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# Theoretical Insights into Enantioselective Catalysis: The Mechanism of the Kharasch–Sosnovsky Reaction

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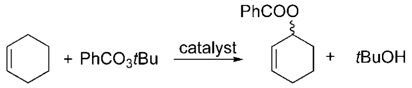
**Abstract:** The mechanism of the Kharasch–Sosnovsky reaction has been investigated using B3LYP/6-31G* calculations on a chiral reaction model [cyclohexene + *tert*-butyl perbenzoate → cyclohex-2-enyl benzoate + *tert*-butyl alcohol, catalyzed by a chiral bisoxazoline-copper(I) complex]. Although two previous reaction mechanisms have been considered, the results are consistent with a new mechanistic pathway. This path involves ligand exchange between the catalyst–cyclohexene complex with *tert*-butyl perbenzoate to give a catalyst–perester complex, which undergoes an (either one- or two-step) oxidative addition reaction to yield a copper(III) complex. The limiting step of the Kharasch–Sosnovsky reaction consists of an intramolecular step involving the abstraction of an allylic hydrogen from cyclohexene [which is π-bound to the copper(III) complex]. The resulting allyl-copper(III) complex (subsequent to the loss of *tert*-butanol) can undergo a haptotropic rearrangement by means of an $\eta^1$-allyl/$\eta^3$-allyl equilibrium, leading to scrambling between vinylic and allylic positions when an isotopically labeled substrate is used. The allyl-copper(III) ion undergoes a stereospecific reductive elimination involving the π-bond migration to yield a reaction product–catalyst complex, which can regenerate the alkene-copper(I) complex by ligand exchange. The proposed reaction mechanism is consistent with all known experimental results (including enantioselectivity data).

**Keywords:** copper · density-functional calculations · homogeneous catalysis · oxidation · reaction mechanisms

## Introduction

The allylic acyloxylation of olefins (named the Kharasch–Sosnovsky reaction) catalyzed by optically active copper complexes has become a powerful tool for the enantioselective synthesis of allylic esters.[1,2] High yields and chiral inductions can be achieved in Kharasch–Sosnovsky reactions when appropriate conditions are used. Both copper(I) and copper(II) derivatives can be used as catalysts,[3] although the large acceleration induced in $Cu^{2+}$ reactions by phenylhydrazine (acting as an in situ reducing reagent)[4] shows that the true catalyst of the Kharasch–Sosnovsky reaction is a copper(I) compound. Although several peresters or hydroperoxides can be efficiently used in the Kharasch–Sosnovsky reaction, *tert*-butyl perbenzoate has become the standard oxidant in recent years.[1] Either acyclic or cyclic alkenes can be successfully used as substrates, though better yields are usually obtained for reactions involving cyclic olefins. In particular, the use of symmetrical cycloalkenes is preferred in order to avoid obtaining mixtures of regioisomers.

Particular attention has been paid to the enantioselective synthesis of allylic esters using chiral copper–ligand complexes as catalysts for the Kharasch–Sosnovsky reaction. Indeed, a large number of copper complexes that incorporate chiral ligands have been tested as catalysts for a benchmark reaction (cyclohexene + *tert*-butyl perbenzoate, see Scheme 1),[5] since the (*S*)-enantiomer of the corresponding reaction product (cyclohex-2-enyl benzoate) can be used as a key intermediate in the leukotriene $B_4$ synthesis.[6] Particular emphasis has been placed on the use of several substituted $C_2$-symmetric bisoxazolines[7] because of their ease of synthesis and high chiral induction.



Scheme 1. Kharasch–Sosnovsky reaction between cyclohexene and *tert*-butyl perbenzoate.

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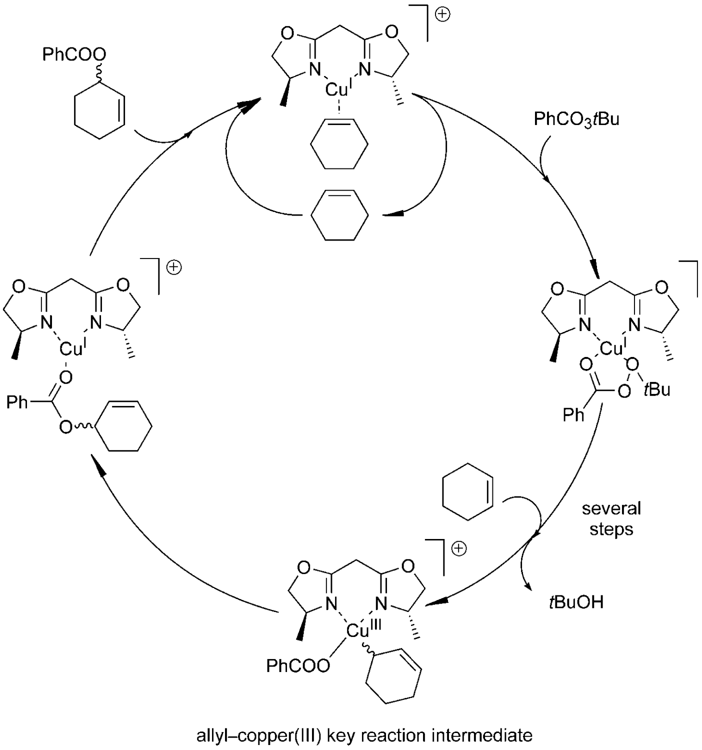
Despite a considerable amount of literature is available concerning synthetic and mechanistic aspects of the Kharasch–Sosnovsky reaction, two crucial points have remained unclear up to now: the detailed steps of the mechanism and the factors that determine the stereochemical control of the reaction.

Although only limited knowledge of the mechanism of the Kharasch–Sosnovsky reaction is currently available,[1,2] some global aspects have been well established. The main features of the benchmark reaction are represented in Scheme 2, in which the copper(I) complex of bis[(*S*)-4-methyl-4,5-dihydrooxazol-2-yl]methane (this ligand is hereafter referred to as “mebox”) is considered as the catalyst.



Scheme 2. Global mechanism of the Kharasch–Sosnovsky reaction.

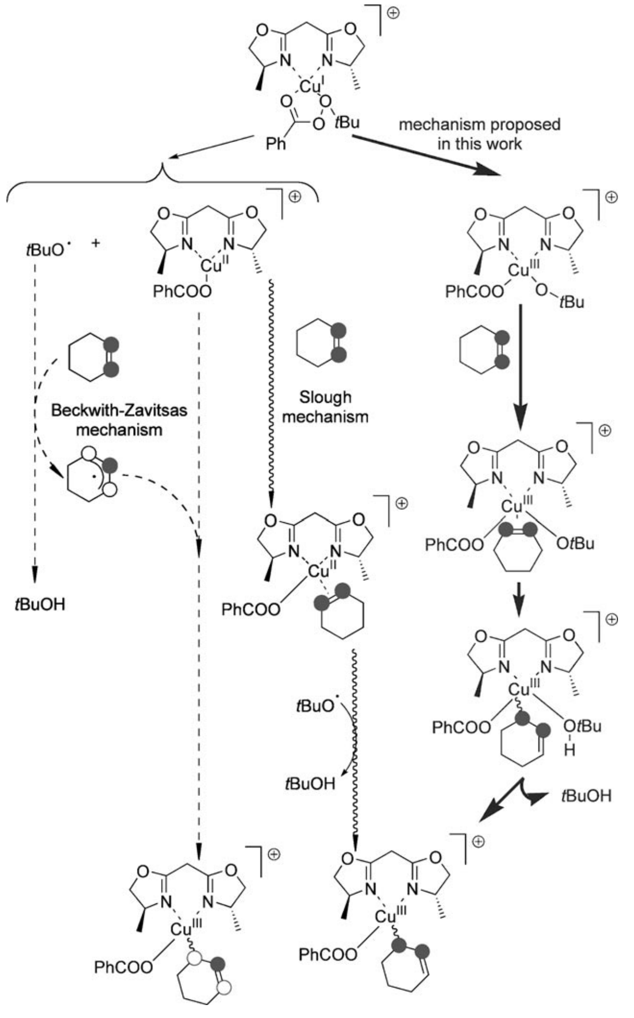
The process takes place through a catalytic cycle involving the variation of the oxidation state of the copper atom. In Kharasch–Sosnovsky reactions by using a non-coordinating solvent in the presence of a large excess of olefin, most catalyst ions must be present in the reaction mixture as a copper(I)-alkene complex,[8] a situation consistent with kinetic data on a closely-related allylic amination reaction.[9] The first step of the catalytic cycle is the formation of a perester–catalyst complex through the ligand exchange of the alkene-copper(I) complex with *tert*-butyl perbenzoate.

