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Enantioselective Cleavage of Cyclobutanols Through Ir-Catalyzed C–C Bond Activation: Mechanistic and Synthetic Aspects

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Abstract: The Ir-catalyzed conversion of prochiral tert-cyclobutanols to β-methyl-substituted ketones proceeds under comparably mild conditions in toluene (45–110 °C) and is particularly suited for the enantioselective desymmetrization of β-oxy-substituted substrates to give products with a quaternary chirality center with up to 95% ee using DTBM-SegPhos as a chiral ligand. Deuteration experiments and kinetic isotope effect measurements revealed major mechanistic differences to related Rh-catalyzed transformations. Supported by DFT calculations we propose the initial formation of an IrIII hydride intermediate, which then undergoes a β-C elimination (C–C bond activation) prior to reductive C–H elimination. The computational model also allows the prediction of the stereochemical outcome. The Ir-catalyzed cyclobutanol cleavage is broadly applicable but fails for substrates bearing strongly coordinating groups. The method is of particular value for the stereo-controlled synthesis of substituted chromanes related to the tocopherols and other natural products.

Introduction

The transition metal-catalyzed activation of C–C single bonds has opened some unconventional strategies for the atom-economic synthesis of complex molecules.[1,2] In many cases cyclobutane derivatives have been employed as substrates because the energy gain (22–26 kcal mol⁻¹) associated with the opening of a strained four-membered ring[3] represents a strong driving force. Mechanistically, the cleavage of cyclobutanes through metal-catalyzed C–C bond activation can follow different pathways. For instance, cyclobutanones can undergo oxidative addition to Rh[4] or Pd[5] to form reactive five-membered metalla-cycles, which can then further react downstream in different ways as reported by Murakami et al.[6] Also other cyclobutane derivatives, such as biphenylenes,[7] cyclobutenediones, or cyclobutenones, can be activated by different transition metals (e.g., Ni, Pt, Rh, or Ru).[8] Furthermore, Ag[9] and Mn[10] reagents are able to induce the ring-opening of cyclobutanols via radical processes (homolytic C–C bond cleavage).

From a synthetic point of view Pd[11] and Rh[12]-catalyzed transformations of tert-cyclobutanols to ring-opened ketones are of particular interest because such reactions can be exploited for the enantioselective synthesis of β-substituted carbonyl compounds if prochiral substrates are employed in the presence of a chiral metal catalyst (Scheme 1).

Scheme 1. Selected metal-catalyzed cyclobutanol cleavage reactions according to the groups of Uemura,[13a] Murakami,[14a] and Cramer.[16]
As a first impressive example, Uemura and co-workers reported the enantioselective Pd-catalyzed reaction of cyclobutanol of type 1 into γ-arylated products (2) in the presence of the chiral ferrocene-derived ligand L1. In contrast, the groups of Murakami and Cramer used Rh catalysts to achieve the enantioselective conversion of prochiral cyclobutanol to β-methyl-substituted carbonyl compounds (such as 4 or 5) in the presence of SegPhos ligands L2 or L3, respectively. Extensive mechanistic studies (including deuterium-labeling experiments) suggested these transformations to proceed according to the general mechanism shown in Scheme 2. At first, the cyclobutanol substrate (6) is supposed to react with the catalyst to form a Rh cyclobutanolate 8, which then undergoes a β-C elimination as the key ring-opening step. In agreement to the outcome of deuteration experiments, the resulting alkyl-Rh intermediate 9 then isomerizes to a more stable Rh enolate 10 via 1,3-hydrogen shift. Final hydrolysis of 10 then closes the catalytic cycle and affords the (α-deuterated) product 7.

Results and Discussion

Initial experiments

Using the spirocyclobutanol 11a as a model substrate, we first reinvestigated different conditions for the metal-mediated ring-opening reaction to demonstrate the pronounced reactivity differences between the Rh- and the Ir-based catalysts (Table 1). In all cases, a solution of the substrate and the catalyst precursors (metal salt and ligand) in toluene was stirred under argon atmosphere for 30–60 min at room temperature before the mixture was heated to the specified temperature and the conversion was monitored by means of TLC. Although the catalyst generated in situ from [Rh(COD)Cl]2 (cod = 1,5-cyclooctadiene) and rac-BINAP proved to be completely inactive, the expected product 12a was cleanly formed upon addition of Cs2CO3 as a base (Table 1, entries 1, 2). Remarkably, the use of Cs2CO3 as a base (Table 1, entries 1, 2).}

![Scheme 2. General mechanism of the Rh-catalyzed cleavage of cyclobutanol as suggested by the groups of Murakami and Cramer based on deuteration studies.](image)

![Scheme 3. Ir-catalyzed cleavage of spirocyclobutanol as a key step of our total synthesis of (2R)-α-tocopherol.](image)

![Table 1. Rh- versus Ir-catalyzed cleavage of cyclobutanol 11a.](table)
of the hydroxy complex \([\text{Rh(COD)OH}]_2\) as the rhodium source also resulted in a smooth conversion without the necessity of a base additive (entry 3). However, virtually no enantioselectivity was observed under Rh catalysis when rac-BINAP was replaced by either \((R)-\text{BINAP}\) or \((R)-\text{DTBM-SegPhos}\) (entry-L3), the latter corresponding to the original conditions of Seiser and Cramer (entry 4).

In contrast, the Ir-based catalyst generated from the chloride salt \([\text{Ir(COD)Cl}_2]\), and rac-BINAP were found to be active even without a base additive. Moreover, a dramatic ligand acceleration was observed upon replacing BINAP by the \((R)-\text{DTBM-SegPhos}\) ligand in the Ir-catalyzed reaction. In this case, the desired transformation proceeded smoothly already at 70°C to give the product \((R)-12\ a\) in 98% isolated yield and with 93% ee (entry 6).

