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FULL PAPER

Transition-metal-free ring-opening reaction of 2-halocyclobutanols via ring contraction

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Dedicated to prof. Ei-ichi Negishi for his outstanding contribution to science.

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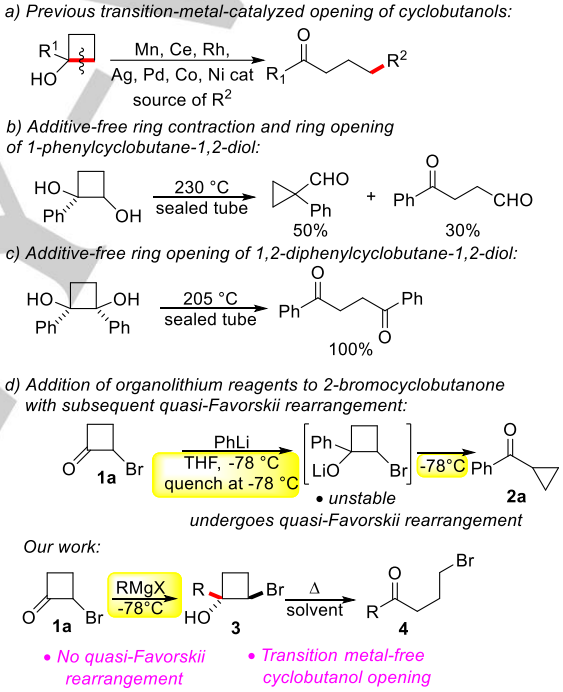
Abstract: The present work describes the preparation of halohydrins from 2-halocyclobutanones by means of reactions with Grignard reagents at -78 °C. We discovered that the prepared cyclobutanols underwent a thermal ring-opening reaction. Depending on the structure of the starting cyclobutanol, different products were formed. More specifically, 1-substituted 2-bromocyclobutan-1-ol was found to open to γ-substituted butyrophenones. A novel 1,3-dihydro-2H-inden-2-ylidene derivative was obtained for indene-derived cyclobutanols. Based on the outcomes of the performed experiments, a mechanism for the ring-opening of cyclobutanols can be proposed.

Introduction

Cyclobutane is a four-membered cyclic hydrocarbon that forms part of a number of natural substances, including alkaloids[1] and katsumadin C.[2] Substituted cyclobutanes can be used as starting materials for the preparation of a wide range of compounds.[3] The potential use of cyclobutane derivatives for the preparation of functionalized molecules is exemplified by the preparation of γ-substituted butyrophenones. These γ-substituted butyrophenones form pharmaco-active substances and they also serve as key intermediates in organic synthesis. Haloperidol is an example of such a biologically active compound.[4] The synthesis of γ-substituted butyrophenones is usually achieved by means of transition-metal-mediated cyclobutanol ring-opening processes (Scheme 1a).[5] Thus, manganese-,[6] cerium-,[7] rhodium-,[8] silver-,[9] palladium,[10] and nickel-mediated[11] reactions are typical examples of such reactivity. From a mechanistic perspective, the vast majority of transition-metal-mediated cyclobutanol ring-opening reactions proceed through a radical mechanism, whereas radical transition-metal-free cyclobutanol ring-opening reactions require the presence of a suitable initiator[12] or electrolyser.[13] However, palladium,[10] and rhodium[8] open cyclobutanols through β-elimination.



Scheme 1 General scheme representing the topic of our work.

Cyclobutane-1,2-diols are structurally related to cyclobutanols and their preparation include cyclocarbopalladation,[14] pinacol coupling[15] or addition of Grignard reagents to cyclobutane-1,2-dione.[16] Cyclobutane-1,2-diols are part of natural substances or have been used for their preparation.[17] In addition, chemical transformations of cyclobutene-1,2-diols have been described including retro-ene reaction,[18] pinacol rearrangement,[19] ring enlargement[20] or ring-opening reactions.[21] Ring contraction and ring expansion reactions of cyclobutanols or cyclobutane-1,2-diols usually proceed under basic or acidic conditions.[22] However, phenylcyclobutane-1,2-diol undergoes additive-free thermal ring opening and ring contraction to form a mixture of aldehydes (Scheme 1b).[22] In contrast, 1,2-diphenylcyclobutane-1,2-diol is thermally opened to 1,4-diphenylbutane-1,4-dione (Scheme 1c).

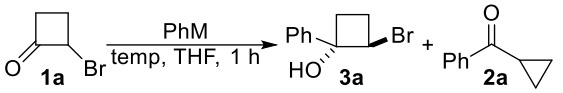
[22] Our research interest in the chemistry of cyclobutanes[23] and the simplicity of thermal opening of substituted cyclobutane-1,2-diols intrigued us and we decided to study the thermal stability of 2-bromocyclobutane-1-ols **3**. In this case, the formation of halogenated products can be expected, allowing their further modification (Scheme 1, our work).

However, the preparation of halocyclobutanols strongly depends on the substitution of the cyclobutane ring. 2-Bromocyclobutanone **1a** reacts with organolithium reagents, including phenyllithium, to form quasi-Favorskii rearrangement products[24a-c] even at low temperature.[24d] Polysubstituted halocyclobutanols are resistant to the quasi-Favorskii rearrangement as illustrated by the addition of 2-furyllithium reagent to disubstituted 2-bromocyclobutanone at -78 °C.[25] Similar trend in reactivity was also observed in the addition of organocerium reagents to dichloro ketones.[26] Other approaches for the preparation of halocyclobutanols cover carbonyl group reduction,[27] double-bond hydroxylation,[28] epoxide opening,[29] and other means.[30] It is worth noting that the relative configuration of substituents for 2-bromocyclobutanols **3** has not been determined. Therefore, the preparation of bromohydrins **3** by addition of Grignard reagents to 2-bromocyclobutanone (**1a**) and the determination of the relative configuration of alcohols **3** is the next objective of this work.

Results and Discussion

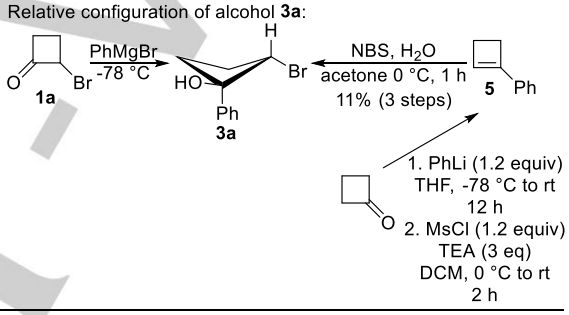
Our initial experiments with phenyllithium showed the complete of the ketone **1a** into the product of the quasi-Favorskii rearrangement **2a**, even at -78 °C, in a 53% isolated yield (Table 1, entry 1). The use of a phenylcerium reagent proved inefficient and the ketone **2a** was formed in a 48% yield (Table 1, entry 2). The same reactivity was observed in relation to phenylmagnesium bromide when the crude reaction mixture was warmed to an ambient temperature (Table 1, entry 3). Maintaining the reaction temperature at -78 °C and quenching the reaction mixture with a solution of acetic acid in methanol gave the bromohydrin **3a** in a 74% isolated yield (Table 1, entry 4). A similar result was obtained with regard to tetrahydrofuran (THF) at -40 °C, although a significant amount of the ketone **2a** was formed at -20 °C (Table 1, entries 5 and 6). A lower isolated yield of the cyclobutanol **3a** was obtained when the reaction mixture was quenched with a solution of water in methanol (Table 1, entry 7). The obtained results suggest that the inhibition of the quasi-Favorskii rearrangement, during the addition of the Grignard reagent to 2-bromocyclobutanone, is caused by the higher polarity of the O–Mg bond compared with O–Li bond. The relative configuration of alcohol **3a** was determined to be *trans.* The relative configuration of alcohol **3a** was confirmed by comparison of ^{1}H NMR spectra of alcohol **3a** prepared by the addition of phenylmagnesium bromide to 2-bromocyclobutanone and the alcohol obtained by addition of NBS to cyclobutene **5**, which proceeds as an *anti*-addition.[31] Formation of the *cis* isomer was ruled out by detailed analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. This finding contrasts with the formation of *cis*-chlorohydrins by addition of methyl lithium to substituted chlorocyclohexanones.[32] Unfortunately, the reasons for this reactivity remain unknown and will be the subject of further study.