The resulting perester-copper(I) complex reacts with cyclohexene through a mechanism involving several steps to yield the benzoate-$\eta^1$-cyclohex-2-enyl-mebox-copper(III) ion (named hereafter as the allyl-copper(III) key reaction intermediate), which is analogous to a substituted cyclohexenyl-copper(III) reaction intermediate detected by NMR in the addition of an organocuprate to cyclohex-2-enone.[10]

The C−O bond formation between the cyclohexenyl and benzoate groups takes place through a reductive elimination of the copper(III) complex,[1] though little information on such a step has been available up to now. The catalyst–reaction product complex can release the reaction product through ligand exchange with cyclohexene by generating the starting olefin–catalyst complex.

Three different reaction mechanisms for the Kharasch–Sosnovsky reaction (shown in Scheme 3) will be discussed in this work. In most studies on this process, it is assumed that the catalyst–perester complex can undergo a homolytic dissociation of the perester through coordination of a copper(I) salt, leading to the formation of a benzoate-copper(II) complex and *tert*-butoxyl radical.[11]

Two alternative mechanistic pathways can be considered at this point. According to the mechanism proposed by



Scheme 3. Mechanisms proposed by Beckwith–Zavitsas (dashed arrows), Slough (wavy arrows), and in this study (solid arrows) for the generation of the allyl-copper(III) key reaction intermediate. Carbon atoms proceeding from the vinylic atoms of cyclohexene are shown as solid circles, whereas vinylic/allylic scrambled atoms are represented by open circles.

Beckwith and Zavitsas in 1986,[12] an allylicic hydrogen from a cyclohexene molecule is abstracted by a *tert*-butoxyl radical, leading to the cyclohexenyl radical and *tert*-butanol. In a subsequent step, the allylic radical binds to the copper atom of the benzoate-copper(II) cation to generate the corresponding allyl-copper(III) key reaction intermediate.

A different reaction mechanism has recently been proposed by Slough for the Kharasch–Sosnovsky reaction.[9] Accordingly, hydrogen abstraction takes place between the *tert*-butoxyl radical and the ligand-bound benzoate-cyclohexene-copper(I) ion to yield a Cu−C σ-bond in an intermolecular reaction, a process that involves formal π-bond migration in the organometallic species.

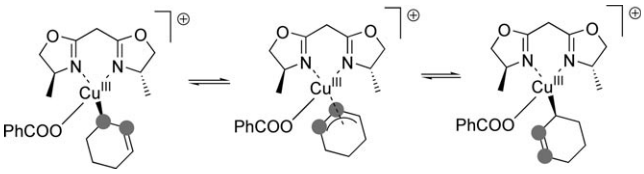
Although both the Beckwith–Zavitsas and Slough mechanisms are based on the intermediacy of *tert*-butoxyl free radical, no such a species is necessarily required in the Kharasch–Sosnovsky reaction. For example, a concerted mechanism for the acyloxylation of the catalyst–olefin complex may be envisaged, in an analogous way to the pathway proposed for the allylic amination of alkenes with phenylhydroxylamine catalyzed by iron–phthalocyanine.[13] However, such a concerted mechanism is incompatible with experimental results on the Kharasch–Sosnovsky reaction between cyclohexene and $^{18}$O-carbonyl-labeled *tert*-butyl perbenzoate, which indicate scrambling between both oxygen atoms in the reaction product.[14]

Experimental studies on the $H_2O_2$ decomposition by several copper(I) complexes have shown the existence of elementary reactions that are very similar to oxidation processes induced by the $HO^{\bullet}$ radical, although the corresponding reaction rates are lower by several orders of magnitude.[15,16] In fact, the reactivity of $H_2O_2$/copper(I) systems with a number of radical scavengers can be attributed to the participation of "crypto-OH radicals",[17] probably corresponding to transient copper(III) complexes.[16] Similarly, we postulate that the real oxidant species of the Kharasch–Sosnovsky reaction is a copper(III) complex ("crypto-alkoxyl radical"), which is analogous to the stable coordination compound generated by oxidative addition of dibenzoyl peroxide to copper(I) chloride in pyridine.[18]

It is known that some copper(III) complexes can abstract hydrogen atoms from C−H bonds.[19] Accordingly, we propose here the abstraction of an allylic hydrogen atom of cyclohexene by a *tert*-butoxo group [bound to a benzoate-mebox-copper(III) complex] rather than a *tert*-butoxyl free radical, as assumed by Slough. The corresponding reaction mechanism involving a "crypto-alkoxyl radical" is similar to that proposed in 1959 by Denney et al.,[14] albeit modified to replace the original copper(II) cation by a $Cu^+$ ion (as suggested by Berglund and Lawesson).[20] The allyl-copper(III) key reaction intermediate is thus formed, in an analogous way to the reaction mechanisms proposed by Beckwith–Zavitsas and Slough.

A major difference between the Beckwith–Zavitsas reaction mechanism and those proposed by Slough and us lies on the possibility of scrambling between the vinylic and allylic carbon atoms in the final product. Thus, the participation of an allylic free radical in the Beckwith–Zavitsas reaction mechanism leads to the equivalence of vinylic and allylic carbon atoms, whereas the pathways involving the hydrogen abstraction of a copper–alkene complex (proposed by Slough and us) can explain a different fate for both types of atoms.

Nevertheless, a reaction pathway allowing the scrambling of former vinylic and allylic hydrogens from cyclohexene can also be involved irrespective of the mechanism for the formation of the allyl-copper(III) intermediate. In particular, we postulate here the haptotropic rearrangement between (*R*)- and (*S*)-epimers of the allyl-copper(III) key reaction intermediate (Scheme 4). Such a reaction mechanism is analogous to the pathways invoked to explain the results on regio- or stereoselectivity on several kinds of reactions involving allyl-copper(III) reaction intermediates.[21] Furthermore, theoretical calculations have indicated that allyl-copper(III) compounds can adopt both $\eta^1$- and $\eta^3$-coordination types, which can readily interconvert,[22,23] (in a similar way to the well-known $\eta^3 \rightarrow \eta^1 \rightarrow \eta^3$ isomerization of allyl-palladium complexes).[24]

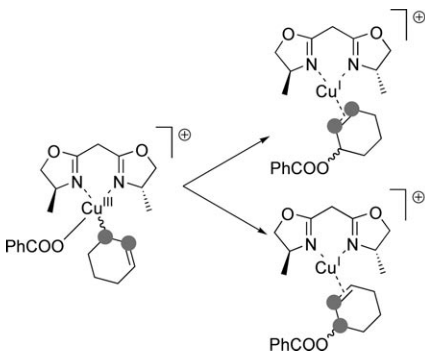


Scheme 4. Haptotropic rearrangement between (*R*)- (left) and (*S*)-(right) diastereomers of the allyl-copper(III) key reaction intermediate through an $\eta^3$ isomer (middle). Carbon atoms from the vinylic atoms of cyclohexene (according to the reaction mechanisms proposed by Slough or us) are shown as filled cirles.

