Synthesis A. G. Griesbeck et al. Feature

Photocaged Hydrocarbons, Aldehydes, Ketones, Enones, and Carboxylic Acids and Esters that Release by the Norrish II Cleavage Protocol and Beyond: Controlled Photoinduced Fragrance Release

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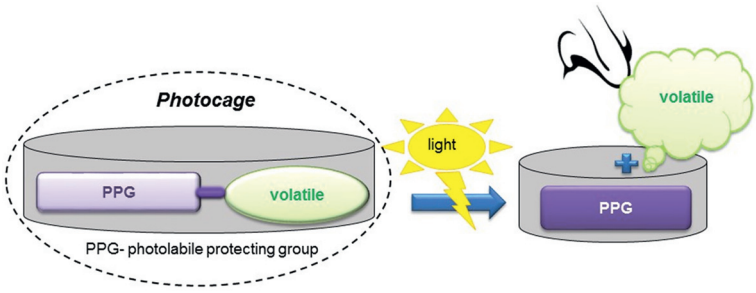

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Abstract Five families of caged fragrance compounds that allow the storage and release of the following small volatile organic molecules are described: terpene hydrocarbons, aldehydes, ketones, Michael-type α,β-unsaturated enones, and carboxylic acids and esters. These caged molecules are released by photoexcitation via carbonyl-directed hydrogen-transfer processes and subsequent C–C bond cleavage (Norrish Type II) or by didenitrogenation of diazirines.

Key words caged molecules, photochemistry, hydrogen transfer, carbonyl compounds, dinitrogen release

Chemical caging describes a technique that makes molecules more stable, easier transportable, less reactive (or less volatile, less sensitive, less aggressive) and eventually releasable under controlled conditions.[1–3] The term *caging* is somewhat misleading because it is reminiscent of a bird in a cage, i.e. a noncovalent interaction in a supramolecular host–guest complex (like the legendary hemicarcerand-caged cyclobutadiene).[4] Many examples, however, refer to covalently linked structures where specific chemical bonds are designed that can be cleaved by controlled methods. The tools for release can be diverse and include pH changes, enzymatic processes, thermolysis or photolysis, to mention just a few. It is of course relevant that the initial fragments generated by *decaging* be rapidly converted into the desired molecules and not lead to secondary chemistry as, for example, in the concept of photoaffinity labeling.[5,6] *Photocages* are compounds that release the desired molecule either by direct electronic excitation,[7] by triplet sensitization[8] or by photoinduced electron-transfer mechanisms.[9] They are especially valuable because light, a traceless reagent, is used for all cases and, thus, the absorptive properties (excitation wavelength, absorbance, quantum yields of chemical versus nonchemical pathways) and not chemical properties are crucial for the *decaging* efficiency. The molecules that are released by the different release mechanisms can have a wide variety of potential functions. Clearly, pharmacologically active molecules are the most relevant group of targets that have to be selectively transported and site-specifically released.[10] Possible advantages of the cage-and-release concept can be summarized as follows: a) lower amounts of the active compound are needed because of less undesired effects during transport, b) spatial control of the release is possible with spatially controllable techniques such as one- or two-photon excitation by UV or visible light for photorelease or magnetic field activation for thermal release, c) temporal control is possible for photoexcitation using on/off irradiation periods and variable irradiation power. Besides applications in drug release,[11] use in numerous other fields is conceivable such as pheromone release,[12] synthetic chemistry as photolabile protecting groups (PPGs)[13–15] and immunoassay screening.[16,17] The caged molecules can be as simple as nitrous oxide[18,19] or carbon monoxide,[3] or of medium complexity such as aliphatic ketones or lactones[20] up to large proteins useful for cell penetration and release.[21]

In the context of this concept, we have developed several families of fragrance photocages. Fragrances are extracted from natural sources or produced on large scales industrially for numerous applications. In cleaning agents, fragrances mask the odor of other components; in perfumes, fragrances are used to maintain the desired long-lasting olfactory effects. A characteristic property of fragrances is their volatility, obviously the basic requirement for olfactory detection. This directly implies that the application of

Biographical Sketches

Axel Griesbeck studied chemistry at the University of Munich and graduated in the group of Klaus Gollnick in 1984. After postdoctoral research at the University of Würzburg, ETH Zürich and Weizmann Institute, Rehovot (with Profs. Adam, Seebach and Fischer), he finished his Habilitation at the University of Würzburg. After a guest professorship at the University of Madison at Wisconsin, he was appointed Professor of Organic Chemistry at the University of Cologne. He has been a guest professor at the Universities of Tsukuba and Taipei, an IUPAC fellow and secretary of the Organic Chemistry Division and chairman of the Photochemistry Section of the German Chemical Society, and has published more than 275 papers and 20 patents in the area of organic photochemistry. Currently, he is an editor of *ChemPhotoChem*.

Björn Porschen studied chemistry at the University of Cologne from 2002–2011 (Diploma). He joined Prof. Griesbeck's group and, within four years of research, he earned his doctorate degree studying the photorelease of limonene from photocages.

Christian Kropf studied chemistry at Saarland University (1986–1991) and the Leibniz Institute for New Materials (1992, Diploma thesis), both in Saarbrücken, Germany. Under the supervision of Prof. Dr. Helmut K. Schmidt, he earned his doctorate degree studying nanotechnology (1998). In 1998, he joined Henkel AG & Co. KGaA, Düsseldorf, as a laboratory manager in corporate research. From 2001–2002 he worked as a technical director for SusTech GmbH & Co. KGaA, Darmstadt, a nanotechnology and materials science start-up initiated by Henkel. After that, he returned to Henkel corporate research as a group leader. Since 2008, he has been head of the synthesis group within the international research department of Henkel's laundry and home care division.

Agnieszka Landes came from Kędzierzyn-Koźle, Poland in 2005 to study chemistry at the University of Cologne. In 2011 she was awarded with her Diploma and in 2015 she received her PhD in the working group of Prof. Griesbeck studying the synthesis and photochemical as well as photophysical properties of photocage compounds.

Olga Mayer (formerly Hinze) studied agricultural science at the Agricultural Academy in Yaroslavl, Russia (1995–2000, Dipl. Ing.) and chemistry at the University of Cologne (2002–2007, Dipl. Chem.). She joined Prof. Griesbeck's group at the University of Cologne in 2007 and obtained her PhD in 2011. From 2012, Dr. Mayer has been working at Dr. Knoell Consult GmbH.

Ursula Huchel studied chemistry at the University of Konstanz from 1989–1995 and received her doctorate degree (1998) in the field of carbohydrate chemistry with Prof. Dr. R. R. Schmidt as supervisor. In 1999 Uschi started her profession with Henkel AG& Co KGaA as technical marketer and changed to corporate research in 2000 as laboratory manager. From 2007 to 2015 she worked as head of R&D for the Henkel Fragrance Center. Since 2015, Uschi leads a group with focus on fragrance innovation in Henkel's laundry and home care division.

Thomas Gerke studied chemistry at the Technical University in (West) Berlin from 1976 to 1982, finishing with a Diploma degree in the group of Prof. Kleinkauf. He then joined Prof. Ferdinand Bohlmann's group at the same university and, in 1986, received his doctorate degree working on structure elucidation and synthesis of natural compounds. In 1987, he started working at the Düsseldorf-based Henkel AG & Co. KGaA in various positions and countries. He is an inventor in the field of active ingredients, mainly fragrance and cosmetic chemistry.

fragrances as flavoring agents or as perfume components is time limited, because of the fragrance volatility. This could be a disadvantage in commercial applications when, by premature volatilization, intended effects of fragrances are reduced or even completely lost. A solution to this problem can be pro-perfumes, which are also termed fragcages.[22] From these cages, fragrances can be released by cleaving a covalent bond induced by an appropriate reaction.[23] In the following sections, we concentrate on photochemical release processes and describe the principles and a set of photocage families. Representative examples of fragrances for these families are limonene (**1**), octanal (**2**), ethyl cinnamate (**3**) and δ-damascone (**4**) (Figure 1).

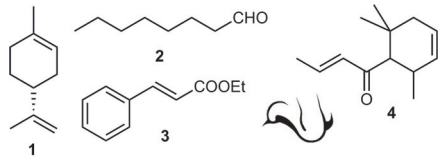
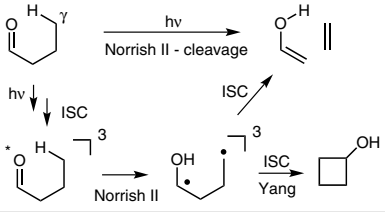


Figure 1 Characteristic fragrance model compounds for caging

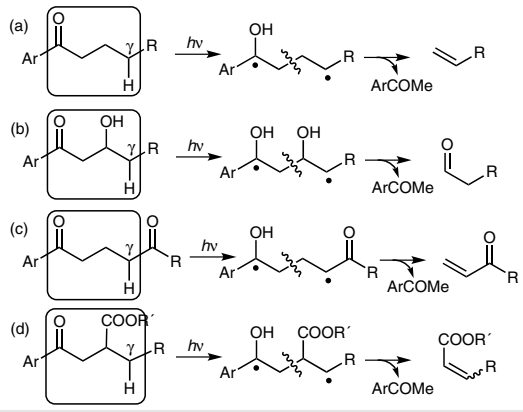
The Norrish Type II Photochemical Cleavage in a Nutshell

The hydrogen transfer from a γ-CH position followed by cleavage of the α,β-carbon–carbon single bond, initiated from an electronically excited state (singlet or triplet) of a carbonyl compound, is one of the archetype reactions in organic photochemistry.[24] Numerous carbonyl compounds undergo this intramolecular hydrogen atom abstraction and form 1-hydroxy-1,4-biradicals.[25] These open-shell species, that are well characterized when formed from their triplet precursors, can undergo two competing reactions: radical–radical coupling to produce cyclobutanols versus homolytic cleavage of the central C2–C3 bond to produce alkenes and enols (Scheme 1).



Scheme 1 Norrish II carbonyl photochemistry involving triplet states (ISC = intersystem crossing)

The dominating path following an intramolecular hydrogen abstraction is the Type II photoelimination discovered by Norrish, who described that dialkyl ketones with at least one γ-C–H bond cleave to ketones and alkenes rather than to acyl and alkyl radicals.[26] The Norrish Type I path is observed in the carbonyl photochemistry of substrates without γ-C–H bonds that can form stabilized C-radicals, such as *tert*-butyl phenyl ketone. Cleavage and cyclization processes do compete in certain ketones and the overall quantum yields are particularly low whenever the Type II process occurs. From a mechanistic point of view, the Type II cleavage reaction can, in principle, be considered as a concerted 1,5-hydrogen transfer accompanied by C–C bond cleavage in a six-atom cyclic transition state leading to an alkene and the enol tautomer, which was initially verified by Calvert and Pitts using transient IR spectroscopy.[27] The competing cyclobutanol formation was discovered by Yang and Yang, and they also suggested that cleavage and cyclization both arise from a 1,4-biradical intermediate formed by γ-hydrogen abstraction by the excited carbonyl group.[28] Subsequent trapping experiments and electron-transfer experiments involving the intermediate 1-hydroxy-1,4-biradicals, and eventually transient absorption spectroscopy,[29] established these species in the nano- to microsecond lifetime regime.[30,31] In order to release diverse structure families, the basic Norrish II substrates (that are able to produce alkenes (a) beside the primary enols) have to be tuned to the desired products by introducing further functional groups that lead to the formation of aldehydes (b), Michael ketones (c) or α,β-unsaturated carboxylic acid derivatives (d) (Scheme 2).

