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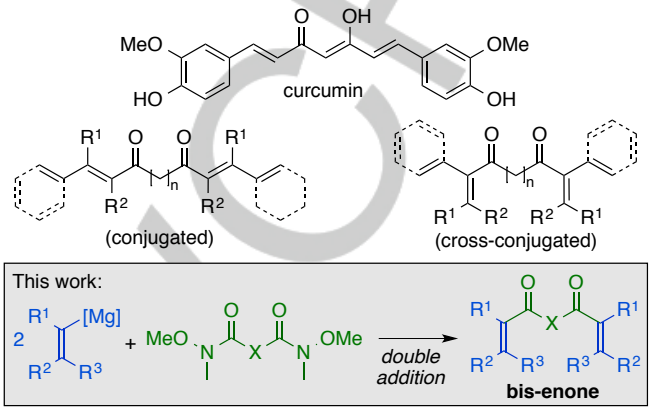
Synthesis of α,ω-Bis-Enones by the Double Addition of Alkenyl Grignard Reagents to Diacid Weinreb Amides

Stefan Wiesler,[a] Michael A. Bau,[a] Thomas Niepel,[a] Sara L. Younas,[a] Hieu-Trinh Luu,[a] and Jan Streuff*[a]

Abstract: An efficient double addition of substituted alkenylmagnesium bromides to bis-Weinreb amides has been developed, giving α,ω-bis-enones that are building blocks for certain drugs and polymers. Furthermore, reliable protocols for the preparation of the required substituted alkenyl magnesium reagents from substituted non-activated alkenyl bromides are reported. The double addition is demonstrated on 25 examples, including enantiopure as well as conjugated and cross-conjugated bis-enones. The addition to a cyclohexane-1,2-dicarboxamide was found to lead to a selective mono addition, giving access to cyclohexyl γ-ketoamides that are core motifs of several pharmaceutical agents and promising drug candidates.



Scheme 1. Curcumin and examples of conjugated and cross-conjugated α,ω-bisenones (top). Envisioned double-Grignard addition to bis-Weinreb amides (bottom).

Introduction

Symmetric α,ω-bisenones have been of interest to researchers over the past decades. Curcumin and related compounds belonging to the family of the bis-chalcones, have been heavily examined for potential biological properties, although it has recently been uncovered that curcumin returns deceptively false results (Scheme 1).[1,2] Furthermore, bis-chalcones are also widely used as photosensitizers and precursors of organic dyes.[3] While these compounds can be easily accessed via aldol condensation reactions, the corresponding cross-conjugated bis-enones exhibit a much higher reactivity and tendency to polymerization and, hence, have been much less studied. Still, such cross-conjugated bis-enones are of interest as precursors in organic synthesis and polymer chemistry.[4]

More general methods to access bis-enone compounds are scarce and do not always give satisfying results.[5] One approach to double unsaturated 1,4-diketones with a saturated C_2-tether are oxidative coupling protocols, which unfortunately cannot be transferred to the preparation of linked enones having a longer connecting chain.[6] An alternative is the 1,2-addition of alkenyllithium and Grignard reagents to α,ω–diacid derivatives.[4,7] But since the preparation of Grignard reagents from non-activated and substituted alkenylbromides is not always straightforward,[7a] such double-additions have only been reported with commercially available vinyl- or 2-propenyl-magnesium bromide solutions and in typically low to moderate yields.[4,7b,c] In this context, it should be noted that the addition of aryl or alkyl Grignard and lithium reagents to bis-Weinreb amides has been reported.[8,9] Recent studies further show that such nucleophilic acyl substitution reactions can be even carried out in protic media under air, efficiently suppressing the over-addition in the addition of organometallic reagents to simple *N,N*-dialkylamides.[10]

We have recently published a broadly applicable synthesis of chiral *ansa*-metallocenes, which featured the double addition of alkenyl Grignard reagents to α,ω-bis-Weinreb amides for the formation of the key bisenone intermediates.[11] Herein, the development and scope of this double addition is reported, including reliable methods for the preparation of substituted alkenyl Grignard reagents.

Results and Discussion

The alkenyl bromides for the formation of the Grignard reagents were prepared from the corresponding ketones by treatment with bromine, triphenylphosphite and triethylamine, if not noted otherwise.[12] The bis-Weinreb amides were conveniently synthesized either from the diesters by reaction with *N*-methoxy-*N*-methylamine hydrochloride and trimethylaluminum, or by a T3P-promoted amide formation using the free diacid, or from the diacid chloride, HN(Me)OMe•HCl and triethylamine.[13,14]

In order to achieve good yields for the envisioned double addition reaction, the procedure for the formation of the required Grignard reagents was optimized using cyclohexenyl bromide (**1**) as test substrate.[15] In Table 1, the results of the condition screening are given, each entry showing the result of the largest scale reaction as indicated. In detail, common conditions using Mg^0 turnings and 5 mol-% of iodine for activation gave

[a] *S. Wiesler, M. A. Bau, T. Niepel, S. L. Younas, H.-T. Luu, Dr. J. Streuff*
Institut für Organische Chemie
Albert-Ludwigs-Universität Freiburg
Albertstr. 12, 79104 Freiburg im Breisgau, Germany
E-mail: jan.streuff@ocbc.uni-freiburg.de
Homepage: https://portal.uni-freiburg.de/streuff

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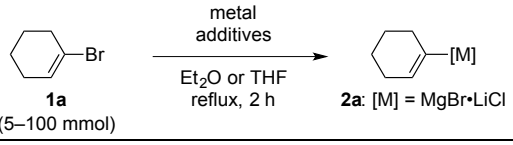
Table 1. Optimization of the Grignard reagent formation.



1a (5–100 mmol) **2a**: [M] = MgBr•LiCl

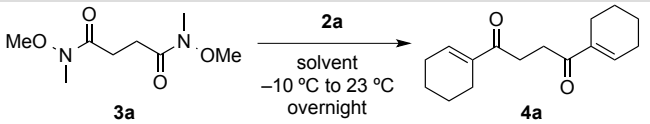
Entry	Metal (equiv)	Additives (equiv)	Solvent	[M] =	c / M[a] (c_{max})[b]	Conversion / %[c]
1	Mg^0 turnings (1.00)	I_2 (0.05)	THF	MgBr	0.34–0.40 (0.80)	43–50[d,e]
2	Mg^0 turnings (1.00)	I_2 (0.05), $(BrCH_2)_2$ (0.05), LiCl (1.25)	THF	MgBr•LiCl	0.42–0.63 (0.80)	53–79[f]
3	Mg^0 powder (2.50)	TMSCl (0.01), $(BrCH_2)_2$ (0.05), LiCl (1.25)	THF	MgBr•LiCl	0.28 (0.40)	70[g]
4	Mg^0 powder (2.50)	TMSCl (0.01), $(BrCH_2)_2$ (0.10), LiCl (1.25)	THF	MgBr•LiCl	0.35 (0.40)	88[h]
5	Mg^0 powder (2.50)	TMSCl (0.01), $(BrCH_2)_2$ (0.05), LiCl (1.25)	Et_2O	MgBr•LiCl	0.06 (0.40)	16[g]
6	*i*PrMgCl•LiCl	none	THF	MgCl•LiCl	-- (0.40)	0[g]
7	Zn^0 powder (1.50)	TMSCl (0.01), $(BrCH_2)_2$ (0.05), LiCl (1.50)	THF	ZnBr•LiCl	-- (0.40)	0[g]

[a] Determined by titration against 2-hydroxybenzaldehyde-*N*-phenylhydrazone.[16] [b] c_{max} = theoretical maximum concentration. [c] Determined from c/c_{max}. [d] Significant Wurtz-coupling was observed. [e] 10 mmol scale. The range in yield of several reactions is given. [f] 100 mmol scale. The range in yield of several reactions is given. [g] 5 mmol scale. [h] 80 mmol scale.

cyclohexenylmagnesium bromide in yields of only 43–50%, the main issue being the formation of undesired byproducts (entry 1).[17] The reaction was more efficient in the presence of dry lithium chloride, which is known to facilitate Grignard reagent formation.[18] Small amounts of dibromoethane and iodine further activated the magnesium metal and enabled the visualization of the reaction initiation by the vanishing iodine color (entry 2).[19] This protocol gave good and reproducible concentrations of the alkenyl magnesium bromide lithium chloride **2a** in a range of c = 0.42–0.63 M (theoretical maximum concentration: 0.8 M). As an alternative procedure, an excess of Mg^0 powder in combination with lithium chloride and chlorotrimethylsilane / dibromoethane for the activation was successful (entry 3). While the concentrations of the reagent prepared this way varied on small scale, this protocol gave reliably high concentrations and yields of **2a** on a 50–80 mmol scale (up to 88%, entry 4). In either case, using THF as solvent for the preparation of **2a** was crucial, since the conversion was poor in diethyl ether (entry 5). Furthermore, the purity of alkenyl bromide **1a** was important for achieving a high concentration of the reagent. We also briefly tested alternative conditions via transmetallation from *i*PrMgCl•LiCl (entry 6) and the formation of the corresponding oranozinc species (entry 7), but the desired organometallic reagents were not formed.[7a,20] Following the conditions of entries 2 (designated method A) or 4 (designated method B), non-activated substituted alkenyl bromides could be efficiently transformed into the corresponding alkenylmagnesium bromide lithium chlorides with good conversion. The resulting solutions were of suitable molarities for the subsequent double 1,2-addition reactions.

We then investigated the addition of **2a** to the bis-Weinreb amide of succinic acid (**3a**) as limiting reagent. The reaction required a careful optimization in order to achieve good results for the double addition and, in particular, the choice of solvent was important (Table 2). It was found that pure THF as solvent was insufficient (entry 1). Preparing the organomagnesium reagent in THF and adding it to a solution of the bis-Weinreb amide in the same volume of diethyl ether, however, gave satisfactory results (entry 2). The yield of diketone **4a** was further increased by a higher concentration of the organomagnesium reagent and by increasing the amount to three equivalents (based on **3a**, = 1.5 equiv/amide). This way, diketone **4a** was received in 70% yield on an 8 mmol scale (entry 3). Importantly, no mono addition product was observed

Table 2. Optimization of the addition of **2a** to **3a**.

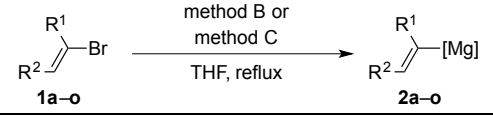


3a **4a**

Entry	[**2a**] / M	Equiv **2a**[a]	**3a** dissolved in	Yield / %[b]
1	0.21 in THF	2.2	THF	15
2	0.21 in THF	2.4	Et_2O (THF:Et_2O = 1:1)[c]	54
3	0.37 in THF	3.0	Et_2O (THF:Et_2O = 1:1)[c]	70[d]
4	0.06 in Et_2O	3.0	neat	99

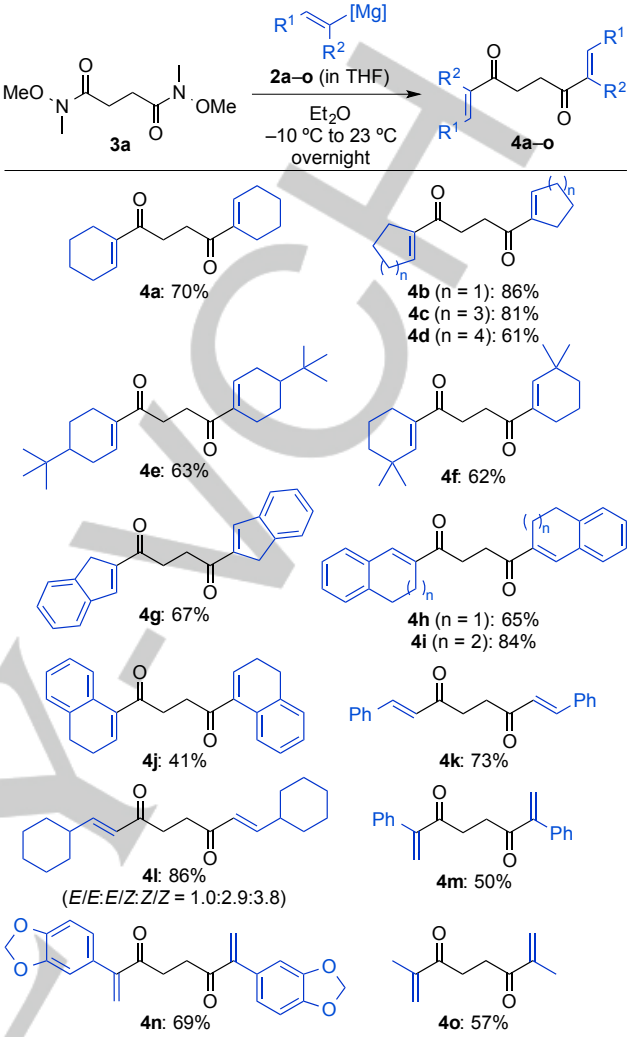
[a] Based on 3a. [b] Yield of isolated product. [c] Final THF/Et_2O ratio (v/v) after the addition. [d] Reaction on an 8 mmol scale.

Table 3. Grignard reagent preparation.



Entry	Reagent	Method[a]	Additives[b]	[2] / M (c_{max})[c,d]
1	**2a**	B	TMSCl, $(BrCH_2)_2$	0.30–0.40 (0.41)
2	**2b**	B	TMSCl, $(BrCH_2)_2$	0.35–0.45 (0.70)
3	**2c**	B	TMSCl, $(BrCH_2)_2$	0.07–0.21 (0.41)
4	**2d**	B	TMSCl, $(BrCH_2)_2$	0.12–0.33 (0.41)
5	**2e**	A	I_2, $(BrCH_2)_2$	0.18 (0.50)
6	**2f**	A	I_2, $(BrCH_2)_2$	0.38 (0.93)
7	**2g**	A	I_2, $(BrCH_2)_2$	0.27 (0.53)
8	**2h**	B	TMSCl, $(BrCH_2)_2$	0.24 (0.41)
9	**2i**	C	-	0.78–0.81 (1.00)
10	**2j**	B	TMSCl, $(BrCH_2)_2$	0.41–0.43 (0.43)[e]
11	**2k**	C	-	0.56 (1.00)
12	**2l**	C	-	0.50–0.68 (1.00)
13	**2m**	A	I_2, $(BrCH_2)_2$	0.23 (0.56)
14	**2n**	A	I_2, $(BrCH_2)_2$	0.17 (0.40)
15	**2o**	A	I_2, $(BrCH_2)_2$	0.40 (0.50)

[a] Method A: see Table 1, entry 2. Method B: see Table 1, entry 4. Method C: Mg^0 turnings (2.5 equiv), alkenyl bromide (1.0 equiv), THF, reflux, 2 h. [b] The additives were added in quantities of 0.3–10 mol-% to start and maintain the Grignard formation. See the experimental details. [c] Determined by titration against 2-hydroxybenzaldehyde-*N*-phenylhydrazone. [d] c_{max} = theoretical maximum concentration. [e] Using method C, reagent **2j** was formed in a concentration of c = 0.76 M (c_{max} = 1.00 M).