Table 1 The addition of phenylmagnesium bromide to the 2-bromocyclobutanone (**1a**).

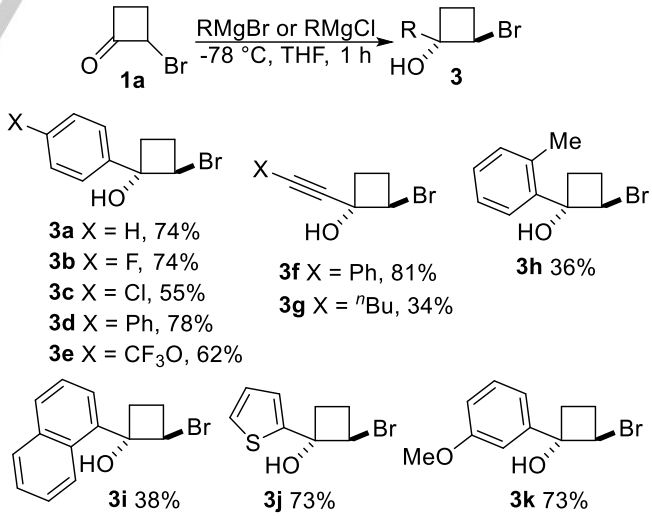


Entry	Temp [°C]	M	**3a** [%][a,b]	**2a** [%][a]
1	-78	Li	–	53
2	-78 to 23	$CeCl_2$	–	48[c]
3	-78 to 23	MgBr	–	50
4	-78	MgBr	74	–
5	-40	MgBr	73	–
6	-20	MgBr	63	<10
7	-78	MgBr	63[d]	–

Relative configuration of alcohol **3a**:



[a] Isolated yield. [b] A solution of phenylmagnesium bromide (1.2 equiv) was added to a solution of ketone (1.0 equiv) in dry THF (4 mL/mmol) and then cooled to the indicated temperature. After one hour, the reaction mixture was quenched with acetic acid (2 M solution in methanol). [c] ^{1}H NMR yield. [d] The reaction mixture was quenched with a solution of water in methanol.

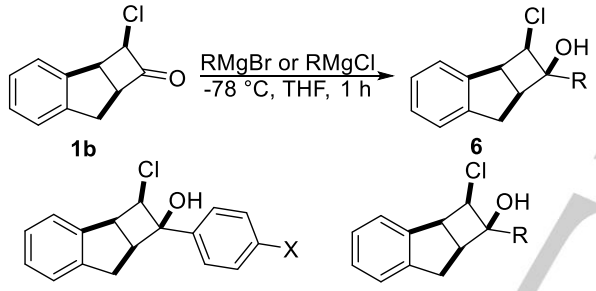


Scheme 2 The scope of the Grignard reagent addition to the 2-bromocyclobutanone (**1a**).

Optimized reaction conditions for the preparation of the bromocyclobutanol **3a** were used to study the effect of the Grignard reagent structure on the formation of cyclobutanols (Scheme 2). The addition of 4-substituted phenylmagnesium

halides gave rise to very good yields of the alcohols **3a**–**3e** (ranging from 55–78%). The cyclobutanols **3f** and **3g**, which both featured a triple bond in their molecules, were also successfully prepared. The use of bulkier Grignard reagents resulted in decreased yields of the alcohols **3h** and **3i**. The 2-thienylmagnesium bromide **3j** and the 3-methoxyphenylmagnesium chloride **3k** showed similar reactivity to the 4-substituted phenylmagnesium halides.

The starting chloroketone **1b** was prepared by [2+2] cycloaddition between dichloroketene and indene,[26] which proceed diastereoselectively,[33] followed by reduction with zinc.[34] The relative configuration of the chlorine atom was determined by NOE experiments. Attempts to prepare chlorocyclobutanones by [2+2] cycloaddition of styrene, allylbenzene, oct-1-ene with dichloroketene and subsequent reduction with zinc[34] led to the formation of a mixture of diastereomers which failed to separate. The substituted chlorocyclobutanone **1b** reacted with the aliphatic, aromatic, vinyl, and ethynyl Grignard reagents to give the tertiary alcohols **6a**–**6i** in high yields (Scheme 3). It is worth noting that the reaction of 1-naphthylmagnesium bromide with the ketone **1b** gave the alcohol **6f** in a substantially lower yield, while phenylethynylmagnesium chloride required a temperature of -50 °C and a 2 h reaction time to accomplish the formation of the tertiary alcohol **6i**.



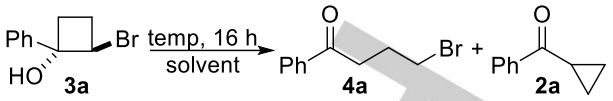
6a X = H, 90%
6b X = Cl, 93%
6c X = Ph, 74%

6d R = $(CH_2)_7CH_3$, 70%
6e R = CH_2=CH, 80%
6f R = 1-naphthyl, 56%
6g R = 3-$MeOC_6H_4$, 94%
6h R = CH_2CH=CH_2, 85%
6i R = PhCC, 87% (-50 °C, 2 h)

Scheme 3 The scope of the Grignard reagent addition to the chlorocyclobutanone **1b**.

Next, we decided to study the ability of the prepared alcohols to undergo ring-expansion and ring-contraction reactions. Therefore, we heated the isolated alcohol **3a** in different solvents (Table 2). After heating the alcohol **3a** in xylene to 140 °C, the formation of the cyclopropyl ketone **2a** and the butyrophenone **4a** were observed (Table 2, entry 1). *N*,*N*-Dimethylacetamide (DMA) gave a similar yield of the ketone **4a**, although the reaction product was present within a complex mixture of difficult-to-identify substances (Table 2, entry 2). With regard to acetonitrile, the almost complete conversion of the starting material into the ketone **4a**, which was obtained in a 75% yield, was observed. We discovered that it was necessary to maintain the reaction time at 16 h, as shortening the reaction time to 4 h resulted in a mixture of the ketones **4a** and **2a** (Table 2, entry 4). In contrast, prolonging the reaction time did not affect the yield of the butyrophenone **4a** (Table 2, entry 5).

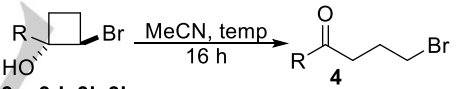
Table 2 Heating of the cyclobutanol **3a**.



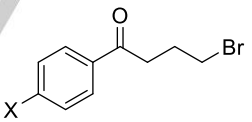
Entry	Solvent	Temp [°C]	**4a** [%][a]	**2a** [%][a]
1	xylene	140	17	54
2	DMA	140	16	–[b]
3	MeCN	80	75	9
4	MeCN	80[c]	50	43
5	MeCN	80[d]	76	7

[a] ^{1}H NMR yield. [b] The formation of a complex reaction mixture was observed. [c] The reaction time was 4 h. [d] The reaction time was 24 h.

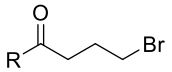
Optimized reaction conditions were applied to a series of the prepared cyclobutanols **3a–3d, 3i** and **3k** (Scheme 4). The thermal opening of bromocyclobutanols bearing 4-substituted phenyl substituents led to the expected butyrophenones **4a**–**4d** in good yields. Similar results were obtained for substances with the 1-naphthyl **4i** and the 3-methoxyphenyl **4k** substituents. It is worth noting that the ketone **4b** proved to be a key intermediate in relation to the preparation of melperone.[35] Thus, the preparation of the butyrophenone **4b** with a 4-fluorophenyl substituent complements the reported procedures for the synthesis of butyrophenone **4b** by means of the acylation of fluorobenzene,[36] light-enabled benzylic oxidation,[37] the cerium-mediated oxidative coupling of cyclobutanols,[7] and the ionic-liquid-mediated opening of cyclopropyl ketones.[38]