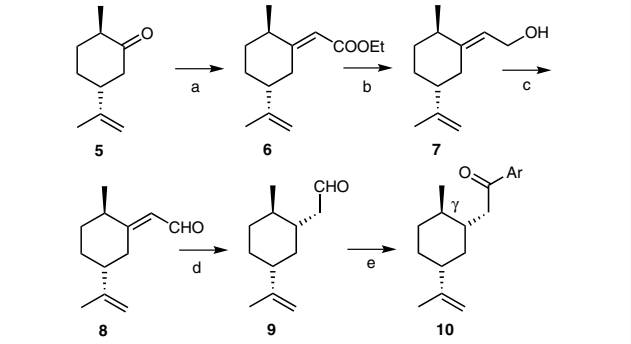


Scheme 2 Cage and release strategies for four Norrish II carbonyl routes

Two Different Norrish Type II Approaches for Limonene

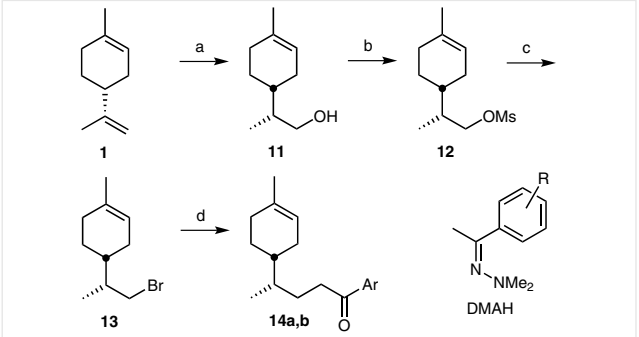
Limonene (**1**) is an inexpensive fragrance component, utilized in nearly every cosmetics or laundry formulation. As such, it might be the natural terpene to which humans have the highest exposure. Due to its hydrophobicity and volatility, limonene is often applied in excess in numerous applications. Controlled release from a stable and less volatile photocage stimulated by light therefore appeared as a useful alternative. Limonene is an unfunctionalized 1,5-diene and therefore a tricky substrate for the introduction of photoreleasing groups: no anchoring groups are present and the two double bonds have to be differentiated in the caging strategy.

In a first approach, we designed a cage pathway generating the *endocyclic double bond* of limonene by photocleavage: the appropriate substrates for this photocage are (*R*)-limonene (**1**) itself and dihydrocarvone (**5**). Both are commercially available, dihydrocarvone as a mixture of isomers contains a small amount of isodihydrocarvone; however, this undesired byproduct can be easily separated during the synthetic steps. Starting from (+)-dihydrocarvone (**5**), cage compounds **9** and **10** were synthesized by HWE olefination to give the vinyl ester **6**, followed by a reduction to the allyl alcohol **7** as described by Srikrishna et al.[32] Oxidation of **7** with manganese dioxide results in enal **8**, the desired substrate for enantioselective reduction of the carbon–carbon double bond of the Michael system with Hantzsch esters as hydride donor.[33] We envisaged the synthesis of both possible diastereoisomers of **9** in order to investigate the differences in photorelease. Conversely, under all conditions investigated, isomer **9** was formed as sole product with all substituents of the cyclohexane chair in equatorial position (Scheme 3). This is a result of complete substrate control, so that the *tert*-butyl group of the reduction catalyst was not able to control the stereochemistry. Aldehyde **9** was subjected to arylation with phenyllithium or 4-methoxyphenyllithium[34] and eventually by *in situ* oxidation gave the phenones **10** (**10a**, Ar = Ph; **10b**, Ar = *p*-$MeOC_6H_4$).[35] The overall yields for these Norrish II cages **10a** and **10b** were 10% and 17%, respectively.



Scheme 3 *Reagents and conditions*: a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, r.t., 16 h, 95%; b) $LiAlH_4$, Et_2O, reflux, 1 h, 92%; c) MnO_2, CH_2Cl_2, r.t., 64 h, 60%; d) Hantzsch ester, MacMillan catalyst, $CHCl_3$, –30 °C, 18 h, 79%; e) 1. ArBr, *n*-BuLi, Et_2O, r.t., 16 h; 2. *t*-BuOOH, CrO_3, CH_2Cl_2 (**10a**, Ar = Ph, 25%; **10b**, Ar = *p*-$MeOC_6H_4$, 42%).

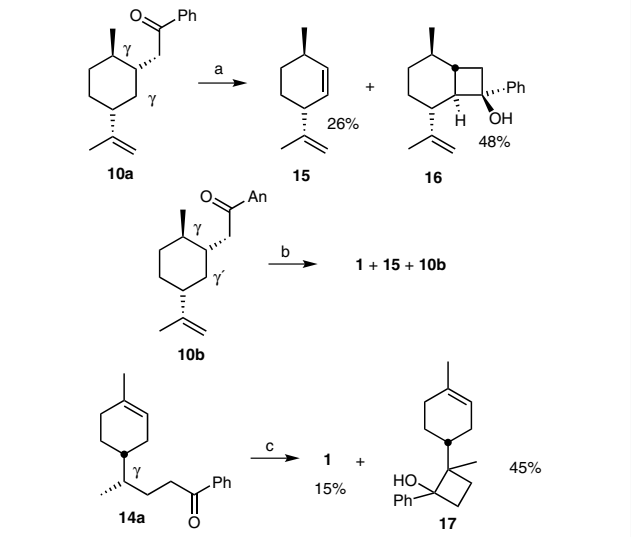
The second approach targets the *exocyclic double bond* of limonene. Hydroboration of the less hindered double bond using disiamylborane is highly regioselective and delivers a 3:2 mixture of diastereoisomers (major shown in Scheme 4).[36] The major stereoisomer was purified via the corresponding 3,5-dinitrobenzoates[37] and transformed into the bromide **13** via the mesylate **12**.[38] The phenone cages **14a**,**b** were synthesized from **13** by treatment with the corresponding deprotonated acetophenone *N*,*N*-dimethylhydrazones.[39]



Scheme 4 *Reagents and conditions*: a) 1. Sia_2BH, Et_2O, r.t., 3 h; 2. H_2O_2, NaOH, THF, 16 h, r.t., 80%; b) MsCl, pyridine, r.t., 18 h, 99%; c) LiBr, THF, reflux, 4 h, 65%; d) 1. *n*-BuLi, DMAH (R = H, *p*-OMe), 0 °C, 1 h; 2. **13**, r.t., 24 h (**14a**, Ar = Ph, 42%; **14b**, Ar = *p*-$MeOC_6H_4$, 16%).

These different cage compounds **10a**,**b** and **14a**,**b** in methanol solutions were irradiated with the emission of a coated mercury low-pressure lamp centered around 350 nm. We discovered a distinct substituent effect on the photochemistry of the cage compounds **10a**,**b** (Scheme 5): whereas the phenyl derivative **10a** was completely converted after 3 hours, the anisyl compound **10b** needed more than 18 hours for 75% conversion. From both substrates, isolimonene (**15**) was formed as the major Norrish II cleavage product and, in the case of the phenyl substrate **10a**, also large amounts of the Norrish–Yang cyclization product **16** were formed. After longer irradiation time, the anisyl derivative **10b** delivered an inseparable mixture of isomeric limonenes, substrate and further photoproducts that could not be identified.

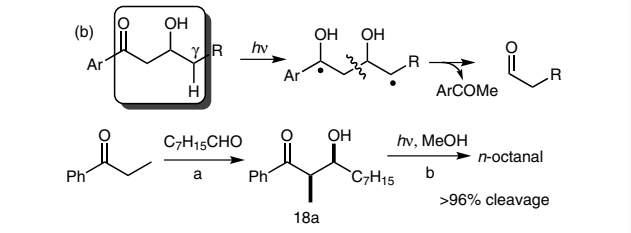
From the cage **14a**, limonene and acetophenone were the sole Norrish II cleavage products, however accompanied by large amounts of the Yang cyclization product **17**. **14b** did not deliver limonene even after prolonged irradiation time. Thus, none of the Norrish II cages that were synthesized from dihydrocarvone or limonene proved to be efficient for limonene release. For compound **10a**, this is most probably a result of the energetically preferred chair-like six-membered transition state for hydrogen transfer. Because all substituents are equatorial in the lowest energy conformation, equatorial hydrogen transfer occurs preferentially from the γ′-position, and either cleavage to give isolimonene (**15**) or cyclization follows. As we have already found for other phenacyl cages,[40] 4-methoxyphenacyl compounds such as **10b** show retarded photochemistry and, for the first time, also limonene formation was observed from **10b** beside the dominating isolimonene (**15**) without Yang cyclization products. The alternative photocage **14a** showed fast and selective hydrogen transfer, however with preferential formation of the Yang photocyclization product **17**. Limonene (**1**) was released in a maximum yield of 15% after full conversion (Scheme 5).



Scheme 5 *Reagents and conditions*: 20 mM cage solutions in MeOH, *hν* (coated mercury low-pressure lamp, λ = 350 ± 20 nm), r.t., argon purging; a) 3 h for full conversion; b) 18 h for 75% conversion (An = anisyl); c) 8 h for full conversion. GC yields are given; acetophenone could not be detected quantitatively.

The Photo-Retro-Aldol Approach for Cyclic and Long-Chain Aliphatic Aldehydes and Michael Ketones

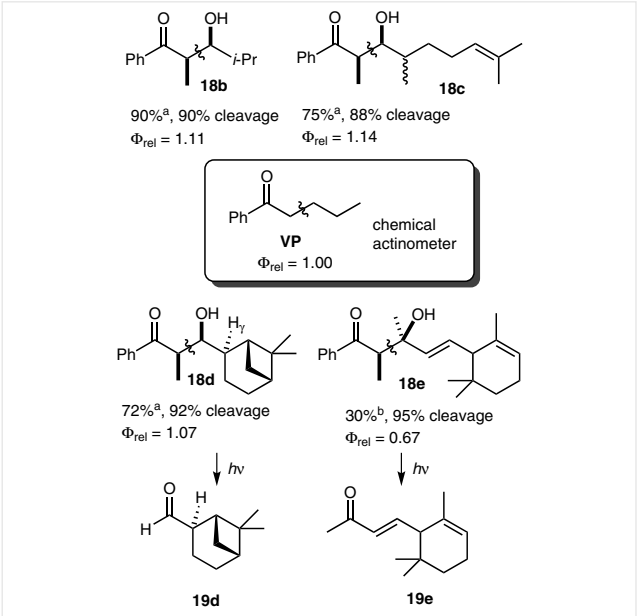
The photochemical release of aliphatic aldehydes follows the aldol route (b) as described in Scheme 2.[40] Although aldols are *per se* able to function as thermal cages for the substrate carbonyl compounds because of their notorious retro-aldol reactivity, controlled release without competing condensation to give Michael products is cumbersome. This is, fortunately, not the case for the photo-retro-aldol route.[41] For the model compound octanal (**2**), the photochemical release process was compared with the valerophenone actinometer ($\Phi_{313\,nm}$ = 0.65 for acetophenone formation)[42] and a 112% relative activity of cleavage product formation was determined for the 300 nm photolysis of cage **18a**, resulting in a Φ_{cl} = 0.73. In methanol as solvent, no other products were detected beside octanal and acetophenone, corresponding to a >96% cleavage efficiency



Scheme 6 *Reagents and conditions*: a) $TiCl_4$, Bu_3N, CH_2Cl_2, −78 °C, 80%, *syn*/*anti* 95:5; b) 20 mM cage solution in MeOH, *hν* (coated mercury low-pressure lamp, λ = 350 ± 20 nm), r.t.