Scheme 2. Double-addition of various Grignard reagents to bis-Weinreb amide **3a**.

under these conditions. A longer reaction time of 72 h did not further improve the reaction outcome. A reaction run in diethyl ether as sole solvent, which was carried out by the addition of an ethereal solution of **2a** to neat **3a**, was quantitative (entry 4). But since the formation of Grignard reagent **2a** was inferior in diethyl ether, the conversion based on alkenyl bromide was low, resulting in the impracticable requirement of a large excess of the bromide. A corresponding addition of **2a** prepared in THF to neat **3a** gave only 52% yield, further showing the importance of Et_2O as co-solvent. Overall, entry 3 provided the best conditions for the addition step.

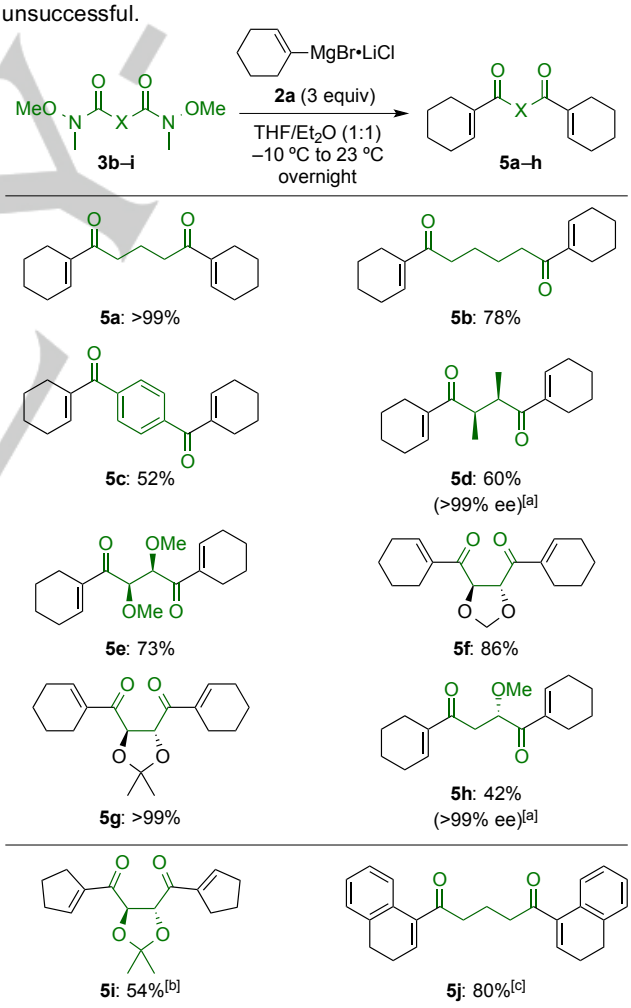
One possible origin for the positive effect of Et_2O on the reaction yield and the high chemoselectivity towards the double addition was the poor solubility of **3a** in Et_2O. The mono addition intermediate, on the other hand, was expected to be more soluble and, hence, the addition to this intermediate would be preferred over the addition to **3a**.

To demonstrate the scope of the double addition, several structurally diverse alkenyl Grignard reagents were prepared. Table 3 shows the concentrations of the reagents that were typically prepared on a 40–70 mmol scale. Several alkenyl bromides, in particular those activated by conjugation, were sufficiently reactive to form the Grignard reagent without the addition of lithium chloride or other additives (designated method C). The addition of each freshly prepared reagents to **3a** then led to a number of substituted bisenones (Scheme 2). In detail, the reaction was tested for five- to eight-membered alkenylmagnesium reagents resulting in isolated yields of 61–86% (**4a–d**). A 4-*tert*-butyl substituted cyclohexenyl Grignard reagent (**2e**) underwent the double addition in 63% yield giving bisenone **4e** and a gem-dimethyl substituted cyclohexene motif could be double-added in 62% yield to give **4f**. It was then tested whether a conjugation of the alkene with an aromatic ring was

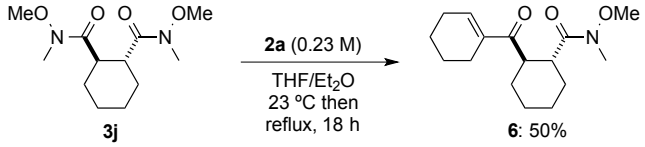
tolerated. Gratifyingly, the addition of 2-indenylmagnesium bromide lithium chloride (**2g**) took place and product **4g** was formed in 67% yield. The fully conjugated bis-enol tautomer of **4g** was not observed. This was also the case for products **4h** and **4i** that were obtained in 65% and 84% yield. The corresponding organomagnesium precursors (**2h**,**i**) were prepared from α-tetralone and benzosuberone, respectively, in a three-step sequence. In analogy, the cross-conjugated bisenone **4j** was prepared, albeit in a 41% yield. A plausible cause for this reduced outcome was the increased steric demand of the Grignard reagent. The formation of the aryl-conjugated Grignard reagents was greatly facilitated and occurred readily in presence of Mg^0 turnings without further additives (method C). However, in the case of **2j**, a higher conversion of the alkenyl bromide (up to >99%) could be achieved using method B (entry 10). Next, acyclic alkenyl-Grignard reagents were examined. The linear phenyl- and cyclohexyl-substituted bisenones **4k** and **4l** bearing 1,2-disubstituted alkene moieties were prepared from the corresponding β-styryl and 2-cyclohexylethenyl reagents **2k,l** in good to excellent yield (73% and 86%). Since **2l** was employed as a mixture of double bond isomers, **4l** was received as a 1.0:2.9:3.8 (*E*/*E*:*E*/*Z*:*Z*/*Z*) stereoisomeric mixture. For characterization purposes, the isomers were successfully separated by chromatography. For the preparation of cross-conjugated bisenones, the Grignard reagents **2m**–**o** were added to **3a** and, to our delight, the products **4m**–**o** could be isolated in moderate to good yields. However, these products were found to be prone to polymerization, which required a rapid purification and characterization. In the cases of **4m** and **4o**, this polymerization tendency led to the slightly reduced yields of 50% and 57%. Along these lines, it should be noted that the α- and β-styryl based bromoalkene precursors for the arene-conjugated Grignard reagents, in particular **1j**,**m**,**n**, were also found to polymerize easily. The corresponding bromoalkene precursors had therefore to be used immediately after their preparation.

The scope of the bis-Weinreb amide was explored as well and a number of aliphatic, aromatic, and chiral bis-amides were prepared from the corresponding readily-available diacids (Scheme 3). Here, elongating the central carbon chain to three and four carbons led to high yields of >99% and 78% (**5a**,**b**). A terephthalic acid derivative was also smoothly converted into the bisenone product (**5c**). Importantly, the enantiopure 2,3-dimethyldiacid derivative **3e** could be converted in 60% yield into bisenone **5d** without any loss of enantiopurity. This encouraged us to prepare further enantiopure 1,4-bisenones using tartaric and malic acid-derived building blocks (**5e**–**h**). The dimethoxy derivative **3f**, prepared from a tartrate by methyl ether formation with silver(I) oxide and subsequent amide formation, gave **5e** in 73% yield. Particularly good yields of 86% and >99% were achieved for the cyclic acetal-containing products (**5f**,**g**). The double addition to the malic acid bisamide **3i** gave **5h** in a moderate yield of 42%. For this product, it was confirmed again that the reaction occurred without any erosion of the enantiopurity. Finally, we prepared bis-enones **5i** and **5j** in 54% and 80% yields by adding cyclopentenyl and dihydroindenyl reagents **2b** and **2j** to bis-Weinreb amides **3h** and **3b**, respectively. Hence, simultaneous variations of both reagents were tolerated as well.

As an interesting exception, cyclohexane-1,2-dicarboxamide **3j** turned out to be a poor substrate for the double addition. Instead, a selective formation of the mono addition product *rac*-**6** took place, which was isolated in 50% yield (Scheme 4). Moreover, no reaction took place when the isolated mono addition product *rac*-**6** was resubmitted to the 1,2-addition conditions. We hypothesized that an unusually stable coordination complex involving both carbonyl groups may be formed in these cases, hampering the second addition of the organometallic reagent. This selective mono addition may be a useful alternative for the preparation of analogous cyclohexyl γ-ketoamides.[21] These are central motifs of compounds with various biological activities, ranging from potential agents against chagas disease and hepatitis C, orexin receptor and MCH antagonists, neuroleptic drug models, as well as FLAP and Pin1 inhibitors, for example.[22] Attempts to further explore the selective mono addition or even a sequential addition of two different Grignard reagents to bis-Weinreb amide **3a** were unsuccessful.



Scheme 3. Addition of **2a** to various bis-Weinreb amides. [a] Determined by chiral HPLC. [b] Prepared using **2b** and **3h**. [c] Prepared using **2j** and **3b**.



Scheme 4. Observed selective mono addition to a substrate with both amides in close proximity.

Conclusions

A double Grignard addition strategy for the synthesis of symmetrical α,ω-bis-enones has been developed. The method has been demonstrated on the synthesis of a range of aliphatic, conjugated, and cross-conjugated α,ω-bisenones and it can be applied to enantiopure diacid building blocks without a loss of enantiopurity. In contrast, the addition of cyclohexenyl magnesium reagent **2a** to a substrate with both amide functionalities in close proximity leads to a selective mono addition, giving the corresponding γ-ketoamide. Since the products obtained from these double- and mono addition reactions are of potential interest as building blocks for biological and polymer chemistry as well as dendralene synthesis, the methods reported herein could find future applications in these areas. The herein reported optimized protocols for the formation of substituted alkenyl Grignard reagents from the corresponding bromoalkenes may facilitate the future use of such substituted alkenylmagnesium reagents in synthesis in general.

Experimental Section

Materials and methods. All reactions have been carried out in flame-dried Schlenk flasks equipped with a magnetic stir bar under argon atmosphere (argon 5.0) using absolute solvents unless noticed otherwise. For reactions run under refluxing conditions, the reaction vessel was equipped with an appropriate reflux condenser. Absolute THF was dried over potassium under argon atmosphere and freshly distilled prior to use. Absolute Et_2O was obtained from a M. Braun Solvent Purification System 800 equipped with activated molecular sieves (MS 2Å). Ethyl acetate and cyclohexane for column chromatography were purchased in technical quality and purified by destillation with a rotary evaporator. 2-Bromoindene (**1g**) was purchased from ChemPur, 2-bromopropene (**1o**) was purchased from AlfaAesar. *N,O*-Dimethylhydroxylamine hydrochloride was purchased from ChemPur and was freshly crystallized from chloroform. Triethylamine was purified by distillation over calcium hydride. Propylphosphonic anhydride (T3P) was purchased from ChemPur. Glutaryl chloride was purchased from ChemPur. Lithium chloride was purchased from VWR. Magnesium powder was purchased from Grüssing and magnesium turnings were purchased from Roth. All other chemicals were purchased from Aldrich, AlfaAesar, or Acros and used as received unless noted otherwise. An IKAmag temperature modulator in combination with an oil bath was used to control the reaction temperatures. NMR spectra were recorded on a Bruker Avance III 300 (300 MHz) or a Bruker Avance II 400 (400 MHz and 100 MHz) spectrometer and reported to residual $CHCl_3$ (^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm), C_6D_5H (^{1}H: δ = 7.16 ppm, ^{13}C: δ = 128.00 ppm), or acetone-d_5 (^{1}H: δ = 2.05 ppm, ^{13}C: δ = 29.84 ppm). The following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, br = broad signal. IR spectra were recorded on a Thermo Scientific Nicolet iS10 FT-IR spectrometer equipped with a diamond ATR unit and are reported in frequency of absorption. Low- and high-resolution mass analyses were performed by the service department at the Institute for Organic Chemistry and Biochemistry, Freiburg University using a Thermo Finnigan TSQ 700 for electron impact ionization (EI) at 70 eV, 200 °C. High resolution mass analyses (HRMS) were carried out on a Thermo Exactive spectrometer with Orbitrap-Analyzer using atmospheric pressure chemical ionization (APCI) or electron spray ionization (ESI). HPLC analyses were carried out by the HPLC Analytics Service of the Institute of Organic Chemistry of the University of Freiburg using a Merck Hitachi LaChrom HPLC system.

Preparation of alkenyl bromides 1a–o

1-Bromocyclohex-1-ene (1a). Synthesized from cyclohexanone (19.6 g, 20.7 ml, 200 mmol) according to a literature procedure in 87% yield (28.1 g, 174.5 mmol).[12] The analytical data matched the previously published values. This compound is also commercially available. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.58-1.64 (m, 2H), 1.71-1.77 (m, 2H), 2.05-2.10 (m, 2H), 2.36-2.43 (m, 2H), 6.03 (dddd, *J* = 1.8, 1.8, 4.0, 4.0 Hz, 1H).

1-Bromocyclopent-1-ene (1b). Synthesized from cyclopentanone (16.8 g, 17.7 ml, 200 mmol) according to a literature procedure in 43% yield (12.5 g, 85.0 mmol).[12] The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.91-2.01 (m, 2H), 2.27-2.35 (m, 2H), 2.52-2.60 (m, 2H), 5.80-5.84 (m, 1H).

1-Bromocyclohept-1-ene (1c). Synthesized from cycloheptanone (22.4 g, 23.6 ml, 200 mmol) according to a literature procedure in 96% yield (33.6 g, 192 mmol).[12] The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.53-1.76 (m, 6H), 2.04-2.11 (m, 2H), 2.66-2.70 (m, 2H), 6.20 (tt, *J* = 0.7, 6.6 Hz, 1H).

1-Bromocyclooct-1-ene (1d). Synthesized from cyclooctanone (25.2 g, 200 mmol) according to a literature procedure in 75% yield (28.3 g, 150 mmol).[12] The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.50-1.56 (m, 6H), 1.59-1.68 (m, 2H), 2.07-2.13 (m, 2H), 2.59-2.63 (m, 2H), 6.03 (t, *J* = 8.5 Hz, 1H).

1-Bromo-4-(*tert*-butyl)cyclohex-1-ene (1e). Synthesized from 4-(*tert*-butyl)cyclohexanone (3.09 g, 20.0 mmol) following the literature for **1a**–**d** in 90% yield (3.91 g, 18.0 mmol).[12] The analytical data matched the previously published values.[23] ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 0.89 (s, 9H), 1.26-1.47 (m, 2H), 1.83-1.93 (m, 2H), 2.07-2.17 (m, 1H), 2.46-2.50 (m, 2H), 6.02-6.05 (m, 1H).

2,2-Dimethylcyclohexanone (7). 2-Methylcyclohexanone (39.3 g, 350 mmol) was methylated following a literature procedure.[24] A mixture of **7**, 2,6-dimethylcyclohexanone, 2,2,6-trimethylcyclohexanone, and 2,2,6,6-tetramethylcyclohexanone was received (>99%). Ketone **7** and unreacted 2-methylcyclohexanone were then separated from the other polymethylated ketones following a literature procedure consisting of a selective formylation, an acid-base extraction, and a deformylation. Fractional distillation under reduced pressure (bp 60 °C at *p* = 19 mbar) using a 20 cm Vigreux column gave pure **7** in 23% overall yield (10.2 g, 80.8 mmol).[25] The analytical data matched the previously published values. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.11 (s, 6H), 1.63-1.68 (m, 2H), 1.70-1.77 (m, 2H), 1.79-1.86 (m, 2H), 2.37-2.43 (m, 2H).