3a–3d, **3i**, **3k**



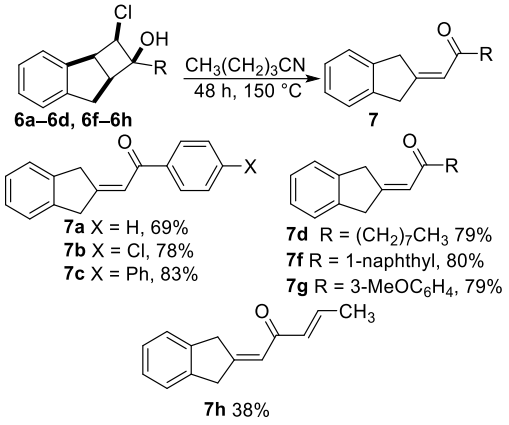
4a, X = H, 67% (80 °C)
4b, X = F, 48% (100 °C)
4c, X = Cl, 82% (100 °C)
4d, X = Ph, 65% (150 °C)



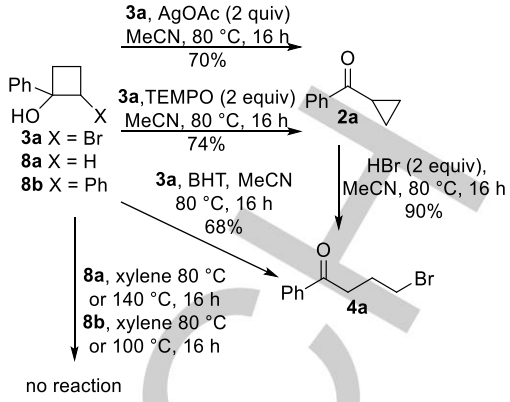
4i R = 1-naphthyl, 67% (120 °C)
4k R = 3-$MeOC_6H_4$, 97% (100 °C)

Scheme 4 The scope of the thermal ring-opening of the cyclobutanols **3a–3d**, **3i**, **3k**.

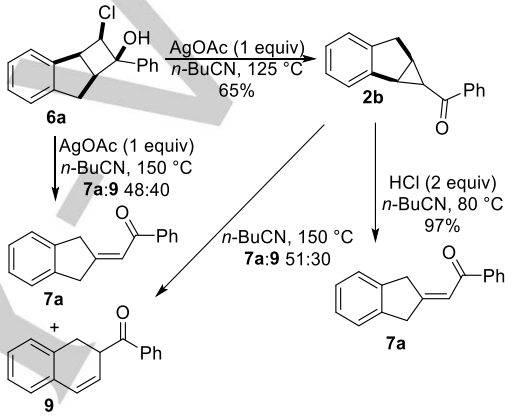
The substrates with fused cyclobutanones **6a**–**6d** and **6f**–**6h** were heated in valeronitrile at 150 °C, although in this case the formation of α,β-unsaturated ketones **7** was observed (Scheme 5). The isolated yields of the α,β-unsaturated ketones **7a**–**7c** were similar with the yields of the butyrophenones **4a**, **4c** and **4d**. The isomerization of alcohols with the 1-naphthyl **6f** and the 3-methoxyphenyl **6g** substituents was performed in a similar manner. Likewise, a high yield of the ketone **7d** was achieved with the octyl substituent. The cyclobutanol with the allyl substituent **6h** gave the product of the double-bond isomerization **7h** in a 38% yield. It is worth noting here that the structural motif represented by the unsaturated ketones **7a**–**7h** has not yet been synthesized.



Scheme 5 The thermal ring-opening of the cyclobutanols **6a–6d** and **6f–6h**.



Scheme 6 Mechanistic study for the conversion of alcohol **3a** to ketone **4a**.

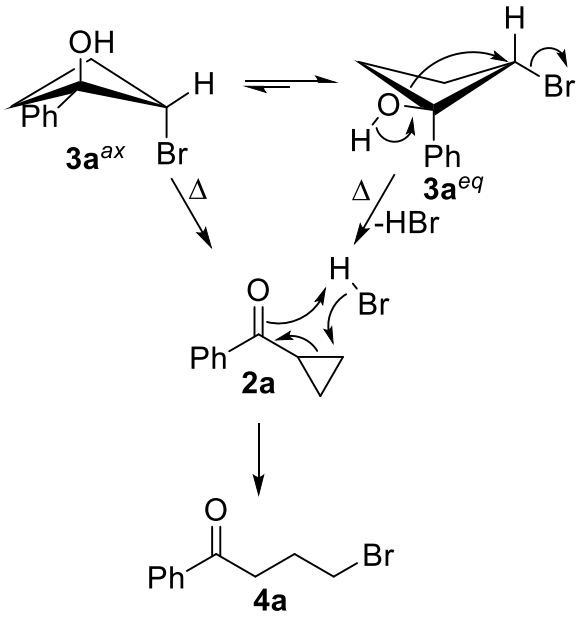


Scheme 7 Mechanistic study for the conversion of alcohol **6a** to ketone **7a**.

The results obtained during the optimization of the ring-opening of the cyclobutanol **3a** suggest cyclopropyl ketone **2a** to be a potential intermediate during the conversion of the substituted cyclobutanols **3** into the butyrophenones **4**. Therefore, we studied the course of the discovered transformation (Scheme 6). We first verified that the presence of a halogen atom is necessary for the formation of the butyrophenone **4a** from the alcohol **3a**, as the alcohols **8a** and **8b** did not react either in acetonitrile at 80 °C or at elevated temperatures in xylene. The formation of the butyrophenone **4a** was inhibited by performing the ring-opening reaction of the alcohol **3a** in the presence of a bromide ion scavenger, which afforded the cyclopropyl ketone **2a** in a 70% yield. Next, we eliminated the radical course by heating the alcohol **3a** in the presence of butylhydroxytoluene (BHT) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). In the case of the BHT, the reaction proceeded to give the ketone **4a** in a 68% yield. The TEMPO provided the cyclopropyl ketone **2a**, indicating that TEMPO acts as a hydrobromic acid scavenger. We further verified that the cyclopropyl ketone **2a** undergoes conversion into the butyrophenone **4a** via the reaction with hydrobromic acid in acetonitrile at 80 °C.

Similar results were also obtained in experiments involving the indene derivative **6a** (Scheme 7). Silver acetate, as a halide ion scavenger, allowed for the formation of the fused cyclopropane derivative **2b** in a 65% yield. Heating the cyclopropyl ketone **2b** in valeronitrile to 150 °C gave the two alkenes **7a** and **9**. However, the reaction of the ketone **2b** with hydrogen chloride at 80 °C completed the formation of the ketone **7a** in a 97% yield.

Based on previous observations and quantum chemical calculations,[39] it can be expected that the wing-shape cyclobutane conformers **3a**^{ax} and **3a**^{eq} will prefer an equatorial arrangement of the hydroxyl group and bromine atom (Scheme 8). Then, the alcohol **3a**^{eq} undergoes conversion into the cyclopropyl ketone **2a** via an additive-free ring contraction. We assume that the ring contraction proceeds by a concerted mechanism because ^{1}H NMR analysis of the crude reaction mixture showed the presence of only ketone **4a**, unreacted starting compound **3a** or cyclopropyl ketone **2a**. Attempts to detect radical or ionic intermediates by heating of the alcohol **3a** in the presence of styrene, methyl acrylate, benzyl bromide, homobenzyl iodide, acetic acid did not show the formation of any by-products. Then, the resulting ketone **2a** is opened to the butyrophenone **4a** via the reaction with either hydrogen bromide. This is consistent with the decreasing yield of cyclopropyl ketone **2a** with increasing reaction time (Table 2, entries 3 and 4). A similar progression can be expected for alcohols **6a**–**6d** and **6f**–**6h** to unsaturated ketones **7a**–**7h**. The more difficult course of the isomerization reaction in this case can be explained by the *cis* relative configuration of the hydroxyl group and the bromine atom.



Scheme 8 Proposed mechanism for the formation of the butyrophenone **4a**.

Conclusion

In conclusion, we have developed a procedure for the preparation of 1-substituted 2-bromocyclobutanols that relies on the reaction of 2-bromocyclobutanone with Grignard reagents at -78 °C. The relative configuration of the hydroxy group and bromine atom of the prepared 1-substituted 2-bromocyclobutanols was determined to be *trans*. The developed procedure can be easily extended to the preparation of substituted halocyclobutanols. We further studied the properties of the prepared alcohols and determined that heating 1-substituted 2-bromocyclobutan-1-ol in acetonitrile to 80 °C produces substituted butyrophenones. In contrast, cyclobutanols with fused indene open to unsaturated ketones with an indenylidene moiety. Based on the performed experiments, we believe that the formation of thermal ring-opening products involves an additive-free cyclobutanes contraction into substituted aryl cyclopropyl ketones. Then the resulting cyclopropane derivatives are opened by means of hydrogen halide.