(Scheme 6). In aqueous solutions, the Norrish II cleavage of valerophenone proceeds with near unity quantum yields in an irradiation window of 290–330 nm.[43]

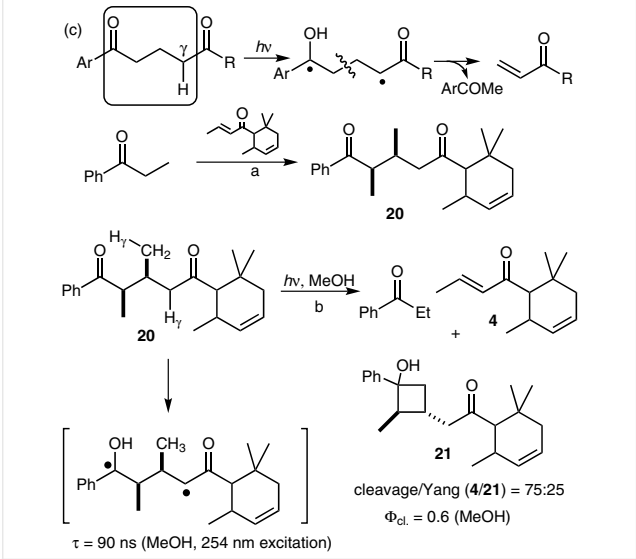
The octanal photocage **18a** and many analogous compounds (selected examples **18b–e** are shown in Scheme 7) were synthesized by *syn*-selective Mukaiyama aldol reactions using titanium[44] or tin enolate routes.[45] In all cases, photolyses of these photocages delivered the protected carbonyl compounds, among them important fragrance molecules like myrtanal (**19d**) from **18d** and the Michael system α-ionone (**19e**) from **18e**. The latter example is special in two ways: a Michael ketone is formed in moderate quantum yield and the hydrogen abstraction occurs only from a nonactivated methyl group. The relative quantum yield for this cleavage reaction (determined by GC for the formation of propiophenone) is 0.67 relative to the chemical actinometer, resulting in an absolute quantum yield for bond cleavage of 0.44. This reflects the less efficient hydrogen transfer from a methyl group relative to a tertiary hydrogen as in the myrtanal cage **18d**. In comparison with the other carbonyl cages, **18e** was very selective in Norrish II cleavage, also indicating that a high-energy intermediate (i.e., the triplet 1,4-biradical) is formed from this substrate that is even more reactive than the corresponding intermediates from **18a–d**.



Scheme 7 A series of phenacyl cages **18b–e**, with their synthetic yields and release properties. *Reagents and conditions*: [a] $TiCl_4$, Bu_3N, CH_2Cl_2, −78 °C; [b] $Sn(OTf)_2$, *N*-ethylpiperidine, 0 °C; cleavage: 20 mM cage solutions in MeOH, *hν* (coated mercury low-pressure lamp, λ = 350 ± 20 nm), r.t. Relative quantum yields for decay were determined by GC with respect to the decay quantum yield of valerophenone (**VP**), in part from ref. 40.

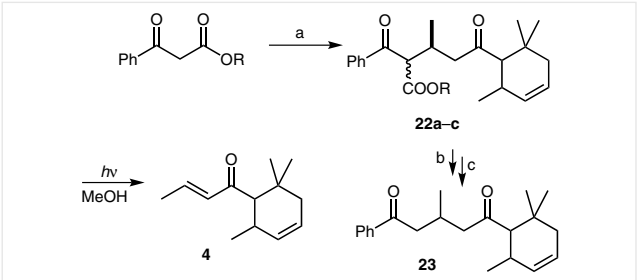
Two Norrish Type II Approaches for the Model Enone δ-Damascone

The damascones constitute a class of highly relevant fragrance components. Several constitutional isomers exist, with the δ-isomer as one of the most prominent and industrial relevant representatives.[46] In contrast to α-ionone (**19e**, see Scheme 7), δ-damascone (**4**) cannot be caged by a classical aldol route. As shown in Scheme 8, a *syn*-selective cerium enolate route[47] was successfully applied for the synthesis of 1,5-diketone **20** from propiophenone and δ-damascone. Photocage **20** has two possible γ-hydrogen positions than can be activated by the electronically excited phenacyl chromophore: the β-methyl group and the methylene group of the linear hydrocarbon chain. Hydrogen transfer from the methyl group and subsequent Norrish cleavage would lead to the deconjugated damascone isomer, that was not observed. The cyclization ('Yang') product **21** is the only product from this obviously less efficient hydrogen transfer. In a detailed mechanistic study,[40] we have detected two transients with the short-lived component (absorbing at 400 nm) interpreted as the triplet 1,4-biradical derived from γ-hydrogen transfer from the CH_2 group. The solvent-dependent lifetimes span 60–120 nanoseconds and the transients are quenched by oxygen, in agreement with literature data.[29]



Scheme 8 *Reagents and conditions*: a) LDA, THF, –78 °C, then $CeCl_3$, then δ-damascone, 80%, *syn*/*anti* >95:5; b) 20 mM cage solution in MeOH, *hv* (coated mercury low-pressure lamp, λ = 350 ± 20 nm), r.t.; from ref. 40.

Due to the fact that the syntheses of **20** and other enone cages were somewhat elaborate and could not easily be upscaled, we searched for more convenient routes to these photocages. Useful alternative structures were benzoylacetate cages that could be synthesized following the $FeCl_3$ catalysis route developed by Christoffers (Scheme 9).[48] This route proved to be highly flexible and directly delivered photoactive compounds that release enones in high yields after short to medium irradiation times. As an additional benefit, diverse ester groups can be introduced right from the start, e.g. benzyl groups as in **22b** or long alkyl chains as in **22c** that make these cages amphiphilic (from the corresponding benzyl[49] or dodecyl esters). Saponification and acidic workup leads to the decarboxylated cage compound **23** (α-demethylated analogue of **20**) with similar δ-damascone release properties. The iron-catalyzed Michael addition also works smoothly with other enones; only β,β′-disubstituted enones gave lower yields (e.g., **25** from mesityl oxide, Figure 2).[50]



Scheme 9 *Reagents and conditions*: a) δ-damascone (1 equiv), $FeCl_3 \cdot 6\,H_2O$ (10–20 mol%), $CHCl_3$, 50 °C (**22a**, R = Et, 85%; **22b**, R = Bn, 86%; **22c**, R = n-$C_{12}H_{25}$, 88%; *syn*/*anti* ca. 55:45); b) from **22a**: KOH, MeOH, reflux, 16 h; then c) HCl to pH 1, 65%.

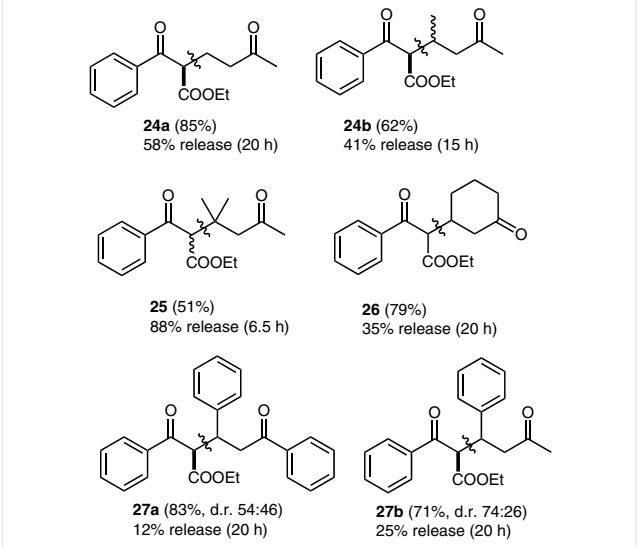


Figure 2 A series of benzoylacetate cages **24**–**27**, with their synthetic yields ($FeCl_3$ route) and release properties. *Reagents and conditions*: 20 mM cage solutions in MeOH, *hv* (coated mercury low-pressure lamp, λ = 350 ± 20 nm), r.t. Cleavage determined by GC measurement of ethyl benzoylacetate formation.

The benzoylacetate cages show slow photoinduced Norrish II cleavage in solution, with maximum conversions of 60–90%. This is a consequence of the internal filter effect that arises from the released benzoylacetate that complete-

ly covers the cage absorption at higher conversions. From the diastereoisomeric mixture of cage **27**, *E*/*Z*-chalcones are released that add to this filter effect. As a characteristic example, the UV/Vis absorption spectra of ethyl ester **22a** and its two cleavage products, in methanol, are shown in Figure 3. Two starting materials were detected by GC, corresponding to the keto and enol form of **22a** with the enol form absorption redshifted in the UV spectrum. This effect increases for ethyl benzoylacetate, indicating that even more enol form is present in the equilibrium.[51]

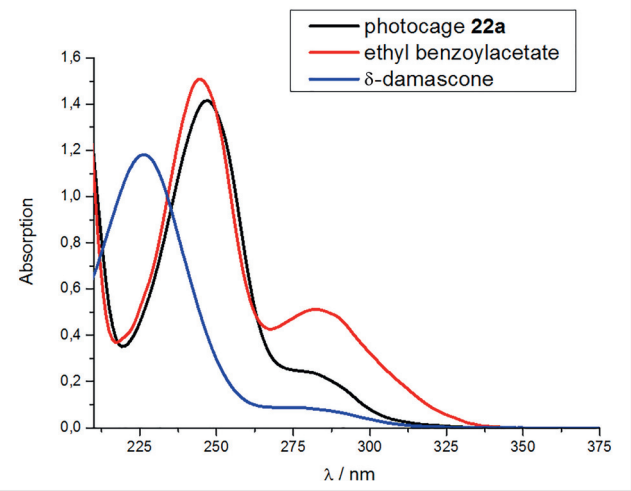


Figure 3 UV absorption properties of the photocage **22a** and its release products: the 290 nm maximum originates from the enol form of ethyl benzoylacetate

The time profile for the photocage cleavage of dodecyl ester **22c** is shown in Figure 4. The photolysis mixture consists of the keto isomer of **22c** that is rapidly degraded and the enol isomer that slowly disappears because of slow tautomerization and subsequent photocleavage. The *E*,*Z*-damascones increase in signal intensity and level out at 80% conversion. The *E*/*Z* ratio of δ-damascone (**4**) remained constant (10:1) over the whole irradiation period, indicating that there is no direct or sensitized *E*/*Z* isomerization of **4**. As an additional route, Yang cyclization results in the formation of a cyclobutanol of unknown structure (from GC/MS analysis).