6-Bromo-2,2-dimethylcyclohexanone (8). This compound was literature-known but no preparation procedure or characterization data could be found.[26] A flame-dried, argon-filled 500 ml Schlenk flask equipped with a magnetic stir bar was charged with 2,2-

dimethylcyclohexanone (**7**) (2.52 g, 20.0 mmol, 1.0 equiv) followed by addition of CH_2Cl_2 (240 ml) and MeOH (100 ml). Stirring was started and tetrabutylammonium tribromide (10.61 g, 22.0 mmol, 1.1 equiv) was added at room temperature. The mixture was further stirred until the orange color turned yellow (about 2.5 h). The solvent was removed under reduced pressure and the residue was extracted with Et_2O (4 × 80 ml). The ether extracts were combined, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The product was received as a colorless solid in 94% yield (3.84 g, 18.7 mmol) and it was used without further purification. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.21 (s, 3H), 1.21 (s, 3H), 1.67 (ddd, *J* = 4.4, 11.9, 13.5 Hz, 1H), 1.75-1.97 (m, 3H), 2.11 (ddd, *J* = 4.4, 11.9, 13.5 Hz, 1H), 2.54-2.62 (m, 1H), 4.87 (dd, *J* = 5.9, 11.9 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.13, 25.45, 26.84, 39.77, 40.87, 46.64, 54.09, 206.6. MS (EI, 70 eV): m/z (%) = 204.0 $[M]^+$ (10), 125.1 (11), 97.1 (56), 81.1 (19), 69.1 (51), 55.1 (100), 41.1 (88), 39.0 (67). HRMS (pos. APCI) calcd for $C_8H_{17}ONBr^+$ $[M+NH_4]^+$: 222.0488, found: 222.0486. IR (ATR): ν [cm^{-1}] = 2941, 2868, 1723, 1452, 1386, 1367, 1300, 1202, 1079, 1052, 991, 942, 863, 752, 711.

***cis*-6-Bromo-2,2-dimethylcyclohexanol (9a) and *trans*-6-Bromo-2,2-dimethylcyclohexanol (9b) (4:1 mixture).** These compounds were literature-known but no preparation procedure or characterization data could be found.[26] A flame-dried, argon-filled 250 ml Schlenk flask equipped with a magnetic stir bar was charged with a solution of 6-bromo-2,2-dimethylcyclohexanone (**8**) (5.01 g, 24.4 mmol, 1.0 equiv) in THF (25.0 ml) and MeOH (14.4 ml). The solution was cooled to 0 ºC and $NaBH_4$ (0.92 g, 24.4 mmol, 1.0 equiv) was added in small portions. After stirring the reaction mixture for 15 min at 0 ºC, it was allowed to warm to room temperature and then stirred for additional 40 min. Then, aq. HCl (1 M, 100 ml) was added to the mixture. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 ml). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The bromohydrins **9a** and **9b** were isolated as a 4:1 *cis*/*trans* mixture in form of a colorless oil in 91% yield (4.60 g, 22.2 mmol). The NMR data is reported for the **9a**/**9b**, 4:1 mixture. ^{1}H NMR (500.2 MHz, $CDCl_3$): δ = 0.91 (s, 0.6H, trans), 0.96 (s, 2.4H, cis), 1.05 (s, 2.4H, cis), 1.08 (s, 0.6H, trans), 1.12-1.16 (m, 0.8H, trans), 1.44-1.66 (m, 3.2H, cis), 1.82-1.91 (m, 0.2H, trans) , 1.93-1.98 (m, 0.8H, cis), 2.06-2.14 (m, 1.6H, cis), 2.31-2.36 (m, 0.4H, trans), 3.32 (dd, *J* = 2.3, 10.1 Hz, 0.2H, trans), 3.52 (s, 0.8H, cis), 4.14 (ddd, *J* = 4.6, 10.1, 12.5 Hz, 0.2H, trans), 4.56 (ddd, *J* = 2.3, 4.6, 12.5 Hz, 0.8H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 18.07, 22.97, 23.09, 24.54, 28.66, 29.91, 31.09, 31.45, 37.13, 37.31, 37.87, 39.16, 58.74, 60.54, 77.82, 81.83. MS (CI): m/z (%) = 224.0 $[M+NH_4]^+$ (16), 144.1 (18), 126.1 (11), 109.1 (100). HRMS (pos. APCI) calcd for $C_8H_{19}ONBr^+$ $[M+NH_4]^+$: 224.0645, found: 224.0639. IR (ATR): ν [cm^{-1}] = 2938, 2866, 1449, 1351, 1278, 1226, 1200, 1177, 1116, 1008, 985, 957, 937, 913, 846, 699.

1-Bromo-3,3-dimethylcyclohexene (1f). This compound was literature-known but no preparation procedure or characterization data could be found.[26] It was synthesized following a modified dehydration procedure from the literature as follows.[27] A flame-dried, argon-filled 1000 ml Schlenk flask equipped with a magnetic stir bar was charged with a solution of *cis*/*trans* 6-bromo-2,2-dimethylcyclohexanol (**9a**/**9b**, 4:1) (4.60 g, 22.2 mmol, 1.0 equiv) in CH_2Cl_2 (222 ml). Stirring was started and the mixture was cooled to 0 °C. DMAP (270 mg, 2.22 mmol, 10 mol-%) and Tf_2O (6.89 g, 24.4 mmol, 1.1 equiv) were added and stirring was continued for 10 min. Then, pyridine (8.96 ml, 111 mmol, 5.0 equiv) was added and the mixture was allowed to slowly warm to room temperature. The reaction was stirred for an additional 16 h and then quenched by addition of H_2O (300 ml). After the transfer to a separation funnel, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 80 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (pentane) and obtained as a colorless liquid in 51% yield (2.14 g, 11.3 mmol). R_f (pentane) = 0.8. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.01 (s, 6H), 1.41-1.44 (m, 2H), 1.71-1.78 (m, 2H), 2.37 (dt, *J* = 1.8, 6.3 Hz, 2H), 5.81 (t, *J* = 1.8 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.61, 29.45, 35.28, 35.58, 35.96, 121.14, 138.84. MS (EI, 70 eV): m/z (%) = 187.9 $[M]^+$ (6), 109.0 (100), 93.0 (90), 81.0 (28), 77.0 (31), 67.0 (82), 53.0 (8), 41.0 (7), 39.0 (7). HRMS (pos. APCI) calcd for $C_8H_{12}OBr^+$ $[M+O–H]^+$: 203.0066, found: 203.0067. IR (ATR): ν [cm^{-1}] = 2936, 2859, 1631, 1494, 1449, 1431, 1386, 1342, 1306, 1272, 1252, 1241, 1132, 1112, 972, 928, 891, 852, 829, 740, 695. The product was found to be unstable under the conditions for the high-resolution mass analysis (APCI and ESI conditions). The measured molecule mass matched the corresponding enone (e.g. 2-bromo-6,6-dimethylcyclohex-2-en-1-one), which was probably formed by an oxidation of the allylic CH_2 group to a ketone.

3-Bromo-1,2-dihydronaphthalene (1h). Synthesized from α-tetralone (8.77 g, 60.0 mmol) following a three-steps literature procedure in 87% yield (10.9 g, 52.1 mmol).[28] The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.75-2.81 (m, 2H), 2.96 (t, *J* = 8.3 Hz, 2H), 6.80 (s, 1H), 6.95-7.01 (m, 1H), 7.06-7.20 (m, 3H).

8-Bromo-6,7-dihydro-5*H*-benzo[7]annulene (1i).[11] This compound was literature known, but the characterization data was incomplete.[29] It was synthesized from 1-benzosuberone (20.8 g, 130 mmol) in analogy to **1h** via the same literature procedure in 95% yield (27.5 g, 123.3 mmol, 3 steps).[28] ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.97-2.02 (m, 2H), 2.87-2.89 (m, 2H), 2.96 (t, *J* = 6.5 Hz, 2H), 7.01 (s, 1H), 7.10-7.22 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.31, 35.22, 43.04, 126.32, 127.47, 128.56, 129.30, 131.00, 133.26, 134.39, 141.14. MS (EI, 70 eV): m/z (%) = 224.0 $[M]^+$ (35), 222.0 (38), 143.1 (100), 128.1 (61), 115.0 (33), 89.0 (5). HRMS (pos. APCI) calcd for $C_{11}H_{11}Br^+$ $[M]^+$: 222.0039, found: 222.0036. IR (ATR): ν [cm^{-1}] = 3056, 3017, 2929, 2859, 1633, 1572, 1491, 1446, 1421, 1378, 1343, 1255, 1197, 1161, 1110, 1076, 1038, 938, 883, 866, 856, 832, 747, 726, 594, 572.

4-Bromo-1,2-dihydronaphthalene (1j). Synthesized from 1-tetralone (29.2 g, 200 mmol) according to a literature procedure in 75% yield (31.4 g, 150.2 mmol).[23] The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.35-2.42 (m, 2H), 2.86 (dd, *J* = 8.1, 8.1 Hz, 2H), 6.46 (dd, *J* = 4.8, 4.8 Hz, 1H), 7.10-7.13 (m, 1H), 7.18-7.29 (m, 2H), 7.57 (dd, *J* = 1.7, 7.5 Hz, 1H).

(*E*)-(2-Bromovinyl)benzene (1k). Synthesized from (*E*)-cinnamic acid (1.48 g, 10.0 mmol) according to a literature procedure in 76% yield (1.39 g, 7.59 mmol).[30] The analytical data matched previously published values.[23] ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 13.9 Hz, 1H), 7.12 (d, *J* = 13.9 Hz, 1H), 7.27-7.37 (m, 5H).

(2-Bromovinyl)cyclohexane (1l), *E*/*Z* mixture. A flame-dried, argon-filled 500 ml Schlenk flask equipped with a magnetic stir bar was charged with (bromomethyl)triphenylphosphonium bromide (17.4 g, 40.0 mmol, 2.0 equiv) and THF (130 ml). The resulting suspension was stirred, cooled to –78 ºC, and KO*t*-Bu (4.04 g, 36.0 mmol, 1.8 equiv) was added. After 30 min, a solution of cyclohexanecarbaldehyde (2.24 g, 20.0 mmol, 1.0 equiv) in THF (32 ml) was added dropwise to the yellow reaction mixture. The cooling bath was slowly warmed to –20 ºC (over 2 h). The reaction mixture was diluted with Et_2O (160 ml) and filtered over silica (hexanes/EtOAc, 9:1). The solvent was removed under reduced pressure and purification by column chromatography (hexanes) gave **1l** as a mixture of *E*/*Z* isomers (1:1.6) as a colorless liquid in 56% yield (2.12 g, 11.19 mmol). The NMR data is reported for the mixture. A partially assignment to the double bond isomers was possible. The NMR data

matched the previously reported values for the *E* and the *Z* isomer.[31] ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.04-1.40 (m, 5.0H), 1.61-1.77 (m, 5.0H), 1.95-2.07 (m, 0.4H, *E*), 2.45-2.57 (m, 0.6H, *Z*), 5.92 (dd, *J* = 7.0, 8.8 Hz, 0.6H, *Z*), 5.99 (dd, *J* = 1.1, 13.6 Hz, 0.4H, *E*), 6.04 (dd, *J* = 0.9, 7.0 Hz, 0.6H, *Z*), 6.14 (dd, *J* = 7.1, 13.6 Hz, 0.4H, *E*).

(1-Bromovinyl)benzene (1m). Synthesized from acetophenone (9.61 g, 9.33 ml, 80.0 mmol) following the literature procedure for the synthesis of **1a** in 47% yield (6.86 g, 37.5 mmol).[12] The analytical data matched the previously published values.[32] ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 5.79 (d, *J* = 2.0 Hz, 1H), 6.13 (d, *J* = 2.0 Hz, 1H), 7.32-7.39 (m, 3H), 7.57-7.62 (m, 2H).

5-(1-Bomovinyl)benzodioxole (1n). Synthesized from benzo-1,3-dioxol-5-yl methyl ketone (4.6 g, 28.0 mmol) following the literature procedure for the synthesis of **1a** in 52% yield (3.29 g, 14.5 mmol).[12] The analytical data matched the previously published values.[33] ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 5.67 (d, *J* = 2.0 Hz, 1H), 5.98 (d, *J* = 2.0 Hz, 1H), 5.99 (s, 2H), 6.77 (dd, *J* = 0.4, 8.2 Hz, 1H), 7.07 (dd, *J* = 0.4, 2.0 Hz, 1H), 7.11 (dd, *J* = 2.0, 8.2 Hz, 1H).

Preparation of Grignard reagents 2a–o.

Method A (Mg turnings, LiCl, I_2, dibromoethane): A 250 ml 3-necked flask, equipped with a magnetic stir bar, a reflux condenser, a stopper, and a septum, was charged with magnesium turnings (1.22 g, 50.0 mmol, 1.00 equiv) and with LiCl (2.65 g, 62.5 mmol, 1.25 equiv). Stirring was started and the solids were dried in vacuo for 20 min using a heat gun. After cooling down to room temperature (23 ºC), THF (46 ml) was added, followed by iodine (32 mg, 0.13 mmol, 0.3 mol-%). The stopper was replaced by an internal thermometer and the orange-brown suspension was heated to 40 ºC (internal temperature). The alkenyl bromide (50.00 mmol, 1.00 equiv) was weighed out in a separate vessel and about 0.25 ml of the alkenyl bromide were then added in one portion using a syringe. Stirring was continued at 40 ºC (internal temperature) and 1,2-dibromoethane (58 µl, 0.68 mmol, 1.4 mol-%) was added. Once the mixture turned colorless (indicating the initiation of the reaction), the remaining alkenyl bromide was added neat via syringe over 50 min while keeping the internal temperature between 40 ºC and 50 ºC. The used vessels and syringes were rinsed with additional THF (4 ml, total THF volume = 50 ml) into the reaction mixture. The reaction was then heated to a gentle reflux (80 ºC oil bath temperature) for 30 min and then cooled to room temperature. A sample of the resulting solution of the Grignard reagent was titrated against 2-hydroxybenzaldehyde-*N*-phenylhydrazone.[16] The Grignard reagent was used immediately.