Experimental Section

All reactions were performed under argon atmosphere. NMR spectra were measured on Varian MercuryPlus 300 (^{1}H, 300.13 MHz; ^{13}C, 75.46 MHz), Agilent 400MR DD2 (^{1}H, 400.13 MHz; ^{13}C, 100.61 MHz) at 298 K unless otherwise stated. Mass spectra were measured on ZAB-SEQ (VG Analytical). Compounds **1a**,[23d] **8a**,[7] **8b**,[7] **5**[36] were prepared according to published procedures. Silica gel (Merck, Silica Gel 60, 40–63 µm or Merck Silica Gel 60, 63-200 µm) was used for column chromatography. Grignard reagents were prepared by reacting aryl halides with magnesium in dry THF. Concentration of Grignard reagents was determined by titration using iodine in dry THF before use. *n*-BuLi (2.5 M solution in hexane), and other compounds were purchased from Sigma-Aldrich, FLuorochem and Acros Organics. Valeronitrile was dried over molecular sieves before use. Other solvents were prepared by PureSolv MD7. Concentration of BuLi was determined by titration using menthol and 1,10-phenanthroline in dry THF before use.

Preparation of starting compound

2-Chloro-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-one (1b)

To a stirred solution of the 2,2-dichloro-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-one (681 mg, 3 mmol) in acetic acid (100 mL) was added zinc dust (2.2 g, 33 mmol). The reaction mixture was then stirred at room temperature. After 20 min the zinc was removed by filtration on celite, and the filtrate was concentrated in vacuo. To the resulting mixture was added aqueous ammonia (33%) at 0 °C. The crude reaction mixture was diluted with ether (10 mL) and the organic phase was washed with water (10 mL) and brine (10 mL). The solvents were dried over $MgSO_4$ and removed under reduce pressure. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.30) gave 0.445 g (77 %) of the title compound as a white solid, Mp 104.2–105.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.35 (m, 1H), 7.29–7.24 (m, 3H), 5.32 (dd, *J* = 4, 12 Hz, 1H), 4.40–4.36 (m, 1H), 4.07 (dddd, *J* = 9.0, 7.6, 2.8, 1.3 Hz, 1H), 3.38 (d, *J* = 16.6 Hz, 1H), 3.15 (dd, *J* = 16.7, 9.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.2, 143.8, 137.9, 128.6, 128.3, 127.0, 125.6, 65.7, 59.0, 45.1, 34.9. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{11}H_9ClO$ 193.0415; Found 193.0414.

General procedure for reaction of halocyclobutanones with Grignard reagents (GP1)

A solution of Grignard reagents (1.2 equiv) was added to a solution of halocyclobutanones **1a** or **1b** (1.0 equiv) in dry THF (5 mL/mmol) cooled to -78 °C. The resultant mixture was stirred at -78 °C for the indicated time. Then an acetic acid (2 M solution in methanol) was added and the reaction mixture was warmed to 23 °C. The crude reaction mixture was diluted with ether (10 mL/mmol) and the organic phase was washed with acidic water (10 mL of water and 1 mL of 1 M HCl/mmol), water (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$, the solvents were removed under reduce pressured and the products were isolated by column chromatography (silica gel).

General procedure for thermal opening of cyclobutanols (GP2)

A solution of cyclobutanols **3** or **6** in dry acetonitrile or valeronitrile (6 mL/mmol) was stirred at elevated temperature for the indicated time. Then the solvents were removed under reduce pressured and the products were isolated by column chromatography (Silica gel).

Cyclopropyl(phenyl)methanone (2a)

A solution of phenylmagnesium bromide (0.67 mL, 1.2 mmol) was added to a solution of bromocyclobutanones (149 mg, 1.0 mmol) in dry THF (5 mL) cooled to -78 °C. The resultant mixture was stirred at 23 °C for 1 h. Then an acetic acid (1 mL, 2 M solution in methanol) was added, and the crude reaction mixture was diluted with ether (10 mL) and the organic phase was washed with acidic water (10 mL of water and 1 mL of 1 M HCl/mmol), water (10 mL) and brine (10 mL). The solvents were dried over $MgSO_4$ and removed under reduce pressure. Column chromatography (Hexane/AcOEt 20:1, $R_f \approx 0.55$) gave 0.073 g (50%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–8.00 (m, 2H), 7.59–7.44 (m, 3H), 2.73–2.64 (m, 1H), 1.27–1.22 (m, 2H), 1.08–1.01 (m, 2H), in accordance with literature.[40]

Phenyl(1,1a,6,6a-tetrahydrocyclopropa[a]inden-1-yl)methanone (2b)

According to modificated GP 2 cyclobutanol **3l** (162 mg, 0.6 mmol) was stirred in valeronitrile (3 mL) with silver acetate (100 mg, 0.6 mmol) at 125 °C for 16 h. The solvent was removed under reduce pressure and column chromatography (Hexane/AcOEt 9:1, R_f = 0.46) gave 91 mg (65%) of the title compound as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–

7.84 (m, 2H), 7.50–7.44 (m, 1H), 7.40–7.34 (m, 2H), 7.16–7.12 (m, 2H), 7.09–7.01 (m, 1H), 7.00–6.93 (m, 1H), 3.58 (d, *J* = 17.0 Hz, 1H), 3.26–3.17 (m, 2H), 2.71–2.64 (m, 1H), 2.51–2.41 (m, 1H), in accordance with literature.[32] $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.7, 144.0, 139.8, 138.16, 132.52, 128.24, 127.96, 126.48, 125.96, 124.58, 124.25, 33.76, 32.45, 28.46, 24.46, in accordance with literature.[41]

2-Bromo-1-phenylcyclobutan-1-ol (3a)

2-Bromocyclobutanone (1.49 g, 10.0 mmol) and phenylmagnesium bromide (6.67 mL, 12.0 mmol) was stirred for 1 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, $R_f \approx 0.35$) gave 1.674 g (74%) of the title compound as a yellow oil. Alternatively, the title compound was prepared from a solution of crude phenylcyclobutene (**6**) in acetone/water (15 mL, 2:1) cooled to 0 °C followed by addition of *N*-bromosuccinimide (1.815 g, 10.2 mmol, 1.02 eq). The resultant mixture was stirred at 0°C for 1 h. Then, the crude reaction mixture was diluted with ether (50 mL) and the organic phase was washed with diluted hydrochloric acid (10 mL of water and 1 mL of 1 M HCl/mmol), water (10 mL) and brine (10 mL). The solvents were dried over $MgSO_4$ and removed under reduce pressure. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.37) gave 0.244 g (10%) of the title compound as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.30 (m, 5H), 4.85–4.79 (m, 1H), 2.67–2.38 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.7, 128.7, 128.0, 124.8, 79.1, 53.2, 32.9, 29.1. IR (ATR): ν 2518 (m), 3439 (m), 3059 (w), 3027 (w), 3002 (w), 2953 (m), 1495 (m), 1447 (m), 1288 (m), 1249 (m), 1223 (m), 1189 (m), 1122 (m), 1074 (m), 1018 (m) cm^{-1}. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{10}H_{11}BrO$ 208.9966; Found 208.9967.

2-Bromo-1-(4-fluorophenyl)cyclobutan-1-ol (3b)

2-Bromocyclobutanone (298 mg, 2 mmol) and 4-fluorophenylmagnesium chloride (3.1 mL, 2.4 mmol) was stirred for 1 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.34) gave 363 mg (74%) of the title compound as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2H), 7.07–7.03 (m, 2H), 4.80–4.76 (m, 1H), 2.69 (br s, 1H), 2.63–2.53 (m, 3H), 2.40–2.33 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.5 (d, *J* = 246.4 Hz), 139.7 (d, *J* = 4.0 Hz), 126.7 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 22.1 Hz), 78.6, 53.3, 33.0, 29.0. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{10}H_{10}BrFO$ 226.9866; Found 226.9866.