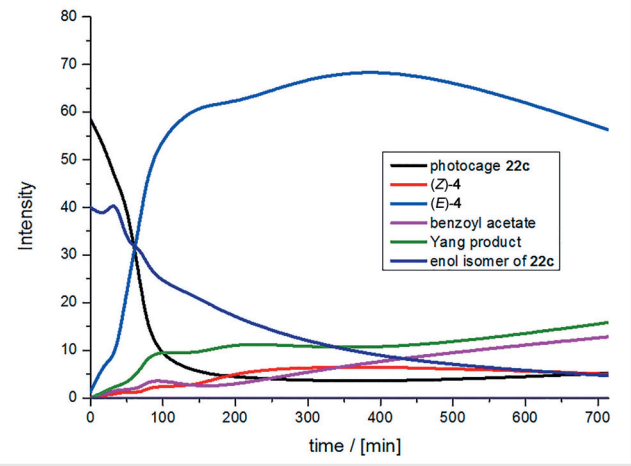


Figure 4 Time profile for the photolysis (350 nm) of **22c** in MeOH (by GC/MS); relative intensities of GC signals are shown with respect to 100% for the keto/enol mixture of **22c**.

Another useful analytical tool to quantify cage release during irradiation of a textile sample is diffuse reflectance UV spectroscopy (DRS).[52] Figure 5 shows the time profile for the release of δ-damascone from the benzyl cage **22b** using this technique. Strongly absorbing compounds at the surface of a solid sample lead to a corresponding decrease in reflectance. This effect occurred in parallel with a redshift, also indicating the formation of the benzoylacetate and its enol form.

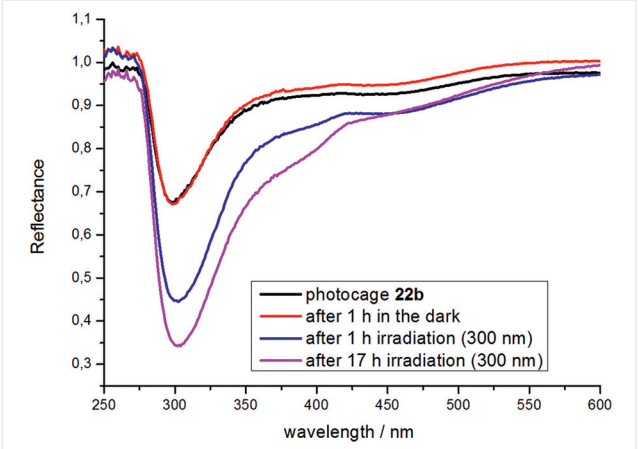
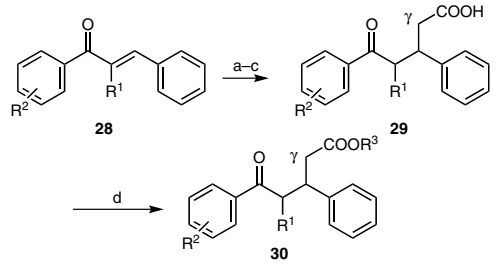


Figure 5 Diffuse reflectance UV/Vis spectroscopy (DRS) of photocage **22b** impregnated on a white cotton sample, before and after photolysis

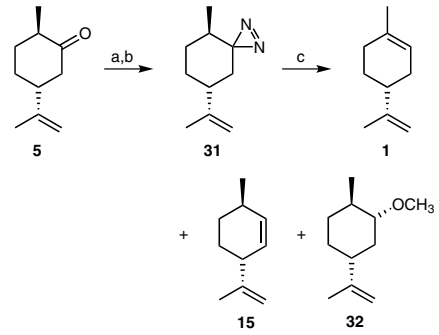
Norrish Type II Approach for Cinnamates: Reluctant, Why?

Cinnamates constitute another important class of fragrance molecules and the Norrish II protocol was also applied to these compounds. Knoevenagel condensation of chalcones with dialkyl malonates and subsequent saponification and decarboxylation delivered the cinnamic acid cages **29** in good yields (Scheme 10);[53] esterification gave the cinnamate cages **30**.

From a dozen of these compounds **29**, **30**, however, we did not detect notable release (only 5–10% cinnamates were detected by GC and NMR spectroscopy, as *E*/*Z* mixtures), even after prolonged irradiation. This effect was even stronger than that already observed for the chalcone cage **27** (Figure 2) which is also rather reluctant under photolysis conditions. Clearly, the β-phenyl substitution is obstructive and precludes γ-hydrogen transfer in these cases. The absorption and emission properties of these photocages are not altered relative to other phenone derivatives; taking



Scheme 10 Synthesis of cinnamic acid and cinnamate cages **29** and **30**. *Reagents and conditions*: a) diethyl malonate, piperidine; b) NaOH; c) HCl; d) R^3OH, acid catalysis. R^1 = H, Me; R^2 = H, 4-Me, 4-OMe; R^3 = Me, Et.



Scheme 11 Diazirine synthesis and photolysis. *Reagents and conditions*: a) NH_3, MeOH, H_2NOSO_3H; b) CrO_3, H_2SO_4; c) 2 mM cage solution in MeOH, *hv* (coated mercury low-pressure lamp, λ = 350 ± 20 nm), r.t.; for product GC, see Figure 6.

this into account, a possible explanation is that reversible β-hydrogen transfer occurs from the more reactive β-CH position with formation of the better stabilized benzylic radical that, as part of a triplet 1,3-biradical, cannot undergo C–C bond cleavage. Hydrogen abstraction from the β-CH position in triplet excited carbonyls is often not detected because cyclopropane formation is less favored.[54]

A New Diazirine Approach to Limonene by Photodidenitrogenation

An alternative approach to a photolabile limonene cage (the phenone compounds **10** and **14** have already been described, see Schemes 3 and 4) is the carbene route. As extensively investigated by the Brinker group[55,56] and others,[57] diazirines photochemically release dinitrogen with formation of a carbene that undergoes, among other reactions, 1,2-hydrogen rearrangement to give the corresponding alkene. For limonene (**1**) release, diazirine **31** was synthesized from dihydrocarvone (**5**) (Scheme 11), already used as starting material for the phenone cage **10** (see Scheme 3). One disadvantage of cage **31** is its low absorbance in the UV-A region:[58] the extinction coefficient at λ_{max} (366 nm) for the strongly forbidden nπ* transition is around 50 which is somewhat compensated by the excellent quantum yields for didenitrogenation. The solution photochemistry (Figure 6) is efficient and selectively delivers limonene [with less than 10% isolimonene (**15**) in the product mixture] and the

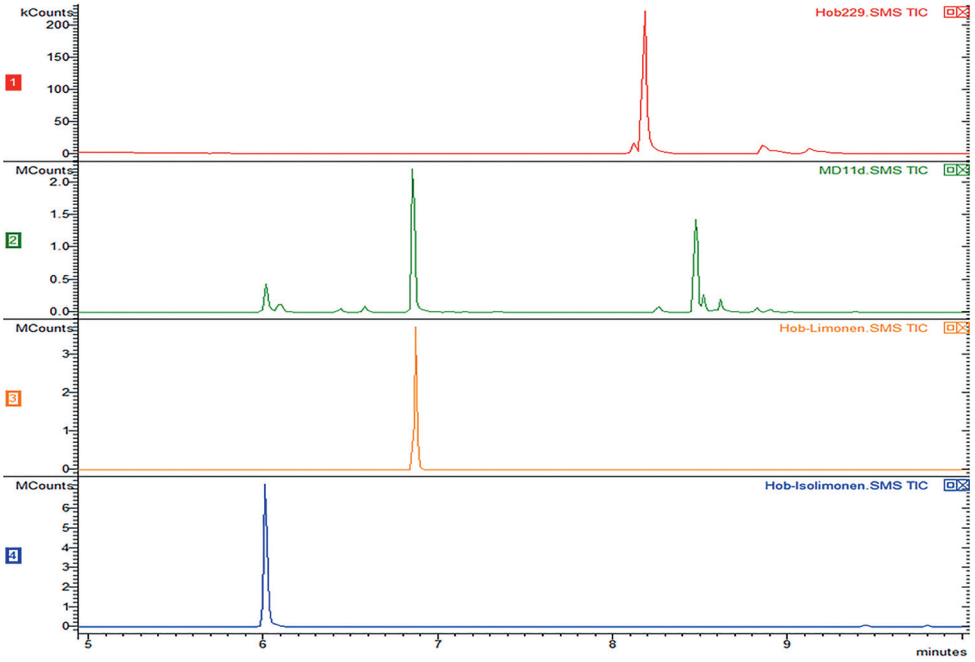


Figure 6 Gas chromatograms (from bottom to top) of isolimonene (**15**) (trace 4), limonene (**1**) (trace 3), cage **31** after photolysis for 2 h (trace 2), and cage **31** (trace 1).

methanol-trapping product **32**. When higher concentrations of **31** were used, the well-known azine formation (addition of the carbene to the starting material) was also observed. The preferred formation of the higher-substituted alkene was also observed by Brinker and co-workers for the diazirine from 2-methylcyclohexanone.[59] From the viewpoint of selective release, photocage **31** is highly useful. For application as a pro-perfume, however, the volatility is too high (in the same range as limonene itself).

Photocaged Compounds: Is There a Perfect Solution?

In most applications of photocage release, the focus is on the biologically active molecule or molecular fragment and not on the supporting chromophore that is concurrently released. In the best case, this second fragment is unreactive, easily separated and invisible (i.e., does not absorb in the photocage region and thus does not operate as an internal filter). In reality, this is generally not the case. Even worse, secondary photochemistry and undesired effects such as oxidative aging can lead to colorization in solution and on surfaces. Thus, better solutions are highly desirable (Figure 7). From a substance-economic point of view, the release of two target molecules from one photocage is an improvement (**A**), the generation of a nonabsorbing volatile component (e.g. molecular nitrogen or carbon dioxide) is better (**B**) and the release of two target molecules without any byproduct would be optimal (**C**). We have developed examples for the first two alternatives: the dimeric cage **33** is available from δ-damascone and the bis-cerium enolate from ethylenediol-linked bis-propiophenone. In the UV/Vis absorption spectrum, cage **33** has a slightly redshifted and hyperchromic absorption relative to the monomeric cage compounds **34** and **35** that bear trialkylamino and tetraalkylammonium side chains as a means of improving the solubility properties (Figure 8).[60]

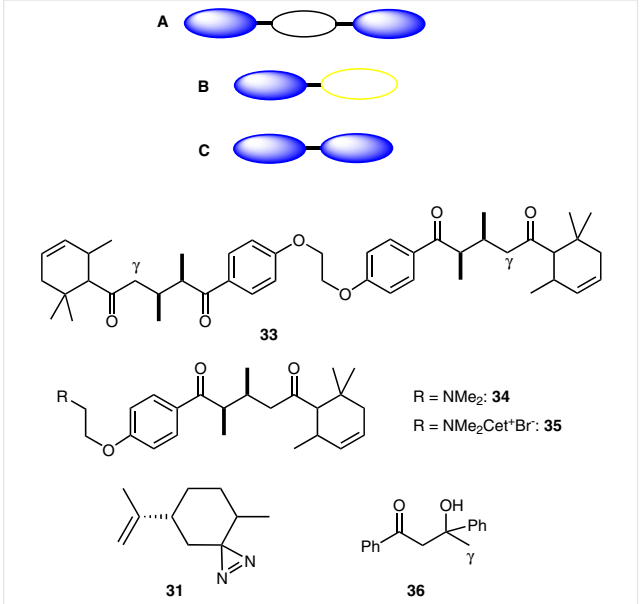


Figure 7 The three *golden routes* and three examples of photocages (**33**, **31**, **36**) that realize these concepts

