dd, J = 16.4, 7.6 Hz, 2H), 3.65 (s, 3H).

Preparation of Cyclohexa-1,3-dienecarboxylic Acid Methyl Ester (3).[14] (3-Methoxycarbonyl-allyl)-triphenylphosphonium bromide (56.5 g, 0.128 mol) was dissolved in CH_2Cl_2 (1.0 L). Saturated sodium bicarbonate (800 mL) and acrolein (8.8 mL, 0.128 mmol, 95%) were added. The reaction mixture was stirred under a nitrogen atmosphere for 3 days. The phases were separated, and the organic phase was concentrated by rotary evaporation. The residue was dissolved in CH_2Cl_2, evaporated on silica gel and then filtered through a plug of silica gel eluting with CH_2Cl_2, and finally distilled under reduced pressure to give 15.4 g of a clear oil (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (dd, J = 5.2, 1.2 Hz, 1H), 6.17−6.11 (m, 1H), 6.09−6.02 (m, 1H), 3.75 (s, 3H), 2.49−2.41 (m, 2H), 2.30−2.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 133.5, 133.2, 127.0, 123.9, 51.6, 22.8, 20.7. IR 1717 cm^{-1} (COOMe).

Preparation of Cyclohexa-1,3-dienecarboxylic Acid (4).[14] Cyclohexa-1,3-dienecarboxylic acid methyl ester (2 g, 14.5 mmol) was dissolved in MeOH (20 mL), and NaOH (1 M, 40 mL) was added in two portions. The reaction was stirred at ambient temperature for 3 h. The aqueous phase was washed once with petroleum ether, acidified with concentrated aqueous HCl, and extracted four times with CH_2Cl_2. The organic phase was concentrated by rotary evaporation, and the residue was purified by flash chromatography using petroleum ether/EtOAc/AcOH [79:20:1] as the eluent. White crystals were obtained (1.27 g, 70%). ^{1}H NMR (400 MHz, MeOD): δ 6.99 (dd, J = 6.8, 2.0 Hz, 1H), 6.19−6.14 (m, 1H), 6.11−6.07 (m, 1H), 2.43−2.35 (m, 2H), 2.30−2.22 (m, 2H). ^{13}C NMR (100 MHz, MeOD): δ 170.9, 134.7, 134.7, 128.8, 125.2, 24.0, 21.9.

Preparation of Tricarbonyl(cyclohexa-1,3-dienecarboxylic acid)iron (5).[15] Dioxane (15 mL) was added to iron nonacarbonyl (10 g, 27.5 mmol) to form a slurry. Cyclohexa-1,3-dienecarboxylic acid (1.48 g, 11.9 mmol) was dissolved in dioxane (5 mL) and added to the slurry. The reaction mixture was flushed with nitrogen and stirred at 55 °C under a nitrogen atmosphere for 4 h. The reaction mixture was evaporated on silica gel and filtered through a plug of silica gel with petroleum ether/EtOAc/AcOH [59:40:1]. The yellow solution was again evaporated on silica gel and purified by flash chromatography using a stepwise gradient of petroleum ether/EtOAc [95:5], petroleum ether/EtOAc [80:20], and finally, petroleum ether/EtOAc/AcOH [79:20:1], yielding 2.5 g of yellow crystals (79%). ^{1}H NMR (400 MHz, MeOD): δ 6.08 (d, J = 4.0 Hz, 1H), 5.51 (t, J = 4.8 Hz, 1H), 3.45 (br s, 1H), 2.17−2.13 (m, 1H), 1.95−1.87 (m, 1H), 1.76−1.63 (m, 1H), 1.46−1.39 (m, 1H). ^{13}C NMR (100 MHz, MeOD): δ 175.7, 90.2, 86.8, 66.6, 65.0, 26.3, 24.1.