Method B (Mg powder, LiCl, TMSCl, dibromoethane): A flame-dried, argon-filled 500 ml three-necked flask equipped with a magnetic stir bar and a reflux condenser was charged with LiCl (3.71 g, 87.5 mmol, 1.25 equiv) and heated under high vacuum with a heat gun until the LiCl was dry (no further gas evolution visible, the powder stopped moving; ca. 15-20 min). Then, the flask was back-filled with argon and magnesium powder (4.25 g, 175 mmol, 2.50 equiv) was added. The flask was again heated under high vacuum for about 10 min. After cooling to room temperature, abs. THF (155 ml) and TMSCl (89 µl, 0.7 mmol, 1 mol-%) were added. While stirring, the suspension was heated to reflux for 1 min and then allowed to cool down for 5 min. Then, 1,2-dibromoethane (5–10 mol-%) was added dropwise. At this point, a vigorous reaction occurred and the solvent started to reflux (if no reaction was observed, gentle warming with a heat gun would usually initiate the reaction). The alkenyl bromide (70.0 mmol, 1.0 equiv) was added slowly by syringe in such way that a gentle reflux was maintained. The syringe was rinsed with abs. THF (20 ml, total THF volume = 175 ml). The reaction mixture was heated to reflux for 4–6 h and then allowed to cool to room temperature. A sample of the resulting solution of the Grignard reagent was titrated against 2-hydroxybenzaldehyde-*N*-phenylhydrazone.[16] The Grignard reagent was used immediately.

Method C (Mg turnings): A flame-dried, argon-filled 100 ml three-necked flask equipped with a magnetic stir bar and a reflux condenser was charged with Mg-turnings (608 mg, 25.0 mmol, 2.5 equiv), and stirred overnight. Then, abs. THF (6.7 ml) was added and the alkenyl bromide (10.0 mmol, 1.0 equiv, in total) was weighed into a separate vessel. A small amount was added neat (about 0.3 g) and then the remaining alkenyl bromide was added as a solution in abs. THF (3.3 ml). The reaction mixture was refluxed for 2 h and then allowed to cool to room temperature. A sample of the resulting solution of the Grignard reagent was titrated with 2-hydroxybenzaldehyde-*N*-phenylhydrazone.[16] The Grignard reagent was used immediately.

Cyclohexen-1-ylmagnesium bromide lithium chloride (2a).[11] Prepared following method B on scales of 30-100 mmol. The concentration determined by titration was in the range of *c* = 0.3–0.4 M.

Cyclopenten-1-ylmagnesium bromide lithium chloride (2b). Prepared following method B on scales of 10-50 mmol. The amount of THF was adjusted to give a theoretical maximum reagent concentration of c_{max} = 0.7 M. The concentration determined by titration was in the range of *c* = 0.35–0.45 M.

Cyclohepten-1-ylmagnesium bromide lithium chloride (2c).[11] Prepared following method B on scales of 30–50 mmol. The concentration determined by titration was in the range of *c* = 0.07–0.21 M.

Cycloocten-1-ylmagnesium bromide lithium chloride (2d).[11] Prepared following method B on scales of 30–70 mmol. The concentration determined by titration

(4-(*tert*-Butyl)cyclohexen-1-yl)magnesium bromide lithium chloride (2e). Prepared following method A on scales of 10-40 mmol. The amount of THF was adjusted to give a theoretical maximum reagent concentration of c_{max} = 0.50 M. The concentration determined by titration was in the range of *c* = 0.12–0.20 M.

(3,3-Dimethylcyclohexen-1-yl)magnesium bromide lithium chloride (2f). Prepared following method A on a 10.5 mmol scale. The amount of THF was adjusted to give a theoretical maximum reagent concentration of c_{max} = 0.93 M. The concentration determined by titration was *c* = 0.38 M.

(1*H*-Inden-2-yl)magnesium bromide lithium chloride (2g). Prepared following method A on scales of 10-30 mmol. The amount of THF was adjusted to give a theoretical maximum reagent concentration of c_{max} = 0.50 M. The concentration determined by titration was *c* = 0.25–0.27 M.

(3,4-Dihydronaphthalen-2-yl)magnesium bromide (2h). Prepared following method B on scales of 30 mmol scale. The concentration determined by titration was *c* = 0.24 M.

(6,7-Dihydro-5H-benzo[7]annulen-8-yl)magnesium bromide (2i).[11] Prepared following method C on scales of 36–123 mmol. The concentration of the Grignard reagent was in the range of *c* = 0.78–0.81 M.

(3,4-Dihydronaphthalen-1-yl)magnesium bromide lithium chloride (2j). Prepared following method B on scales of 15–30 mmol. The amount

of THF was adjusted to give a theoretical maximum reagent concentration of c_{max} = 0.43 M. The concentration determined by titration was in the range c = 0.41–0.43 M.

(*E*)-Styrylmagnesium bromide (2k). Prepared following method C on a 30 mmol scale. The concentration determined by titration was c = 0.56 M.

(2-Cyclohexylvinyl)magnesium bromide (2l). Prepared following method C on scales of 10-23 mmol. The concentration determined by titration was in the range of c = 0.50–0.68 M.

(1-Phenylvinyl)magnesium bromide lithium chloride (2m). Prepared following method A on a 30 mmol scale. The amount of THF was adjusted to give a theoretical maximum reagent concentration of c_{max} = 0.56 M. The concentration determined by titration was c = 0.23 M.

(1-(Benzodioxol-5-yl)vinyl)magnesium bromide lithium chloride (2n). Prepared following method A on a 8.4 mmol scale. The amount of THF was adjusted to give a theoretical maximum reagent concentration of c_{max} = 0.40 m. The concentration determined by titration was c = 0.17 M.

(1-Propen-2-ylmagnesium bromide lithium chloride (2o). Prepared following method A on a 10 mmol scale. The amount of THF was adjusted to give a theoretical maximum reagent concentration of c_{max} = 0.50 M. The concentration determined by titration was c = 0.40 M.

Preparation of Weinreb amides 3a–j.

***N,N'*-Dimethoxy-*N,N'*-dimethylsuccinamide (3a).** This compound was literature known.[34] A flame-dried, argon-filled 100 ml Schlenk flask equipped with a magnetic stir bar was charged with *N,O*-dimethylhydroxylamine hydrochloride (1.18 g, 12.0 mmol, 3.0 equiv, freshly crystallized from chloroform), DMAP (48 mg, 0.4 mmol, 10 mol-%) and CH_2Cl_2 (10 ml). Then, freshly distilled succinyl chloride (440 µl, 4.0 mmol, 1.0 equiv) was added. Stirring was started and the mixture was cooled to –10 °C. Then, freshly distilled triethylamine (1.7 ml, 24.0 mmol, 6.0 equiv) was added slowly. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (60 ml) and the mixture was transferred into a separation funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 35 ml). The combined organic layers were washed with aq. HCl (1 M, 60 ml) and brine (60 ml). After drying over Na_2SO_4 and filtration, the solvent was removed under reduced pressure. The crude product **3a** was of sufficient purity and used as such in the next step (696 mg, 3.41 mmol, 85%). The reaction was repeated on a 70 mmol scale and **3a** was received in 75% yield (10.7 g, 52.5 mmol). The analytical data matched the previously published values.[34] ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.75 (s, 4H), 3.16 (s, 6H), 3.71 (s, 6H).

***N,N'*-Dimethoxy-*N,N'*-dimethylglutaramide (3b).** Synthesized from glutaryl chloride (9.45 ml, 74 mmol) according to a literature procedure in 88% yield (14.25 g, 65.3 mmol).[9a] The analytical data matched the previously published values.[34] ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.91 (quint, J = 7.2 Hz, 2H), 2.46 (t, J = 7.2 Hz, 4H), 3.12 (s, 6H), 3.62 (s, 6H).

***N,N'*-Dimethoxy-*N,N'*-dimethyladipamide (3c).** Synthesized from adipoyl chloride (7.27 ml, 50 mmol) according to a literature procedure in 65% yield (7.59 g, 32.7 mmol).[35] The analytical data matched the previously published values.[36] ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.66-1.71 (m, 6H), 2.42-2.49 (m, 6H), 3.17 (s, 8H), 3.68 (s, 8H).

***N,N'*-Dimethoxy-*N,N'*-dimethylterephthalamide (3d).** This compound was prepared from terephthaloyl chloride (4.06 g, 20.0 mmol) in analogy to **3a** in 95% yield (4.76 g, 18.9 mmol). The analytical data matched the previously published values.[34] ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 3.37 (s, 6H), 3.54 (s, 6H), 7.70 (s, 4H).

(*R,R*)-2,3-Dimethylsuccinic acid (10). Synthesized from propionyl chloride (4.39 ml, 50.3 mmol) according to a three-step literature procedure involving a dimerization in 60% overall yield (2.20 g, 15.1 mmol).[37] The analytical data matched the previously published values. $[\alpha]_D^{25}$ = +7.8° (c 1.02, H_2O). ^{1}H NMR (400.1 MHz, CD_3OD): δ = 1.14-1.18 (m, 6H), 2.71-2.79 (m, 2H), 4.82 (br, 2H). ^{13}C NMR (100.6 MHz, CD_3OD): δ = 14.12, 42.97, 179.19.

(*R,R*)-*N,N'*-Dimethoxy-*N,N'*,2,3-tetramethylsuccinamide (3e).[11] A flame-dried and argon-filled 250 ml Schlenk flask was charged with (*R,R*)-2,3-dimethylsuccinic acid (**10**) (1.572 g, 10.76 mmol) and with freshly recrystallized *N,O*-dimethylhydroxylammonium chloride (3.147 g, 32.26 mmol, 3.0 equiv). While stirring, the flask was evacuated and backfilled with argon three times. The solids were suspended in THF (65 ml) and the suspension was cooled to 0 °C. A solution of propylphosphonic anhydride (T3P, 50% w/w in toluene, 10.54 g, 16.56 mmol, 1.5 equiv) in THF (24 ml) was added dropwise and subsequently freshly dried and distilled diisopropylethylamine (12.5 ml, 9.50 g, 73.5 mmol, 6.8 equiv) was added dropwise, the mixture was stirred for 5 min at 0 °C, the cooling bath was removed and the mixture was stirred for further 18.5 h at room temperature. Additional diisopropylethylamine (3.0 ml, 2.3 g, 18 mmol, 1.7 equiv) was added and the mixture was stirred for 2 h and 20 min at room temperature. Afterwards, the reaction mixture was cooled to 0 °C, the reaction was quenched by addition of a saturated aq. solution of $NaHCO_3$ (100 ml) (gas evolution!) and then diluted with H_2O (50 ml). The organic solvent (THF) was removed from the mixture under reduced pressure. Otherwise no proper separation of the organic and aqueous was achieved in the next step. The remaining contents of the flask were transferred to a separatory funnel followed by rinsing with CH_2Cl_2 and H_2O. The mixture was then extracted with CH_2Cl_2 (5 × 40 ml). The combined organic layers were consecutively washed with saturated aq. NH_4Cl (50 ml), H_2O (2 × 50 ml) and brine (50 ml) and then dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc). The title compound was obtained as a colorless oil, which solidified upon removal of the solvents by freeze-drying in 72% yield (1.789 g, 7.702 mmol). R_f (EtOAc) = 0.2. Mp 55 °C. $[\alpha]_D^{25}$ = +12.7° (c 1.00, $CHCl_3$). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.12-1.15 (m, 6H), 3.09 (br, 2H), 3.15 (br, 6H), 3.80 (br, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.83, 32.21 (br), 38.53, 61.45, 177.23 (br). MS (CI): m/z (%) = 233.2 $[M+H]^+$ (100), 172.1 (27). HRMS (APCI) calcd for $C_{10}H_{21}N_2O_4$ $[M+H]^+$: 233.1496, found: 233.1494. IR (ATR): ν [cm^{-1}] = 2977, 2942, 2908, 2881, 1652, 1457, 1422, 1386, 1365, 1178, 1086, 987, 733, 562.

Diethyl (*R,R*)-2,3-dimethoxysuccinate (11). This compound was literature-known and prepared according to a modified procedure as follows:[38] A flame-dried and argon-filled 100 ml Schlenk flask was charged with MeI (20 ml, 46 g, 320 mmol, 12.8 equiv) and the liquid was cooled to 0 °C. While stirring, (+)-diethyl (*R,R*)-L-tartrate (4.3 ml, 5.2 g, 25 mmol) was added dropwise, followed by a portion-wise addition of Ag_2O (26.14 g, 112.8 mmol, 4.5 equiv). The reaction mixture was heated to reflux for 19 h and after cooling to room temperature the remaining MeI was removed by vacuum condensation. Et_2O (200 ml) was added to the residue and the obtained suspension was filtered through a plug of diatomaceous earth, followed by rinsing with additional Et_2O (300 ml). The solvent was removed under reduced pressure and the title compound was obtained as a colorless liquid in 96% yield (5.628 g, 24.03 mmol). The analytical data matched the previously published values.[39] ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.2 Hz, 6H), 3.43

(s, 6H), 4.18 (s, 2H), 4.16-4.31 (m, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.31, 59.67, 61.31, 81.29, 169.22. MS (EI, 70 eV): m/z (%) = 234.1 $[M]^+$ (1), 173.1 (14), 161.1 (23), 133.1 (80), 117.1 (100), 89.1 (41), 77.1 (21), 61.0 (36), 45.1 (53). HRMS (APCI) calcd for $C_{10}H_{22}NO_6$ $[M+NH_4]^+$: 252.1442, found: 252.1443. IR (ATR): ν [cm^{-1}] = 2984, 2937, 2833, 1754, 1730, 1447, 1369, 1267, 1185, 1149, 1108, 1026, 923, 858, 703.

(*R*,*R*)-*N*,*N'*,2,3-Tetramethoxy-*N*,*N'*-dimethylsuccinamide (3f). A flame-dried and argon-filled 50 ml Schlenk flask was charged with freshly recrystallized *N*,*O*-dimethylhydroxylammonium chloride (1.114 g, 11.42 mmol, 4.6 equiv) and evacuated and backfilled with argon with stirring three times. CH_2Cl_2 (12.5 ml) was added and the resulting suspension was cooled to 0 °C. Within 5 min trimethylaluminum (2.0 m solution in *n*-hexane, 5.7 ml, 11 mmol, 4.4 equiv) was added dropwise and the obtained homogeneous, colorless solution was stirred for 5 min at 0 °C, then 5 min at room temperature and was then cooled to −18 °C. A solution of diethyl (*R*,*R*)-2,3-dimethoxysuccinate (**11**) (587 mg, 2.51 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise and the mixture was stirred for 4 h between −18 °C and −10 °C. Afterwards, the mixture was stirred for 1 h at room temperature and it was then poured carefully on aq. HCl (1 M, 15 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were washed with brine (25 ml), dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography (EtOAc/MeOH, 20:1) and the title compound was obtained as a colorless solid in 72% yield (478 mg, 1.81 mmol). R_f (EtOAc/MeOH, 20:1) = 0.3. Mp 82 °C. $[\alpha]_D^{25}$ = +78.0° (*c* 1.49, $CDCl_3$). ^{1}H NMR (500.2 MHz, $CDCl_3$): δ = 3.18 (br, 6H), 3.51 (s, 6H), 3.79 (s, 6H), 4.59 (br, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 32.00, 59.17, 61.58, 77.72, 169.66. MS (ESI, 70 eV): m/z (%) = 287.1 $[M+Na]^+$ (100), 168.1 (74), 138.1 (6), 74.1 (42). HRMS (ESI) calcd for $C_{10}H_{20}N_2O_6Na$ $[M+Na]^+$: 287.1214, found: 287.1214. IR (ATR): ν [cm^{-1}] = 2940, 2830, 1655, 1442, 1389, 1330, 1179, 1098, 1062, 984, 937, 823, 721, 628.