Interestingly, experimental studies on the vinylic/allylic scrambling in Kharasch–Sosnovsky reactions show different results depending on the particular reaction conditions. Thus, the different regioselectivities observed in the reactions of allylbenzene (71:29) and (*E*)-prop-1-enylbenzene (100:0) under the same conditions (*tert*-butyl peracetate, catalyzed by CuCl at 70 °C)[25] indicate that a common reaction intermediate (cinnamyl free radical) cannot participate in both processes. Instead, a study using 3,3,6,6-tetradeuterocyclohexene showed a slight preference for the reaction compound involving a net π-bond migration,[9] that we attribute to the shift of the thermodynamic equilibrium between two isotopomers of the allyl-copper(III) key reaction intermediate, similarly to experimental results on deuterated cyclohex-2-enol.[26]

The difficulty of distinguishing between the reaction mechanisms proposed by Slough and us on the basis of common experimental data must be remarked. Thus, the formation of acetone in some Kharasch–Sosnovsky reactions has been attributed to the β-scission of *tert*-butoxyl radical,[27] whereas we think that such a feature can also be justified by means of the participation of a crypto-alkoxyl radical.

Two alternative reaction mechanisms for the reductive elimination of the allyl-copper(III) key reaction intermediate can be envisaged. Thus, a step involving the migration of the π-bond (named by some authors as a pericyclic reaction) has been usually assumed.[1] In contrast, a step involving the π-bond retention has been proposed for the reductive elimination of a different allyl-copper(III) complex (see Scheme 5).[28]



Scheme 5. Reductive elimination of the allyl-copper(III) key reaction intermediate involving migration (top) or retention (bottom) of the π-bond. Carbon atoms from the vinylic atoms of cyclohexene (according to reaction mechanisms proposed by Slough and us) are shown in purple.

A great challenge for chemists working on the Kharasch–Sosnovsky reaction catalyzed by chiral complexes concerns understanding the factors affecting the stereochemical control of the reaction, an area that would allow a better design of catalysts. In this respect, particular attention has been paid to understanding the reductive elimination of the allyl-copper(III) intermediate. Although a reaction model was proposed by Andrus and co-workers[29] for the Kharasch–Sosnovsky reaction between cyclohexene and *tert*-butyl perbenzoate catalyzed by chiral bisoxazolines, neither experimental nor theoretical evidence of the interactions that determine the stereoselectivity have been provided.

To the best of our knowledge, the work described here involves the first theoretical study on the mechanism of the Kharasch–Sosnovsky reaction. A typical benchmark reaction (cyclohexene + *tert*-butyl benzoate → cyclohex-2-enyl benzoate + *tert*-butyl alcohol) has been considered. As a chiral catalyst model, we considered the complex of the copper(I) ion with mebox, which can be considered as a model for typical $C_2$-symmetric bisoxazolines.[7]

## Computational Methods

A comprehensive mechanistic study of the Kharasch–Sosnovsky reaction was carried out using a medium-sized model including the following reactants: mebox-copper(I) cation as the catalyst, cyclohexene as the olefin, and *tert*-butyl perbenzoate as the perester.

The B3LYP functional was used throughout the study because of its good performance on binding energies for Cu$^{I}$[30,31] and Cu$^{II}$[30] ions with small organic molecules, as well as the reactivity of organocopper(I) and organocopper(III) species.[32] The 6-31G* basis set was chosen because of its good performance in several studies on copper derivatives as well as a number of copper-catalyzed reactions (such as formation of carbene-copper complexes,[33] cyclopropanation,[34] conjugate addition,[35] amine addition to diynes,[36] and cyclization of carbonyl ylides).[37] RB3LYP calculations were used for closed-shell models, whereas UB3LYP computations were applied to open-shell systems.

All energy minima and transition states (TS) were fully optimized. No solvent correction was considered since all Cu complexes bear the same charge, namely +1e. Analytical frequencies were calculated at the B3LYP/6-31G* level and the nature of each stationary point was determined according to the appropriate number of negative eigenvalues of the exact Hessian matrix. Non-scaled frequencies were used for the computation of thermodynamic properties. All calculations were carried out using the Gaussian03 package.[38]

Unless stated otherwise, Gibbs free energies at 25 °C are used for the discussion on the relative stabilities of the chemical structures considered throughout this work. Hard data on geometries, electronic energies, and Gibbs free energies of all structures considered are available as Supporting Information.

## Results and Discussion

### Formation of the allyl-copper(III) key reaction intermediate

**Ligand exchange**: The ligand exchange between cyclohexene and *tert*-butyl perbenzoate for the catalyst complex can take place through a mebox-copper(I) complex binding both ligands (Figure 1, left). According to our calculations, the formation of such a species is slightly favored (by 2.1 kcal mol$^{-1}$), whereas the subsequent step leading to the catalyst–perester chelate (Figure 1, right) is slightly disfavored (by 0.2 kcal mol$^{-1}$). As a consequence, the perester/cyclohexene ligand exchange is slightly favored (by 1.9 kcal mol$^{-1}$). It can be observed that both copper(I) complexes show a tetrahedral geometry around the metal atom, in agreement with typical tetracoordinated copper(I) complexes.[39]

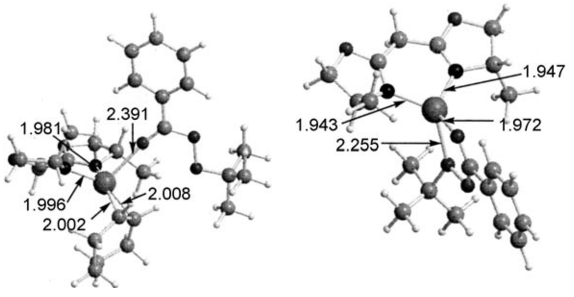


Figure 1. Geometries of the *tert*-butyl perbenzoate-cyclohexene-mebox-copper(I) complex (left) and the *tert*-butyl perbenzoate-mebox-copper(I) ion (right), according to B3LYP/6-31G* calculations. Some selected bond lengths (Å) are also shown.

The allyl-copper(III) key reaction intermediate plays a major role in the mechanism of the Kharasch–Sosnovsky reaction according to all three reaction mechanisms considered (Beckwith–Zavitsas, Slough and our own model). Interestingly, four isomers (depending on the geometrical arrangement of copper and the absolute configuration of the copper-bound carbon atom) for such a species can be found (shown in Figure 2).

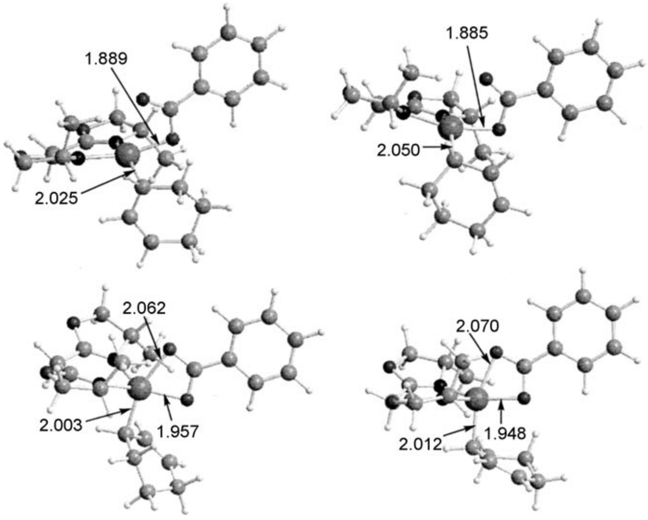


Figure 2. Geometries of four isomers of the allyl-copper(III) key reaction intermediate, according to B3LYP/6-31G* calculations. Structures showing a square-planar tetracoordinated (trigonal bipyramidal pentacoordinated) geometry are gathered on top (bottom), whereas species with the *R* (*S*) absolute configuration are shown on the left (right). Some selected distances (Å) are also shown.