Preparation of Tricarbonyl(cyclohexa-1,3-dienecarboxylic acid 4-nitro-phenyl ester)iron (6). CH_2Cl_2 (10 mL) was added to tricarbonyl(cyclohexa-1,3-dienecarboxylic acid)-iron (614 mg, 2.33 mmol) to form a slurry. 4-Nitrophenol (357 mg, 2.57 mmol), DIC (402 μL, 2.57 mmol), and DMAP (5 mg) were added. The reaction mixture was stirred under a nitrogen atmosphere at ambient temperature for 3 days. The precipitate was removed by filtration, and the filtrate was evaporated on silica gel and purified by flash chromatography using CH_2Cl_2/petroleum ether [1:1] as the eluent. Yellow crystals were obtained (920 mg, 99%). ^{1}H NMR δ (400 MHz, $CDCl_3$): 8.27 (d, J = 9.4 Hz, 2H), 7.29 (d, J = 9.4 Hz, 2H), 6.21 (d, J = 4.6 Hz, 1H), 5.47 (dd, J = 4.6, 1.2 Hz, 1H), 3.56−3.50 (m, 1H), 2.32−2.22 (m, 1H), 2.08−1.98 (m, 1H), 1.84−1.74 (m, 1H), 1.62−1.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.0, 155.6, 145.1, 125.1, 122.4, 88.5, 85.9, 64.1, 62.5, 25.3, 22.8. IR 2046 (CO), 1979 (CO), 1714 (COOAr) cm^{-1}. mp 143−144 °C. Anal. Calcd for $C_{16}H_{11}FeNO_7$: C, 49.90; H, 2.88. Found: C, 50.08; H, 2.85.

Preparation of Tricarbonyl(cyclohexa-1,3-dienylcarboxylic acid 4-nitro-phenyl ester)iron Hexafluorophosphate (7). Triphenylcarbenium hexafluorophosphate (1.97 g, 5.08 mmol) was dissolved in dry CH_2Cl_2 (11 mL) and added to tricarbonyl(cyclohexa-1,3-dienecarboxylic acid 4-nitro-phenyl ester)iron (1.86 g, 4.84 mmol) dissolved in dry CH_2Cl_2 (9 mL). The reaction mixture was stirred under a nitrogen atmosphere for 24 h at ambient temperature. The precipitated cation was removed by filtration and washed with CH_2Cl_2. Yellow crystals were formed (2.0 g, 78%). ^{1}H NMR (400 MHz, CD_3CN): δ 8.32 (d, J = 8.8, 2H), 7.45 (d, J = 8.8, 2H), 7.38 (t, J = 4.4 Hz, 1H), 6.82 (d, J = 5.6 Hz, 1H), 5.98 (t, J = 5.2 Hz, 1H), 4.84 (t, J = 6.4 Hz, 1H), 3.41 (dd, J = 15.2, 6.4 Hz, 1H), 2.02 (d, J = 15.2 Hz, 1H). Anal. Calcd for $C_{16}H_{10}F_6FeNO_7P$: C, 36.32; H, 1.91. Found: C, 36.18; H, 1.97.

General Procedure A for the Reaction of Cation 7 with Nucleophiles. Tricarbonyl(cyclohexa-1,3-dienylcarboxylic acid 4-nitro-phenyl ester)iron hexafluorophosphate (0.15 mmol) and PS-DIEA (0.15 mmol) were suspended in dry CH_2Cl_2 (1 mL), and the nucleophile (0.13 mmol) dissolved in 100 μL of dry CH_2Cl_2 was added. The reaction mixture was stirred at ambient temperature overnight. PS-Trisamine (0.15 mmol) was added, and the reaction mixture was stirred at ambient temperature for 3 h. The polymer was removed by filtration, and the solvent was evaporated with a stream of nitrogen and finally dried under vacuum.