**Mechanistic studies**

The experiments summarized in Table 1 indicate the Ir- and the Rh-catalyzed reactions to follow different mechanistic pathways. The fact that the Rh-catalyzed reaction either essentially requires a base additive or the employment of the hydroxy complex as catalyst precursor suggested the formation of a rhodium cyclobutanolate intermediate of type 8 according to the established mechanism shown in Scheme 2. However, we were puzzled by the question why the Ir-catalyzed reaction proceeds smoothly in the absence of a base under “acidic” conditions using the chloro complex for the in situ generation of the active catalyst. We hypothesized that the primary intermediate 14 formed by coordination of the cyclobutanol substrate to the Ir-catalyst does not lead to a cyclobutanolate complex 13 (related to 8) in the absence of a base (Scheme 4). Instead, it appeared feasible that the iridium center in 14 might undergo oxidative addition (O–H bond activation) to generate an Ir\(^{II}\) hydride complex of type 15, which (as a 16 valence electron intermediate) could then be involved in the subsequent C–C bond activation step.

![Scheme 4. Possible reactions of the supposed primary Ir intermediate 14. Base-mediated generation of a cyclobutanolate 13 versus formation of an Ir\(^{II}\) hydride 15 by oxidative addition into the O–H bond.](image)

We started our experimental investigation of the mechanism of the Ir-catalyzed reaction with a deuteration experiment. For this purpose, the substrate D-11 a was prepared by O-deuteration of 11 a either by partitioning between D\(_2\)O/EtOAc (ca. 60% D) or by treatment of an ethereal solution of 11 a with 1.5 equiv of nBuLi followed by quenching the resulting lithium alkoxide with D\(_2\)O/DCI (ca. 70% D). The success of the O-deuteration was confirmed by IR analysis (see the Supporting Information). The reaction of D-11 a under the proven conditions then proceeded cleanly (Scheme 5) to afford the ring-opened ketone D-12 a with the deuterium label located at the newly formed (angular) methyl group according to NMR analysis (see the Supporting Information). Only a minor degree of deuteration (≤ 10%) was also detected at the terminal \(\alpha\)-carbonyl position.

The outcome of this experiment (Scheme 5) unambiguously proves the Ir-catalyzed process to mechanistically differ from the Rh-catalyzed reaction as virtually no deuteration occurred under Ir catalysis at the methylene position next to the keto function (compare Scheme 2). Thus, an 1,3-hydrogen shift leading to a metal enolate, as a characteristic feature of the Murakami/Cramer mechanism, could be excluded. Also, these authors never observed any deuteration of the newly formed methyl group during their studies of the Rh-catalyzed cyclobutanol cleavage.

Based on our experimental results we devised the mechanism shown in Scheme 6 for the Ir-catalyzed transformation. This mechanism starts with the oxidative addition of the \(\text{Ir}^{II}\)-complex into the O–D bond of D-11 a leading to the \(\text{Ir}^{III}\)-hydride 16. Now, the iridium center is supposed to activate the adjacent C–C bond to induce a \(\beta\)-carbon elimination via a transition state (TS) of type TS(16–17). The resulting \(\text{Ir}^{III}\)-alkyl-intermediate 17 finally undergoes reductive elimination to release the product D-12 a under regeneration of the Ir-catalyst.

When the Ir-catalyzed reaction of either 11 a or D-11 a was performed in the presence of excess D\(_2\)O (in toluene/D\(_2\)O = 4:1), the product D-12 a again contained a (single) deuterium

**Scheme 5. Selective deuteration of the angular methyl group in the Ir-catalyzed conversion of D-11 a.**

**Scheme 6. Proposed mechanism for the Ir-catalyzed cleavage of cyclobutanol D-11 a that takes into account the specific deuteration outcome.**
atom at the angular methyl group—in agreement with the proposed mechanism. In this case, however, the α-carbonyl methyl group was completely deuterated as well while still almost no deuterium (<10% D) was observed at the methylene group. This indicates the additional α-deuteration to occur at the stage of the ketone product (D-12a) via kinetically controlled enolization, preferentially to the terminal position.

To support the hypothesis that an iridium hydride species is involved in the (rate-determining) key step of the proposed mechanism we decided to also investigate the kinetic isotope effect (KIE) of the reaction. For this purpose, we performed four parallel reactions (two with H-11a and two with D-11a) and monitored the reaction rates by means of NMR. To minimize the experimental error, these reactions were carried out very carefully under absolutely identical conditions as follows: A stock solution containing [Ir(COD)Cl]2 and the chiral ligand L3 in dry toluene was stirred for 60 min at room temperature before equal amounts of this solution were transferred by syringe to the four reaction vials containing the substrate (H/D-11a) to give a 0.12 M solution in toluene. After heating the stirred reaction mixtures to 73 °C, small samples were taken after 30, 60, 90, 120, and 180 min. Two of the four reactions were stirred for another 90 min to ensure full conversion. The taken samples were immediately filtered through a tiny plug of silica and analyzed by 'H NMR spectroscopy. The degree of conversion was calculated based on the integral changes of four selected signals: Product signals at 2.79 ppm (d, 1H) and 1.86 ppm (m, 1H) and signals of the starting material at 2.31 ppm (m, 2H) and 2.01 ppm (t, 2H). The results of these measurements are depicted in Figure 1 and clearly reveal that the deuterated cyclobutanol D-11a reacts slower than the non-deuterated cyclobutanol 11a, which indicates a significant kinetic isotope effect.

To quantify the kinetic isotope effect, the rate constants for H (kH) and D (kD) were calculated by determining the slope of the line for the initial reaction rate (Figure 1). From the average value of kH (0.872 min⁻¹) and kD (0.520 min⁻¹) a KIE of 1.68 was calculated for the Ir-catalyzed cyclobutanol cleavage. Taking a deuterium degree of 70% for D-11a into account, the corrected KIE calculates to 2.4. This corresponds to a primary kinetic isotope effect and supports our mechanistic proposal (Scheme 6) that a O–H (or O–D) bond activation is involved (even as a rate-determining step) in the catalytic cycle.

To probe the role of the chloride ligand and in particular whether it possibly dissociates from iridium during the catalytic process, we added varying amounts of AgOTf to the reaction mixture and monitored the conversion of 11a into 12a under standard conditions (4 mol% [Ir(COD)Cl]2, 12 mol% L3, toluene, 73 °C). While addition of 2 mol% of AgOTf had no significant effect, the reaction was much slower upon addition of 8 mol% and completely inhibited in the presence of an excess of AgOTf (40 mol%). This may be a hint that the chloride ligand plays a certain role; however, oxidation of the Ir-catalyst by Ag+ would also cause inhibition of the reaction. Therefore, a cationic Ir-complex cannot be fully excluded.