(*R*,*R*)-Dimethyl-1,3-dioxolane-4,5-dicarboxylate (12). Synthesized from (+)-dimethyl (*R*,*R*)-L-tartrate (8.92 g, 50 mmol) according to a literature procedure in 87% yield (8.26 g, 43.4 mmol).[40] The analytical data matched previously published values.[41] ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.81 (s, 6H), 4.75 (s, 2H), 5.24 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 52.93, 76.84, 97.60, 169.70.

(*R*,*R*)-*N*,*N'*-Dimethoxy-*N*,*N'*-dimethyl-1,3-dioxolane-4,5-dicarboxamide (3g). This compound was prepared from (*R*,*R*)-dimethyl-1,3-dioxolane-4,5-dicarboxylate (**12**) (380 mg, 2.00 mmol) following the procedure for diamide **3f** with the following modification: The dropwise addition of **12** was carried out over 1.5 h at temperatures between −18 °C and −10 °C. Afterwards, stirring was continued for 30 min at room temperature. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 30:1) giving the title compound as a yellow oil in 77% yield (382 mg, 1.54 mmol). R_f (CH_2Cl_2/MeOH 30:1) = 0.3. $[\alpha]_D^{25}$ = −22.2° (*c* 1.73, $CHCl_3$). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.20 (br s, 6H), 3.67 (s, 6H), 5.07 (br s, 2H), 5.15 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 32.48, 61.75, 74.67, 97.07, 169.56. MS (EI, 70eV): m/z (%) = 248.1 $[M]^+$ (3), 217.1 (7), 186.1 (16), 160.1 (48), 142.1 (13), 130.1 (20), 102.1 (100), 88.1 (29), 71.1 (30), 60.1 (30), 42.1 (22). HRMS (APCI) calcd for $C_9H_{17}N_2O_6$ $[M+H]^+$: 249.1081, found: 249.1082. IR (ATR): ν [cm^{-1}] = 2977, 2942, 1667, 1463, 1443, 1391, 1332, 1169, 1119, 1083, 1053, 988, 935, 856.

(*R*,*R*)-*N*,*N'*-Dimethoxy-*N*,*N'*-2,2-tetramethyl-1,3-dioxolane-4,5-dicarboxamide (3h). Synthesized from commercially available (*R*,*R*)-diethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (4.93 g, 20.0 mmol) according to a literature procedure in 91% yield (5.01 g, 18.1 mmol).[9c] The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.48 (s, 6H), 3.19 (s, 6H), 3.66 (s, 6H), 5.13 (s, 2H).

(*S*)-Dimethyl-2-hydroxysuccinate (13). Synthesized from commercially available L-malic acid (6.70 g, 50.0 mmol) according to a literature procedure in 92% yield (7.47 g, 46.1 mmol).[42] The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.70-2.86 (m, 2H), 3.65 (s, 3H), 3.75 (s, 3H), 4.44 (dd, *J* = 4.6, 6.1 Hz, 1H).

(*S*)-Dimethyl-2-methoxysuccinate (14). Synthesized from (*S*)-dimethyl-2-hydroxysuccinate (**13**, 2.81 g, 17.3 mmol) according to a literature procedure in 92% yield (2.83 g, 16.0 mmol).[43] The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.73 (dd, *J* = 7.7, 16.2 Hz, 1H), 2.80 (dd, *J* = 5.1, 16.1 Hz, 1H), 3.46 (s, 3H), 3.71 (s, 3H), 3.78 (s, 3H), 4.20 (dd, *J* = 5.1, 7.7 Hz, 1H).

(*S*)-2-Methoxysuccinic acid (15). Synthesized from (*S*)-dimethyl-2-methoxysuccinate (**14**, 1.68 g, 9.51 mmol) according to a literature procedure in 73% yield (1.02 g, 6.90 mmol).[44] The analytical data matched the previously published values.[45] ^{1}H NMR (300.1 MHz, acetone-d_6): δ = 2.64 (dd, *J* = 8.2, 16.2 Hz, 1H), 2.80 (dd, *J* = 4.4, 16.2 Hz, 1H), 3.39 (s, 3H), 4.16 (dd, *J* = 4.4, 8.2 Hz, 1H).

(*S*)-*N*,*N'*,2-Trimethoxy-*N*,*N'*-dimethylsuccinamide (3i). A flame-dried, argon-filled 25 ml Schlenk tube was charged with (*S*)-2-methoxysuccinic acid (**15**) (148 mg, 1.0 mmol, 1.0 equiv) and with freshly recrystallized *N*,*O*-dimethylhydroxylammonium chloride (292 mg, 3.0 mmol, 3.0 equiv). While stirring, the vessel was evacuated and backfilled with argon three times. The solids were suspended in THF (6 ml) and the suspension was cooled to 0 °C. A solution of propylphosphonic anhydride (T3P, 50% *w*/*w* in toluene, 1.9 g, 3.0 mmol, 3.0 equiv) in THF (1.5 ml) was added dropwise and then subsequently freshly dried and distilled diisopropylethylamine (1.4 ml, 8.0 mmol, 8.0 equiv) was added dropwise. The mixture was stirred for 5 min at 0 °C, then the cooling bath was removed and the mixture was stirred for further 15 h at room temperature. The reaction mixture was then cooled to 0 °C and saturated aq. $NaHCO_3$ solution (10 ml) (gas evolution!) was added. The mixture was diluted with H_2O (5 ml) and extracted with CH_2Cl_2 (5 × 5 ml). The combined organic layers were consecutively washed with saturated aq. NH_4Cl (5 ml), H_2O (2 × 5 ml) and brine (5 ml) and dried over Na_2SO_4. After filtration and concentration, the product was purified by column chromatography (CH_2Cl_2/MeOH, 20:1) and obtained as a colorless oil in 73% yield (172 mg, 0.73 mmol). R_f (CH_2Cl_2/MeOH, 20:1) = 0.4. $[\alpha]_D^{25}$ = –4.0° (*c* 1.00; $CHCl_3$). ^{1}H NMR (400.1 MHz, $CDCl_3$, 333K): δ = 2.78 (dd, *J* = 5.8, 16.2 Hz, 1H), 2.85 (dd, *J* = 7.1, 16.2 Hz, 1H), 3.12 (s, 3H), 3.18 (s, 3H), 3.33 (s, 3H), 3.66 (s, 3H), 3.72 (s, 3H), 4.65 (dd, *J* = 5.8, 7.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, 333K): δ = 32.33, 32.62, 34.54, 57.52, 61.33, 61.50, 74.22, 171.12, 171.88. MS (EI, 70 eV): m/z (%) = 174.0 $[M–C_2H_4O_2^+]$ (97), 146.0 (100), 142.0 (73), 113.0 (10), 104.0 (100), 85.0 (12), 72.0 (7), 60.0 (20), 58.0 (13). HRMS (pos. ESI) calcd for $C_9H_{18}N_2O_5Na^+$ $[M+Na]^+$: 257.1108, found: 257.1109. IR (ATR): ν [cm^{-1}] = 2939, 2826, 1653, 1422, 1386, 1325, 1275, 1177, 1101, 986, 945, 845, 732, 700, 616.

rac-**3i** was prepared as follows:

***N*-Tolyl maleimide (16).** Synthesized from *para*-toluidine (5.36 g, 50.0 mmol) according to a literature procedure in 89% yield (8.29 g, 44.3 mmol).[46] If necessary, the product can be recrystallized from hot *i*-PrOH. The analytical data matched the previously published values.[45] ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 6.82 (s, 2H), 7.21-7.24 (m, 2H), 7.27-7.30 (m, 2H).

***rac*-2-Methoxysuccinic acid (*rac*-15).** Synthesized from *N*-tolyl maleimide (**16**, 2.81 g, 15.0 mmol) according to a literature procedure in 75% yield (1.67 g, 11.28 mmol).[45] The following modification was applied: 9 mol-% of K_2CO_3 were used. The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, acetone-d_6): δ = 2.63 (dd, *J* = 8.2, 16.2 Hz, 1H), 2.80 (dd, *J* = 4.4, 16.2 Hz, 1H), 3.39 (s, 3H), 4.17 (dd, *J* = 4.4, 8.2 Hz, 1H).

***rac*-*N*,*N*'-2-Trimethoxy-*N*,*N*'-dimethylsuccinamide (*rac*-3i).** This compound was prepared from *rac*-2-methoxysuccinic acid (*rac*-**15**, 603 mg, 4.07 mmol) in analogy to (*S*)-*N*,*N*',2-trimethoxy-*N*,*N*'-dimethylsuccinamide (**3i**). The product was purified by column chromatography (CH_2Cl_2/MeOH, 20:1, R_f = 0.4) and obtained as a colorless oil in 69% yield (655 mg, 2.79 mmol). ^{1}H NMR (400.1 MHz, $CDCl_3$, 333K): δ = 2.78 (dd, *J* = 5.8, 16.2 Hz, 1H), 2.85 (dd, *J* = 7.1, 16.2 Hz, 1H), 3.12 (s, 3H), 3.18 (s, 3H), 3.33 (s, 3H), 3.66 (s, 3H), 3.72 (s, 3H), 4.65 (dd, *J* = 5.8, 7.1 Hz, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$, 333K): δ = 32.33, 32.62, 34.54, 57.52, 61.33, 61.50, 74.22, 171.12, 171.88. MS (CI): m/z (%) = 235.1 $[M+H]^+$ (100), 174.0 (53), 146.0 (6), 142.0 (6), 131.0 (5), 104.0 (6). HRMS (pos. APCI) calcd for $C_9H_{19}N_2O_5^+$ $[M+H]^+$: 235.1288, found: 235.1287. IR (ATR): ν [cm^{-1}] = 2939, 2826, 1655, 1423, 1386, 1324, 1178, 1103, 989, 917, 844, 726, 646, 608.

***rac*-*trans*-Cyclohexane-1,2-dicarbonyldichloride (17).** Synthesized from commercially available *rac*-*trans*-cyclohexane-1,2-dicarboxylic acid (1.72 g, 10.0 mmol) according to a literature procedure with the following modification: the reaction time was shortened to 16 h.[47] The crude diacid dichloride was used immediately in the next step. The analytical data matched the previously published values. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 1.32-1.52 (m, 4H), 1.87-1.97 (m, 2H), 2.35-2.44 (m, 2H), 3.03-3.12 (m, 2H).

***rac*-*trans*-*N*,*N*'-Dimethoxy-*N*,*N*'-dimethylcyclohexane-1,2-dicarboxamide (3j).** This compound was prepared from *rac*-*trans*-cyclohexane-1,2-dicarbonyldichloride (**17**, 2.09 g, 10.0 mmol) in analogy to **3a**. The desired bis-Weinreb amide was obtained in analytically pure form as a yellow solid in 82% yield (2.114 g, 8.184 mmol). The product can be recrystallized by slow evaporation at room temperature of a saturated solution in Et_2O/*n*-pentane = 4:1 (v/v). Mp 56-58 °C. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.23-1.36 (m, 4H), 1.72-1.82 (m, 2H), 1.90-2.04 (m, 2H), 2.99-3.20 (m, 8H), 3.79 (br, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.76, 28.71, 32.08 (br), 41.73, 61.54, 176.05 (br). MS (CI): m/z (%) = 276.2 $[M+NH_4]^+$ (9), 259.2 $[M+H]^+$ (100), 229.2 (20), 198.2 (72), 168.1 (16), 142.1 (9), 75.1 (6), 62.1 (19). HRMS (ESI) calcd for $C_{12}H_{22}N_2O_4Na$ $[M+Na]^+$: 281.1472, found: 281.1473. IR (ATR): ν [cm^{-1}] = 2933, 2857, 1652, 1468, 1446, 1385, 1178, 1130, 984, 918, 731.

Grignard addition reactions.

1,4-Di(cyclohex-1-en-1-yl)butane-1,4-dione (4a).[11] A flame-dried, argon-filled 250 ml Schlenk flask equipped with a magnetic stir bar was charged with the bis-Weinreb amide **3a** (1.67 g, 8.18 mmol, 1.0 equiv) and evacuated and backfilled with argon three times while stirring. The solid was suspended in Et_2O (88 ml) and cooled to 0 °C with stirring. A solution of the freshly titrated Grignard reagent **2a** (88 ml, 0.28 M in THF, 24.6 mmol, 3.0 equiv) was added. After 10 minutes, the reaction mixture was allowed to warm to room temperature and stirring was continued for 14–20 h. Then, saturated aq. NH_4Cl solution (35 ml) was added and the mixture was transferred into a separation funnel. The phases were separated and the org. phase was washed with aq. HCl (1 M, 3 × 50 ml). The combined aq. layers were extracted with Et_2O (3 × 75 ml) and the combined org. layers were washed with saturated aq. $NaHCO_3$ (1 × 100 ml) and brine (1 × 100 ml). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The product was purified by column chromatography (*n*-pentane/EtOAc, 20:1) and obtained as a colorless solid in 70% yield (1.402 g, 5.69 mmol). R_f (*n*-pentane/EtOAc, 6:1) = 0.3. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.55-1.65 (m, 8H), 2.19-2.26 (m, 8H), 2.95 (s, 4H), 6.97-6.99 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.74, 22.13, 23.33, 26.20, 31.26, 139.16, 139.92, 200.08. MS (EI, 70 eV): m/z (%) = 246.1 $[M]^+$ (11), 165.1 (9), 137.1 (25), 109.1 (100), 91.1 (6), 81.1 (61), 79.0 (49), 77.0 (11), 55.1 (10), 53.1 (19), 41.2 (9). HRMS (pos. APCI) calcd for $C_{16}H_{23}O_2^+$ $[M+H]^+$: 247.16926, found: 247.16949. IR (ATR): ν [cm^{-1}] = 2935, 1660, 1638, 1423, 1387, 1262, 1214, 1168, 1135, 1097, 994, 923, 746, 667.

1,4-Di(cyclopent-1-en-1-yl)butane-1,4-dione (4b). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (2.37 g, 11.6 mmol) and Grignard reagent **2b** (70 ml, 0.45 M in THF, 31.5 mmol, 2.7 equiv). The product was purified by column chromatography (hexanes/EtOAc, 10:1) and obtained as a colorless solid in 86% yield (2.19 g, 10.0 mmol). R_f (hexanes/EtOAc, 10:1) = 0.1. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.87-1.94 (m, 4H), 2.50-2.58 (m, 8H), 2.99 (m, 4H), 6.79-6.81 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.93, 30.84, 32.96, 34.09, 143.66, 145.49, 197.63. MS (EI, 70 eV): m/z (%) = 218.1 $[M]^+$ (20), 123.1 (22), 95.0 (100), 67.1 (11), 41.1 (7). HRMS (pos. APCI) calcd for $C_{14}H_{19}O_2^+$ $[M+H]^+$: 219.1380, found: 219.1379. IR (ATR): ν [cm^{-1}] = 2955, 2324, 2162, 2050, 1980, 1663, 1614, 1412, 1368, 1307, 1259, 1163, 1039, 980, 944, 903, 801, 615.