2-Bromo-1-(4-chlorophenyl)cyclobutan-1-ol (3c)

2-Bromocyclobutanone (298 mg, 2 mmol) and 4-chlorophenylmagnesium chloride (2.5 mL, 2.4 mmol) was stirred at for 1 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.37) gave 288 mg (55%) of the title compound as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 4H), 4.79–4.75 (m, 1H), 2.72 (br s, 1H), 2.65–2.52 (m, 3H), 2.39–2.32 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.2, 134.0, 128.8, 126.4, 78.6, 53.2, 33.0, 29.0. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{10}H_{10}BrClO$ 244.9550; Found 244.9547.

1-([1,1'-Biphenyl]-4-yl)-2-bromocyclobutan-1-ol (3d)

2-Bromocyclobutanone (298 mg, 2 mmol) and 4-biphenylmagnesium bromide (5.5 mL, 2.4 mmol) was stirred for 1 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.33) gave 473 mg (78%) of the title compound as a white solid, Mp 71.5–73 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.57 (m, 4H), 7.52–7.43 (m, 4H)7.38–7.34 (m, 1H), 4.89–4.85 (m, 1H), 2.73 (d, *J* = 4.0 Hz, 1H), 2.69–2.56 (m, 3H), 2.46–2.42 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.7, 141.1, 140.7, 129.0, 127.6, 127.5, 127.3, 125.3, 79.0, 53.4, 33.1, 29.1. IR (ATR): ν 3502 (s), 3421 (s), 3028 (m), 2956 (m), 1486 (s), 1447 (m), 1428 (w), 1397 (m), 1352 (m), 1296 (m), 1246 (m), 1217 (m), 1191 (m), 1126 (m), 1114 (m), 1076 (m), 1034 (w), 1015 (m), 1006 (m) cm^{-1}. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{16}H_{15}BrO$ 285.0273; Found 285.0271.

2-Bromo-1-(4-(trifluoromethoxy)phenyl)cyclobutan-1-ol (3e)

2-Bromocyclobutanone (298 mg, 2 mmol) and 4-(trifluoromethoxy)phenylmagnesium bromide (4.4 mL, 2.4 mmol) was for 1 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.38) gave 386 mg (62%) of the title compound as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.23–7.20 (m, 2H), 4.81–4.77 (m, 1H), 2.74–2.73 (m, 1H), 2.67–2.54 (m, 3H), 2.41–2.36 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 142.4, 126.5, 125.0, 121.2, 120.6 (q, *J* = 258 Hz) 78.5, 53.1, 33.1, 29.0. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{11}H_{10}BrF_3O_2$ 292.9783; Found 292.9782.

2-Bromo-1-(phenylethynyl)cyclobutan-1-ol (3f)

2-Bromocyclobutanone (298 mg, 2 mmol) and phenylethynylmagnesium chloride (5 mL, 2.4 mmol) was stirred for 1.5 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.35) gave 407 mg (81%) of the title compound as a white solid, Mp 40.3–42.7 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2H), 7.34–7.30 (m, 3H), 4.78–4.74 (m, 1H), 2.74 (br s, 1H), 2.61–2.43 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 131.9, 128.9, 128.5, 122.1, 88.9, 85.0, 70.0, 54.1, 34.8, 29.0. HR MS (APCI) m/z: $[(M+H]^+$ Calcd for $C_{12}H_{11}BrO$ 251.0066; Found 251.0064.

2-Bromo-1-(hex-1-yn-1-yl)cyclobutan-1-ol (3g)

2-Bromocyclobutanone (298 mg, 2 mmol) and hex-1-yn-1-ylmagnesium chloride (5 mL, 2.4 mmol) was stirred for 1.5 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.40) gave 157 mg (34%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.62–4.58 (m, 1H), 2.54 (br s, 1H), 2.51–2.29 (m, 4H), 2.21 (t, *J* = 7.0 Hz, 2H), 1.50–1.36 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 86.2, 80.5, 69.8, 54.7, 34.9, 30.6, 28.8, 22.1, 18.5, 13.7. HR MS (APCI) m/z: $[(M+H]^+$ Calcd for $C_{10}H_{15}BrO$ 231.0379; Found 231.0375.

2-Bromo-1-(o-tolyl)cyclobutan-1-ol (3h)

2-Bromocyclobutanone (298 mg, 2 mmol) and o-tolylmagnesium chloride (3.4 mL, 2.4 mmol) was stirred for 1 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.39) gave 174 mg (36%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.28 (m, 1H), 7.22–7.16 (m, 3H), 5.04–5.00 (m, 1H), 2.77–2.48 (m, 3H), 2.42 (s, 3H), 2.38–2.28 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 141.3, 137.3, 131.8, 128.3, 125.9, 124.3, 80.2, 51.5, 33.6, 29.7, 20.0. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{11}H_{13}BrO$ 223.0117; Found 223.0120.

2-Bromo-1-(naphthalen-1-yl)cyclobutan-1-ol (3i)

2-Bromocyclobutanone (298 mg, 2 mmol) and 1-naphthylmagnesium bromide (4.6 mL, 2.4 mmol) was stirred for 1 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.34) gave 211 mg (38%) of the title compound as a white solid, Mp 76.3–77.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.28–8.25 (m, 1H), 7.88–7.85 (m, 1H), 7.82–7.79 (m, 1H), 7.55–7.43 (m, 4H), 5.22–5.18 (m, 1H), 3.05–2.99 (m, 1H), 2.80–2.69 (m, 2H), 2.60 (dtd, *J* = 11.0, 7.9, 3.0 Hz, 1H), 2.52–2.44 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.0, 134.6, 131.0, 129.2, 128.9, 126.3, 126.0, 125.8, 125.0, 122.3, 80.1, 52.0, 34.8, 29.6. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{14}H_{13}BrO$ 259.01169; Found 259.01165.

2-Bromo-1-(thiophen-2-yl)cyclobutan-1-ol (3j)

2-Bromocyclobutanone (298 mg, 2 mmol) and 2-thienylmagnesium bromide (2.2 mL, 2.4 mmol) was stirred for 1 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.40) gave 340 mg (73%) of the title compound as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.27–7.25 (m, 1H), 7.02–6.97 (m, 2H), 4.78–4.73 (m, 1H), 2.95 (br s, 1H), 2.66–2.52 (m, 3H), 2.46–2.39 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 148.4, 127.2,

125.3, 123.2, 77.0, 55.0, 35.2, 28.5. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for C_8H_9BrOS 214.9525; Found 214.9526.

2-Bromo-1-(3-methoxyphenyl)cyclobutan-1-ol (3k)

2-Bromocyclobutanone (298 mg, 2 mmol) and 3-methoxyphenylmagnesium bromide (2.5 mL, 2.4 mmol) was stirred for 1 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.30) gave 375 mg (73%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.27 (m, 1H), 7.01–6.97 (m, 2H), 6.86–6.83 (m, 1H), 4.83–4.79 (m, 1H), 3.82 (s, 3H), 2.67–2.52 (m, 4H), 2.42–2.37 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.9, 145.4, 129.8, 125.0, 117.1, 113.4, 110.8, 79.0, 55.4, 53.3, 33.0, 29.1. IR (ATR): ν 3459 (s), 2942 (w), 1591 (m), 1492 (m), 1462 (m), 1425 (m), 1368 (m), 1328 (m), 1296 (m), 1236 (m), 1209 (w), 1190 (m), 1166 (m), 1125 (m), 1093 (w), 1073 (w), 1045 (w), 1018 (m) cm^{-1}. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{11}H_{13}BrO_2$ 239.0066; Found 239.0067.

2-Chloro-1-phenyl-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-ol (6a)

Chloroketone **1b** (578 mg, 3 mmol) and phenylmagnesium bromide (1.8 mL, 3.6 mmol) was stirred for 2 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.43) gave 731 mg (90%) of the title compound as a white solid, Mp 82.9–83.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.48 (m, 2H), 7.43–7.38 (m, 2H), 7.36–7.23 (m, 5H), 5.15 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.23 (t, *J* = 7.5 Hz, 1H), 3.52–3.47 (m, 2H), 3.14 (dd, *J* = 16.7, 8.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.7, 144.7, 140.4, 128.7, 128.0, 127.9, 127.7, 126.3, 125.0, 124.9, 79.2, 64.5, 49.3, 46.1, 33.3. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{17}H_{15}ClO$ 253.07785; Found 253.07793.