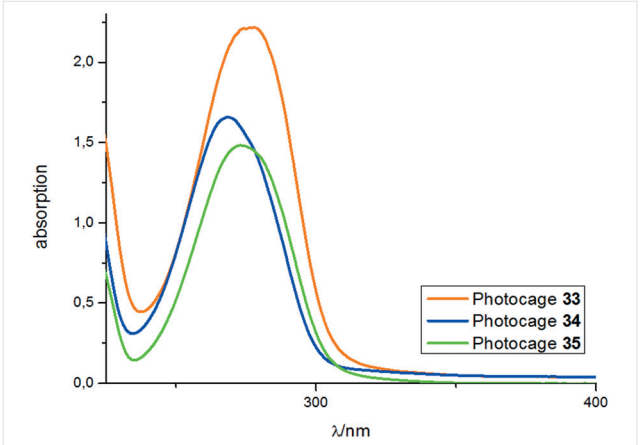


Figure 8 UV spectra of the cage dimer **33** and compounds **34**, **35**

An example for concept (**B**) with an invisible and easily removable carrier (dinitrogen) is the diazirine **31** that we have developed as a volatile photocage for limonene. Finally, the concept of the photo-retro-aldol route (as shown in Scheme 6) might also be used for the realization of concept (**C**): the acetophenone aldol dimer **36** is a labile aldol that undergoes thermal retro-aldol reaction,[61] and also photochemical cleavage can be expected. This might serve as a recipe for the design of ideal photocages.

In summary, we have proven that the Norrish II carbonyl cleavage protocol serves as a highly versatile guideline for the design of photocages for the release of hydrocarbons, cyclic and long-chain alkylated aldehydes and ketones, α,β-unsaturated ketones and, albeit less efficient, also for carboxylic acids and esters. Diazirines, as exemplified by the limonene cage **31**, are another potential class of useful photocages for numerous applications.

The starting materials were commercially available. $CDCl_3$, $CHCl_3$, CH_2Cl_2, MeOH, EtOAc, Et_2O, MTBE, cyclohexane, acetone and THF were used as solvents. ^1H NMR spectra were recorded on Bruker Avance II 300 and Avance 400 spectrometers operating at 300 and 400 MHz or on a Bruker Avance II+ 600 spectrometer operating at 600 MHz. Standard abbreviations are used for coupling patterns. ^{13}C NMR spectra were recorded on the above-mentioned NMR spectrometers operating at 75, 100 and 150 MHz. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Solvent peaks were used as an internal standard in all NMR spectra ($CDCl_3$, δ = 7.26 and 77.2 ppm). Mass spectra and accurate mass determinations were obtained with a Finnigan MAT 900S mass spectrometer by electrospray ionization. Infrared spectra were recorded with a Perkin-Elmer FT-IR-S 1600 fourier-transform spectrometer. Elemental analyses were performed with an Elementar Vario EL analyzer. For all new compounds, satisfactory

elemental analyses or high-resolution mass spectra, as well as HPLC analyses, were obtained confirming >95% purity. For UV/Vis absorption spectra, a Perkin-Elmer Lambda 35 UV/Vis spectrophotometer was used with quartz cuvettes (d = 1.00 cm) and for DRS, a Perkin-Elmer Lambda 1050 UV/Vis/NIR spectrophotometer with a 150 mm InGaAs integrating sphere detector was used. For photolysis studies, Rayonet RPR-208 chamber photoreactors equipped with 8 lamps (phosphor coated with an emission maximum at 300 or 350 nm; 800 W) or a Luzchem LZC-4V photoreactor with 254, 300 or 350 nm (center line positions) were used for irradiation.

Ethyl (*E*)-2-[(2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohexylidene]acetate (6)[32]

A suspension of NaH (60% in paraffin; 3.7 g, 91.5 mmol, 1.5 equiv) in THF (70 mL) under argon atmosphere was cooled to 0 °C. Triethyl phosphonoacetate (20.6 mL, 103.7 mmol, 1.7 equiv) in THF (14 mL) was added dropwise. After stirring for 0.5 h at r.t., the mixture was cooled to 0 °C and (+)-dihydrocarvone (**5**) (10 mL, 61.0 mmol, 1.0 equiv) in THF (9 mL) was added dropwise. After 16 h at r.t., sat. aq NH_4Cl solution (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 19:1) to afford **6** as a yellow oil; yield: 12.9 g (58.0 mmol, 95%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.53 (s, 1 H), 4.67 (m, 2 H), 4.08 (m, 2 H), 2.29–1.63 (m, 8 H), 1.68 (s, 3 H), 1.22 (m, 3 H), 1.09 (d, J = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.0 (C_q), 166.4 (C_q), 149.1 (C_q), 110.5 (CH), 108.9 (CH_2), 59.4 (CH_2), 47.2 (CH), 43.7 (CH), 41.4 (CH_2), 38.1 (CH_2), 32.5 (CH_2), 20.6 (CH_3), 18.3 (CH_3), 14.3 (CH_3).

MS (EI): m/z (%) = 222.1 (19) [M$^+$], 193.1 (23), 179.1 (95), 177.1 (23), 176.1 (56), 161.1 (22), 151.1 (35), 149.1 (23), 148.2 (39), 147.2 (26), 133.1 (59), 121.1 (29), 119.1 (48), 109.1 (25), 107.1 (60), 105.1 (100), 93.1 (66), 91.1 (76), 79.1 (62), 77.1 (31), 67.1 (28), 65 (20).

(*E*)-2-[(2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohexylidene]ethanol (7)[32]

$LiAlH_4$ (6.6 g, 172.6 mmol, 2.0 equiv) was suspended in Et_2O (173 mL) and ethyl (*E*)-2-[(2*R*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohexylidene]acetate (**6**) (19.2 g, 86.3 mmol, 1.0 equiv) dissolved in Et_2O (35 mL) was added dropwise. After reflux for 1 h, the mixture was cooled to 0 °C and water was added dropwise until no more hydrogen gas was formed. The precipitate was dissolved by adding 2.5 M aq H_2SO_4. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ solution (200 mL) and brine (200 mL), and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 9:1) (R_f = 0.45) to afford **7** as a colorless liquid; yield: 14.3 g (79.4 mmol, 92%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.26 (t, J = 6.7 Hz, 1 H), 4.65 (m, 2 H), 4.12 (m, 2 H), 2.64 (m, 2 H), 2.00–1.46 (m, 6 H), 1.67 (s, 3 H), 0.99 (d, J = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 149.7 (C_q), 146.3 (C_q), 118.3 (CH), 108.6 (CH_2), 58.5 (CH_2), 46.8 (CH), 37.8 (CH), 36.6 (CH_2), 34.6 (CH_2), 31.9 (CH_2), 20.7 (CH_3), 18.0 (CH_3).

MS (EI): m/z (%) = 147.2 (26), 119.1 (66), 107.1 (23), 105.1 (69), 93.1 (46), 91.1 (100), 81.1 (22), 79.1 (85), 77.1 (60), 67.1 (39), 65.1 (21).

(*E*)-2-[(2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohexylidene]acetaldehyde (8)

(*E*)-2-[(2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohexylidene]ethanol (**7**) (11.8 g, 64.9 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (65 mL) and MnO_2 (electrolytically precipitated) (84.6 g, 973.4 mmol, 15.0 equiv) was added. After stirring for 64 h at r.t., MnO_2 was removed by filtration over Celite. The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 5:1) (R_f = 0.48) to afford **8** as a yellow liquid; yield: 6.9 g (39.9 mmol, 60%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.99 (d, J = 8.0 Hz, 1 H), 5.74 (d, J = 8.0 Hz, 2 H), 4.68 (s, 1 H), 3.37 (m, 1 H), 2.15 (m, 1 H), 2.04 (m, 1 H), 1.94 (m, 2 H), 1.90 (m, 1 H), 1.79 (m, 1 H), 1.67 (s, 3 H), 1.42 (ddd, J = 3.9, 13.0, 25.3 Hz, 1 H), 1.00 (d, J = 6.5 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 190.6 (CH), 170.2 (C_q), 148.3 (C_q), 122.6 (CH), 109.4 (CH_2), 47.5 (CH), 39.4 (CH), 36.4 (CH_2), 35.0 (CH_2), 31.4 (CH_2), 20.5 (CH_3), 17.4 (CH_3).

MS (EI): m/z (%) = 178.2 (54) [M$^+$], 163.1 (20), 145.1 (29), 135.2 (40), 121.1 (44), 119.1 (41), 117.1 (40), 115.1 (53), 107.1 (71), 105.1 (53), 95.1 (31), 93.1 (67), 91.1 (100), 81.1 (27), 79.1 (79), 77.1 (67), 67.2 (52), 65.1 (33), 53.1 (20), 51.1 (24).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{19}O$: 179.14304; found: 179.14332.

2-[(1*S*,2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohexyl]acetaldehyde (9)

(*E*)-2-[(2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohexylidene]acetaldehyde (**8**) (3.5 g, 19.6 mmol, 1.0 equiv) was dissolved in $CHCl_3$ (98 mL) and cooled to –30 °C. 2-*tert*-Butyl-3-methyl-4-oxoimidazolidin-1-ium trifluoroacetate (1.1 g, 3.9 mmol, 0.2 equiv) and diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6.0 g, 23.6 mmol, 1.2 equiv) were added and the mixture was stirred for 18 h at –30 °C. Then, Et_2O (100 mL) was added and the solution was filtered over silica gel. The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 5:1) (R_f = 0.56) to afford **9** as a yellow liquid; yield: 2.8 g (15.5 mmol, 79%).

IR (ATR): 2921 (w), 2857 (w), 1724 (vs), 1643 (w), 1597 (w), 1448 (m), 1372 (m), 1284 (m), 1230 (s), 1044 (m), 805 (m), 773 cm^{-1} (m).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.69 (dd, J = 2.6, 1.3 Hz, 1 H), 4.60 (d, J = 5.2 Hz, 2 H), 2.40 (dd, J = 15.6, 4.6 Hz, 1 H), 2.34 (m, 1 H), 2.28 (ddd, J = 15.6, 8.5, 2.7 Hz, 1 H), 1.69–1.67 (m, 1 H), 1.64 (m, 1 H), 1.61 (s, 3 H), 1.58 (m, 2 H), 1.46–1.37 (m, 3 H), 1.08 (dd, J = 12.6, 3.1 Hz, 1 H), 0.79 (d, J = 7.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 203.0 (CH), 149.7 (C_q), 108.5 (CH_2), 41.6 (CH_2), 38.5 (CH), 36.1 (CH_2), 34.5 (CH), 33.4 (CH), 31.3 (CH_2), 29.4 (CH_2), 20.9 (CH_3), 19.6 (CH_3).

MS (EI): m/z (%) = 136.1 (68), 121.1 (89), 119.1 (23), 107.1 (45), 105.1 (26), 95.1 (20), 93.1 (100), 92.1 (24), 91.1 (49), 81.1 (27), 79.1 (81), 77.1 (44), 67.2 (63).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{21}O$: 181.15869; found: 181.15884.