Computational investigations

To shed additional light on the proposed mechanism of the Ir-catalyzed cyclobutanol cleavage we performed DFT (PW6B95D3) computations.[23] Using a simplified test system (with L = PH3) the theoretical analysis confirmed the feasibility of the proposed mechanism (Figure 2). The calculations suggest the oxidative addition of the iridium center to the O–H bond of the cyclobutanol (14 to 15) to be the step with the highest activation energy ($E_A = 26.8$ kcal mol⁻¹). This is in accordance with the experimentally found KIE of 2.4 as the activation energy of the β-C elimination step (16.2 kcal mol⁻¹) is significantly lower. The final reductive C–H elimination ($E_A = 23.5$ kcal mol⁻¹) leads to a complex, which, according to the calculations, dissociates without any barrier to liberate the product and the catalyst.

Understanding enantioselectivity

Although the absolute (S)-configuration of the product 12a, prepared by Ir-catalyzed fragmentation of 11a in the presence of (S)-DTBM-SegPhos (L3) as a chiral ligand, had been unambiguously assigned by its conversion into (2R)-t-cocopherol,[19] we felt challenged to rationalize the stereochemical outcome. For this reason, we took a closer look at the β-carbon elimination as the stereo-determining step of the catalytic cycle.[24] A first configurational analysis (supported by DFT calculations) revealed that four types of transition states (TS) can be distinguished, which are all characterized by a pseudo-octahedral coordination geometry of the iridium center with the bidentate P,P-ligand in maximum distance to the activated C–C bond (Figure 3). Two of these transition states lead to the (S)- and the other two to the (R)-product, and in both series the
hydride and chloride ligands are oriented either cis or trans to each other.

Orienting DFT calculations on a small model system (see the Supporting Information) suggested transition structures with trans-oriented H and Cl ligands and the O–C–C-substrate atoms aligned in-plane with the PIr ring being energetically most favored for electronic reasons (Figure 4).

To prepare for the computation of the competing transition states (leading to the different enantiomers of 12a) at a higher level of theory, the conformation of the axially chiral ligand (L3) coordinated to the iridium metal center was analyzed. As shown in Figure 5, two of the P-bound aryl groups adopt an axial and the other two an equatorial position. The axial P-aryl groups are fixed in coplanar orientation to the adjacent benzo-dioxole moieties of the biaryl unit, whereas the equatorial P-aryl groups were found to be conformationally more flexible and able to intensely interact with the substrate. All in all, the (S)-DTBM-SegPhos-iridium unit was found to adopt a right-turning C2-symmetric propeller shape.

To limit the number of conformations, transition-state optimizations were performed initially only with an in-in-in-in orientation of the methoxy groups, which can either point towards the adjacent aryl unit (inwards) or away from it (outwards). Further calculations to rationalize the origins of the enantioselectivity were then performed on the complete system generated from cyclobutanol 11a and (S)-DTBM-SegPhos-IrCl. The quantitative energetic analysis then revealed a clear preference for the (S)-enantiotopic transition structure with a calculated ee of 95% (for details see the Supporting Information).

This result, which is in excellent agreement with the experimental facts, can be “explained” as follows. In the most favorable (S) transition state both the favorable anti H–Cl
Figure 4. DFT computations (PW6B95D3/6–311G**(C,H,O,P,Cl)/SDD (+ ECP, Ir)-SCRF(toluene)/ONIOM/B97D3/SDD (+ ECP, Ir), D95 (C,H,O,P,Cl):PM6) of a simplified model system show the energetically most favorable transition structures with a trans-orientation of H and Cl ligands and an in-plane alignment of the P–P–Ir′ plane and the metal-bound O–C–C unit of the substrate.

Figure 5. Schematic view of the conformation of the C2-symmetric (S)-DTBM-SegPhos ligand (L3) coordinated to the iridium center.

In contrast, in the lowest energy (R)-transition state (Figure 7) such a co-planar alignment of an equatorial P-aryl group with the substrate is only possible at the expense of an energetically unfavorable out-of-plane orientation of the P2Ir and the C–C–O units (H–Cl cis) (Figure 7).

Substrate scope

To explore the substrate scope of the Ir-catalyzed cyclobutanol cleavage we initially used the easily accessible spirocyclobutane 

allyl-MgBr) react with 18 in a cis-selective fashion while trans-products are favored in diethyl ether. This behavior might result from a different aggregation of the reagents in the different solvents. Noteworthy, the branched Grignard reagent iso-Pr-MgCl afforded the addition product only in low yield because mainly reduction of the carbonyl group occurred in this case to yield a 1:1 mixture of diastereomers (11/11′ with R=H). Fortunately, the cis- and trans-diastereomers could be separated by column chromatography in all cases (Table 2).

Additional substrates of type 11/11′ were prepared from the readily accessible vinylated compound 11′i (Scheme 7). Hydroboration of 11′i with 9-BBN (9-borabicyclo[3.3.1]nonane) and subsequent oxidation with H2O2 gave the diol 19′, which in turn could easily be protected selectively at the primary OH group to give substrates 11′f (OAc), 11′g (OMOM), and 11′h (O8n).
Robocyclobutanol 11a, which yields the methyl ketone 12a with high enantioselectivity, the corresponding cis-diastereomer 11’a gave the product ent-12a with only 18% ee (non-optimized). Nevertheless, other cis-configured substrates, that is, 11b–11d, gave rise to the expected products (12b–12d) with satisfying enantioselectivity.

Interestingly, the investigation of the three cis-cyclobutanols 11b–11d with different spacer lengths between the phenyl group and the cyclobutanol unit showed that the reactivity drops with an increasing bulk of the side chain. Actually, the phenyl-substituted substrate 11b proved to be rather unreactive and the addition of water[16] was required to achieve at least a decent yield (44%). In the case of 11c, the catalyst load had to be increased to ensure a high yield. The enantioselectivity of the reaction of 11c to 12c increased from 78% to 87% ee upon lowering the temperature to 100 °C but at the expense of conversion (34% yield). The bulky iso-propyl-substituted substrate (prepared according to Table 2, entry 11) did not react at all under the standard conditions. In contrast, the 2-oxy-ethyl substituted substrates, especially the TBS-protected (11e) and the benzyl-protected (11f) compounds, reacted smoothly to give the products 12e and 12f, respectively, in high yield and enantioselectivity (92–93% ee). The corresponding acetyl-protected substrate 11f, however, proved to be completely unreactive and the MOM-derivative 11g only reacted very slowly, and unreacted starting material could be partly resolated. Possibly, the catalysis is inhibited in the latter cases by coordination of the Ir atom to the polar functional groups.