General Procedure B for the Reaction of Cation 7 with Nucleophiles. Tricarbonyl(cyclohexa-1,3-dienylcarboxylic acid 4-nitro-phenyl ester)iron hexafluorophosphate (0.15 mmol) and PS-DIEA (0.15 mmol) were suspended in dry CH_2Cl_2 (1 mL), and the nucleophile (0.3 mmol) dissolved in 222 μL of dry CH_2Cl_2 was added. The reaction mixture

was stirred at ambient temperature overnight. PS-Trisamine (0.15 mmol) and the appropriate scavenger (0.6 mmol) (MP-Isocyanate for amines, PS-TsCl for alcohol, MP-Carbonate for thiophenol) were added, and the reaction mixture was stirred at ambient temperature for 3 h. The polymer was removed by filtration, and the solvent was evaporated using a stream of nitrogen and finally dried under vacuum.

General Procedure for the Reaction of Cation 7 with Volatile Nucleophiles. Tricarbonyl(cyclohexa-1,3-dienyl-carboxylic acid 4-nitro-phenyl ester)iron hexafluorophosphate (0.15 mmol) and PS-DIEA (0.15 mmol) were suspended in dry CH_2Cl_2 (1 mL), and the nucleophile (**a**−**j**) was added (500 μL). The reaction mixture was stirred at ambient temperature overnight. PS-Trisamine (0.15 mmol) was added, and the reaction mixture was stirred at ambient temperature for 3 h. The polymer was removed by filtration, and the solvent was evaporated using a stream of nitrogen and, finally, dried under vacuum.

General Procedure for the Aminolysis of Nitroesters 9 (Formation of 10 and 11). Ester **9** (0.068 mmol) was dissolved in CH_3CN (1 mL), and the amine was added (1.6 mmol) and heated to 50 °C overnight. MP-Carbonate (0.27 mmol) was added, and the reaction mixture was stirred for 3 h at ambient temperature. The polymer was removed by filtration, and the solvent was evaporated using a stream of nitrogen and finally dried under vacuum.

General Procedure for the Oxidative Decomplexation (Formation of 12 and 13). The iron tricarbonyl-protected dienes (0.068 mmol) were dissolved in MeOH (1.4 mL), and H_2O_2 (430 μL, 30%) was added. The reaction mixture was stirred at 0 °C, and NaOH (430 μL, 1 M in H_2O/MeOH) was added in three portions. The reaction mixture was stirred for 5 min at 0 °C, diluted with ether (8 mL), and washed three times with brine. The organic phase was evaporated under a stream of nitrogen. To remove iron-byproducts, the residue was dissolved in CH_2Cl_2 and absorbed on a small plug of silica (0.5 g), washed with CH_2Cl_2, and eluted with 5% MeOH in CH_2Cl_2. The organic solvent was evaporated using a stream of nitrogen and dried under vacuum.

5-(3-Phenyl-propoxy)-cyclohexa-1,3-dienecarboxylic Acid Diethylamide (12a). Yield: 12.1 mg (57%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, J = 7.0 Hz, 2H), 7.23−7.14 (m, 3H), 6.15 (dd, J = 9.6, 5.2 Hz, 1H), 6.07 (d, J = 5.6 Hz, 1H), 6.18 (dd, J = 9.6, 4.8 Hz, 1H), 4.06 and 3.69 (dd, J = 11.2, 6.4 Hz, 1H), 3.51−3.32 (m, 6H), 2.68−2.62 (m, 4H), 1.93−1.82 (m, 2H), 1.16 (t, J = 7.2 Hz, 6H). MS (ES) m/z 314.13 (MH^+), 336.07 (MNa^+).

5-(2,4-Dimethoxy-phenyl)-cyclohexa-1,3-dienecarboxylic Acid Diethylamide (12b). Yield: 16 mg (74%); purity (ELS) 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, J = 8.0 Hz, 1H), 6.48−6.39 (m, 2H), 6.18−6.10 (m, 1H), 6.04 (d, J = 4.8 Hz, 1H), 5.90 (dd, J = 9.6, 4.0 Hz, 1H), 4.10−3.96 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.40−3.16 (br s, 4H), 2.71 (dd, J = 17.2, 9.2 Hz, 1H), 2.47 (dd, J = 17.2, 10.8 Hz, 1H), 1.06 (br s, 6H), small singlet at δ 3.83 indicates trace amounts of another isomer. MS (ES) m/z 316.28 (MH^+).