2-[(1*S*,2*R*,5*R*)-2-Methyl-5-(prop-1-en-2-yl)cyclohexyl]-1-phenylethanone (10a)

PhBr (1.8 mL, 16.6 mmol, 1.5 equiv) was dissolved in Et_2O (16 mL) and cooled to 0 °C. *n*-BuLi (2.5 M in *n*-hexane; 5.3 mL, 13.3 mmol, 1.2 equiv) was added dropwise. The mixture was stirred for 10 min at 0 °C and 20 min at r.t. After cooling to 0 °C, aldehyde **9** (2.0 g,

11.1 mmol, 1.0 equiv) in Et_2O (8 mL) was added dropwise. The mixture was stirred for a further 16 h at r.t. and then sat. aq NH_4Cl solution (30 mL) was added. The layers were separated, the aqueous layer was extracted with Et_2O (2 × 30 mL), and the combined organic layers were washed with brine. After drying over $MgSO_4$, the solvent was evaporated. The intermediate was added to a solution of CrO_3 (56 mg, 555 µmol, 0.05 equiv) and *t*-BuOOH (9.1 mL, 66.6 mmol, 6.0 equiv) in CH_2Cl_2 (56 mL). After stirring for 2 h, sat. aq $NaSO_3$ solution was added until no more gas evolved. The layers were separated and the aqueous layer was extracted with Et_2O (2 ×). The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 9:1) (R_f = 0.20) to afford **10a** as a yellow liquid; yield: 0.7 g (2.8 mmol, 25%).

IR (ATR): 2919 (w), 2852 (w), 1682 (s), 1643 (w), 1597 (w), 1448 (m), 1373 (w), 1209 (m), 1159 (m), 1108 (m), 1014 (m), 885 (m), 752 (s), 690 (s), 654 cm^{-1} (m).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.8 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.49 (t, *J* = 7.7 Hz, 2 H), 4.66 (s, 2 H), 3.03 (dd, *J* = 16.0, 4.5 Hz, 1 H), 2.91 (dd, *J* = 15.9, 9.4 Hz, 1 H), 2.52 (m, 2 H), 2.11 (t, *J* = 11.5 Hz, 1 H), 1.79–1.70 (m, 3 H), 1.67 (s, 3 H), 1.55 (m, 1 H), 1.31–1.25 (m, 2 H), 0.93 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 201.1 (C_q), 151.0 (C_q), 138.2 (C_q), 133.3 (CH), 129.1 (CH), 128.6 (CH), 108.6 (CH_2), 39.3 (CH), 36.3 (CH_2), 36.2 (CH_2), 35.7 (CH), 35.6 (CH), 32.1 (CH_2), 30.2 (CH_2), 21.2 (CH_3), 20.0 (CH_3).

MS (EI): *m*/*z* (%) = 105.0 (62), 93.0 (32), 79.0 (34), 77.0 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}O$: 257.18999; found: 257.19017.

1-(4-Methoxyphenyl)-2-[(1*S*,2*R*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohexyl]ethanone (10b)

4-Bromoanisole (2.1 mL, 16.6 mmol, 1.5 equiv) was dissolved in Et_2O (16 mL) and cooled to 0 °C. *n*-BuLi (2.5 M in *n*-hexane; 5.3 mL, 13.3 mmol, 1.2 equiv) was added dropwise. The mixture was stirred for 10 min at 0 °C and 20 min at r.t. After cooling to 0 °C, aldehyde **9** (2.0 g, 11.1 mmol, 1.0 equiv) in Et_2O (8 mL) was added dropwise. The mixture was stirred for a further 16 h at r.t. and then sat. aq NH_4Cl solution (30 mL) was added. The layers were separated, the aqueous layer was extracted with Et_2O (2 × 30 mL), and the combined organic layers were washed with brine. After drying over $MgSO_4$, the solvent was evaporated. The intermediate was added to a solution of CrO_3 (56 mg, 555 µmol, 0.05 equiv) and *t*-BuOOH (9.1 mL, 66.6 mmol, 6.0 equiv) in CH_2Cl_2 (56 mL). After stirring for 2 h, sat. aq $NaSO_3$ solution was added until no more gas evolved. The layers were separated and the aqueous layer was extracted with Et_2O (2 ×). The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 9:1) (R_f = 0.22) to afford **10b** as a yellow liquid; yield: 1.3 g (4.4 mmol, 42%).

IR (ATR): 2927 (w), 1656 (vs), 1614 (m), 1597 (w), 1442 (m), 1371 (w), 1254 (s), 1158 (w), 1110 (m), 1024 (m), 869 (m), 756 (s), 685 cm^{-1} (s).

^1H NMR (600 MHz, $CDCl_3$): δ = 7.96 (m, 2 H), 6.96 (m, 2 H), 4.67 (m, 2 H), 3.86 (s, 3 H), 2.88–2.75 (m, 1 H), 2.64–2.50 (m, 1 H), 2.13–1.13 (m, 9 H), 1.67 (s, 3 H), 0.94 (m, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.5 (C_q), 163.9 (C_q), 151.0 (C_q), 131.2 (C_q), 130.8 (CH), 114.2 (CH), 108.6 (CH_2), 56.0 (CH_3), 45.8 (CH), 43.7 (CH_2), 38.0 (CH), 36.3 (CH_2), 35.6 (CH), 32.1 (CH_2), 30.2 (CH_2), 21.3 (CH_3), 20.0 (CH_3).

MS (EI): *m*/*z* (%) = 150.1 (35), 136.1 (22), 135.1 (100), 121.1 (20), 92.1 (25), 79.1 (20), 77.1 (50).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{27}O_2$: 287.20056; found: 287.20102.

(2*R*)-2-[(1*R*)-4-Methylcyclohex-3-en-1-yl]propan-1-ol (11)[36]

Borane–dimethyl sulfide complex (25.0 mL, 263.6 mmol, 1.0 equiv) was cooled to –21 °C. 2-Methyl-2-butene (58.7 mL, 553.6 mmol, 2.1 equiv) was added dropwise and the mixture was stirred for 1.5 h at 0 °C. Then, Et_2O (41 mL) was added and the mixture was stirred for 1 h at r.t. Then, the thus-formed disiamylborane was added dropwise at 0 °C to (+)-limonene (38.5 mL, 237.3 mmol, 0.9 equiv) and the mixture was stirred for 3 h at r.t. After that, all volatile components were removed in vacuo and the remaining liquid was dissolved in THF (475 mL). The solution was cooled to 0 °C and 3.0 M aq NaOH (79.1 mL, 237.3 mmol, 0.9 equiv) was added dropwise. Finally, 30% H_2O_2 (80.8 mL, 790.9 mmol, 3.0 equiv) was added dropwise and the mixture was stirred for 16 h at r.t. Then, NaCl was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 150 mL) and the combined organic layers were washed with brine. After drying over $MgSO_4$, the solvent was evaporated. The crude product was purified by fractional distillation (120 °C/35 mbar) to afford product **11** as a colorless liquid; yield: 29.1 g (188.7 mmol, 80%; 3:2 mixture of isomers).

Next, the isomeric mixture of **11** (29.1 g, 188.7 mmol, 1.0 equiv) was dissolved in pyridine (377 mL) and 3,5-dinitrobenzoyl chloride (69.6 g, 301.9 mmol, 1.6 equiv) was added. After 4 h of stirring, water (400 mL) was added and the mixture was extracted with Et_2O (3 × 400 mL). The combined organic layers were washed with sat. aq $CuSO_4$ solution (3 × 200 mL) and brine (1 × 200 mL). After drying over $MgSO_4$, the solvent was evaporated. The crude product was recrystallized from *n*-heptane–DCE (2:1), then from *n*-hexane at –23 °C and finally from *n*-hexane at r.t. to afford (2*R*)-2-[(1*R*)-4-methylcyclohex-3-en-1-yl]propyl 3,5-dinitrobenzoate as a colorless solid; yield: 10.5 g (30.2 mmol, 16%); mp 70–72 °C.

Finally, the 3,5-dinitrobenzoate (5.1 g, 14.7 mmol, 1.0 equiv) was suspended in MeOH (50 mL) and KOH (1.5 g, 26.5 mmol, 1.8 equiv) was added. After reflux for 18 h, water (100 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 300 mL) and the combined organic layers were washed with brine (300 mL). After drying over $MgSO_4$, the solvent was evaporated and the crude product was purified by bulb-to-bulb distillation to afford product **11** as a colorless liquid; yield: 2.0 g (13.0 mmol, 88%).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.33 (s, 1 H), 3.56 (m, 1 H), 3.40 (m, 1 H), 1.90 (m, 3 H), 1.67 (m, 2 H), 1.59 (s, 3 H), 1.53 (m, 2 H), 1.30 (m, 1 H), 0.85 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.9 (C_q), 120.7 (CH), 66.1 (CH_2), 40.1 (CH), 35.0 (CH), 30.8 (CH_2), 27.5 (CH_2), 27.3 (CH_2), 23.5 (CH_3), 13.2 (CH_3).

MS (EI): *m*/*z* (%) = 121.0 (26), 107.0 (32), 95.0 (40), 94.0 (100), 93.0 (78), 91.0 (37), 81.0 (45), 79.0 (95), 77.0 (34), 68.0 (44), 67.0 (81), 55.0 (28), 53.0 (20).

(2*R*)-2-[(1*R*)-4-Methylcyclohex-3-en-1-yl]propyl Methanesulfonate (12)[62]

(2*R*)-2-[(1*R*)-4-Methylcyclohex-3-en-1-yl]propan-1-ol (**11**) (20.0 g, 129.7 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (260 mL) and cooled to 0 °C. Pyridine (27.0 mL, 194.5 mmol, 1.5 equiv) was added, and then MsCl (11.0 mL, 142.6 mmol, 1.1 equiv) was added dropwise. The mixture was stirred for 0.5 h at 0 °C and 18 h at r.t. Then, sat. aq

$NaHCO_3$ solution (200 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2 ×). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated to afford **12** as a colorless liquid; yield: 30.1 g (129.6 mmol, 99%).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.33 (s, 1 H), 4.19 (dt, *J* = 9.4, 4.6 Hz, 1 H), 4.07 (m, 1 H), 2.98 (s, 3 H), 1.97–1.67 (m, 6 H), 1.61 (s, 3 H), 1.57–1.11 (m, 2 H), 0.96 (t, *J* = 7.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.0 (C_q), 120.2 (CH), 73.2 (CH_2), 37.3 (CH), 37.1 (CH_3), 35.0 (CH), 30.5 (CH_2), 27.7 (CH_2), 26.9 (CH_2), 23.4 (CH_3), 13.3 (CH_3).

MS (EI): *m*/*z* (%) = 94.0 (53), 93.0 (31), 91.0 (28), 79.0 (100), 77.0 (24), 67.0 (39).