While the examples given in Scheme 8 illustrate a fair scope of the method, a number of substrates with unsaturated side-chains failed to undergo the expected Ir-catalyzed cyclobutanol cleavage (Scheme 9). For instance, the vinyl-cyclobutanol 11i and the related higher substituted allylic alcohol 11k mainly afforded the dienes 20 and 21, respectively, possibly via formation of a π-allyl-Ir intermediate and subsequent β-H elimination. Chiral GC analysis indicated that both of these compounds were formed as racemic mixtures.

In a similar fashion the trans-isomer 19 (obtained from 11l) was prepared to use the TBS-protected (TBS = tert-butylidemethylsilyl) substrate 11e (structures shown in Scheme 8). We also employed the vinyl-substituted cyclobutanol 19 to prepare the substrate 11d with a phenylethyl sidechain through Pd-catalyzed reductive Heck reaction.[22] Remarkably, this transformation proceeded smoothly to afford the product 11d in high yield without any significant Pd-mediated cyclobutanol cleavage (as described by Uemura and co-workers[13a] compare Scheme 1).

With the various spirocyclobutanol substrates in our hands, the stage was set for the investigation of their performance in the Ir-catalyzed ring opening. As a first important result we found that (using the same chiral ligand L3) the diastereomers 11a and 11’a afforded the products with opposite absolute configuration (Scheme 8). However, in contrast to the trans-spirocyclobutanol 11a, which yields the methyl ketone 12a with high enantioselectivity, the corresponding cis-diastereomer 11’a gave the product ent-12a with only 18% ee (non-optimized). Nevertheless, other cis-configured substrates, that is, 11b–11d, gave rise to the expected products (12b–12d) with satisfying enantioselectivity.

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To further probe the scope of the Ir-based methodology employing simpler prochiral cyclobutanols lacking the spirocromane moiety we converted the easily accessible cyclobutanol 23[18] through addition of alkyl Grignard reagents and functional group manipulation into the substituted tertiary cyclobutanols 26 and 27 (Scheme 10). Noteworthy, the addition of MeMgBr in Et2O to the ketone 27 proceeds diastereoselectively to afford the trans-product 28 in high yield as the only isolated product.
Under the proven conditions of the Ir-catalyzed cyclobutanol cleavage both of these substrates (26 and 28) afforded the corresponding chiral ketones (29 and 30, respectively) with high yields and good enantioselectivity (Scheme 11). Noteworthy, when 28 was treated with the corresponding Rh(OH) catalyst under the conditions of Seiser and Cramer, a 2:1 mixture of the enone 31 and its non-conjugated isomer 32 was formed, probably through elimination of TBS-OH from the primary product 30. This again proves the advantage of our Ir-based protocol for the enantioselective cleavage of 3-oxy-substituted cyclobutanols.

Enantioselective synthesis of chromanes related to natural products

As already mentioned above, the starting point of the present study was our synthesis of \( \alpha \)-tocopherol (13) (Scheme 3) and in particular the discovery that the enantioselective opening of the prochiral spirocyclobutanol 11a to the methylketone 12a could be efficiently achieved using an Ir catalyst, whereas the related Rh-based protocol only afforded the racemic product. In a similar fashion, the Ir-catalyzed reaction of the more elaborated substrate 11q afforded the \( \alpha \)-tocopherol precursor 12q with virtually complete stereocontrol (Scheme 12).

Against this background, we asked ourselves whether the methodology could be applied also to the synthesis of other tocopherol-related compounds such as the antimalarial chromane natural product 33 recently isolated from Koeberlinia spinosa, which displays an interesting activity against the malaria parasite *Plasmodium falciparum* (IC\(_{50} = 24 \mu M*) (Figure 8).

To probe the installation of an unsaturated (enone) sidechain, we used the substrate 11r, which was obtained by TBS deprotection of an intermediate of our \( \alpha \)-tocopherol synthesis. In this case (Scheme 13), the trisubstituted olefin in the side chain was well tolerated and the desired desymmetrized ketone 12r was obtained in excellent yield (98%) and diaste-

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**Scheme 8.** Enantioselective conversion of various substrates of type 11 or 11' in the Ir-catalyzed cyclobutanol cleavage. Standard conditions: 5 mol % [Ir(COD)Cl]2, 15 mol % L3, 0.1 m solution of substrate in dry toluene, 110 °C (color change). [a] 1 mol % cat., 3 mol % L3, 70 °C; [b] 9 mol % cat., 26 mol % L3, toluene/H\(_2\)O 4:1; [c] 10 mol % cat., 30 mol % L3; [d] 7 mol % cat., 19 mol % L3; [e] 85–95 °C; [f] 7 mol % cat., 23 mol % L3; [g] 8 mol % cat., 24 mol % L3; [h] 7 mol % cat., 23 mol % L3; [i] 8 mol % cat., 24 mol % L3; (for details see the Supporting Information).
reoselectivity (dr = 98.5:1.5; determined by HPLC after transformation into \( \alpha \)-tocopherol methyl ether, see the Supporting Information).

Treatment of the \( \beta,\gamma \)-enone 12r with trifluoromethane sulfonic acid in dichloromethane resulted in the migration of the double bond to give of the more stable conjugated enone 34 as a separable mixture of \( E \) and \( Z \) isomers (Scheme 13). Although \( E \)-34 already displays some characteristic structural features of the natural product 33, we decided to also probe the Ir-catalyzed cyclobutanol opening employing the spirochromane 38 with an aromatic substitution pattern related to 33 (Scheme 14). For this purpose, the literature-known building blocks 35[29] and 36[19] were first fused to 37 in a Friedel–Crafts-related condensation. While the use of BF\(_3\)-Et\(_2\)O as a Lewis acid[19] was not successful in this case, the desired reaction took place in the presence of an excess (4 equiv) of methane sulfonic acid in dichloromethane to afford 37 in 38% yield as a mixture of cis and trans isomers. Subsequent saponification of the ester moiety, oxidation,[30] and reaction of the resulting ketone with MeMgBr in diethyl ether then cleanly afforded the trans-cyclobutanol 38 as the desired desymmetrization precur-