1,4-Di(cyclohept-1-en-1-yl)butane-1,4-dione (4c).[11] This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (204 mg, 1.0 mmol) and Grignard reagent **2c** (38.6 ml, 0.07 M in THF, 2.7 mmol, 2.7 equiv). The product was purified by column chromatography (*n*-pentane/EtOAc, 20:1) and obtained as a colorless solid in 81% yield (223 mg, 0.81 mmol). R_f (*n*-pentane/EtOAc, 10:1) = 0.3. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.41-1.47 (m, 4H), 1.51-1.57 (m, 4H), 1.73-1.79 (m, 4H), 2.31-2.36 (m, 4H), 2.46-2.49 (m, 4H), 2.96 (s, 4H), 7.14 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.86, 25.93, 26.26, 29.21, 31.70, 32.33, 144.39, 146.02, 200.04. MS (EI, 70 eV): m/z (%) = 276.3 (19), 275.2 $[M]^+$ (100), 274 (13), 257.2 (3), 179.2 (4), 151.2 (7), 123.1 (27), 95.0 (12), 67.1 (5). HRMS (pos. APCI) calcd for $C_{18}H_{27}O_2^+$ $[M+H]^+$: 275.2006, found: 275.2003. IR (ATR): ν [cm^{-1}] = 2919, 2850, 1662, 1636, 1448, 1387, 1330, 1299,1276, 1234, 1215, 1187, 1173, 1132, 1101, 1077, 1025, 968, 917, 856, 778, 732, 649.

1,4-Di(cyclooct-1-en-1-yl)butane-1,4-dione (4d).[11] This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (511 mg, 2.5 mmol) and Grignard reagent **2d** (56 ml, 0.12 M in THF, 6.75 mmol, 2.7 equiv). The product was purified by column chromatography (*n*-pentane/EtOAc, 20:1) and obtained as a colorless solid in 61% yield (464 mg, 1.53 mmol). R_f (*n*-pentane/EtOAc, 10:1) = 0.2. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.39-1.55 (m, 12H), 1.59-1.65 (m, 4H), 2.31-2.36 (m, 4H), 2.43-2.46 (m, 4H), 3.00 (s, 4H), 6.96 (t, *J* = 8.4 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.87, 26.28, 26.75, 27.64, 29.21, 29.37, 31.67, 142.48, 142.59, 199.90. MS (EI, 70 eV): m/z (%) = 302.3 $[M]^+$ (28), 193.2 (33), 165.2 (58), 137.1 (100), 109.1 (16), 81.1 (23), 67.1 (88), 55.1 (33), 41.2 (21). HRMS (pos. APCI) calcd for $C_{20}H_{31}O_2^+$ $[M+H]^+$: 303.2319, found: 303.2318. IR (ATR): ν [cm^{-1}] = 2922, 2851, 1662, 1636, 1465, 1446, 1402, 1383, 1358, 1324, 1265, 1189, 1167, 1089, 1026, 976, 896, 847, 777.

1,4-Bis(4-(*tert*-butyl)cyclohexen-1-yl)butane-1,4-dione (4e). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (98 mg, 0.48 mmol) and Grignard reagent **2e** (14 ml, 0.09 M in THF, 1.3 mmol, 3.0 equiv). The product was purified by column chromatography (hexanes/EtOAc, 9:1) and obtained as a colorless solid in 63% yield (108 mg, 0.30 mmol). R_f (hexanes/ ethyl acetate, 9:1) = 0.4. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 0.89 (s, 18H), 1.04-1.14 (m, 2H), 1.23-

1.31 (m, 2H), 1.88-1.93 (m, 2H), 1.96-2.09 (m, 4H), 2.27-2.34 (m, 2H), 2.52-2.57 (m, 2H), 2.96 (s, 4H), 6.99-7.01 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.62, 24.86, 27.28, 28.01, 31.39, 32.31, 43.64, 139.08, 140.43, 199.92. MS (EI, 70 eV): m/z (%) = 358.3 $[M]^+$ (100), 343.3 (22), 301.2 (36), 193.3 (11), 165.3 (36), 57.1 (9). HRMS (pos. APCI) calcd for $C_{24}H_{39}O_2^+$ $[M+H]^+$: 359.2945, found: 359.2936. IR (ATR): ν [cm^{-1}] = 2958, 2868, 1658, 1642, 1420, 1385, 1364, 1320, 1288, 1246, 1184, 1159, 1020, 977, 915, 765.

1,4-Bis(3,3-dimethylcyclohexen-1-yl)butane-1,4-dione (4f). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (293 mg, 1.43 mmol) and Grignard reagent **2f** (11 ml, 0.38 M in THF, 4.3 mmol, 3.0 equiv). The product was purified by column chromatography (hexanes/EtOAc, 9:1) and obtained as a colorless oil in 62% yield (268 mg, 0.89 mmol). R_f (hexanes/ ethyl acetate, 9:1) = 0.4. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.07 (s, 12H), 1.43-1.46 (m, 4H), 1.60-1.67 (m, 4H), 2.18 (td, *J* = 1.7, 6.2 Hz, 4H), 2.97 (s, 4H), 6.64 (t, *J* = 1.7 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.30, 23.53, 29.36, 31.39, 32.87, 36.61, 136.77, 148.82, 200.65. MS (EI, 70 eV): m/z (%) = 303.2 $[M]^+$ (6), 193.1 (32), 177.0 (13), 165.1 (67), 151.1 (11), 147.1 (14), 137.0 (83), 133.1 (31), 109.0 (100), 93.0 (14), 79.0 (18), 67.0 (49), 55.0 (7). HRMS (pos. APCI) calcd for $C_{20}H_{31}O_2^+$ $[M+H]^+$: 303.2319, found: 303.2314. IR (ATR): ν [cm^{-1}] = 2954, 2929, 2864, 1665, 1635, 1469, 1453, 1391, 1360, 1339, 1298, 1268, 1214, 1154, 1062, 1035, 1000, 990, 937, 870, 591.

1,4-Di(1*H*-inden-2-yl)butane-1,4-dione (4g). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (131 mg, 0.64 mmol) and Grignard reagent **2g** (7.0 ml, 0.28 M in THF, 1.9 mmol, 3.0 equiv). The product was purified by column chromatography (hexanes/EtOAc, 9:1) and obtained as a colorless oil in 67% yield (135 mg, 0.43 mmol). R_f (hexanes/EtOAc, 9:1) = 0.4. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.38 (s, 4H), 3.61 (d, *J* = 2.1 Hz, 4H), 7.27 (td, *J* = 1.2, 7.4 Hz, 2H), 7.32-7.36 (m, 2H), 7.48-7.50 (m, 2H), 7.53 (t, *J* = 2.1 Hz, 2H), 8.20 (dt, *J* = 0.9, 7.7 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 33.61, 38.87, 123.53, 123.80, 125.94, 126.87, 141.03, 143.27, 143.30, 144.19, 196.91. MS (EI, 70 eV): m/z (%) = 314.0 $[M]^+$ (31), 286.1 (67), 271.0 (6), 240.9 (6), 199.0 (100), 171.1 (14), 157.1 (8). 143.1 (26), 129.1 (10), 115.2 (69), 55.2 (6). HRMS (pos. APCI) calcd for $C_{22}H_{19}O_2^+$ $[M+H]^+$: 315.1380, found: 315.1379. IR (ATR): ν [cm^{-1}] = 3074, 2917, 1709, 1674, 1662, 1604, 1581, 1561, 1461, 1455, 1398, 1387, 1375, 1296, 1246, 1205, 1189, 1086, 1019, 910, 885, 791, 763, 722, 716.

1,4-Bis(3,4-dihydronaphthalen-2-yl)butane-1,4-dione (4h). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (476 mg, 2.33 mmol) and Grignard reagent **2h** (26.8 ml, 0.235 M in THF, 6.3 mmol, 2.7 equiv). The product was purified by column chromatography (*n*-pentane/EtOAc, 10:1) and obtained as a colorless solid in 65% yield (518 mg, 1.51 mmol). R_f (*n*-pentane/EtOAc, 10:1) = 0.1. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.62 (t, *J* = 8.2 Hz, 4H), 2.85 (t, *J* = 8.2 Hz, 4H), 3.23 (s, 4H), 7.17-7.29 (m, 8H), 7.54 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.40, 27.61, 31.65, 126.87, 127.84, 128.88, 129.91, 132.72, 136.58, 137.59, 137.70, 199.30. MS (EI, 70 eV): m/z (%) = 342.3 $[M]^+$ (13), 211.2 (20), 185.2 (13), 172.1 (100), 157.2 (52), 128.2 (28), 77.1 (6). HRMS (pos. ESI) calcd for $C_{24}H_{23}O_2^+$ $[M+H]^+$: 343.1693, found: 343.1695. IR (ATR): ν [cm^{-1}] = 3016, 2931, 2835, 1655, 1622, 1567, 1485, 1452, 1439, 1384, 1345, 1313, 1297, 1269, 1249, 1206, 1189, 1171, 1154, 1107, 1030, 1011, 945, 892, 851, 756, 724.

1,4-Bis(6,7-dihydro-5*H*-benzo[7]annulen-8-yl)butane-1,4-dione (4i).[11] This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (544 mg, 2.66 mmol) and Grignard reagent **2i** (32 ml, 0.29 M in THF, 9.3 mmol, 3.5 equiv). The product was purified by column chromatography (*n*-pentane/EtOAc, 20:1) and obtained as a colorless solid in 84% yield (827 mg, 2.23 mmol). R_f (*n*-pentane/EtOAc, 10:1) = 0.4. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.06-2.12 (m, 4H), 2.59 (ddd, *J* = 1.1, 6.2, 6.2 Hz, 4H), 2.78-2.81 (m, 4H), 3.26 (s, 4H), 7.16-7.21 (m, 2H), 7.22-7.27 (m, 4H), 7.31-7.35 (m, 2H), 7.67 (s, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.35, 28.92, 32.29, 34.99, 126.30, 129.01, 129.58, 132.30, 134.94, 139.71, 141.46, 143.20, 200.68. MS (EI, 70 eV): m/z (%) = 370.1 $[M]^+$ (80), 226.0 (17), 198.2 (8), 171.0 (100), 143.2 (18), 128.1 (54), 118.0 (11). HRMS (pos. ESI) calcd for $C_{26}H_{26}O_2Na^+$ $[M+Na]^+$: 393.1825, found: 393.1829. IR (ATR): ν [cm^{-1}] = 3060, 3015, 2926, 2859, 1659, 1627, 1570, 1492, 1447, 1417, 1340, 1303, 1283, 1260, 1224, 1188, 1152, 1109, 1079, 1044, 949, 907, 868, 798, 754, 731.

1,4-Bis(3,4-dihydronaphthalen-1-yl)butane-1,4-dione (4j). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (204 mg, 1.0 mmol) and Grignard reagent **2j** (4.5 ml, 0.67 M in THF, 3.0 mmol, 3.0 equiv). The product was purified by column chromatography (*n*-pentane/EtOAc, 10:1) and obtained as a colorless solid in 41% yield (139 mg, 0.41 mmol). R_f (*n*-pentane/EtOAc, 10:1) = 0.2. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 2.43-2.48 (m, 4H), 2.78 (t, *J* = 7.9 Hz, 4H), 3.22 (s, 4H), 7.08 (t, *J* = 4.9 Hz, 2H), 7.17-7.26 (m, 6H), 7.68-7.70 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.55, 27.45, 34.01, 126.36, 126.44, 127.53, 127.60, 130.99, 136.36, 137.57, 139.07, 200.49. MS (EI, 70 eV): m/z (%) = 342.3 $[M]^+$ (18), 314.3 (56), 211.1 (100), 183.2 (18), 172.2 (52), 157.2 (97), 141.2 (10), 128.2 (57), 102.1 (7), 77.1 (10), 55.1 (9). HRMS (pos. ESI) calcd for $C_{24}H_{23}O_2^+$ $[M+H]^+$: 343.1693, found: 343.1693. IR (ATR): ν [cm^{-1}] = 3058, 2937, 2886, 2831, 2248, 1670, 1613, 1598, 1567, 1483, 1450, 1424, 1380, 1327, 1242, 1191, 1139, 1093, 1044, 1020, 956, 911, 873, 817, 787, 763, 735, 679.

(*E*,*E*)-1,8-diphenylocta-1,7-diene-3,6-dione (4k). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (515 mg, 2.52 mmol) and Grignard reagent **2k** (11.3 ml, 0.56 M in THF, 6.3 mmol, 2.5 equiv). The product was purified by column chromatography (*n*-pentane/EtOAc, 10:1 to 5:1) and obtained as a colorless solid in 73% yield (536 mg, 1.85 mmol). R_f (*n*-pentane/EtOAc, 3:1) = 0.2. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.09 (s, 4H), 6.79 (d, *J* = 16.3 Hz, 2H), 7.37-7.41 (m, 4H), 7.53-7.58 (m, 4H), 7.62 (d, *J* = 16.3 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 34.53, 126.22, 128.40, 129.02, 130.54, 134.62, 142.87, 198.63. MS (EI, 70 eV): m/z (%) = 290.2 $[M]^+$ (9), 272.1 (7), 180.1 (5), 159.1 (5), 144.1 (23), 131.1 (100), 103.1 (38), 77.1 (14). HRMS (pos. ESI) calcd for $C_{20}H_{19}O_2^+$ $[M+H]^+$: 291.1380, found: 291.1380. IR (ATR): ν [cm^{-1}] = 3056, 3032, 2906, 1690, 1668, 1613, 1576, 1494, 1449, 1395, 1361, 1236, 1192, 1164, 1097, 1086, 1009, 979, 970, 944, 903, 783, 743, 688.