(4*R*)-4-[(2*R*)-1-Bromopropan-2-yl]-1-methylcyclohex-1-ene (13)[38]

LiBr (33.8 g, 388.7 mmol, 3.0 equiv) was suspended in THF (555 mL), and methanesulfonate **12** (30.1 g, 129.6 mmol, 1.0 equiv) was added. After reflux for 4 h, water (300 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by fractional distillation (98 °C/1.7 mbar) to afford **13** as a colorless liquid; yield: 18.3 g (84.2 mmol, 65%).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.32 (s, 1 H), 3.43 (m, 1 H), 3.37 (m, 1 H), 2.01–1.88 (m, 3 H), 1.70 (m, 4 H), 1.62 (s, 3 H), 1.32–1.22 (m, 1 H), 0.98 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.9 (C_q), 120.4 (CH), 40.0 (CH_2), 39.6 (CH), 36.5 (CH), 30.5 (CH_2), 27.7 (CH_2), 27.0 (CH_2), 23.6 (CH_3), 15.7 (CH_3).

MS (EI): *m*/*z* (%) = 95.0 (88), 93.0 (39), 91.0 (44), 81.0 (64), 79.0 (71), 77.0 (47), 67.1 (100).

(4*S*)-4-[(1*R*)-4-Methylcyclohex-3-en-1-yl]-1-phenylpentan-1-one (14a)

n-BuLi (2.5 M in hexane; 5.4 mL, 13.4 mmol, 1.2 equiv) was added dropwise to (*E*)-1,1-dimethyl-2-(1-phenylethylidene)hydrazine (2.1 mL, 12.3 mmol, 1.1 equiv) in THF (25 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C, and **13** (2.4 g, 11.2 mmol, 1.0 equiv) was added. After stirring for 15 h at r.t., 2.0 M aq HCl (15 mL) was added and the mixture was stirred for 24 h. The solution was treated with sat. aq $NaHCO_3$ solution (2 ×) and the combined aqueous layers were extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 9:1) (R_f = 0.52) to afford **14a** as a yellow liquid; yield: 1.2 g (4.7 mmol, 42%).

IR (ATR): 2913 (w), 1685 (s), 1597 (w), 1580 (w), 1448 (w), 1377 (w), 1267 (w), 1206 (m), 1178 (m), 1116 (w), 1001 (m), 974 (m), 914 (w), 797 (m), 741 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.1 Hz, 2 H), 7.51 (ddd, *J* = 7.4, 2.7, 1.3 Hz, 1 H), 7.41 (td, *J* = 7.5, 1.9 Hz, 2 H), 5.35 (s, 1 H), 2.94 (m, 2 H), 2.00–1.18 (m, 10 H), 1.61 (s, 3 H), 0.81 (t, *J* = 5.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.5 (C_q), 137.1 (C_q), 133.8 (C_q), 132.8 (CH), 128.5 (CH), 128.0 (CH), 120.9 (CH), 38.2 (CH), 37.0 (CH), 36.5 (CH_2), 30.9 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 27.1 (CH_2), 23.4 (CH_3), 15.8 (CH_3).

MS (EI): *m*/*z* (%) = 119.1 (52), 105.0 (71), 79.0 (36), 77.0 (100), 67.0 (29).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}O$: 257.18999; found: 257.18841.

(4*S*)-1-(4-Methoxyphenyl)-4-[(1*R*)-4-methylcyclohex-3-en-1-yl]pentan-1-one (14b)

n-BuLi (2.5 M in hexane; 5.4 mL, 13.4 mmol, 1.2 equiv) was added dropwise to (*E*)-2-[1-(4-methoxyphenyl)ethylidene]-1,1-dimethylhydrazine (2.4 g, 12.3 mmol, 1.1 equiv) in THF (25 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C, and **13** (2.4 g, 11.2 mmol, 1.0 equiv) was added. After stirring for 15 h at r.t., 2.0 M aq HCl (15 mL) was added and the mixture was stirred for 24 h. The solution was washed with sat. aq $NaHCO_3$ solution (2 ×) and the combined aqueous layers were extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 9:1) (R_f = 0.23) to afford **14b** as a colorless solid; yield: 0.5 g (1.8 mmol, 16%); mp 62 °C.

IR (ATR): 2923 (w), 1672 (vs), 1564 (w), 1404 (m), 1354 (w), 1207 (m), 1168 (m), 1111 (m), 1009 (m), 976 (m), 801 (s), 686 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 8.9 Hz, 2 H), 5.34 (s, 1 H), 3.82 (s, 3 H), 2.88 (m, 2 H), 2.01–1.17 (m, 10 H), 1.61 (s, 3 H), 0.88 (t, *J* = 6.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3 (C_q), 163.3 (C_q), 133.9 (C_q), 130.3 (CH), 130.2 (C_q), 120.9 (CH), 113.7 (CH), 55.4 (CH_3), 38.2 (CH), 37.1 (CH), 36.3 (CH_2), 30.9 (CH_2), 29.0 (CH_2), 27.6 (CH_2), 27.1 (CH_2), 23.5 (CH_3), 15.8 (CH_3).

MS (EI): *m*/*z* = 150.1 (30), 135.1 (100), 121.1 (30), 119.1 (39), 77.0 (53).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{27}O_2$: 287.20056; found: 287.19941.

Ethyl 2-Benzoyl-3-methyl-5-oxo-5-(2,6,6-trimethylcyclohex-3-enyl)pentanoate (22a)

A mixture of ethyl benzoylacetate (1.73 g, 1.56 mL, 9.00 mmol, 1.0 equiv), δ-damascone (1.73 g, 1.86 mL, 9.00 mmol, 1.0 equiv) and $FeCl_3 \cdot 6\,H_2O$ (243.0 mg, 0.90 mmol, 0.1 equiv) in $CHCl_3$ (2 mL) was stirred for 24 h at 50 °C. Column chromatography (MTBE–cyclohexane, 1:4) gave **22a** as a yellow oil; yield: 2.94 g (7.65 mmol, 85%).

IR (ATR): 3018 (w), 2960 (m), 2878 (m), 1737 (s), 1686 (s), 1448 (m), 1367 (m), 1261 (m), 1213 cm^{-1} (m).

^1H NMR (600 MHz, $CDCl_3$): δ (mixture of diastereoisomers) = 8.40–7.95 (m, 2 H), 7.55–7.53 (m, 1 H), 7.46–7.42 (m, 2 H), 5.48 (m, 1 H), 5.39 (m, 1 H), 4.62–4.48 (m, 1 H), 4.09–4.07 (m, 2 H), 2.89 (m, 2 H), 2.66 (m, 1 H), 2.44 (m, 1 H), 2.15 (m, 1 H), 1.94–1.89 (m, 1 H), 1.66–1.62 (m, 1 H), 1.30 (m, 3 H), 1.10 (m, 3 H), 0.90 (m, 3 H), 0.85 (m, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (mixture of diastereoisomers) = 213.5, 213.3 (2 × C_q), 195.1 (C_q), 169.2 (C_q), 136.5, 136.4 (2 × C_q), 133.6 (CH), 131.9 (CH), 128.6 (CH), 128.5 (CH), 124.2, 124.1 (2 × CH), 62.6, 62.5 (2 × CH), 61.2, 61.1 (2 × CH_2), 57.6, 57.3 (2 × CH), 52.1 (2 × CH_2), 41.8 (2 × CH_2), 35.7 (C_q), 31.7, 31.6 (2 × CH), 28.8 (CH_3), 28.7 (CH), 20.7, 20.6 (2 × CH_3), 17.2, 17.2 (2 × CH_3), 14.2 (CH_3).

GC/MS [50 °C (5 min), 20 °C/min, 280 °C (10 min); H_2, 2.0 mL/min]: isomer A: t_R = 16.457 min, *m*/*z* (%) = 261 (42) [M – C_9H_{15}], 105 (100), 81 (24), 77 (57); isomer B: t_R = 16.407 min, *m*/*z* (%) = 261 (36) [M – C_9H_{15}], 105 (100), 81 (25), 77 (61).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{33}O_4$: 385.23733; found: 385.23782.

UV/Vis (MeOH, *c* = 10^{-4} M, *d* = 1 cm): λ_{max} (log ε) = 247 (4.15), 281 nm (3.38).

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.40; H, 8.31.

Benzyl 2-Benzoyl-3-methyl-5-oxo-5-(2,6,6-trimethylcyclohex-3-enyl)pentanoate (22b)

A mixture of benzyl benzoylacetate (2.29 g, 9.00 mmol, 1.0 equiv), δ-damascone (1.73 g, 1.86 mL, 9.00 mmol, 1.0 equiv) and $FeCl_3·6\ H_2O$ (486.0 mg, 1.80 mmol, 0.2 equiv) in $CHCl_3$ (2 mL) was stirred for 48 h at 50 °C. Column chromatography (MTBE–cyclohexane, 1:4) gave **22b** as a yellow oil; yield: 3.46 g (7.74 mmol, 86%).

IR (ATR): 3012 (w), 2959 (m), 2883 (m), 2832 (w), 1740 (s), 1686 (s), 1449 (m), 1366 (s), 1264 (s), 1212 cm^{-1} (s).

^1H NMR (600 MHz, $CDCl_3$): δ (mixture of diastereoisomers) = 8.40–7.95 (m, 2 H), 7.56–7.54 (m, 1 H), 7.44–7.42 (m, 2 H), 7.25 (m, 3 H), 7.19 (m, 2 H), 5.50 (m, 1 H), 5.41 (m, 1 H), 5.09 (m, 2 H), 4.72–4.55 (m, 1 H), 2.96–2.93 (m, 1 H), 2.72–2.59 (m, 1 H), 2.50–2.40 (m, 2 H), 2.20–2.12 (m, 1 H), 1.94–1.90 (m, 1 H), 1.66–1.64 (m, 1 H), 1.08–1.04 (m, 3 H), 0.96–0.80 (m, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (mixture of diastereoisomers) = 213.7, 213.5, 213.3 (3 × C_q), 195.0, 194.9 (2 × C_q), 169.1, 169.0 (2 × C_q), 136.7 (C_q), 135.4 (C_q), 133.6 (CH), 131.9, 131.8 (2 × CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.3, 128.2 (2 × CH), 124.3, 124.2 (2 × CH), 66.9 (CH_2), 62.7, 62.6, 62.5 (3 × CH), 57.8, 57.6, 57.3 (3 × CH), 52.1 (CH_2), 41.7 (CH_2), 33.1, 33.0 (2 × C_q), 31.8, 31.7 (2 × CH), 29.3, 29.0 (2 × CH_3), 28.8, 28.6 (2 × CH), 20.8, 20.7 (2 × CH_3).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{29}H_{34}O_4Na$: 469.23493; found: 469.23452.

UV/Vis (MeOH, *c* = 10^{-4} M, *d* = 1 cm): λ_{max} (log ε) = 247 (4.14), 281 nm (3.40).

Anal. Calcd for $C_{29}H_{34}O_4$: C, 78.00; H, 7.67. Found: C, 78.01; H, 7.78.

Dodecyl 2-Benzoyl-3-methyl-5-oxo-5-(2,6,6-trimethylcyclohex-3-enyl)pentanoate (22c)

A mixture of dodecyl benzoylacetate (2.99 g, 9.00 mmol, 1.0 equiv), δ-damascone (1.73 g, 1.86 mL, 9.00 mmol, 1.0 equiv) and $FeCl_3·6\ H_2O$ (243.0 mg, 0.90 mmol, 0.1 equiv) in $CHCl_3$ (2 mL) was stirred for 48 h at 50 °C. Column chromatography (MTBE–cyclohexane, 1:5) gave **22c** as an orange oil; yield: 4.16 g (7.93 mmol, 88%).