2-Chloro-1-(4-chlorophenyl)-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-ol (6b)

Chloroketone **1b** (385 mg, 2 mmol) and 4-chlorophenylmagnesium chloride (2.5 mL, 2.4 mmol) was stirred for 2 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.42) gave 568 mg (93%) of the title compound as a white solid, Mp 109.1–110.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2H), 7.38–7.23 (m, 6H), 5.08 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.23 (t, *J* = 7.5 Hz, 1H), 3.48–3.43 (m, 2H), 3.13 (dd, *J* = 16.7, 8.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.5, 143.1, 140.2, 133.8, 128.8, 128.2, 127.7, 126.6, 126.4, 124.9, 78.8, 64.6, 49.2, 46.2, 33.2. IR (ATR): ν 3511 (s), 3071 (w), 3056 (w), 2983 (w), 2964 (w), 2930 (w), 2891 (w), 2821 (w), 1489 (m), 1478 (m), 1456 (m), 1418 (m), 1396 (m), 1316 (m), 1291 (m), 1254 (w), 1214 (w), 1174 (w), 1137 (w), 1119 (w), 1091 (m), 1013 (m) cm^{-1}. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{14}Cl_2O$ 287.0389; Found 287.0387.

1-([1,1'-Biphenyl]-4-yl)-2-chloro-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-ol (6c)

Chloroketone **1b** (385 mg, 2 mmol) and 4-biphenylmagnesium bromide (5.5 mL, 2.4 mmol) was stirred for 2 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.39) gave 513 mg (74%) of the title compound as a white solid, Mp 135.9–136.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.55 (m, 6H), 7.48–7.42 (m, 2H), 7.38–7.24 (m, 5H), 5.20–5.16 (m, 1H), 4.29–4.23 (m, 1H), 3.56–3.48 (m, 2H), 3.20–3.11 (m, 1H), 2.22–2.20 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.6, 143.6, 140.9, 140.8, 140.4, 129.0, 128.1, 127.7, 127.6, 127.5, 127.3, 126.3, 125.5, 124.9, 79.1, 64.6, 49.3, 46.2, 33.3. IR (ATR): ν 3521 (m), 3450 (m), 3068 (m), 3033 (m), 2927 (m), 2909 (m), 1487 (m), 1477 (m), 1456 (m), 1369 (m), 1310 (m), 1282 (m), 1264 (m), 1235 (m), 1217 (m),1193 (m), 1136 (m), 1164 (m), 1113 (m), 1084 (w), 1024 (w), 1007 (w) cm^{-1}. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{23}H_{19}ClO$ 329.1092; Found 329.1087.

2-Chloro-1-octyl-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-ol (6d)

Chloroketone **1b** (385 mg, 2 mmol) and octylmagnesium chloride (1.3 mL, 2.4 mmol) was stirred for 2 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.53) gave 430 mg (70%) of the title compound as a white solid, Mp 60.3–61.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (m, 4H), 4.66 (dd, *J* = 7.9, 0.9 Hz, 1H), 4.07 (t, *J* = 7.2 Hz, 1H), 3.29 (d, *J* = 15.6 Hz, 1H), 3.06–2.95 (m, 2H), 1.73 (s, 1H), 1.66–1.61 (m, 2H), 1.41–1.24 (m, 12H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.4, 140.7, 127.8, 127.7, 126.1, 124.9, 78.6, 63.6, 48.9, 45.1, 41.6, 33.2, 32.0, 30.0, 29.7, 29.4, 23.0, 22.8, 14.3. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{19}H_{27}O$ 289.1718; Found 289.1712.

2-Chloro-1-vinyl-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-ol (6e)

Chloroketone **1b** (385 mg, 2 mmol) and vinylmagnesium bromide (2.7 mL, 2.4 mmol) was stirred for 2 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.44) gave 366 mg (83 %) of the title compound as a white solid, Mp 74.2–75.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.19 (m, 4H), 5.98 (dd, *J* = 17.1, 10.6 Hz, 1H), 5.36 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.16 (dd, *J* = 10.6, 1.2 Hz, 1H), 4.83 (dd, *J* = 7.9, 1.0 Hz, 1H), 4.12 (t, *J* = 7.3 Hz, 1H), 3.32 (d, *J* = 15.6 Hz, 1H), 3.19–3.15 (m, 1H), 3.04 (dd, *J* = 16.6, 8.2 Hz, 1H), 1.85 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.5, 141.0, 140.4, 127.9, 127.6, 126.2, 124.8, 114.1, 77.9, 63.3, 49.2, 44.8, 32.8. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{13}H_{13}ClO$ 203.0622; Found 203.0623.

2-Chloro-1-(naphthalen-1-yl)-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-ol (6f)

Chloroketone **1b** (385 mg, 2 mmol) and 1-naphthylmagnesium bromide (4.6 mL, 2.4 mmol) was stirred for 2 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.37) gave 359 mg (56%) of the title compound as a white solid, Mp 149.5–151.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31–8.29 (m, 1H), 7.91–7.82 (m, 2H), 7.62–7.28 (m, 8H), 5.61 (d, *J* = 8.1 Hz, 1H), 4.24 (t, *J* = 7.9 Hz, 1H), 4.02 (d, *J* = 16.6 Hz, 1H), 3.68 (ddt, *J* = 8.5, 7.2, 1.2 Hz, 1H), 3.44 (dd, *J* = 16.5, 8.6 Hz, 1H), 2.32 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 146.1, 140.7, 140.6, 134.7, 130.7, 129.3, 129.2, 128.0, 127.6, 126.34, 126.29, 125.9, 125.8, 125.1, 124.7, 124.0, 80.4, 63.0, 48.9, 46.3, 34.8. IR (ATR): ν 3521 (s), 3019 (w), 2962 (w), 2909 (w), 1508 (m), 1481 (m), 1459 (w), 1345 (w), 1308 (w), 1282 (w), 1242 (w), 1222 (w), 1179 (w), 1138 (w), 1115 (m), 1065 (w), 1022 (w) cm^{-1}. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{21}H_{17}ClO$ 303.0935; Found 303.0932.

2-Chloro-1-(3-methoxyphenyl)-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-ol (6g)

Chloroketone **1b** (385 mg, 2 mmol) and 3-methoxyphenylmagnesium bromide (2.5 mL, 2.4 mmol) was stirred for 2 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.33) gave 565 mg (94%) of the title compound as a white solid, Mp 111.3–113.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.23 (m, 5H), 7.10–7.05 (m, 2H), 6.88–6.84 (m, 1H), 5.14 (dd, *J* = 8.1, 1.1 Hz, 1H), 4.23 (t, *J* = 7.5 Hz, 1H), 3.84 (s, 3H), 3.51–3.46 (m, 2H), 3.13 (dd, *J* = 16.7, 8.3 Hz, 1H), 2.18–2.17 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.9, 146.6, 146.4, 140.4, 129.8, 128.0, 127.7, 126.2, 124.9, 117.3, 113.1, 111.0, 79.1, 64.6, 55.4, 49.2, 46.2, 33.3. IR (ATR): ν 3532 (s), 3016 (w), 2978 (w), 2946 (w), 2925 (w), 2848 (w), 1610 (s), 1582 (s), 1477 (s), 1443 (s), 1331 (m), 1278 (s), 1245 (s), 1214 (m), 1161 (m), 1135 (m), 1111 (s), 1046 (m), 1024 (m) cm^{-1}. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{18}H_{17}ClO_2$ 283.08842; Found 283.08840.

1-Allyl-2-chloro-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-ol (6h)

Chloroketone **1b** (385 mg, 2 mmol) and allylmagnesium chloride (1.7 mL, 2.4 mmol) was stirred for 2 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.45) gave 399 mg (85 %) of the title compound as a white solid, Mp 51.6–52.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.19 (m, 4H), 5.91–5.81 (m, 1H), 5.21–5.19 (m, 1H), 5.17–5.15 (m, 1H), 4.71

(dd, *J* = 8.0, 0.9 Hz, 1H), 4.10–4.06 (m, 1H), 3.33–3.26 (m, 1H), 3.06–2.99 (m, 2H), 2.41 (d, *J* = 7.2 Hz, 1H), 1.89 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 146.3, 140.6, 132.4, 127.9, 127.7, 126.2, 124.9, 119.1, 77.7, 62.7, 48.9, 45.7, 44.6, 33.0. HR MS (APCI) m/z: $[(M-H_2O)+H]^+$ Calcd for $C_{14}H_{15}ClO$ 217.0779; Found 217.0777.