1,8-Dicyclohexylocta-1,7-diene-3,6-dione, mixture of double bond isomers (4l). This compound was prepared in analogy to **4a** on using bis-Weinreb amide **3a** (204 mg, 1.0 mmol) and Grignard reagent **2l** (4.4 ml, 0.68 M in THF, 3.0 mmol, 3.0 equiv). The product was purified by column chromatography (hexanes/EtOAc, 25:1) and obtained as a colorless solid in 86% yield (259 mg, 0.86 mmol) as a mixture of double bond isomers (*E*/*E* : *E*/*Z* : *Z*/*Z* = 1.0:2.9:3.8). For characterization purposes the olefin isomers were separated using an *Interchim* Puriflash system equipped with a normal phase silica gel column (type PF-SIHP/12g, 30 µm particle size) eluting with hexanes/EtOAc, 50:1→25:1. *E*/*E* isomer: R_f (hexanes/EtOAc, 10:1) = 0.43. ^{1}H NMR (400.1 MHz, C_6D_6): δ = 0.87-1.12 (m, 6H), 1.18-1.33 (m, 4H), 1.47-1.62 (m, 6H), 1.70-1.78 (m, 4H), 2.49 (s, 4H), 3.40-3.54 (m, 2H), 5.60 (dd, *J* = 9.6, 11.4 Hz, 2H), 5.81 (dd, *J* = 1.0, 11.4 Hz, 2H). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 25.83, 26.31, 32.75, 37.69, 37.85, 125.24, 152.76, 198.46. MS (EI, 70 eV): m/z (%) = 302.2 $[M]^+$ (16), 208.1 (10), 193.1 (45), 175.1 (18), 165.1 (25), 157.1 (7), 147.1 (15), 133.1 (46), 119.1 (5), 113.1 (32), 105.1 (6), 95.1 (29), 81.0 (100), 67.0 (25), 55.0 (8). HRMS (pos. ESI) calcd for $C_{20}H_{31}O_2^+$ $[M+H]^+$: 303.2319, found: 303.2321. IR (ATR): ν [cm^{-1}] = 2922,

2850, 2206, 1787, 1683, 1620, 1448, 1407, 1349, 1273, 1185, 1073, 1029, 962, 891, 838, 817, 762, 687. *E*/*Z* isomer: R_f (hexanes/EtOAc, 10:1) = 0.41. ^{1}H NMR (400.1 MHz, C_6D_6): δ = 0.82-1.11 (m, 8H), 1.26 (tq, *J* = 3.2, 12.6 Hz, 2H), 1.47-1.61 (m, 8H), 1.71-1.80 (m, 3H) 2.57-2.65 (m, 4H), 3.44-3.54 (m, 1H), 5.62 (dd, *J* = 9.6, 11.4 Hz, 1H), 5.85 (dd, *J* = 1.0, 11.4 Hz, 1H), 5.99 (dd, *J* = 1.4, 16.0 Hz, 1H), 6.66 (dd, *J* = 6.8, 16.0 Hz, 1H). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 25.84, 26.00, 26.22, 26.31, 31.90, 32.77, 34.00, 37.72, 37.91, 40.60, 125.29, 128.22, 151.21, 152.79, 197.60, 198.65. MS (EI, 70 eV): m/z (%) = 302.2 $[M]^+$ (9), 208.1 (6), 193.1 (24), 175.0 (6), 165.1 (5), 150.1 (9), 133.0 (12), 111.0 (100), 99.0 (20), 83.0 (8), 67.0 (12), 55.0 (8). HRMS (pos. ESI) calcd for $C_{20}H_{31}O_2^+$ $[M+H]^+$: 303.2319, found: 303.2319. IR (ATR): ν [cm^{-1}] = 2922, 2850, 2206, 1787, 1683, 1620, 1448, 1407, 1349, 1273, 1185, 1073, 1029, 962, 891, 838, 817, 762, 687. *Z*/*Z* isomer: R_f (hexanes/EtOAc, 10:1) = 0.39. ^{1}H NMR (400.1 MHz, C_6D_6): δ = 0.81-1.12 (m, 10H), 1.46-1.58 (m, 10H), 1.73-1.82 (m, 2H), 2.74 (s, 4H), 6.02 (dd, *J* = 9.6, 11.4 Hz, 2H), 6.69 (dd, *J* = 1.0, 11.4 Hz, 2H). ^{13}C NMR (100.6 MHz, C_6D_6): δ = 26.01, 26.23, 31.91, 34.07, 40.63, 128.30, 151.28, 197.84. MS (EI, 70 eV): m/z (%) = 302.1 $[M]^+$ (26), 208.1 (8), 193.1 (22), 165.0 (32), 150.1 (48), 147.1 (12), 137.0 (100), 119.0 (21), 111.0 (82), 95.0 (26), 83.0 (19), 67.0 (31), 55.0 (89). HRMS (pos. ESI) calcd for $C_{20}H_{31}O_2^+$ $[M+H]^+$:303.2319, found: 303.2320. IR (ATR): ν [cm^{-1}] = 2922, 2850, 2206, 1787, 1683, 1620, 1448, 1407, 1349, 1273, 1185, 1073, 1029, 962, 891, 838, 817, 762, 687.

2,7-Diphenylocta-1,7-diene-3,6-dione (4m). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (843 mg, 4.13 mmol) and Grignard reagent **2m** (54 ml, 0.23 M in THF, 12.4 mmol, 3.0 equiv). The product was purified by column chromatography (hexanes/EtOAc, 6:1) and obtained as a colorless solid in 50% yield (595 mg, 2.05 mmol). R_f (hexanes/EtOAc, 6:1) = 0.2. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.14 (s, 4H), 5.93 (d, *J* = 0.6 Hz, 2H), 6.22 (d, *J* = 0.6 Hz, 2H), 7.32-7.40 (m, 10H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 33.86, 124.60, 128.20, 128.30, 128.49, 137.30, 149.28, 200.34. MS (EI, 70 eV): m/z (%) = 290.2 $[M]^+$ (1) 261.9 (100), 187.0 (16), 159.0 (8), 142.1 (11), 131.1 (9), 117.1 (8), 105.1 (7), 103.1 (51), 77.2 (13). HRMS (pos. APCI) calcd for $C_{20}H_{19}O_2^+$ $[M+H]^+$: 291.1380, found: 291.1375. IR (ATR): ν [cm^{-1}] = 3077, 2905, 1672, 1603, 1503, 1487, 1441, 1364, 1354, 1155, 1114, 1037.

2,7-Bis(benzodioxol-5-yl)octa-1,7-diene-3,6-dione (4n). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (127 mg, 0.62 mmol) and Grignard reagent **2n** (10 ml, 0.17 M in THF, 1.7 mmol, 2.7 equiv). The product was purified by column chromatography (hexanes/EtOAc, 9:1) and obtained as a colorless solid in 69% yield (163 mg, 0.43 mmol). R_f (hexanes/EtOAc, 9:1) = 0.2. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 3.11 (s, 4H), 5.86 (d, *J* = 0.4 Hz, 2H), 5.96 (s, 4H), 6.11 (d, *J* = 0.4 Hz, 2H), 6.78-6.83 (m, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 33.98, 101.29, 108.29, 109.12, 122.34, 123.80, 131.24, 147.66, 147.80, 148.91, 200.64. MS (EI, 70 eV): m/z (%) = 378.1 $[M]^+$ (8), 349.9 (79), 320.0 (12), 201.0 (9), 186.0 (44), 147.1 (100), 117.0 (13), 89.2 (22), 63.2 (5). HRMS (pos. APCI) calcd for $C_{22}H_{22}O_6N^+$ $[M+NH_4]^+$: 396.1442, found: 396.1442. IR (ATR): ν [cm^{-1}] = 3079, 2919, 1670, 1626, 1603, 1503, 1493, 1444, 1408, 1344, 1262, 1229, 1167, 1148, 1121, 1081, 1031, 939, 935, 867, 822, 811, 753, 736.

2,7-Dimethylocta-1,7-diene-3,6-dione (4o). This product was literature known.[4] This compound was prepared in analogy to **4a** using bis-Weinreb amide **3a** (408 mg, 2.0 mmol) and Grignard reagent **2o** (15 ml, 0.40 M in THF, 6.0 mmol, 3.0 equiv). The product was purified by column chromatography (hexanes/EtOAc, 9:1) and obtained as a colorless solid in 57% yield (190 mg, 1.14 mmol). The NMR data matched the previously reported values. R_f (hexanes/EtOAc, 9:1) = 0.4. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.88 (dd, *J* = 0.9, 1.5 Hz, 6H), 3.03 (s, 4H), 5.78 (qd, *J* = 0.7, 1.5 Hz, 2H), 6.05 (quint, *J* = 0.9 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.74, 31.68, 124.77, 144.42, 200.53.

1,5-Di(cyclohex-1-en-1-yl)pentane-1,5-dione (5a).[11] This compound was prepared in analogy to **4a** using bis-Weinreb amide **3b** (611 mg, 2.8 mmol) and Grignard reagent **2a** (21.6 ml, 0.35 M in THF, 7.56 mmol, 2.7 equiv). The product was purified by column chromatography (*n*-pentane/EtOAc, 20:1) and obtained as a colorless solid in quantitative yield (>99%, 727 mg, 2.79 mmol). R_f (*n*-pentane/EtOAc, 10:1) = 0.2. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.46-1.57 (m, 8H), 1.81 (quint, *J* = 7.1 Hz, 2H), 2.09-2.17 (m, 8H), 2.58 (t, *J* = 7.1 Hz, 4H), 6.81-6.83 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.75, 21.54, 21.94, 23.07, 25.99, 36.15, 139.02, 139.72, 200.92. MS (EI, 70 eV): m/z (%) = 260.2 $[M]^+$ (22), 207.0 (7), 179.1 (8), 151.2 (19), 136.1 (24), 124.1 (15), 109.1 (100), 91.1 (9), 81.1 (62), 79.1 (41), 67.1 (6), 53.1 (17), 41.1 (13). HRMS (pos. APCI) calcd for $C_{17}H_{25}O_2^+$ $[M+H]^+$: 261.1849, found: 261.1848. IR (ATR): ν [cm^{-1}] = 2933, 2860, 2251, 1660, 1636, 1449, 1434, 1423, 1386, 1344, 1312, 1269, 1249, 1204, 1136, 1082, 990, 909, 843, 828, 792, 727, 647.

1,6-Di(cyclohex-1-en-1-yl)hexane-1,6-dione (5b). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3c** (1.56 g, 6.7 mmol) and Grignard-reagent **2a** (33.5 ml, 0.60 M, 20.1 mmol, 3.0 equiv). The product was purified by column chromatography (petroleum ether/EtOAc, 10:1) and obtained as a colorless solid in 78% yield (1.44 g, 5.24 mmol). R_f (hexanes/EtOAc, 10:1) = 0.3. ^{1}H-NMR (400.1 MHz, $CDCl_3$): δ = 1.57-1.65 (m, 12H), 2.19-2.26, M, 8H), 2.62-2.66 (m, 4H), 6.87-6.89 (m, 2H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 21.75, 22.15, 23.31, 24.71, 26.22, 37.00, 139.36, 139.78, 201.45. MS (EI, 70 eV): m/z (%) = 274.2 $[M]^+$ (25), 256.2 (10), 150.1 (60), 148.2 (15), 124.1 (30), 109.1 (100), 91.2 (5), 81.2 (50), 53.2 (10). HRMS (pos. ESI) m/z $[M+Na]^+$ calcd for $C_{18}H_{26}O_2Na$ 297.1825, found: 297.1821. IR (ATR): ν [cm^{-1}] = 2927, 2857, 1686, 1659, 1638, 1617, 1462, 1432, 1414, 1387, 1354, 1271, 1271, 1250, 1173, 1140, 1075, 986, 938, 901, 849, 796, 732, 708.

1,4-Phenylenebis(cyclohexen-1-ylmethanone) (5c). This compound was prepared in analogy to **4a** using bis-Weinreb amide **3d** (499 mg, 1.98 mmol) and Grignard reagent **2a** (13.5 ml, 0.44 M in THF, 5.94 mmol, 3.0 equiv). The product was purified by column chromatography (hexanes/EtOAc, 9:1) and obtained as a colorless solid in 52% yield (301 mg, 1.02 mmol). R_f (hexanes/EtOAc, 9:1) = 0.4. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.64-1.76 (m, 8H), 2.24-2.29 (m, 4H), 2.39-2.43 (m, 4H), 6.58-6.60 (m, 2H), 7.62 (s, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.72, 22.06, 23.88, 26.34, 128.73, 138.89, 141.19, 145.27, 197.65. MS (EI, 70 eV): m/z (%) = 294.3 $[M]^+$ (41), 277.2 (8), 266.2 (24), 248.1 (24), 238.1 (11), 213.2 (19), 198.1 (23), 185.0 (100), 157.0 (38), 143.0 (42), 129.0 (41), 115.0 (17), 109.0 (39), 91.0 (8), 81.0 (49), 79.0 (32), 53.0 (9). HRMS (pos. APCI) calcd for $C_{20}H_{23}O_2^+$ $[M+H]^+$: 295.1693, found: 295.1693. IR (ATR): ν [cm^{-1}] = 3054, 2931, 1630, 1496, 1448, 1431, 1421, 1401, 1344, 1307, 1265, 1251, 1237, 1132, 1114, 1013, 972, 932, 893, 853, 824, 733, 702, 605.

(*R*,*R*)-1,4-Di(cyclohex-1-en-1-yl)-2,3-dimethylbutane-1,4-dione (5d).[11] It was observed that the yield of this reaction was reduced by >10% if it was run on a larger scale than 4.0 mmol. Hence, two identical reactions were set up in parallel and then combined in the workup procedure as follows: Two flame-dried, argon-filled 250 ml Schlenk flasks equipped with magnetic stir bars were charged with bis-Weinreb amide **2e** (930 mg, 4.00 mmol, 1.0 equiv each flask) and evacuated and backfilled with argon three times while stirring. Stirring was started, the solid was dissolved in Et_2O (55 ml each flask) and the mixtures were cooled to 0 ºC. A solution of the freshly titrated Grignard reagent **2a** (24.5 ml, 0.49 M in THF, 12.0 mmol, 3.0 equiv) was added to each flask. After 10 minutes, the reaction mixtures were allowed to warm to room temperature and stirring was continued for 16 h. Then, saturated aq.

NH_4Cl solution (50 ml) and H_2O (25 ml) were added to each flask and the mixtures were combined in a separation funnel. The remaining workup was performed as described for diketone **4a**. Purification of the crude mixture by column chromatography (cyclohexane/EtOAc, 20:1) gave the title compound as a yellow oil in 60% yield (1.314 g, 4.789 mmol). The enaniomeric purity was determined to be >99% ee by chiral HPLC (Chiralpak AD-3, heptane/2-propanol = 99:1, 0.5 ml min^{-1}, 22 ºC, t_{major} = 12.85 min, t_{minor} = 11.76 min).[11] R_f (cyclohexane/EtOAc, 20:1) = 0.2. $[\alpha]_D^{25}$ = +90.6º (*c* 1.41; $CHCl_3$). ^1H NMR (500.2 MHz, $CDCl_3$): δ = 1.06-1.11 (m, 6H), 1.55-1.66 (m, 8H), 2.05-2.28 (m, 8H), 3.44-3.52 (m, 2H), 6.93-6.95 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.19, 21.70, 22.15, 23.48, 26.22, 42.32, 138.06, 139.66, 205.54. MS (EI, 70eV): m/z (%) = 274.1 $[M]^+$ (27), 193 (5), 165.1 (25), 109.1 (100), 81.2 (25), 53.2 (5). HRMS (ESI) calcd for $C_{18}H_{26}O_2Na$ $[M+Na]^+$: 297.1825, found: 297.1827. IR (ATR): ν $[cm^{-1}]$ = 2970, 2930, 2875, 2859, 1657, 1636, 1449, 1433, 1385, 1267, 1211, 1187, 1171, 1135, 933, 915, 843, 734, 690.