5-(1-Methyl-indol-3-yl)-cyclohexa-1,3-dienecarboxylic Acid Diethylamide (12c). Yield: 13.5 mg (64%); purity (ELS) 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.23 (t, J = 7.2 Hz, 1H), 6.98 (s, 1H), 6.10 (br s, 3H), 4.01 (t, J = 10.0 Hz, 1H), 3.75 (s, 3H), 3.50−3.28 (m, 4H), 2.67−2.85 (m, 2H), 1.25−0.95 (m, 6H). MS (ES) m/z 309.13 (MH^+).

5-Isopropoxy-cyclohexa-1,3-dienecarboxylic Acid Diethylamide (12d). Yield: 10.7 mg (66%); purity (UV) 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (dd, J = 9.2, 5.2 Hz, 1H), 6.06 (d, J = 4.4 Hz, 1H), 5.96 (dd, J = 9.2, 4.4 Hz, 1H), 4.13 (q, J = 6.0 Hz, 1H), 3.73 (t, J = 6.0 Hz, 1H), 3.50−3.32 (m, 4H), 2.68−2.52 (m, 2H), 1.19−1.13 (m, 12H). MS (ES) m/z 238.07 (MH^+).

2-(5-Diethylcarbamoyl-cyclohexa-2,4-dienyl)-malonic Acid Diethyl Ester (12e). Yield: 10.5 mg (46%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.03 (br s, 2H), 5.89−5.83 (m, 1H), 4.20 (q, J = 7.2 Hz, 4H), 3.69 (br s, 1H), 3.62−3.30 (m, 4H), 3.30−3.12 (m, 1H), 2.52 (dd, J = 17.2, 8.0 Hz, 1H), 2.34 (dd, J = 17.2, 11.2 Hz, 1H), 1.32−1.20 (m, 6H), 1.16 (t, J = 7.2 Hz, 6H). MS (ES) m/z 338.50 (MH^+), 336.07 ($M-H)^-$.

5-Morpholin-cyclohexa-1,3-dienecarboxylic Acid Diethylamide (12f). Yield: 11.3 mg (63%); purity (ELS) 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (dd, J = 9.2, 5.6 Hz, 1H), 5.95 (d, J = 4.0 Hz, 1H), 5.84 (dd, J = 5.6, 4.0 Hz, 1H), 3.70 (br s, 4H), 3.41 (app q, J = 6.8 Hz, 5H), 2.69 (dd, J = 18.0 8.4 Hz, 1H), 2.53−2.51 (m, 4H), 2.44 (dd, J = 18.0, 10.0 Hz, 1H), 1.17 (t, J = 6.8 Hz, 6H). MS (ES) m/z 265.14 (MH^+), 287.07 (MNa^+).

5-*tert*-Butoxycyclohexa-1,3-dienecarboxylic Acid Diethylamide (12g). Yield: 7.9 mg (46%); purity (ELS) 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (br s, 2H), 5.88−5.82 (m, 1H), 4.26−4.20 (m, 1H), 3.44−3.38 (m, 4H), 2.70−2.45 (m, 2H), 1.19−1.14 (m, 6H). MS (ES) m/z 253.05 (MH^+).

5-Phenylsulfanyl-cyclohexa-1,3-dienecarboxylic Acid Diethylamide (12h). Yield: 9.5 mg (48%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.34 (m, 3H), 7.32−7.22 (m, 2H), 6.16−6.06 (m, 2H), 6.04−5.98 (m, 1H), 4.14−4.10 (m, 1H), 3.46−3.35 (m, 4H), 2.92 (dd, J = 18.0, 5.6 Hz, 1H), 2.62 (dd, J = 18.0, 2.8 Hz, 1H), 1.21−1.08 (m, 6H). MS (ES) m/z 288.10 (MH^+), 310.03 (MNa^+), 286.79 ($M - H)^-$.