Similar energies are found for structures in which the copper is in a square-planar tetracoordinated geometry in comparison with the trigonal bipyramidal pentacoordinated arrangement. A preference (by 1.8 kcal mol$^{-1}$) for the tetracoordinated geometry is observed for the (*R*)-epimer, whereas a slight predilection (by 0.2 kcal mol$^{-1}$) for the pentacoordinated arrangement is found for the (*S*)-stereoisomer. Comparison of the most stable geometries of both enantiomers shows a preference (by 2.2 kcal mol$^{-1}$) for (*R*)-epimer.

The relative stability of the square-planar tetracoordinated geometry of the allyl-copper(III) intermediate is consistent with experimental[10] and theoretical data on a substituted cyclohexenyl-copper(III) complex.[40] Instead, the occurrence of a low-energy trigonal bipyramidal arrangement, analogously to a different copper(III) complex,[41] provides an explanation for the total $^{16}$O/$^{18}$O scrambling in a Kharasch–Sosnovsky reaction product using $^{18}$O-carbonyl-labeled *tert*-butyl perbenzoate.[14]

According to our calculations, the formation of the (*R*)-epimer of the allyl-copper(III) intermediate and *tert*-butanol (starting from the perester–catalyst complex and cyclohexene) is thermodynamically favored (by 37.0 kcal mol$^{-1}$). As a consequence, the formation of the allyl-copper(III) complex can be regarded as essentially irreversible. Three different reaction mechanisms can be considered for such a process and these are discussed below.

**Beckwith–Zavitsas mechanism**: In the reaction mechanisms of Beckwith–Zavitsas[12] and Slough,[9] it is assumed that the *tert*-butyl perbenzoate–catalyst complex undergoes a homolytic dissociation of the perester O−O bond, leading to the formation of the *tert*-butoxyl radical and benzoate-mebox-copper(II) ion[11] (see Scheme 3).

All relevant stationary points of the Beckwith–Zavitsas mechanism have been calculated, the corresponding energies being gathered in the Supporting Information. Interestingly, our computations predict that the recombination of benzoate-mebox-copper(II) ion and cyclohex-2-enyl radical (leading to the allyl-copper(III) key reaction intermediate formation) is thermodynamically disfavored (by 10.8 kcal mol$^{-1}$). Such a surprising result can be attributed to the well-known underestimation of bond energies for organic[42] and organometallic[43] compounds by B3LYP calculations. Such an artifact is a very common error for density functional methods and this has been attributed to the overstabilization of free radicals caused by the self-interaction error.[44] As a consequence, no reliable conclusions by comparing energies of open and closed-shell systems can be drawn at B3LYP level.

According to the Beckwith–Zavitsas mechanism, a non-coordinated molecule of cyclohexene is attacked by a *tert*-butoxyl radical. The calculated TS (shown in Figure 3) has an approximately linear C···H···O arrangement (165°). Our calculations predict a significant activation free energy (12.3 kcal mol$^{-1}$) but a lower value for the activation enthalpy (1.6 kcal mol$^{-1}$), in a similar way to experimental data for the reactions of methoxyl radical + cyclohexene (3.7 kcal mol$^{-1}$)[45] or *tert*-butoxyl radical + cyclopentene (2.35 kcal mol$^{-1}$).[46]

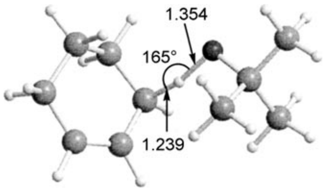


Figure 3. Geometry of the TS corresponding to the Beckwith–Zavitsas mechanism, according to B3LYP/6-31G* calculations. Some selected distances (Å) and an angle are shown.

Some information on the geometry of the C−H···O arrangement (linear vs bent) in TSs of hydrogen-transfer reactions can be obtained from experimental kinetic isotope effects (KIE).[47] For example, the nearly linear C−H···O geometry (165°) calculated for the cyclohexene + *tert*-butoxyl radical reaction is consistent with experimental data for related systems (such as the benzylic hydrogen abstraction from toluene by the photochemically-generated *tert*-butoxyl radical).[48] In contrast, experimental KIEs for the hydrogen abstraction of allylbenzene by the *tert*-butoxyl radical in the presence of Cu$^{+}$ ions can only be explained by assuming a bent C−H···O geometry.[49]

Our theoretical calculations on the TS for the hydrogen abstraction between cyclohexene and the *tert*-butoxyl free radical (indicating a nearly linear C−H···O geometry) allows the Beckwith–Zavitsas mechanism to be ruled out. Such an interpretation is consistent with experimental data on Kharasch–Sosnovsky reactions that show the absence of reaction products derived from the coupling of allylic free radicals. In contrast, significant amounts of 1,1′-bi(cyclohex-2-ene) are formed in cyclohexene oxidation reactions involving free radicals (such as the thermal reaction with acetyl peroxide[50] or some catalyzed oxidation reactions with alkyl hydroperoxides).[51]

**Slough mechanism**: According to the Slough mechanism, the coordination of cyclohexene to the benzoate-mebox-copper(II) ion is considered as a step prior to the hydrogen abstraction reaction. The resulting complex (shown in Figure 4) displays a square-pseudopyramidal arrangement, cyclohexene occupying the apical position. Nevertheless, calculations indicate that the formation of such a complex is thermodynamically disfavored by 7.8 kcal mol$^{-1}$, in agreement with the well-known low affinity of copper(II) complexes for olefins.

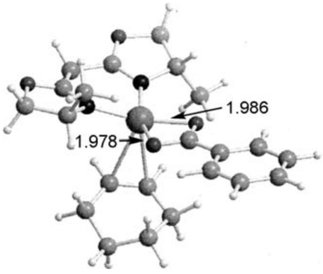


Figure 4. Geometry of the benzoate-cyclohexene-mebox-copper(II) ion, according to B3LYP/6-31G* calculations. Some selected bond lengths (Å) are also shown.

Two different TSs (shown in Figure 5) can be considered for the hydrogen transfer of the Slough mechanism, depending on the absolute configuration of the cyclohexenyl group in the complex being formed.

Interestingly, a bent C−H···O arrangement is predicted in both hydrogen transfer TSs for the Slough mechanism (135° in both structures) and this is in contrast with the nearly linear geometry predicted for the Beckwith–Zavitsas pathway.

Our calculations indicate a slight preference (by 0.9 kcal mol$^{-1}$) for the stereoisomeric TS leading to the (*S*)-epimer of the allyl-copper(III) key reaction intermediate, a situation in agreement with the existence of steric repulsion between a cyclohexene allylic hydrogen and a bisoxazoline substituent. As a consequence, formation of the *S* [rather than *R*] stereoisomer of the allyl-copper(III) key reaction intermediate is predicted to be the fastest for the Slough mechanism. An activation barrier of 49.8 kcal mol$^{-1}$ is calculated for the allylic hydrogen abstraction of the cyclohexene–catalyst complex by the *tert*-butoxyl radical.