**Scheme 9.** Substrates of type 11/11' that did not undergo Ir-catalyzed cyclobutanol cleavage.

**Scheme 10.** Synthesis of cyclobutans 26 and 28. Reagents and conditions: a) nBuMgCl, THF, \(-78^\circ C, 1 \text{ h} \); b) NaOH, EtOH, 30\(^\circ\)C, 24 \text{ h} \); c) TBSOTf, 2,6-lutidine, \( CH_2Cl_2 \), 0\(^\circ\)C to RT, 2.5 \text{ h} \); d) DMP, \( CH_2Cl_2 \), 0\(^\circ\)C to RT, 2 \text{ h} \); e) TBSOTf, 2,6-lutidine, \( CH_2Cl_2 \), 0\(^\circ\)C to RT, 1.5 \text{ h} \); f) MeMgBr (3 \text{ m} in Et\(_2\)O), Et\(_2\)O, \(-78^\circ\)C, 1 \text{ h}.

**Scheme 11.** Ir- and Rh-catalyzed cleavage of cyclobutans 26 and 28.

**Scheme 12.** Ir-catalyzed key step of our total synthesis of \( \alpha \)-tocopherol.

**Figure 8.** Structure of an antiplasmodial chromane 33 isolated from \( Kaeberlinia \) spino.

**Scheme 13.** Synthesis of the enone 34 (as a model compound related to 33) through cyclobutanol fragmentation and subsequent acid-mediated double bond isomerization.

reoselectivity (dr = 98.5:1.5; determined by HPLC after transformation into \( \alpha \)-tocopherol methyl ether, see the Supporting Information).

Treatment of the \( \beta,\gamma \)-enone 12r with trifluoromethane sulfonic acid in dichloromethane resulted in the migration of the double bond to give of the more stable conjugated enone 34 as a separable mixture of \( E \) and \( Z \) isomers (Scheme 13). Although \( E \)-34 already displays some characteristic structural features of the natural product 33, we decided to also probe the Ir-catalyzed cyclobutanol opening employing the spirochromane 38 with an aromatic substitution pattern related to 33 (Scheme 14). For this purpose, the literature-known building blocks 35[29] and 36[19] were first fused to 37 in a Friedel–Crafts-related condensation. While the use of BF\(_3\)-Et\(_2\)O as a Lewis acid[19] was not successful in this case, the desired reaction took place in the presence of an excess (4 equiv) of methane sulfonic acid in dichloromethane to afford 37 in 38% yield as a mixture of cis and trans isomers. Subsequent saponification of the ester moiety, oxidation,[30] and reaction of the resulting ketone with MeMgBr in diethyl ether then cleanly afforded the trans-cyclobutanol 38 as the desired desymmetrization precur-
sor. And much to our satisfaction, the Ir-catalyzed ring opening then proceeded smoothly under the proven conditions to give the ketone 39 in high yield and with excellent enantioselectivity (95 % ee).

The expected absolute (S)-configuration of the chiral 2,2-disubstituted chromane 39 was confirmed by X-ray crystallography (Figure 9).[33]

![Scheme 14. Synthesis of the model chromane 39 (related to 33).](image)

**Figure 9. Structure of 39 in the crystalline state.**

**Conclusions**

We have demonstrated that the Ir-catalyzed conversion of prochiral tert-cyclobutanol proceeds under comparably mild conditions to afford β-methyl-substituted ketones in a variety of cases. In the presence of DTBM-SegPhos as a chiral ligand the products are formed with up to 95 % ee. Our protocol appears to be particularly suited for the enantioselective desymmetrization[32] of prochiral β-oxo-substituted cyclobutanols that fail to react in a similar fashion under Rh catalysis. And indeed, deuteration experiments and kinetic isotope effect measurements revealed major mechanistic differences to related Rh-catalyzed transformations. Based on the experimental data, we derived a plausible mechanism that involves the initial formation of an IrII hydride intermediate by oxidative addition of IrI into the O–H bond of the cyclobutanol substrate. In the key C–C bond activating step, the four-membered ring is cleaved by β-C elimination, and the catalytic cycle is closed by reductive C–H elimination. This mechanism is supported by DFT calculations, and the computational analysis of competing transition states of the enantioselectivity-determining β-carbon elimination step even allowed the prediction of the stereochemical outcome. Although simple tert-cyclobutanols such as 28 could be successfully employed as well, the developed protocol is of particular value for the stereo-controlled synthesis of 2,2-disubstituted chromanes related to natural products such as α-tocopherol. Thus, we are optimistic that the Ir-catalyzed cyclobutanol cleavage will find future application also in other laboratories. At least, it opens a new chapter in the use of Ir-catalyzed reactions in natural product synthesis[21] and also complements existing methods for the catalytic ring opening of cyclic alcohols to generate ketones with a (quaternary) chirality center in β-position.1,12b,13b,17,33 Furthermore, the protocol may find application in the preparation of selectively deuterated (or even tritium-labeled) compounds.[34]

**Experimental Section**

**General procedure for the Ir-catalyzed cyclobutanol cleavage:** A glass vial was charged under argon with [Ir(COD)Cl]2 and (S)-DTBM-SegPhos and the vial was sealed with a septum. After injection of a 0.1 m solution of the respective cyclobutanol in dry toluene at RT the solution was first stirred for 1.5 h and then heated to 85–110 °C. The reaction progress was monitored by TLC. Noteworthy, successful reactions were always associated with a color change of the solution from yellow–orange to dark red. Once the starting material was fully consumed (or nor further conversion was detected), the mixture was cooled to RT and a few milligrams of QuadraSil AP were added. After stirring for 30 min the mixture was filtered over a short pad of silica and all volatiles were removed under reduced pressure. The crude product was finally subjected to column chromatography to yield the ketone product (12) as a colorless oil.