5-*p*-Tolylamino-cyclohexa-1,3-dienecarboxylic Acid Diethylamide (12i). Yield: 9.2 mg (47%); purity (ELS) 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.87 (d, J = 7.6 Hz, 2H), 6.61 (d, J = 7.6 Hz, 2H), 6.23−6.15 (m, 1H), 6.09−6.04 (m, 1H), 5.91 (dd, J = 9.6, 4.0 Hz, 1H), 3.80−3.65 (m, 1H), 3.45−3.25 (m, 4H), 2.80−2.35 (m, 2H), 1.30−1.03 (m, 6H). MS (ES) m/z 285.22 (MH^+).

5-Methoxy-cyclohexa-1,3-dienecarboxylic Acid Diethylamide (12j). Yield: 6.3 mg (44%); purity (UV) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (dd, J = 9.6, 5.6 Hz, 1H), 6.08−6.00 (m, 2H), 4.01−3.95 (m, 1H), 3.46−3.36 (m, 4H), 3.34 (s, 3H), 2.65 (dd, J = 6.4, 1.2 Hz, 2H), 1.16 (t, J = 7.2 Hz, 6H). MS (ES) m/z 210.02 (MH^+).

Morpholin-4-yl-[5-(3-phenyl-propoxy)-cyclohexa-1,3-dienyl]-methanone (13a). Yield: 8.7 mg (39%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, J = 6.8 Hz, 2H), 7.23−7.12 (m, 3H), 6.19−6.09 (m, 2H), 6.06 (dd, J = 9.6, 4.8 Hz, 1H), 4.06−4.00 (m, 1H), 3.72−3.56 (m, 8H),

3.46 (t, J = 5.6 Hz, 2H), 2.68−2.60 (m, 4H), 1.92−1.80 (m, 2H). MS (ES) *m*/*z* 328.12 (MH^+), 350.06 (MNa^+).

[5-(2,4-Dimethoxy-phenyl)-cyclohexa-1,3-dienyl]-morpholin-4-yl-methanon e (13b). Yield: 17 mg (76%); purity (ELS) 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, J = 8.4 Hz, 1H), 6.45 (s, 1H), 6.42 (dd, J = 8.0, 2.4 Hz, 1H), 6.20−6.13 (m, 1H), 6.12 (br s, 1H), 5.96 (dd, J = 9.2, 4.4 Hz, 1H), 4.06−3.94 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.55 (br s, 4H) overlaps with 3.46 (br s, 4H), 2.71 (dd, J = 17.2, 9.2 Hz, 1H), 2.46 (dd, J = 17.2, 10.4 Hz, 1H). MS (ES) *m*/*z* 330.15 (MH^+).

[5-(1-Methyl-1*H*-indol-3-yl)-cyclohexa-1,3-dienyl]-morpholin-4-yl-methano ne (13c). Yield: 11.5 mg (52%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.0 Hz, 1H), 7.34−7.20 (m, 2H), 7.11 (t, J = 6.8 Hz, 1H), 6.93 (s, 1H), 6.15 (br s, 3H), 4.01 (t, J = 8.8 Hz, 1H), 3.75 (s, 3H), 3.75−3.30 (m, 8H), 2.81 (dd, J = 16.8, 8.8 Hz, 1H), 2.71 (dd, J = 16.9, 9.6 Hz, 1H). MS (ES) *m*/*z* 323.11 (MH^+).

(5-Isopropoxy-cyclohexa-1,3-dienyl)-morpholin-4-yl-methanone (13d). Yield: 9.5 mg (55%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (br s, 2H), 6.04−5.98 (m, 1H), 4.12−4.07 (m, 1H), 3.66 (br d, J = 4.4 Hz, 4H), 3.62 (br d, J = 4.4 Hz, 4H), 2.67−2.53 (m, 3H), 1.13 (d, J = 6.0 Hz, 6H). MS (ES) *m*/*z* 252.02 (MH^+), 274.05 (MNa^+).