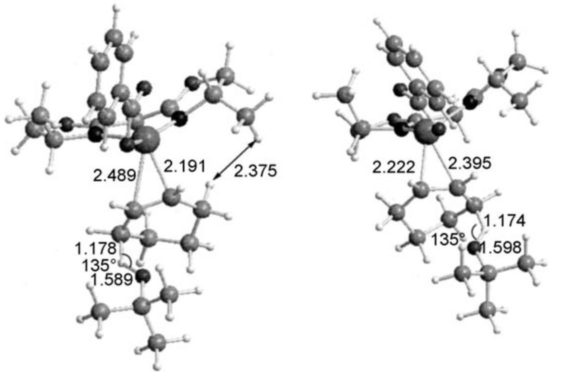


Figure 5. Geometries of both TSs corresponding to the Slough mechanism leading to (*R*)- (left) and (*S*)- (right) epimers of the allyl-copper(III) key reaction intermediate, according to B3LYP/6-31G* calculations. Some selected distances (Å) and angles are also shown.

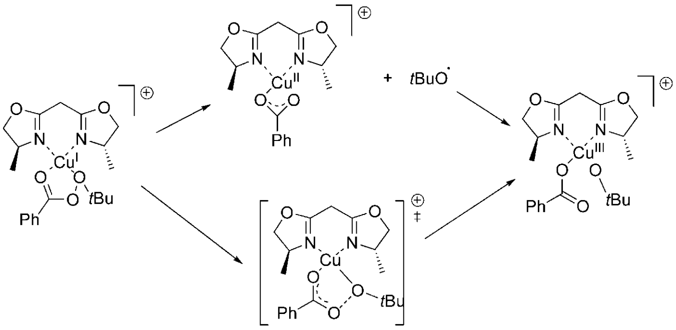
Interestingly, the comparison between the activation barriers of Beckwith–Zavitsas and Slough mechanisms shows that the hydrogen abstraction of cyclohexene by *tert*-butoxyl radical must occur preferably by a naked molecule, in contrast with the conclusions of a related experimental study.[9]

**Proposal of a new reaction mechanism**: B3LYP/6-31G* results corresponding to the O−O bond dissociation of the perester–catalyst complex to yield the allyl-copper(III) key reaction intermediate show that such a reaction is thermodynamically favored (by 21.9 kcal mol$^{-1}$).

Two alternative pathways (Scheme 6) can be envisaged for such a process, in an analogous way to the reaction mechanisms proposed for the oxidative addition of dibenzoyl peroxide to copper(I) chloride in pyridine.[18] One possible route corresponds to a two-step path involving the homolytic cleavage of the O−O bond leading to the formation of the benzoate-mebox-copper(II) ion and *tert*-butoxyl radical, which would subsequently recombine through Cu−O bond formation. As an alternative mechanism, the copper atom of the *tert*-butyl perbenzoate-mebox-copper(I) ion can undergo an one-step oxidative addition of the O−O bond of perester moiety, leading to a copper(III) complex, in an analogous way to the pathway proposed for the dissociation of hydrogen peroxide coordinated to the Fe$^{+}$ ion.[52]

According to B3LYP/6-31G* calculations on the TS corresponding to the concerted cleavage of the peroxide bond, a tetrahedral coordination for the copper atom and an O–O distance of 2.021 Å are found (Figure 6, left).

A low activation barrier (6.5 kcal mol$^{-1}$) for the concerted oxidative addition of the catalyst–perester complex is obtained. Moreover, since calculations show that this process is thermodynamically favored by 21.9 kcal mol$^{-1}$, it can be inferred that the oxidative addition of the perester to the catalyst is essentially irreversible. The low value of the activation barrier calculated for the copper-catalyzed dissociation contrasts with the high experimental value for the non-



Scheme 6. Alternative pathways for the oxidative addition for the *tert*-butyl perbenzoate-mebox-copper(I) ion leading to the allyl-copper(III) key reaction intermediate.

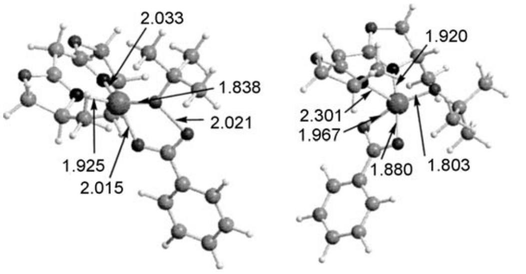


Figure 6. Geometries of the TS (left) and the reaction product (right) for the oxidative addition for the *tert*-butyl perbenzoate-mebox-copper(I) ion, according to B3LYP/6-31G* calculations. Some selected bond lengths (Å) are also shown.

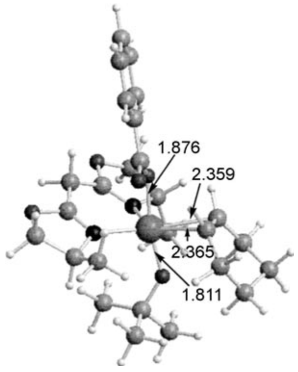


Figure 7. Geometry of the benzoate-*tert*-butoxo-cyclohexene-mebox-copper(III) ion (most stable isomer), according to B3LYP/6-31G* calculations. Some selected distances (Å) are shown.

catalyzed *tert*-butyl perbenzoate reaction (31.4 $\mathrm{kcal\,mol^{-1}}$, extrapolated to 25 °C).[53]

Our computations on the resulting benzoate-*tert*-butoxo-mebox-copper(III) ion in the most stable geometry (Figure 6, right) predict a square-based pyramidal geometry for the copper atom, which is in agreement with X-ray diffraction data for a different pentacoordinated copper(III) compound.[18]

Although an intermolecular mechanism may be proposed for the cyclohexene allylic hydrogen abstraction by the crypto-alkoxyl radical, intrinsic reaction coordinate calculations for such a process have indicated the existence of the benzoate-*tert*-butoxo-cyclohexene-mebox-copper(III) ion (Figure 7) as a reaction intermediate. The occurrence of such a species is consistent with the typical reaction mechanism for the conjugate addition of organocuprate compounds to enoates that involve an olefin-copper(III) ion as a reaction intermediate.[54]

The previous coordination of cyclohexene to the crypto-alkoxyl radical means that the abstraction of the allylic hydrogen atom takes place in an intramolecular step. In the most stable isomer, the cyclohexene ligand of such a reaction intermediate is arranged appropriately for an intramolecular hydrogen transfer with the *tert*-butoxo group.

A trigonal-based bipyramidal coordination for the copper atom is found for the benzoate-*tert*-butoxo-cyclohexene-mebox-copper(III) ion and the equatorial positions are occupied by a mebox ligand and cyclohexene, whereas the apical positions are occupied by benzoate and *tert*-butoxo groups. Depending on the relative orientation of the tetramethylene chain of cyclohexene (included alternatively in the benzoate or *tert*-butoxo hemispheres), two stereoisomers can be envisaged.

According to B3LYP/6-31G* calculations, the binding of cyclohexene to the benzoate-*tert*-butoxo-mebox-copper(III) ion is thermodynamically disfavored (by 25.6 $\mathrm{kcal\,mol^{-1}}$ for the most stable stereoisomer), which is consistent with the experimental preference of the copper(III) ion for tetracoordination and its low affinity for alkene ligands.[55]

Two different TSs (shown in Figure 8) for the intramolecular hydrogen transfer of the benzoate-*tert*-butoxo-cyclohexene-mebox-copper(III) ion can be considered, depending on the absolute configuration of the copper-bound carbon atom of the resulting complex. Our calculations predict a bent C–H···O arrangement (154°) for both TSs, which is similar to the structure predicted in our computations on the Slough mechanism. It must be stressed that such an angular geometry provides an explanation of the experimental KIE on the hydrogen abstraction of allylbenzene by the *tert*-butoxyl radical in the presence of $\mathrm{Cu^+}$ ions.[49] Interestingly, such experimental data have been previously attributed to the occurrence of a stabilizing interaction between the olefin π-bond and the open-shell oxygen atom,[49,56] although previous theoretical studies that have ignored the effect of the copper atom effect are unable to support such a hypothesis.[57] According to our calculations, the hydrogen migration proposed in our mechanism involves a low activation barrier (7.1 $\mathrm{kcal\,mol^{-1}}$ in the preferred TS). As a consequence, a total activation barrier of 32.7 $\mathrm{kcal\,mol^{-1}}$ (by taking cyclohexene and the crypto-alkoxyl radical as references) is calculated.