2-Chloro-1-(phenylethynyl)-2,2a,7,7a-tetrahydro-1H-cyclobuta[a]inden-1-ol (6i)

Chloroketone **1b** (385 mg, 2 mmol) and phenylethynylmagnesium chloride (5 mL, 2.4 mmol) was stirred at -50 °C for 2 h according to GP1. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.37) gave 513 mg (87 %) of the title compound as a white solid, Mp 138.6–140.3 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.44 (m, 2H), 7.36–7.19 (m, 7H), 5.12 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.22 (t, *J* = 8.2 Hz, 1H), 3.55–3.45 (m, 2H), 3.12 (dd, *J* = 16.9, 8.5 Hz, 1H), 2.20 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 146.2, 139.8, 131.8, 128.7, 128.3, 127.9, 127.4, 126.1, 124.7, 122.1, 90.1, 84.7, 70.7, 64.2, 49.5, 47.5, 32.7. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}ClO$ 295.08842; Found 295.08838.

4-Bromo-1-phenylbutan-1-one (4a)

According to GP 2 cyclobutanol **3a** (347 mg, 1.53 mmol) was stirred in acetonitrile (7 mL) at 80 °C for 16 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.45) gave 234 mg (67%) of the title compound as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.01–7.97 (m, 2H), 7.61–7.55 (m, 1H), 7.51–7.45 (m, 2H), 3.56 (t, *J* = 6.1 Hz, 2H), 3.19 (t, *J* = 6.9 Hz, 1H), 2.36–2.27 (m, 2H), in accordance with literature.[42]

4-Bromo-1-(4-fluorophenyl)butan-1-one (4b)

According to GP 2 cyclobutanol **3b** (123 mg, 0.5 mmol) was stirred in acetonitrile (3 mL) at 100 °C for 20 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.41) gave 59 mg (48%) of the title compound as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04–7.99 (m, 2H), 7.17–7.11 (m, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.16 (t, *J* = 6.0 Hz, 2H), 2.31 (p, *J* = 6.0 Hz, 2H), in accordance with literature.[42]

4-Bromo-1-(4-chlorophenyl)butan-1-one (4c)

According to GP 2 cyclobutanol **3c** (131 mg, 0.5 mmol) was stirred in acetonitrile (3 mL) at 100 °C for 20 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.46) gave 107 mg (82%) of the title compound as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9 Hz, 2H), 7.45 (d, *J* = 9 Hz, 2H), 3.55 (t, *J* = 6 Hz, 2H), 3.16 (t, *J* = 6 Hz, 2H), 2.31 (p, *J* = 6 Hz, 2H), in accordance with literature.[42]

1-([1,1'-Biphenyl]-4-yl)-4-bromobutan-1-one (4d)

According to GP 2 cyclobutanol **3d** (152 mg, 0.5 mmol) was stirred in valeronitrile (3 mL) at 150 °C for 16 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.36) gave 94 mg (65%) of the title compound as a yellow solid, Mp 126.9–129.1 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08–8.04 (m, 2H), 7.72–7.69 (m, 2H), 7.65–7.62 (m, 2H), 7.50–7.46 (m, 2H), 7.43–7.39 (m, 1H), 3.58 (t, *J* = 6 Hz, 2H), 3.23 (t, *J* = 6 Hz, 2H), 2.34 (p, *J* = 6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.6, 146.1, 140.0, 129.1, 128.8, 128.4, 127.5, 127.4, 36.8, 33.8, 27.1. IR (ATR): ν 3036 (w), 2923 (w),1678 (s), 1062 (m), 1560 (w),1519 (w), 1484 (w), 1448 (w), 1402 (m), 1371 (m), 1305 (w), 1261 (w), 1236 (w), 1190 (m), 1182 (m) cm^{-1}. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{15}BrO$ 303.0379; Found 303.0383.

4-Bromo-1-(naphthalen-1-yl)butan-1-one (4i)

According to GP 2 cyclobutanol **3i** (166 mg, 0.6 mmol) was stirred in valeronitrile (3 mL) at 120 °C for 16 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.38) gave 111 mg (67%) of the title compound as a white solid, Mp 112.3–115.1 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.61–8.59 (m, 1H), 8.02–7.99 (m, 1H), 7.94–7.87 (m, 1H), 7.62–7.50 (m, 4H), 3.60 (t, *J* = 6 Hz, 2H), 3.28 (t, *J* = 6 Hz, 2H), 2.39 (p, *J* = 6 Hz, 2H), in accordance with literature.[33] $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 203.2, 135.8, 134.1, 133.0, 130.2, 128.6, 128.2, 127.9, 126.7, 125.8, 124.5, 40.1, 33.7, 27.4, in accordance with literature.[42] IR (ATR): ν 3047 (w), 2921 (w), 1676 (s), 1592 (w), 1573 (w), 1507 (m), 1434 (w), 1397 (w), 1354 (w), 1282 (w), 1230 (m), 1172 (w), 1094 (m), 1065 (w), 1023 (w) cm^{-1}.

4-Bromo-1-(3-methoxyphenyl)butan-1-one (4k)

According to GP 2 cyclobutanol **3k** (128 mg, 0.5 mmol) was stirred in acetonitrile (3 mL) at 100 °C for 16 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.33) gave 124 mg (97%) of the title compound as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58–7.49 (m, 1H), 7.50–7.49 (m, 1H), 7.40–7.36 (m, 1H), 7.14–7.11 (m, 1H), 3.86 (s, 3H), 3.55 (t, *J* = 6 Hz, 2H), 3.17 (t, *J* = 6 Hz, 2H), 2.31 (p, *J* = 6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.8, 160.0, 138.2, 129.8, 120.8, 119.8, 112.4, 55.6, 36.8, 33.8, 27.1. IR (ATR): ν 2939 (w), 2835 (w), 1681 (s), 1597 (s), 1582 (s), 1485 (m), 1451 (m), 1428 (m), 1362 (w), 1313 (w), 1285 (m), 1254 (s), 1202 (m), 1164 (w), 1164 (w), 1029 (w) cm^{-1}. HR MS (APCI) m/z: $[M+H]^+$ Calcd For $C_{11}H_{13}BrO_2$ 257.0171; Found 257.0170.

2-(1,3-Dihydro-2H-inden-2-ylidene)-1-phenylethan-1-one (7a)

According to GP 2 cyclobutanol **6a** (271 mg, 1 mmol) was stirred in valeronitrile (6 mL) at 150 °C for 36 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.37) gave 162 mg (69%) of the title compound as a white solid, Mp 127.1–129.4 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04–8.02 (m, 2H), 7.60–7.55 (m, 1H), 7.50–7.45 (m, 2H), 7.40–7.38 (m, 1H), 7.31–7.29 (m, 1H), 7.25–7.21 (m, 1H), 7.15–7.11 (m, 1H), 6.70 (s, 1H), 4.17 (s, 2H), 3.45 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.5, 145.0, 143.6, 142.2, 136.7, 133.4, 130.4, 128.8, 128.7, 126.4, 124.5, 123.6, 120.6, 41.7, 41.6. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{14}O$ 235.1117; Found 235.1119.

1-(4-Chlorophenyl)-2-(1,3-dihydro-2H-inden-2-ylidene)ethan-1-one (7b)

According to GP 2 cyclobutanol **6b** (153 mg, 0.5 mmol) was stirred in valeronitrile (3 mL) at 150 °C for 36 h. Column chromatography (Hexane/AcOEt 1:9, R_f = 0.35) gave 105 mg (78%) of the title compound as a white solid, Mp 135.7–137.2 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98–7.94 (m, 2H), 7.46–7.43 (m, 2H), 7.40–7.38 (m, 1H), 7.31–7.29 (m, 1H), 7.25–7.21 (m, 1H), 7.16–7.12 (m, 1H), 6.69 (s, 1H), 4.14 (s, 2H), 3.44 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.3, 144.8, 143.5, 141.8, 139.9, 134.9, 130.6, 130.1, 129.2, 126.5, 124.6, 123.7, 120.7, 41.6. IR (ATR): ν 3042 (w), 2889 (w), 1680 (s), 1585 (m), 1569 (m), 1485 (m), 1460 (m), 1396 (m), 1333 (m), 1206 (m), 1091 (m) cm^{-1}. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{13}ClO$ 269.0728; Found 269.0730.