2-[5-(Morpholine-4-carbonyl)-cyclohexa-2,4-dienyl]-malonic Acid Diethyl Ester (13e). Yield: 8.7 mg (36%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.10−6.03 (m, 2H), 5.97−5.92 (m, 1H), 4.30−4.15 (m, 4H), 3.69 (br d, J = 4.4 Hz, 4H), 3.64 (br d, J = 4.4 Hz, 4H), 3.45 (d, J = 9.6 Hz, 1H), 3.23−3.12 (m, 1H), 2.55 (dd, J = 17.2, 7.6 Hz, 1H), 2.33 (dd, J = 17.2, 10.4 Hz, 1H), 1.27 (t, J = 7.2 Hz, 6H). MS (ES) *m*/*z* 352.45 (MH^+), 349.99 $(M - H)^-$.

Morpholin-4-yl-(5-morpholin-4-yl-cyclohexa-1,3-dienyl)-methanone (13f). Yield: 2.9 mg (15%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.15 (dd, J = 9.6, 5.6 Hz, 1H), 6.00 (d, J = 3.6 Hz, 1H), 5.89 (dd, J = 9.6, 4.4 Hz, 1H), 3.75−3.54 (m, 8H), 3.18 (t, J = 4.8 Hz, 1H), 2.75−2.65 (m, 1H), 2.65−2.50 (m, 4H), 2.50−2.38 (m, 1H). MS (ES) *m*/*z* 279.12 (MH^+).

(5-*tert*-Butoxy-cyclohexa-1,3-dienyl)-morpholin-4-yl-methanone (13g). Yield: 7.1 mg (39%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (br s, 1H), 6.11−6.05 (m, 1H), 5.90 (dd, J = 9.2, 4.8 Hz, 1H), 4.22−4.16 (m, 1H), 3.75−3.53 (m, 8H), 2.65 (dd, J = 18.0, 7.2 Hz, 1H), 2.46 (dd, J = 18.0, 5.6 Hz, 1H), 1.19 (s, 9H). MS (ES) *m*/*z* 266.03 (MH^+).

Morpholin-4-yl-(5-phenylsulfanyl-cyclohexa-1,3-dienyl)-methanone (13h). Yield: 10.1 mg (49%); purity (ELS) >99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46−7.36 (m, 3H), 7.34−7.22 (m, 2H), 6.18−6.08 (m, 2H), 6.08−6.01 (m, 1H), 4.16−4.11 (m, 1H), 3.65 (br s, 8H), 2.90 (dd, J = 18.4, 6.4 Hz, 1H), 2.64 (dd, J = 18.4, 2.4 Hz, 1H). MS (ES) *m*/*z* 302.08 (MH^+), 324.01 (MNa^+).

Morpholin-4-yl-(5-*p*-tolylamino-cyclohexa-1,3-dienyl)-methanone (13i). Yield: 9.3 mg (46%); purity (ELS) 73%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.88 (d, J = 8.0 Hz, 2H), 6.61 (d, J = 8.0 Hz, 2H), 6.24−6.17 (m, 1H), 6.14 (d, J = 4.8 Hz, 1H), 5.97 (dd, J = 9.6, 3.6 Hz, 1H), 3.58 (br s, 9H), 2.80−2.35 (m, 2H), 2.22 (s, 3H). MS (ES) *m*/*z* 299.18 (MH^+).

(5-Methoxy-cyclohexa-1,3-dienyl)-morpholin-4-yl-methanone (13j). Yield: 6.3 mg (41%); purity (UV) 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (dd, J = 9.6, 5.6 Hz, 1H), 6.12 (d, J = 4.8 Hz, 1H), 6.08 (dd, J = 9.6, 4.8 Hz, 1H), 3.96 (q, J = 5.6 Hz, 1H), 3.74−3.55 (m, 8H), 2.65 (d, J = 6.0 Hz, 2H). MS (ES) *m*/*z* 223.98 (MH^+), 246.02 (MNa^+).

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