A net distinction between all three reaction mechanisms for the formation of the allyl-copper(III) key reaction intermediate can be achieved on the basis of energy results. In this respect, it must be stressed that calculations predict a clear preference (by 15.5 $\mathrm{kcal\,mol^{-1}}$) for the TS corresponding to the intramolecular abstraction (corresponding to the

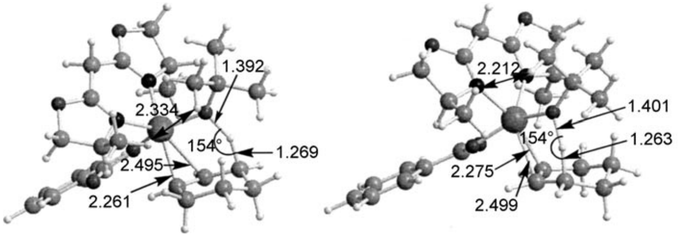


Figure 8. Geometries of both TSs corresponding to the intramolecular hydrogen transfer of benzoate-*tert*-butoxo-cyclohexene-mebox-copper(III) ion to yield the (*R*)- (left) and (*S*)- (right) epimers of the benzoate-*tert*-butanol-η$^1$-cyclohex-2-enyl-mebox-copper(III) ion, according to B3LYP/6-31G* calculations. Some selected distances (Å) and bond angles are shown.

mechanism proposed by us) in comparison with the isomeric intermolecular structure (Slough pathway). As a consequence, the Slough reaction mechanism can be ruled out on the basis of the corresponding high activation energy. It should be noted here that the reaction mechanism proposed here for the formation of the allyl-copper(III) key reaction intermediate is consistent with all available experimental data.

Both calculated stereoisomeric TSs of the intramolecular hydrogen transfer lead to the corresponding epimers of the resulting benzoate-*tert*-butanol-η$^1$-cyclohex-2-enyl-mebox-copper(III) ion (depending on the absolute configuration of the cyclohexenyl group). Our calculations predict a preference for the formation of the (*R*)-isomer of the benzoate-*tert*-butanol-η$^1$-cyclohexenyl-mebox-copper(III) ion rather than the (*S*)-counterpart (shown in Figure 9) in terms of activation barriers (7.1 vs 8.1 kcal mol$^{-1}$) and reaction free energies (−24.0 vs −19.1 kcal mol$^{-1}$). In a subsequent step, both the (*R*)- and (*S*)-epimers of the latter species can lose the *tert*-butanol ligand to yield the corresponding allyl-copper(III) reaction intermediate stereoisomers by following thermodynamically favored processes (by 15.7 and 18.9 kcal mol$^{-1}$, respectively).

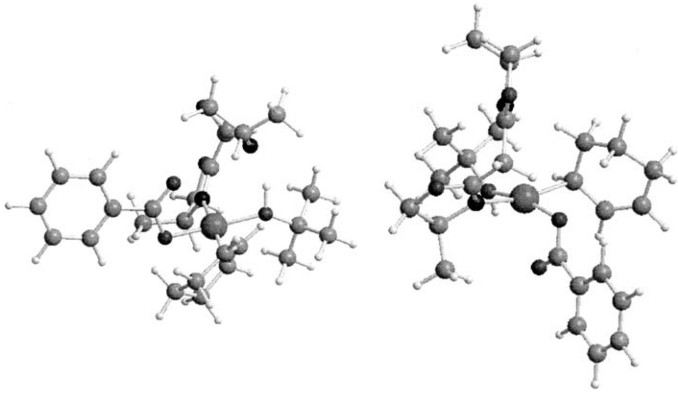


Figure 9. Geometries of (*R*)- (left) and (*S*)- (right) epimers of the benzoate-*tert*-butanol-η$^1$-cyclohex-2-enyl-mebox-copper(III) ion, according to B3LYP/6-31G* calculations.

The results reported here support the new mechanism proposed in this paper. Thus, calculations predict the ready (either one- or two-step) cleavage of the O−O bond in the catalyst–perester complex to yield the crypto-alkoxyl radical. The later species can react with a cyclohexene molecule to yield an intermediate addition complex, which can undergo an intramolecular hydrogen migration to yield the benzoate-*tert*-butanol-η$^1$-cyclohexenyl-mebox-copper(III) ion. The latter species can lose *tert*-butanol to yield the allyl-copper(III) key reaction intermediate.

## Stereoselectivity of the reaction

**Haptotropic rearrangement**: Interconversion between (*R*)- and (*S*)-epimers of the benzoate-*tert*-butoxo-η$^1$-cyclohexenyl-mebox-copper(III) ion can take place through an η$^1$→η$^3$→η$^1$ haptotropic rearrangement. Calculated structures corresponding to energy minima and TSs involved in this process are shown in Figure 10.

B3LYP/6-31G* calculations on the η$^3$ isomer of the allyl-copper(III) key reaction intermediate predict a trigonal pseudo-pyramidal coordination for the copper atom (benzoate group occupying the apical position). Interestingly, a significant tilt in the cyclohexenyl group can be observed in a front view in such way that this ligand is oriented towards

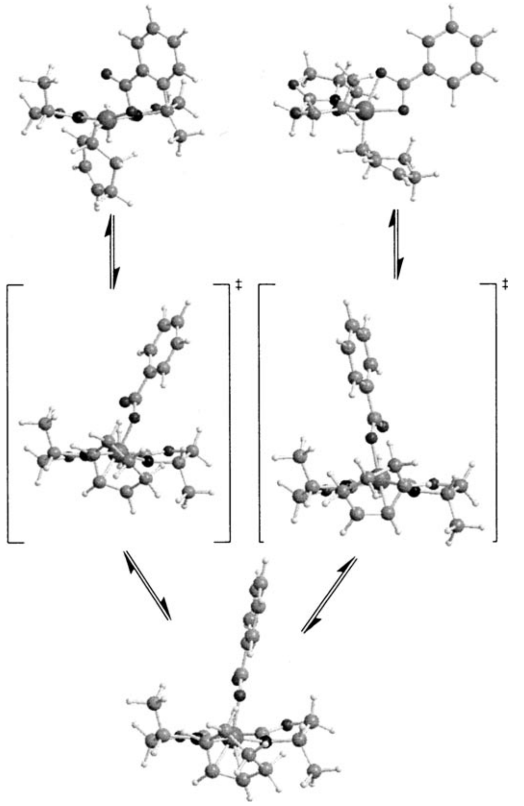


Figure 10. Geometries of the structures involved in the epimerization between (*R*)- (top, left) and (*S*)- (top, right) epimers of the allyl-copper(III) key reaction intermediate via the η$^3$ isomer (bottom), according to B3LYP/6-31G* calculations.

the non-hindered quadrants[7] of the mebox ligand, similar experimental data were found for an $\eta^3$-cyclohexenyl–palladium(II) complex bearing a $C_2$-symmetric ligand.[58] Free energy calculations on the allyl-copper(III) key reaction intermediate show that $\eta^1$-coordination is preferred over $\eta^3$-coordination by 7.6 kcal mol$^{-1}$ (Figure 11), a situation in qualitative agreement with previous calculations on some allyl-copper(III) derivatives.[23]