(5)-1-(6-Methoxy-2,5,7,8-tetramethylchroman-2-yl)propan-2-one (12a): According to the general procedure, a solution of 150 mg (0.543 mmol) of cyclobutanol 11a, 3.7 mg (5.51 μmol, 1 mol%) of [Ir(COD)Cl]2, and 20.0 mg (16.96 μmol, 3 mol%) of (S)-DTBM-SegPhos in 4.5 mL of dry toluene was heated for 18 h to 70 °C to give 142 mg (0.514 mmol, 95 %) of 12a (92 % ee) after purification by column chromatography (SiO2, CH/Hex/EtOAc 12:1). C21H26O3 (M = 276.38 g mol−1). 1H NMR (499 MHz, CDCl3): δ = 6.33 (s, 3H), 2.79 (d, J1,2 = 14.0 Hz, 1H), 2.64 (d, J,2 = 14.0 Hz, 1H), 2.61–2.53 (m, 2H), 2.22 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 1.96 (dt, J1,3 = 13.9 Hz, J2,3 = 7.0 Hz, 1H), 1.86 dt, J1,2 = 13.6 Hz, J,2 = 6.7 Hz, 1H), 1.35 ppm (s, 3H); 13C NMR (125 MHz, CDCl3): δ = 208.0, 150.0, 147.1, 128.3, 126.2, 123.0, 117.4, 74.2, 60.6, 52.8, 32.4, 31.6, 24.4, 20.7, 12.7, 12.1, 11.8 ppm; FTIR (ATR): ν = 1707 (m), 1457 (m), 1404 (m), 1253 (s), 1090 cm−1 (s); GC–MS [m/z]: 276 (M+) 74, 243 (16), 219 (19), 203 (41), 179 (100), 135 (14), 91 (11), 43 (18); HRMS (ESI): calcd 299.16177 [M + Na]+; found 299.16167.

2-(6-Methoxy-2,5,7,8-tetramethylchroman-2-yl)phenylethan-1-one (12b): According to the general procedure, a solution of 12 mg (35.4 μmol) of cyclobutanol 11b, 2.2 mg (3.27 μmol, 9 mol%) of [Ir(COD)Cl]2, and 10.9 mg (9.24 μmol, 26 mol%) of (S)-DTBM-SegPhos in 0.4 mL of dry toluene and 0.1 mL of water was heated for 20 h to 110 °C to give 5.3 mg (15.7 μmol, 44 %) of 12b (92 % ee) after purification by preparative TLC (SiO2, CH/Hex/EtOAc 7:1). C21H26O3 (M = 338.45 g mol−1). 1H NMR (500 MHz, CDCl3): δ = 7.94–7.92 (m, 2H), 7.55–7.52 (m, 1H), 7.04–7.02 (m, 1H), 6.91–6.89 (m, 1H), 4.95 ppm (s, 1H); 13C NMR (125 MHz, CDCl3): δ = 208.0, 150.0, 147.1, 128.3, 126.2, 123.0, 117.4, 74.2, 60.6, 52.8, 32.4, 31.6, 24.4, 20.7, 12.7, 12.1, 11.8 ppm; FTIR (ATR): ν = 1707 (m), 1457 (m), 1404 (m), 1253 (s), 1090 cm−1 (s); GC–MS [m/z]: 338 (M+) 74, 243 (16), 219 (19), 203 (41), 179 (100), 135 (14), 91 (11), 43 (18); HRMS (ESI): calcd 338.3007 [M + Na]+; found 338.2997.
(16) Method-2,5,7,8-tetramethylchroman-2-yl)-4-(methoxy-methoxybutan-2-one (12g) According to the general procedure, a solution of 15 mg (42.8 μmol) of cyclonan 11c, 2.0 mg (200 μmol, 7 mol%) of NaHMDS (23 mol%) of (S)-DTBM-SeqPhos in 0.6 mL of dry toluene was heated for 4.5 h to 110 °C to give 7 mg (20.0 μmol, 47%) of 12g (83% ee) after purification by column chromatography (SiO\textsubscript{2} 600 MHz, CDCl\textsubscript{3}, δ = 207.7, 150.0, 147.1, 128.3, 126.2, 123.0, 117.5, 96.7, 74.3, 62.7, 60.5, 55.4, 52.3, 44.8, 31.5, 24.0, 20.7, 12.7, 11.1 ppm. FTIR (ATR) δ = 1714 (m), 1657 (m), 1543 (m), 1472 (m), 1359 (m), 1319 (m), 1296 (m), 1211 (m), 1141 (s), 1087 (s), 1063 (s) cm\textsuperscript{-1}; HRMS (ESI): found 419.21928 [M+Na\textsuperscript{+}] \textsuperscript{+}; calculated 419.21948.

2-{( tert-Butyldimethylsilyloxy)octan-4-one (29) According to the general procedure, a solution of 30 mg (0.116 mmol) of cyclonan 12b, 2.4 mg (3.57 μmol, 3 mol%) of [Ir(COD)Cl] and 12.5 mg (10.60 μmol, 9 mol%) of (S)-DTBM-SeqPhos in 0.6 mL of dry toluene was heated for 4 h to 110 °C to give 24 mg (0.099 mmol, 80%) of 29 (70% ee), determined after deprotection of the alcohol after purification by column chromatography (SiO\textsubscript{2} 600 MHz, CDCl\textsubscript{3}, δ = 328.5, 283.0, 204.8, 194.3, 151.3, 129.3, 128.8, 128.6, 128.5, 127.8, 127.8, 126.2, 123.0, 117.5, 96.7, 74.3, 62.7, 60.5, 55.4, 52.3, 44.8, 31.5, 24.0, 20.7, 12.7, 11.1 ppm. FTIR (ATR) δ = 1715 (m), 1657 (m), 1543 (m), 1472 (m), 1359 (m), 1319 (m), 1296 (m), 1211 (m), 1141 (s), 1087 (s), 1063 (s) cm\textsuperscript{-1}; HRMS (ESI): found 524.2345 (M+Na\textsuperscript{+}); calculated 524.2344.

4-[(tert-Butyldimethylsilyloxy)oxy]methoxymethoxybutan-2-one (12c) According to the general procedure, a solution of 15 mg (35.7 μmol) of cyclonan 11e, 1.3 mg (1.94 μmol, 5 mol%) of [Ir(COD)Cl] and 6.5 mg (5.51 μmol, 15 mol%) of (S)-DTBM-SeqPhos in 0.5 mL of dry toluene was heated for 2 h to 85 °C, 1 h to 90 °C and 1 h to 95 °C to give 15 mg (35.7 μmol, 99%) of 12c (92% ee) after purification by column chromatography (SiO\textsubscript{2} 600 MHz, CDCl\textsubscript{3}, δ = 328.5, 283.0, 204.8, 194.3, 151.3, 129.3, 128.8, 128.6, 128.5, 127.8, 127.8, 126.2, 123.0, 117.5, 96.7, 74.3, 62.7, 60.5, 55.4, 52.3, 44.8, 31.5, 24.0, 20.7, 12.7, 11.1 ppm. FTIR (ATR) δ = 1715 (m), 1657 (m), 1543 (m), 1472 (m), 1359 (m), 1319 (m), 1296 (m), 1211 (m), 1141 (s), 1087 (s), 1063 (s) cm\textsuperscript{-1}; HRMS (ESI): found 524.2345 (M+Na\textsuperscript{+}); calculated 524.2344.