(*R*,*R*)-1,4-Di(cyclohex-1-en-1-yl)-2,3-dimethoxybutane-1,4-dione (5e). A flame-dried and argon-filled Schlenk flask was charged with bis-Weinreb amide **3f** (1.182 g, 4.473 mmol) and evacuated and backfilled with argon three times while stirring. Et_2O (61 ml) was added and the mixture was cooled to 0 ºC with stirring. Then, cyclohexenylmagnesium bromide lithium chloride adduct **2a** (59.0 ml, 0.23 M in THF, 13.6 mmol, 3.0 equiv) was added. The rest of the reaction was performed following the general procedure for double Grignard additions. After chromatographic purification of the crude mixture (hexanes/EtOAc, 9:4), the title compound (1.005 mg, 3.280 mmol, 73%) was obtained as a yellow oil. R_f (hexanes/EtOAc, 9:4) = 0.3. $[\alpha]_D^{25}$ = +28.7º (*c* 1.16; $CHCl_3$). ^1H NMR (500.2 MHz, $CDCl_3$): δ = 1.55-1.67 (m, 8H), 2.02-2.11 (m, 2H), 2.21-2.32 (m, 6H), 3.36 (s, 6H), 4.65 (s, 2H), 7.04-7.06 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 21.56, 21.96, 23.25, 26.38, 58.63, 82.68, 138.47, 143.07, 198.18. MS (EI, 70eV): m/z (%) = 306.3 $[M]^+$ (1), 197.1 (5), 166.1 (17), 135.1 (24), 109.1 (100), 88.1 (7), 81.1 (32), 53.1 (9). HRMS (ESI) calcd for $C_{18}H_{26}O_4Na$ $[M+Na]^+$: 329.1723, found 329.1723. IR (ATR): ν $[cm^{-1}]$ = 2935, 1722, 1670, 1632, 1450, 1193, 1105.

(*R*,*R*)-(1,3-Dioxolane-4,5-diyl)bis(cyclohex-1-en-1-ylmethanone) (5f). This compound was synthesized in analogy to diketone **5e** using bis-Weinreb amide **3g** (750 mg, 3.02 mmol) as starting material and cyclohexenylmagnesium bromide lithium chloride adduct (14.0 ml, 0.65 M in THF, 9.10 mmol, 3.0 equiv). After chromatographic purification of the crude mixture (cyclohexane/EtOAc, 10:1), the title compound (756 mg, 2.60 mmol, 86%) was obtained as a light yellow oil. R_f (cyclohexane/EtOAc, 10:1) = 0.2. $[\alpha]_D^{25}$ = –131.5º (*c* 2.05; $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.54-1.68 (m, 8H), 2.20-2.37 (m, 8H), 5.12 (s, 2H), 5.31 (s, 2H), 7.12 (dddd, *J* = 1.6, 1.6, 3.9, 3.9 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.54, 21.86, 23.27, 26.50, 77.48, 97.09, 137.76, 144.61, 195.77. MS (EI, 70eV): m/z (%) = 181.1 $[M–C_7H_9O]^+$ (11), 151.1 (6), 109.1 (100), 81.1 (41), 53.1 (10). HRMS (ESI) calcd for $C_{17}H_{22}O_4Na$ $[M+Na]^+$: 313.1410, found: 313.1412. IR (ATR): ν $[cm^{-1}]$ = 2933, 2861, 1729, 1664, 1632, 1449, 1434, 1421, 1387, 1345, 1272, 1213, 1196, 1163, 1089, 985, 940, 874, 729, 696.

(*R*,*R*)-(2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(cyclohex-1-en-1-ylmethanone) (5g). This compound was prepared in analogy diketone **4a** using bis-Weinreb amide **3h** (1.66 g, 6.0 mmol) and Grignard reagent **2a** (60 ml, 0.25 M in THF, 15 mmol, 2.5 equiv). The product was purified by column chromatography (*n*-pentane/EtOAc, 10:1) and obtained as a colorless oil in >99% yield (1.91 g, 6.0 mmol). R_f (*n*-pentane/EtOAc, 10:1) = 0.2. $[\alpha]_D^{25}$ = –43.0º (*c* 0.35; $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.43 (s, 6H), 1.58-1.68 (m, 8H), 2.22-2.32 (m, 8H), 5.36 (s, 2H), 7.14-7.17 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.55, 21.86, 23.24, 26.44, 26.65, 77.55, 112.50, 137.90, 144.57, 196.32. MS (EI, 70 eV): m/z (%) = 318.1 $[M]^+$ (2), 260.0 (6), 209.1 (25), 151.0 (31), 109.0 (100), 85.0 (8), 81.1 (30), 53.1 (6). HRMS (pos. APCI) calcd for $C_{19}H_{27}O_4^+$ $[M+H]^+$: 319.1904, found: 319.1903. IR (ATR): ν $[cm^{-1}]$ = 2987, 2934, 2861, 1666, 1634, 1449, 1435, 1381, 1257, 1200, 1157, 1073, 987, 923, 877, 849, 820, 695, 610.

(*S*)-1,4-Di(cyclohexen-1-yl)-2-methoxybutane-1,4-dione (5h). This compound was prepared in analogy to diketone **4a** using bis-Weinreb amide **3i** (117 mg, 0.5 mmol) and Grignard reagent **2a** (7.1 ml, 0.21 M in THF, 1.5 mmol, 3.0 equiv). The product was purified by column chromatography (hexanes/EtOAc, 10:1) and obtained as a colorless solid in 42% yield (57 mg, 0.21 mmol). The enaniomeric purity was determined to be >99% ee by chiral HPLC (Chiralcel LC-4, heptane/EtOH= 95:5, 0.5 ml min^{-1}, 22 ºC, t_{major} = 11.72 min, t_{minor} = 13.92 min). R_f (hexanes/EtOAc, 10:1) = 0.2. $[\alpha]_D^{25}$ = –35.5º (*c* 1.02; $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.58-1.66 (m, 8H), 2.20-2.30 (m, 8H), 2.86 (dd, *J* = 4.7, 16.6 Hz, 1H), 3.08 (dd, *J* = 7.5, 16.6 Hz, 1H), 3.30 (s, 3H), 5.01 (dd, *J* = 4.7, 7.5 Hz, 1H), 6.91-6.94 (m, 1H), 7.03-7.07 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.65, 22.03, 22.04, 23.24, 23.37, 26.32, 26.37, 39.75, 57.67, 77.28, 138.09, 139.48, 141.43, 141.70, 198.00, 199.50. MS (CI): m/z (%) = 277.1 $[M+H]^+$ (100), 262.1 (14), 245.1 (77), 109.0 (49), 81.0 (5). HRMS (pos. ESI) calcd for $C_{17}H_{24}O_3Na^+$ $[M+Na]^+$: 299.1618, found: 299.1619. IR (ATR): ν $[cm^{-1}]$ = 2932, 2860, 1663, 1634, 1449, 1434, 1422, 1387, 1344, 1286, 1272, 1190, 1117, 993, 908, 729, 647.

***rac*-1,4-Di(cyclohexen-1-yl)-2-methoxybutane-1,4-dione (*rac*-5h).** This compound was prepared in analogy to diketone **4a** using bis-Weinreb amide *rac*-**3i** (234 mg, 1.0 mmol) and Grignard reagent **2a** (10.5 ml, 0.285 M in THF, 3.0 mmol, 3.0 equiv). The product was purified by column chromatography (hexanes/EtOAc, 10:1) and obtained as a colorless solid in 45% yield (125 mg, 0.45 mmol). R_f (hexanes/EtOAc, 10:1) = 0.2. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.58-1.66 (m, 8H), 2.20-2.30 (m, 8H), 2.86 (dd, *J* = 4.7, 16.6 Hz, 1H), 3.08 (dd, *J* = 7.5, 16.6 Hz, 1H), 3.30 (s, 3H), 5.01 (dd, *J* = 4.7, 7.5 Hz, 1H), 6.91-6.94 (m, 1H), 7.03-7.07 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.65, 22.03, 22.04, 23.24, 23.37, 26.32, 26.37, 39.75, 57.67, 77.28, 138.09, 139.48, 141.43, 141.70, 198.00, 199.50. MS (CI): m/z (%) = 277.1 $[M+H]^+$ (100), 262.1 (12), 245.1 (71), 109.0 (55), 81.1 (6). HRMS (pos. ESI) calcd for $C_{17}H_{24}O_3Na^+$ $[M+Na]^+$: 299.1618, found: 299.1619. IR (ATR): ν $[cm^{-1}]$ = 2931, 2860, 1663, 1635, 1449, 1434, 1423, 1387, 1344, 1312, 1272, 1191, 1119, 993, 922, 836, 798, 730.

(*R*,*R*)-(2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(cyclopent-1-en-1-ylmethanone) (5i). This compound was prepared in analogy to diketone **4a** using bis-Weinreb amide **3h** (501 mg, 1.81 mmol) and Grignard reagent **2b** (14 ml, 0.35 M in THF, 4.9 mmol, 2.7 equiv). The product was purified by column chromatography (hexanes/EtOAc, 10:1) and obtained as a colorless oil in 54% yield (285 mg, 0.98 mmol). R_f (hexanes/EtOAc, 10:1) = 0.2. $[\alpha]_D^{25}$ = –48º (*c* 1.00; $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$): δ = 1.42 (s, 6H), 1.86-1.94 (m, 4H), 2.56-2.63 (m, 8H), 5.26 (s, 2H), 7.05-7.07 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.38, 26.73, 31.10, 34.66, 79.48, 112.81, 143.56, 148.01, 194.44. MS (EI, 70 eV): m/z (%) = 290.0 $[M]^+$ (1), 232.0 (5), 195.1 (18), 137.0 (29), 95.0 (100), 67.0 (4), 41.0 (5). HRMS (pos. ESI) calcd for $C_{17}H_{23}O_4^+$ $[M+H]^+$: 291.1591, found: 291.1593. IR (ATR): ν $[cm^{-1}]$ = 2939, 1665, 1609, 1457, 1431, 1381, 1372, 1297, 1259, 1212, 1179, 1155, 1104, 1063, 1041, 980, 896, 857, 809, 782, 727, 611.

1,5-Bis(3,4-dihydronaphthalen-1-yl)pentane-1,5-dione (5j). This compound was prepared in analogy to diketone **2a** using bis-Weinreb amide **3b** (655 mg, 3.0 mmol) and Grignard reagent **2j** (18.1 ml, 0.415 M in THF, 7.5 mmol, 2.5 equiv). The product was purified by column chromatography (hexanes/EtOAc, 10:1) and obtained as a colorless solid in 80% yield (860 mg, 2.41 mmol). R_f (hexanes/EtOAc, 10:1) = 0.5. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 2.11 (quint, *J* = 7.1 Hz, 2H), 2.42 (td, *J* =

4.9, 7.9 Hz, 4H), 2.75 (t, *J* = 7.9 Hz, 4H), 2.90 (t, *J* = 7.1 Hz, 4H), 6.96 (t, *J* = 4.9 Hz, 2H), 7.15-7.23 (m, 6H), 7.62-7.64 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 19.85, 23.71, 27.58, 38.90, 126.40, 126.58, 127.74, 127.81, 131.05, 136.58, 137.96, 139.18, 201.90. MS (EI, 70 eV): m/z (%) = 356.1 $[M]^+$ (100), 338.2 (31), 296.1 (6), 225.1 (42), 197.2 (15), 186.2 (42), 174.2 (13), 165.1 (16), 157.2 (60), 141.1 (15), 128.1 (96), 115.1 (8). HRMS (pos. ESI) calcd for $C_{25}H_{25}O_2^+$ $[M+H]^+$: 357.1849, found: 357.1851. IR (ATR): ν [cm^{-1}] = 3059, 2938, 2831, 2248, 1671, 1612, 1483, 1450, 1425, 1379, 1325, 1241, 1139, 1094, 1044, 1021, 944, 909, 834, 764, 728, 689, 647, 568.

***rac-trans*-2-(Cyclohex-1-ene-1-carbonyl)-*N*-methoxy-*N*-methylcyclohexane-1-carboxamide (6).** A flame-dried and argon-filled 25 ml Schlenk flask was charged with bis-Weinreb amide **3j** (103 mg, 0.40 mmol, 1.0 equiv). While stirring, the vessel was evacuated and backfilled with argon three times. Et_2O (5.6 ml) was added and the solution was cooled to 0 °C. A freshly prepared solution of reagent **2a** (0.23 M in THF, 5.3 ml, 1.2 mmol, 3.0 equiv) was added over 5 min. During the addition, the mixture turned turbid first and then clear again. The mixture was heated to reflux for 21 h (oil bath temperature = 65 °C) and the reaction was quenched after cooling to room temperature by addition of saturated aq. NH_4Cl (5 ml), followed by H_2O (5 ml) and Et_2O (5 ml). The biphasic mixture was stirred for 5 min at room temperature, the layers were separated and the organic layer was washed with aq. HCl (1 M, 3 x 10 ml). The combined aqueous layers were extracted with Et_2O (3 x 15 ml), and the combined organic layers were then washed with saturated aq. $NaHCO_3$ solution (25 ml) and brine (25 ml), dried over Na_2SO_4 and filtered. The solvents were removed under reduced pressure and the residue was purified by column chromatography (cyclohexane/EtOAc, 2:1→0:100). The title compound (55.2 mg, 0.198 mmol, 50%) was obtained as a colorless oil. R_f (cyclohexane/EtOAc, 2:1) = 0.3. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 1.12-1.43 (m, 4H), 1.53-1.65 (m, 4H), 1.73-1.82 (m, 2H), 1.89-2.11 (m, 3H), 2.20-2.32 (m, 3H), 3.12 (br, 4H), 3.44 (ddd, *J* = 3.4, 10.6, 10.6 Hz, 1H), 3.82 (br, 3H), 6.98-7.02 (m, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.65, 22.10, 23.44, 25.87, 26.00, 26.21, 28.86, 30.87, 32.04 (br), 41.63, 45.65, 61.52, 137.79, 140.07, 176.11 (br), 204.73. MS (EI, 70eV): m/z (%) = 249.3 (5), 219.2 $[M–C_2H_6NO]^+$ (100), 191.2 (11), 109.1 (72), 81.1 (27), 79.1 (17), 53.1 (6), 41.1 (7). HRMS (ESI) calcd for $C_{16}H_{25}NO_3Na$ $[M+Na]^+$: 302.1727, found: 302.1726. IR (ATR): ν [cm^{-1}] = 2930, 2857, 1657, 1448, 1384, 1342, 1248, 1186, 1119, 1000, 981.

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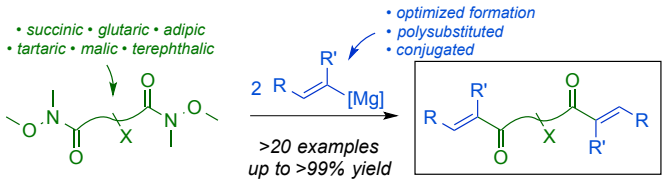

The synthesis of bis-enones from alkenyl bromides and α,ω-bis-Weinreb amides via a double Grignard reaction is reported. The work contains reliable protocols for the double addition and the efficient generation of the required substituted alkenyl Grignard reagents from alkenyl bromide precursors.

Bis-enone Synthesis*

*Stefan Wiesler, Michael A. Bau, Thomas Niepel, Sara L. Younas, Hieu-Trinh Luu, Jan Streuff**

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Synthesis of α,ω-Bis-Enones by the Double Addition of Alkenyl Grignard Reagents to Diacid Weinreb Amides