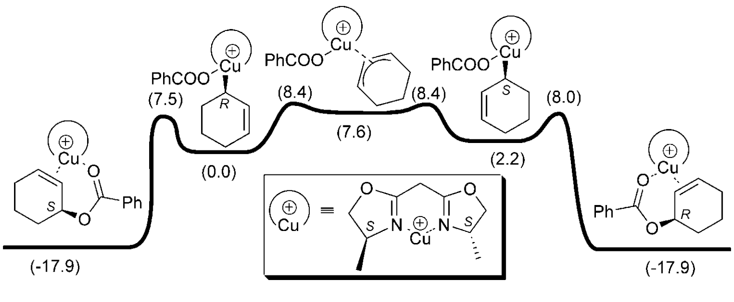


Figure 11. Energy diagram showing the haptotropic rearrangement and reductive elimination of both epimers of the benzoate-cyclohexenyl-mebox-copper(I) ion. B3LYP/6-31G* relative free energies (in kcal mol$^{-1}$) and absolute configurations are shown in parentheses.

Both calculated TSs for the reactions connecting the $\eta^3$-isomer of the allyl-copper(III) key reaction intermediate with the (*R*)- and (*S*)-epimers of the corresponding $\eta^1$-isomer (Figure 10) show a trigonal pseudopyramidal coordination for the copper atom and present similar free energies.

**Reductive elimination**: The binding between cyclohexenyl and benzoate fragments, as well as the regeneration of the +I oxidation state of the copper atom along the catalytic cycle can be explained in terms of a reductive elimination of the allyl-copper(III) key reaction intermediate. The calculated activation energies for both mechanisms of the reductive elimination (see Figure 12) indicate a clear preference for the path involving migration (7.5 kcal mol$^{-1}$, Figure 12) rather than retention (17.7 kcal mol$^{-1}$, Figure 13) of the C=C bond.

These results agree with a theoretical study by Nakamura showing that the reductive elimination of an allyl-copper(III) complex occurs preferentially through the terminal vinylic atom (rather than the copper-bound carbon atom).[22]

Two stereoisomeric approaches can be distinguished for the reductive elimination reaction depending on the (*R*) (Figure 12, top) or (*S*) (Figure 12, bottom) stereochemistry of the allyl-copper(III) key reaction intermediate involving the π-bond migration. Interestingly, the (*R*)-isomer leads to the (*S*)-reaction product, whereas the (*S*)-allyl-copper(III) reaction intermediate yields the (*R*)-final product.

Comparison of the two stereoisomeric TSs in the reductive elimination involving π-bond migration (Figure 12) shows a preference (by 0.5 kcal mol$^{-1}$) for the structure that transforms the (*R*)-allyl-copper(III) intermediate into the catalyst-bound (*S*)-reaction product, whereas the lower stability of the other TS can be attributed to the occurrence of a steric repulsion between the bisoxazoline substituent and the cyclohexene moiety.

Two extreme hypotheses (named as Curtin–Hammett and anti-Curtin–Hammett)[59] can be considered as alternatives to explain the stereochemistry-controlling step in the Kharasch–Sosnovsky reaction. According to the Curtin–Hammett principle, a very fast interconversion (in comparison with the reaction rate of the reductive elimination step) between the two epimers of the allyl-copper(III) key reaction intermediate would occur. As a consequence, the stereochemistry of the Kharasch–Sosnovsky reaction would be determined by the energy difference between the two stereoisomeric TSs corresponding to the reductive elimination step.

According to the anti-Curtin–Hammett hypothesis, no interconversion between the two stereoisomers of the allyl-copper(III) intermediate would take place. In this case, the

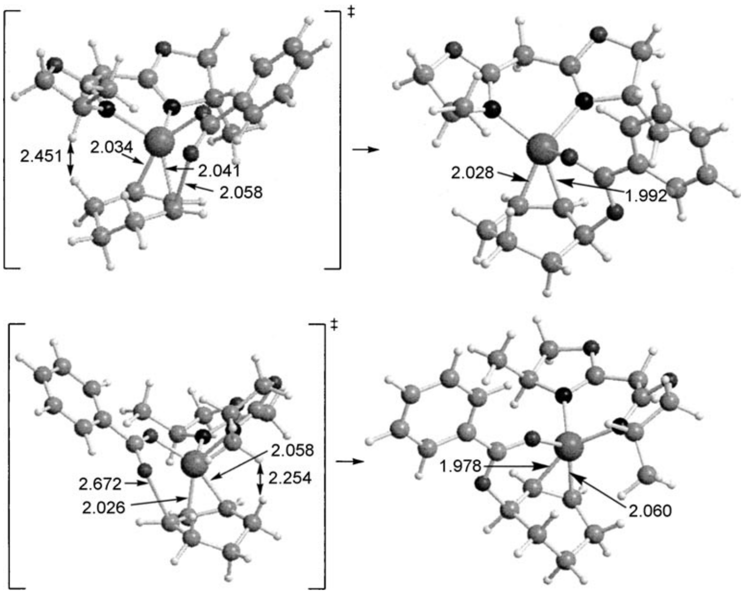


Figure 12. Geometries of the TSs and reaction products for the reductive elimination of (*R*)- (top) and (*S*)- (bottom) stereoisomers of the allyl-copper(III) key reaction intermediate involving π-bond migration, according to B3LYP/6-31G* calculations. Some selected distances (Å) are also shown.

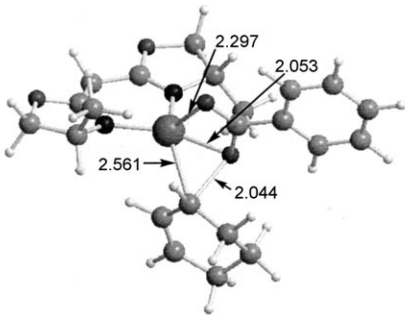


Figure 13. Geometry of the TS of the reductive elimination of the (*R*)-epimer of the allyl-copper(III) key reaction intermediate involving the retention of the π-bond. Some selected bond lengths (Å) are also shown.

stereochemistry of the final product would be controlled by the energy difference between the TSs corresponding to the irreversible formation of the two epimeric reaction intermediates.

Both Curtin–Hammett and anti-Curtin–Hammett hypotheses are incompatible with our computational results since very close activation barriers for the steps involving *R*/*S* interconversion of the allyl-copper(III) key reaction intermediate and the corresponding reductive elimination are found [8.4 and 7.5 kcal mol$^{-1}$, respectively, for the (*R*)-reaction intermediate; 6.2 and 5.9 kcal mol$^{-1}$, respectively, for the (*S*)-reaction intermediate]. Hence, our calculations predict that the enantioselectivity of the Kharasch–Sosnovsky reaction is time-dependent and must follow a complex formula depending on the kinetic constants of all steps involved.[59]

It can be seen from Figure 11 that the reductive elimination reaction of the (*R*)-allyl-copper(III) intermediate leads to the formation of the (*S*)-enantiomer of cyclohex-2-enyl benzoate, whereas the opposite (*S*)-stereoisomer of the starting species yields the (*R*)-reaction product. Interestingly, B3LYP/6-31G* calculations indicate a negligible energy difference (0.0 kcal mol$^{-1}$) for the mebox-copper(I) complexes with (*R*)- and (*S*)-stereoisomers of cyclohex-2-enyl benzoate.