3-{(tert-Butyldimethylsilyloxy)octan-4-one (28) According to the general procedure, a solution of 30 mg (0.116 mmol) of cyclonan 12b, 2.4 mg (3.57 μmol, 3 mol%) of [Ir(COD)Cl] and 12.5 mg (10.60 μmol, 9 mol%) of (S)-DTBM-SeqPhos in 0.6 mL of dry toluene was heated for 4 h to 110 °C to give 24 mg (0.099 mmol, 80%) of 28 (70% ee), determined after deprotection of the alcohol after purification by column chromatography (SiO\textsubscript{2} 600 MHz, CDCl\textsubscript{3}, δ = 328.5, 283.0, 204.8, 194.3, 151.3, 129.3, 128.8, 128.6, 128.5, 127.8, 127.8, 126.2, 123.0, 117.5, 96.7, 74.3, 62.7, 60.5, 55.4, 52.3, 44.8, 31.5, 24.0, 20.7, 12.7, 11.1 ppm. FTIR (ATR) δ = 1715 (m), 1657 (m), 1543 (m), 1472 (m), 1359 (m), 1319 (m), 1296 (m), 1211 (m), 1141 (s), 1087 (s), 1063 (s) cm\textsuperscript{-1}; HRMS (ESI): found 524.2345 (M+Na\textsuperscript{+}); calculated 524.2344.

2-{( tert-Butyldimethylsilyloxy)octan-4-one (28) According to the general procedure, a solution of 30 mg (0.116 mmol) of cyclonan 12b, 2.4 mg (3.57 μmol, 3 mol%) of [Ir(COD)Cl] and 12.5 mg (10.60 μmol, 9 mol%) of (S)-DTBM-SeqPhos in 0.6 mL of dry toluene was heated for 4 h to 110 °C to give 24 mg (0.099 mmol, 80%) of 28 (70% ee), determined after deprotection of the alcohol after purification by column chromatography (SiO\textsubscript{2} 600 MHz, CDCl\textsubscript{3}, δ = 328.5, 283.0, 204.8, 194.3, 151.3, 129.3, 128.8, 128.6, 128.5, 127.8, 127.8, 126.2, 123.0, 117.5, 96.7, 74.3, 62.7, 60.5, 55.4, 52.3, 44.8, 31.5, 24.0, 20.7, 12.7, 11.1 ppm. FTIR (ATR) δ = 1715 (m), 1657 (m), 1543 (m), 1472 (m), 1359 (m), 1319 (m), 1296 (m), 1211 (m), 1141 (s), 1087 (s), 1063 (s) cm\textsuperscript{-1}; HRMS (ESI): found 524.2345 (M+Na\textsuperscript{+}); calculated 524.2344.
4-((tert-Butyldimethylsilyloxy)-4-methyloctan-2-one (30): According to the general procedure, a solution of 45 mg (0.118 mmol) of 4-methyloctan-2-one (28), 2.3 mg (3.28 mmol, 2 mol%) of [Ir(COD)Cl] and 11.7 mg (9.92 μmol, 6 mol%) of (S)-DBTM-SegPhos in 0.8 mL of dry toluene was heated for 5 h to 100 °C to give 44 mg (0.161 mmol, 98%) of 30 (85% ee) after purification by column chromatography (SiO₂, hex/EtOAc 80:1; C₂H₅OH, 0.5 mL). [α]D²⁰ = 28.41° (c = 0.21 in CHCl₃); H NMR (500 MHz, CDCl₃): δ = 2.61 (d, JHH = 13.6 Hz, 1H), 2.48 (d, JHH = 13.6 Hz, 1H), 1.79 (s, 3H), 1.57–1.53 (m, 2H), 1.39–1.20 (m, 4H), 1.31 (s, 3H), 0.90 (t, JHH = 7.1 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 ppm (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ = 208.7, 75.6, 55.0, 43.0, 32.8, 28.1, 26.6, 26.1, 23.3, 18.4, 14.2, −1.7 ppm; FTIR (ATR) ν = 2957 (m), 2930 (m), 1712 (m), 1253 (m), 1075 (m), 1028 (m), 1005 (m), 834 (s), 772 cm⁻¹ (s); GC-MS [m/z]: 1257 min, m/z = 239 (8), 215 (15), 157 (32), 132 (10), 115 (53), 75 (79), 57 (100); HRMS (ESI): calcd. 215.1467 [M-Bu⁺]; found 215.17.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** asymmetric catalysis · C-C bond activation · cyclobutanols · deuteriation · iridium

[1] a) L. Souillart, N. Cramer, Chem. Rev. 2015, 115, 9410–9466; b) Y. Xia, G. Lu, P. Liu, G. Dong, Nature 2016, 539, 546–550; c) K. Ruhlhand, Eur. J. Org. Chem. 2012, 2683–2706; d) L. Souillart, E. Parker, N. Cramer, Asymmetric Transformations via C-C Bond Cleavage, published in: C-C Bond Activation, Vol. 346 (Ed.: G. Dong), Springer-Verlag, Berlin, Heidelberg, 2014, pp 163–193; e) Cleavage of Carbon-Carbon Single Bonds by Transition Metals (Eds.: M. Murakami, N. Chatani), Wiley-VCH, 2016.

[2] T. Seiser, N. Cramer, Org. Biomol. Chem. 2009, 7, 2835–2840.

[3] P. R. Khoury, J. D. Goddard, W. Tam, Tetrahedron 2004, 60, 8103–8112.

[4] M. Murakami, H. Amii, Y. Ito, Nature 1994, 370, 540–541.