1-([1,1'-Biphenyl]-4-yl)-2-(1,3-dihydro-2H-inden-2-ylidene)ethan-1-one (7c)

According to GP 2 cyclobutanol **6c** (173 mg, 0.5 mmol) was stirred in valeronitrile (3 mL) at 150 °C for 48 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.35) gave 129 mg (83%) of the title compound as a white solid, Mp 171.7–173.5 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11–8.09 (m, 2H), 7.70–7.68 (m, 2H), 7.64–7.62 (m, 2H), 7.50–7.46 (m, 2H), 7.42–7.39 (m, 2H), 7.32–7.30 (m, 1H), 7.26–7.21 (m, 1H), 7.16–7.12 (m, 1H), 6.73–6.72 (m, 1H), 4.20 (s, 2H), 3.47 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.1, 146.1, 145.0, 143.6, 142.3, 139.9, 135.3, 130.4, 129.3, 129.1, 128.4, 127.5, 127.4, 126.5, 124.5, 123.7, 120.7, 41.70, 41.67. IR (ATR): ν 3036 (w), 2913 (w), 2882 (w), 1786 (w), 1679 (s), 1597 (m), 1560 (m), 1484 (w), 1459 (m), 1387 (m), 1333 (m), 1217 (w), 1199 (m), 1019 (w) cm^{-1}. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{18}O$ 311.1430; Found 311.1434.

1-(1,3-Dihydro-2H-inden-2-ylidene)decan-2-one (7d)

According to GP 2 cyclobutanol **6d** (153 mg, 0.5 mmol) was stirred in valeronitrile (3 mL) at 150 °C for 36 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.30) gave 102 mg (79%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (m, 1H), 7.33–7.29 (m, 1H), 7.26–7.21 (m, 1H), 7.18–7.11 (m, 1H), 6.68–6.64 (m, 1H), 3.58 (s, 2H), 3.40–3.36 (m, 2H), 2.50 (t, *J* = 7.4 Hz, 2H), 1.63–1.52 (m, 3H), 1.34–1.18 (m, 11H), 0.92–0.82 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 208.3, 144.8, 143.5, 141.8, 130.1, 126.3, 124.3, 123.5, 120.5, 45.5, 42.4, 41.5, 31.8, 29.4, 29.2, 29.1, 23.8, 22.6, 14.1. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{26}O$ 271.2056; Found 271.2060.

2-(1,3-Dihydro-2H-inden-2-ylidene)-1-(naphthalen-1-yl)ethan-1-one (7f)

According to GP 2 cyclobutanol **6f** (160 mg, 0.5 mmol) was stirred in valeronitrile (3 mL) at 150 °C for 48 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.36) gave 114 mg (80%) of the title compound as a white solid, Mp 115.6–117.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66–8.64 (m, 1H), 8.02–7.99 (m, 2H), 7.89–7.87 (m, 1H), 7.62–7.49 (m, 4H), 7.40–7.37 (m, 1H), 7.31–7.28 (m, 1H), 7.24–7.20 (m, 1H), 7.15–7.11 (m, 1H), 6.74–6.72 (m, 1H), 4.27 (s, 2H), 3.48 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 201.3, 145.0, 143.6, 142.4, 135.4, 134.2, 133.2, 130.4, 128.6, 128.4, 128.3, 126.7, 126.5, 125.9, 124.48, 124.46, 123.7, 120.7, 44.9, 41.7. IR (ATR): ν 3038 (m), 2884 (w), 1785 (w), 1673 (s), 1608 (m), 1592 (m), 1570 (m), 1505 (m), 1459 (m), 1431 (m), 1387 (m), 1325 (m), 1298 (m), 1224 (m), 1209 (m), 1169 (m), 1149 (m), 1084 (m) cm^{-1}. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}O$ 285.1274; Found 285.1276.

2-(1,3-Dihydro-2H-inden-2-ylidene)-1-(3-methoxyphenyl)ethan-1-one (7g)

According to GP 2 cyclobutanol **6g** (150 mg, 0.5 mmol) was stirred in valeronitrile (3 mL) at 150 °C for 48 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.33) gave 104 mg (79%) of the title compound as a white solid, Mp 77.8–78.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.60 (m, 1H), 7.55–7.53 (m, 1H), 7.40–7.36 (m, 2H), 7.31–7.29 (m, 1H), 7.25–7.20 (m, 1H), 7.15–7.10 (m, 2H), 6.70–6.69 (m, 1H), 4.16 (s, 2H), 3.86 (s, 3H), 3.45 (m, 2H) ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.4, 160.04, 145.0, 143.6, 142.2, 138.0, 130.4, 129.8, 126.4, 124.5, 123.6, 121.4, 120.6, 119.9, 112.9, 55.6, 41.7, 41.6. IR (ATR): ν 3054 (w), 2985 (w), 2917 (w), 2889 (w), 1678 (s), 1594 (s), 1482 (m), 1461 (m), 1429 (s), 1391 (m), 1338 (m), 1300 (w), 1259 (w), 1223 (w), 1211 (w), 1199 (w), 1165 (m), 1136 (m), 1041 (m), 1017 (m) cm^{-1}. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{16}O_2$ 265.1223; Found 265.1226.

(*E*)-1-(1,3-Dihydro-2H-inden-2-ylidene)pent-3-en-2-one (7h)

According to GP 2 cyclobutanol **6h** (117 mg, 0.5 mmol) was stirred in valeronitrile (3 mL) at 150 °C for 40 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.32) gave 38 mg (38%) of the title compound as a yellow solid, Mp 57.8–58.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (m, 1H), 7.32–7.30 (m, 1H), 7.26–7.21 (m, 1H), 7.16–7.12 (m, 1H), 7.00–6.91 (m, 1H), 6.67–6.66 (m, 1H), 6.23–6.18 (m, 1H), 3.71 (s, 2H), 3.39–3.38 (m, 2H), 1.91–1.89 (m 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 197.2, 145.0, 144.1, 143.7, 142.2, 131.1, 130.3, 126.5, 124.4, 123.7, 120.6, 43.4, 41.6, 18.5. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{14}O$ 199.1117; Found 199.1116.

(1,2-Dihydronaphthalen-2-yl)(phenyl)methanone (9)

According to modified GP2 cyclobutanol **2b** (271 mg, 1 mmol) was stirred in valeronitrile (3 mL) with silver acetate (167 mg, 1 mmol) at 150 °C for 36 h. Column chromatography (Hexane/AcOEt 9:1, R_f = 0.52) gave 94 mg (40%) of the title compound as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.95 (m, 2H), 7.61–7.54 (m, 1H), 7.50–7.41 (m, 3H), 7.41–7.36 (m, 1H), 7.32–7.25 (m, 1H), 7.22–7.16 (m, 1H), 6.86–6.82 (m, 1H), 6.61 (dd, *J* = 5.5, 2.0 Hz, 1H), 4.21–4.13 (m, 1H), 3.42 (dd, *J* = 17.5, 6.1 Hz, 1H), 3.09 (dd, *J* = 17.5, 8.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) 198.8, 147.1, 144.2, 139.1, 136.8, 133.3, 131.3, 128.7, 128.1, 126.9, 125.0, 123.1, 121.2, 45.6, 40.3. HR MS (APCI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{14}O$ 235.1117; Found 235.1119.

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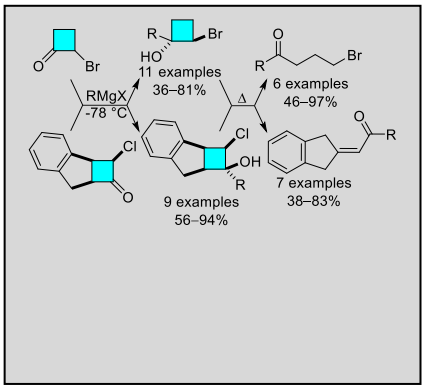

We have developed a new procedure for the preparation of aryl alkyl ketones and α,β-unsaturated ketones by thermal opening of halocyclobutanols. The reaction conditions for the thermal isomerization of cyclobutanols depend on the relative configuration of halohydrins. Based on the experiments performed, we assume that the halocyclobutanols undergo ring contraction to form cyclopropyl ketones, which are isomerized by means of hydrogen halide.

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