A moderate preference (at steady state) can be calculated for the formation (at 25 °C) of the (*S*)-enantiomer of cyclohex-2-enyl benzoate (58 % *ee*), with such a value being intermediate between those calculated for Curtin–Hammett (43 % *ee*) and anti-Curtin–Hammett (69 % *ee*) conditions. The calculated (*S*)-preference is very close to the experimental data (at 23 °C) for reactions involving several (*S*,*S*)-$C_2$-symmetric disubstituted dimethylbisoxazolines (*i*Pr: 61 % *ee*; *t*Bu: 60 % *ee*; Ph: 67 % *ee*).[60] Our calculated TSs allows us to propose a new reaction model for a chiral Kharasch–Sosnovsky reaction, which is based on the stereoselectivity of two reaction steps: the formation of the allyl-copper(III) intermediate and the corresponding reductive elimination. It can be remarked that the remarkable prediction of the enantioselectivity of the Kharasch–Sosnovsky reaction involves a higher degree of complexity degree than that proposed by Andrus, for which only the reductive elimination step was considered.[29]

Since the experimental results from a Kharasch–Sosnovsky reaction involving isotopically labeled cyclohexene indicate a significant scrambling between vinylic and allylic carbon atoms in the reaction product, we can infer that the epimerization of the copper(III) intermediate is produced at a similar rate to the corresponding reductive elimination. This finding is analogous to that reported in an experimental study on several enantiomerically pure η$^1$-cyclohexenyl-metal derivatives (M = Li, Mg, Ti), which showed the competition between the haptotropic rearrangement and the nucleophilic addition to an aldehyde.[61]

It can be stated that a Curtin–Hammett situation would lead to a complete scrambling between vinylic and allylic carbon atoms, whereas no scrambling should be expected for the anti-Curtin–Hammett hypothesis. Thus, our results (indicating partial scrambling) show an intermediate behavior between experimental results corresponding to two related Kharasch–Sosnovsky reactions (suggesting full[9] or scarce scrambling).[25] Evidently, the complexity of the experimental reaction conditions (role of counterion, specific solvent interactions, different catalyst ligand, isotope labeling, etc.) can affect to the significance of carbon scrambling.

A distorted pseudo-tetrahedral coordination sphere is predicted for copper in both TSs of the reductive elimination of the allyl-copper(III) intermediate (Figure 12), in contrast with the distorted square-planar coordination assumed in the model proposed by Andrus and co-workers.[29] In particular, the C=C bond of the cyclohexene ligand is oriented along a line roughly parallel to the pseudo-$C_2$ symmetry axis of the mebox ligand. As a consequence, cyclohexene is placed in a non-hindered quadrant of the catalyst in the TS arising from the (*R*)-stereoisomer of the allyl-copper(III) reaction intermediate, whereas it occupies a hindered quadrant in the structure corresponding to the (*S*)-counterpart.

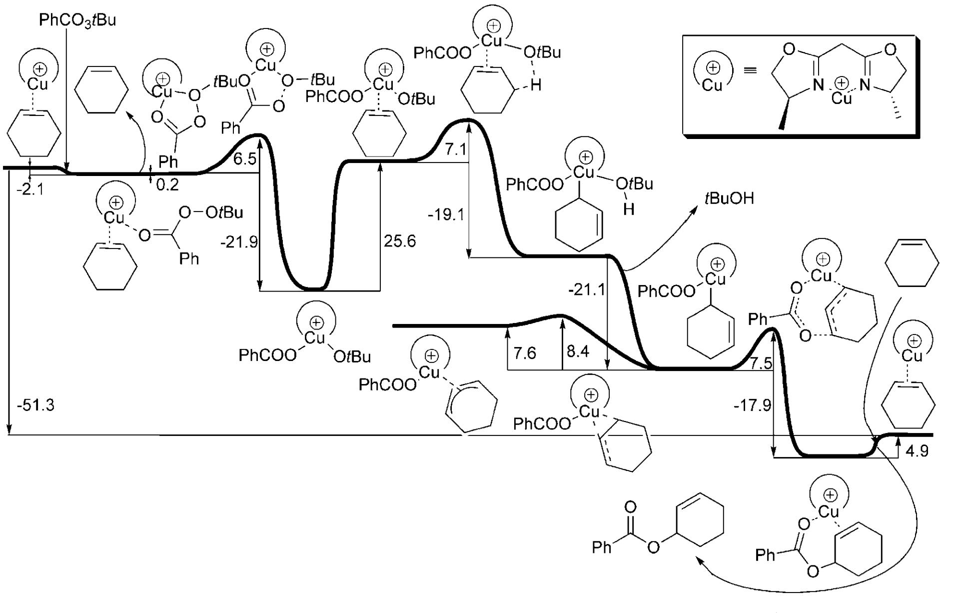


Figure 14. Diagram including activation barriers and reaction free energies (in kcal mol$^{-1}$) for the Kharasch–Sosnovsky reaction through the mechanism proposed here, according to B3LYP/6-31G* calculations. The most stable stereoisomer has been considered for each structure.

**Regeneration of the starting alkene-copper(I) complex**: The Kharasch–Sosnovsky reaction product can be obtained through ligand exchange between the catalyst reaction product complex and cyclohexene, in such way that the catalyst–cyclohexene complex is regenerated. Theoretical calculations indicate that such a process is slightly disfavored (by 4.9 kcal mol$^{-1}$).

### Catalytic cycle

An energy diagram of the Kharasch–Sosnovsky reaction (according to the reaction mechanism proposed here) is shown in Figure 14. The catalytic cycle is thermodynamically favored by 51.3 kcal mol$^{-1}$. Consideration of the energy diagram shows the occurrence of four significant activation barriers along the catalytic cycle (corresponding to oxidative addition, hydrogen transfer, reductive elimination and ligand exchange). Furthermore, comparison between the activation barriers (by taking stable reaction intermediates as a reference) leads to the conclusion that the limiting step of the Kharasch–Sosnovsky reaction corresponds to the intramolecular hydrogen abstraction (Figure 14), which is consistent with kinetic data on such a process that indicate a pseudo-first order for catalyst, olefin, and perester.[62] The corresponding activation barrier [32.7 kcal mol$^{-1}$, if the allyl-copper(III) key reaction intermediate is taken as a reference] is consistent with typical reaction conditions.

## Conclusion

The reaction mechanism of the Kharasch–Sosnovsky reaction has been studied using B3LYP/6-31G* calculations. It was found that the catalytic cycle is thermodynamically favored by 51.3 kcal mol$^{-1}$. A new reaction mechanism has been proposed that excludes the participation of free radicals but includes the oxidative addition of a copper(I) complex as well as the reductive elimination of a copper(III) derivative. Such a process is similar to those found in a number of typical copper salt-catalyzed organic reactions[63] (such as cross-coupling[64] or conjugate addition).[54,65] As an intermediate step, a hydrogen abstraction between the perester–catalyst complex through the *tert*-butoxo group (rather than a *tert*-butoxyl free radical) and cyclohexene is considered and this is analogous to the chemistry of crypto-OH radicals.

The Kharasch–Sosnovsky reaction involves the formation of two epimers of the allyl-copper(III) key reaction intermediate. Our calculations showed that epimerization between the two $\eta^1$-allylic complexes can readily take place through an $\eta^3$-allylic intermediate.

The reductive elimination of the allyl-copper(III) key reaction intermediate takes place through a mechanism involving the $\pi$-bond migration. In particular, two diastereomeric TSs can be calculated for the reductive elimination of the allyl-copper(III) key reaction intermediate, depending on the match/mismatch of benzoate and cyclohexenyl groups with the quadrants defined by the bisoxazoline methyl substituents. The calculated enantioselectivity of the Kharasch–Sosnovsky reaction shows good agreement with experimental results obtained using several bisoxazoline-copper(I) catalysts.

## Acknowledgements

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