IR (ATR): 3012 (w), 2956 (s), 2926 (s), 2854 (m), 1739 (s), 1687 (s), 1466 (m), 1366 (m), 1212 cm^{-1} (m).

^1H NMR (600 MHz, $CDCl_3$): δ (mixture of diastereoisomers) = 8.40–7.95 (m, 2 H), 7.54–7.52 (m, 1 H), 7.45–7.41 (m, 2 H), 5.47 (m, 1 H), 5.40 (m, 1 H), 4.62–4.47 (m, 1 H), 4.03–3.99 (m, 2 H), 2.95–2.87 (m, 1 H), 2.69–2.65 (m, 1 H), 2.59–2.52 (m, 1 H), 2.50–2.40 (m, 1 H), 2.21–2.13 (m, 1 H), 1.94–1.88 (m, 1 H), 1.65–1.60 (m, 1 H), 1.48–1.47 (m, 2 H), 1.21–1.15 (m, 18 H), 1.06–1.01 (m, 3 H), 0.96–0.90 (m, 3 H), 0.87–0.83 (m, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (mixture of diastereoisomers) = 213.7, 213.5, 213.2 (3 × C_q), 194.1, 194.0 (2 × C_q), 169.3, 169.2 (C_q), 136.6, 136.5 (2 × C_q), 133.5 (2 × CH), 131.9, 131.8 (2 × CH), 128.8 (CH), 128.6 (CH), 124.2, 124.1 (2 × CH), 65.1 (CH_2), 62.4, 62.3 (2 × CH), 58.1, 57.7 (2 × CH), 52.1 (CH_2), 41.8 (CH_2), 33.0, 33.1 (2 × C_q), 31.9 (CH_2), 31.8, 31.7, 31.6 (3 × CH), 29.7, 29.6 (2 × CH), 28.7, 28.6 (2 × CH_3), 25.8 (2 × CH_2), 22.7 (CH_2), 20.8, 20.7 (2 × CH_3), 19.8, 19.7 (2 × CH_3), 14.2 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{53}O_4$: 525.39384; found: 525.39415.

UV/Vis (MeOH, *c* = 10^{-4} M, *d* = 1 cm): λ_{max} (log ε) = 246 (4.26), 283 nm (3.45).

Anal. Calcd for $C_{34}H_{52}O_4$: C, 74.82; H, 9.99. Found: C, 74.28; H, 9.94.

Ethyl (*R,*R**)- and (*R**,*S**)-2-Benzoyl-5-oxo-3-phenylhexanoate (27b) (Diastereoisomeric Chalcone Photocages)**

A mixture of ethyl benzoylacetate (1.73 g, 9.00 mmol, 1.0 equiv), benzalacetone (1.32 g, 9.00 mmol, 1.0 equiv) and $FeCl_3·6\ H_2O$ (24.3 mg, 0.09 mmol, 0.01 equiv) in $CHCl_3$ (1.5 mL) was stirred for 24 h at 50 °C. Column chromatography (MTBE–cyclohexane, 1:3) gave a 26:74 diastereoisomeric mixture [yield: 2.48 g (6.39 mmol, 71%)] that was separated into the (*R**,*R**)- and (*R**,*S**)-diastereoisomers by column chromatography.

(*R,*R**)-Isomer**

Yellow solid; mp 70 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.09–8.06 (d, $^3J_{H,H}$ = 7.3 Hz, 2 H), 7.61 (m, 1 H), 7.49 (m, 2 H), 7.35–7.28 (m, 4 H), 7.25–7.22 (m, 1 H), 4.84–4.81 (d, $^3J_{H,H}$ = 10.2 Hz, 1 H), 4.27–4.19 (m, 1 H), 3.87–3.80 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H), 2.86–2.84 (m, 2 H), 2.02 (s, 3 H), 0.92–0.87 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.6 (C_q), 193.7 (C_q), 167.9 (C_q), 140.4 (C_q), 136.5 (C_q), 133.9 (CH), 128.9 (2 × CH), 128.6 (2 × CH), 127.4 (CH), 61.6 (CH_2), 59.8 (CH), 47.1 (CH_2), 41.1 (CH), 30.4 (CH_3), 13.8 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}O_4$: 339.40492; found: 339.40814.

UV/Vis (MeOH, *c* = 10^{-4} M, *d* = 1 cm): λ_{max} (log ε) = 248 (4.01), 289 nm (3.26).

(*R,*S**)-Isomer**

Orange solid; mp 161 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.82 (d, $^3J_{H,H}$ = 7.8 Hz, 2 H), 7.52–7.49 (m, 1 H), 7.40–7.36 (m, 2 H), 7.26–7.08 (m, 5 H), 4.83–4.80 (d, $^3J_{H,H}$ = 9.6 Hz, 1 H), 4.22–4.09 (m, 3 H), 3.02–3.00 (d, $^3J_{H,H}$ = 6.9 Hz, 2 H), 2.04 (s, 3 H), 0.92–0.87 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.5 (C_q), 193.7 (C_q), 168.6 (C_q), 141.0 (C_q), 136.6 (C_q), 133.5 (CH), 128.7 (2 × CH), 128.2 (2 × CH), 127.1 (CH), 61.8 (CH_2), 59.2 (CH), 47.4 (CH_2), 40.8 (CH), 30.4 (CH_3), 14.0 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{23}O_4$: 339.40492; found: 339.405243.

UV/Vis (MeOH, *c* = 10^{-4} M, *d* = 1 cm): λ_{max} (log ε) = 248 (4.25), 285 nm (3.01).

(4*R*,7*R*)-4-Methyl-7-(prop-1-en-2-yl)-1,2-diazaspiro[2.5]oct-1-ene (31)

(+)-Dihydrocarvone (**5**) (5.0 mL, 30.6 mmol, 1.0 equiv) was added dropwise to 7.0 M methanolic NH_3 (44 mL, 305.5 mmol, 10.0 equiv) at 0 °C. After stirring for 2 h, the mixture was cooled to –18 °C and hydroxylamine-*O*-sulfonic acid (8.6 g, 76.4 mmol, 2.5 equiv) was added in portions. The mixture was slowly warmed to r.t. and stirred for 20 h at r.t. Then, the solvent and the remaining ammonia were evaporated and the intermediate was dissolved in acetone (153 mL). CrO_3 (4.6 g, 48.8 mmol, 1.5 equiv) was dissolved in 3.8 M aq H_2SO_4 (66 mL) and added dropwise within 45 min to the solution of the intermediate. After stirring for 4 h, water (150 mL) was added. After extraction with CH_2Cl_2 (3 × 150 mL), the combined organic layers were washed with brine (150 mL) and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 9:1) (R_f = 0.67) to afford **31** as a colorless liquid; yield: 1.8 g (11.0 mmol, 36%).

IR (ATR): 2930 (m), 2855 (w), 1739 (w), 1645 (m), 1569 (m), 1438 (m), 1378 (m), 1179 (m), 1048 (m), 983 (m), 891 (s), 818 (m), 791 (m), 722 (m), 697 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.59 (s, 1 H), 4.56 (s, 1 H), 2.21 (tt, *J* = 12.0, 3.3 Hz, 1 H), 1.90 (m, 1 H), 1.84 (m, 1 H), 1.77 (m, 1 H), 1.67 (m, 1 H), 1.58 (s, 3 H), 1.38 (m, 1 H), 1.20 (m, 1 H), 0.37 (ddd, *J* = 13.8, 3.8, 2.1 Hz, 1 H), 0.11 (d, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3 (C_q), 109.1 (CH_2), 43.4 (CH_2), 37.5 (CH_2), 33.9 (CH), 33.0 (C_q), 31.4 (CH), 31.0 (CH_2), 20.7 (CH_3), 17.1 (CH_3).

MS (EI): *m*/*z* (%) = 93.0 (92), 91.0 (72), 79.0 (100), 77.0 (43), 67.0 (100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{17}N_2$: 165.13863; found: 165.13911.

Bis-damascone Photocage 33

Under an argon atmosphere in a three-neck 50-mL flask, *i*-Pr_2NH (2.02 g, 2.81 mL, 20.00 mmol, 2.0 equiv) in THF (7 mL) was cooled to –78 °C. To this solution, 2.5 M *n*-BuLi in *n*-hexane (9.62 mL, 24 mmol, 2.4 equiv) was added dropwise over 20 min, and then the mixture was stirred for 40 min. Subsequently, a solution of 1,1′-(4,4′-(ethan-1,2-diylbis(oxy))bis(4,1-phenylene))dipropan-1-one (3.26 g, 10 mmol, 1.0 equiv) in THF (20 mL) was added to the LDA solution over 1 h. After an additional hour stirring at –78 °C, $CeCl_3$ (5.77 g, 23.4 mmol, 2.3 equiv) was added over 20 min and, over an additional 30 min, δ-damascone (3.84 g, 4.12 mL, 20.00 mmol, 2.0 equiv) was added. The reaction mixture was stirred for 12 h at 0 °C and then quenched with sat. aq NH_4Cl solution (20 mL) and extracted with Et_2O (3 × 30 mL). The organic phases were combined, washed with sat. aq NaCl solution (30 mL) and dried over $MgSO_4$, and then the solvent was removed by rotary evaporation. Column chromatography (MTBE–cyclohexane, 1:4) gave **33** as a yellow oil; yield: 5.54 g (7.79 mmol, 78%).

IR (ATR): 3336 (w), 3012 (w), 2960 (m), 2868 (m), 2826 (w), 1705 (m), 1670 (s), 1599 (s), 1456 (m), 1366 (s), 1222 (s), 1171 cm^{-1} (s).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93–7.90 (m, 2 H), 6.95–6.93 (m, $^3J_{H,H}$ = 8.4 Hz, 1 H), 6.88–6.86 (m, $^3J_{H,H}$ = 8.6 Hz, 1 H), 5.46–5.35 (m, 2 H), 4.36 (s, 2 H), 3.51–3.43 (m, 1 H), 2.94–2.88 (m, 1 H), 2.47–2.36 (m, 3 H), 2.19–2.14 (m, 1 H), 1.97–1.91 (m, 1 H), 1.69–1.63 (m, 1 H), 0.99–0.98 (m, 3 H), 0.90 (m, 6 H), 0.87 (m, 3 H), 0.72–0.71 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 214.0 (C_q), 202.9 (C_q), 162.3 (C_q), 132.2 (C_q), 130.9 (CH), 130.6 (CH), 124.1 (CH), 114.5 (CH), 66.5 (CH_2), 62.6 (CH), 50.2 (CH_2), 44.4 (CH), 41.7 (CH_2), 33.1 (C_q), 31.4 (CH), 30.7 (CH), 29.8 (CH_3), 20.0 (CH_3), 19.8 (CH_3), 12.7 (CH_3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{46}H_{63}O_6$: 711.46192; found: 711.46216; *m*/*z* [M + Na]$^+$ calcd for $C_{46}H_{62}O_6Na$: 733.44386; found: 733.44349.

UV/Vis (MeOH, *c* = 10^{-4} M, *d* = 1 cm): λ_{max} (log ε) = 286 nm (4.34).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588645.

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