[5] a) N. Ishida, W. Ikemoto, M. Murakami, Org. Lett. 2012, 14, 3230–3233; b) N. Ishida, W. Ikemoto, M. Murakami, J. Am. Chem. Soc. 2014, 136, 5912–5915.

[6] M. Murakami, K. Takahashi, H. Amii, Y. Ito, J. Am. Chem. Soc. 1977, 99, 9307–9308.

[7] W. D. Jones, Mechanistic Studies of Transition Metal-Mediated C-C Bond Activation, published in: C-C Bond Activation, Vol. 346 (Ed.: G. Dong), Springer-Verlag, Berlin, Heidelberg, 2014, pp 1–32.

[8] T. X. A. Demencini, G. Dong, Transition Metal-Catalyzed C-C Bond Activation of Four-Membered Cyclic Ketones, published in: C-C Bond Activation, Vol. 346 (Ed.: G. Dong), Springer, Berlin, Heidelberg, 2014, pp 233–258.

[9] X. H. Zhao, X. Fan, J. Y. Chu, J. Am. Chem. Soc. 2015, 137, 3490–3493.

[10] a) L. Huan, C. Zhu, Org. Chem. Front. 2016, 3, 1467–1471; b) R. Ren, H. Zhao, L. Huan, C. Zhu, Angew. Chem. Int. Ed. 2015, 54, 12692–12696; Angew. Chem. 2015, 127, 12883–12887.

[11] a) A. Zilić, A. Correa, R. Martin, Chem. Commun. 2013, 49, 4286–4288; b) L. Chen, F.-N. Sun, Y.-L. Sun, Z. Xu, Z.-J. Zheng, Y.-M. Cui, J. Cao, L.-W. Xu, Adv. Synth. Catal. 2018, 360, 411–415; c) Q. Wang, R. Chen, J. Lou, D. H. Zhang, Y.-G. Zhou, Z. Yu, ACS Catal. 2019, 9, 11669–11675.

[12] a) Y. Xia, Z. Liu, Z. Liu, R. Ge, F. Ye, M. Hossain, Y. Zhang, J. Wang, J. Am. Chem. Soc. 2014, 136, 3013–3015; b) A. Masarwa, M. Weber, R. Sarpong, J. Am. Chem. Soc. 2015, 137, 6327–6334.

[13] a) S. Matsumura, Y. Maeda, T. Nishimura, S. Uemura, J. Am. Chem. Soc. 2003, 125, 8862–8869; for a recent application of the Pd-catalyzed opening of cyclobutans in total synthesis, see: b) I. Kershgens, A. R. Rovira, R. Sarpong, J. Am. Chem. Soc. 2018, 140, 9810–9813.

[14] a) T. Matsuda, M. Shigeno, M. Murakami, J. Am. Chem. Soc. 2007, 129, 12086–12087; for a more recent mechanistic study on Rh-catalyzed stereoselective C-C/C-H activation of tert-cyclobutans, see also: b) H. Yu, C. Wang, Y. Yang, Z.-M. Dang, Chem. Eur. J. 2014, 20, 3839–3848.

[15] a) T. Matsuda, M. Shigeno, M. Makino, M. Murakami, Org. Lett. 2006, 8, 3379–3381; b) N. Ishida, Y. Nakashima, M. Murakami, Angew. Chem. Int. Ed. 2013, 52, 11875–11878; Angew. Chem. 2013, 125, 12091–12094;

---

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doi.org/10.1002/chem.202004843
\[ E. L. Eliel, S. H. Wilen, M. P. Doyle, J. Am. Chem. Soc. 1981, 103, 4491–4494. \]

\[ A. O. Termath, H. Sebode, W. Schlundt, T. Netscher, W. Bonnath, H.-G. Schmalz, Chem. Eur. J. 2014, 20, 12015–12055; b) A. O. Termath, J. Velder, R. T. Stemmler, T. Netscher, W. Bonnath, H.-G. Schmalz, Eur. J. Org. Chem. 2014, 3337–3340. \]

\[ F. Ratsch, W. Schlundt, D. Albat, A. Zimmer, J.-M. Neudörfl, T. Netscher, H.-G. Schmalz, Chem. Eur. J. 2019, 25, 4941–4945. \]

\[ A. H. Crabtree, R. P. Dion, D. J. Gibbon, D. V. McGrath, E. M. Holt, J. Am. Chem. Soc. 1986, 108, 7222–7227; b) M. Murakami, K. Itami, M. Uubakata, I. Tsuji, Y. Ito, J. Org. Chem. 1998, 63, 4–5; c) T. Nishimura, T. Yoshinaka, Y. Nishiguchi, Y. Maeda, S. Uemura, Angew. Chem. Int. Ed. 2015, 54, 5331–5334; Angew. Chem. 2015, 127, 5441–5444; d) J. Yu, H. Yan, C. Zhu, Angew. Chem. Int. Ed. 2016, 55, 1143–1146; Angew. Chem. 2016, 128, 1155–1158. \]

\[ C. Yuan, B. Liu, Org. Chem. Front. 2018, 5, 106–131; b) P. Chen, Y. Wu, S. Zhu, H. Jiang, Z. Ma, Org. Chem. Front. 2018, 5, 132–150. \]

\[ F. T. Ladipo, M. Kooti, J. S. Merola, Inorg. Chem. 1993, 32, 1681–1688; b) O. Blum, D. Milstein, J. Am. Chem. Soc. 1995, 117, 4582–4594; c) K. Tani, A. Isaki, T. Yamagata, Angew. Chem. Int. Ed. 1998, 37, 3381–3383; Angew. Chem. 1998, 110, 3590–3592; d) P. Klarig, S. Pahl, T. Braun, A. Penner, Dalton Trans. 2011, 40, 6785–6791; e) M. G. Crestani, A. Steffen, A. M. Kenwright, A. S. Batsanov, J. A. K. Howard, T. B. Marder, Organometallics 2009, 28, 2904–2914; for related Rh-studies see: f) J. Yuven, Y. Jiao, W. W. Brennessel, W. D. Jones, Inorg. Chem. 2016, 55, 9482–9491. \]

\[ M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Johnson, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. M. Mirza, J.-G. Zheng, W. Liang, M. Hada, M. Karas, T. Noda, H. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throsell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, D. J. Fox, Gaussian 16, Revision B.01, Gaussian, Inc., Wallingford CT, 2016. \]