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Authors

Osuna, Sílvia
Dermenci, Alpay
Miller, Scott J
et al.

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The roles of counterion and water in a stereoselective cysteine-catalyzed Rauhut-Currier reaction: A challenge for computational chemistry

Sílvia Osuna[1], **Alpay Dermenci**[2], **Scott J. Miller**[2], and **K. N. Houk**[1]

[1]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095

[2]Department of Chemistry, Yale University, 225 Prospect Street, New Haven, Connecticut 06520

Abstract

The stereoselective Rauhut-Currier (RC) reaction catalyzed by a cysteine derivative has been explored computationally with DFT (M06-2X) theory. Both methanethiol and a chiral cysteine derivative were studied as nucleophiles. The complete reaction pathway involves rate-determining elimination of the thiol catalyst from the Michael addition product. The stereoselective Rauhut-Currier reaction, catalyzed by a cysteine derivative as nucleophile, has also been studied in detail. This reaction was experimentally found to be extremely sensitive to the reaction conditions, such as the number of water equivalents and the effect of potassium counterion. The E1cB process for catalyst elimination has been explored computationally for the 8 possible stereoisomers. The effect of explicit water solvation and the presence of counterion (either K^+ or Na^+) has been studied for the lowest energy enantiomer pair (1S, 2R, 3S)/(1R, 2S, 3R).

Introduction

The Rauhut-Currier (RC) and the Morita-Baylis-Hillman (MBH) reactions involve a nucleophilic conjugate addition to generate an enolate intermediate.[1,2] This class of reactions has been known for over four decades, but many developments and applications have been reported only recently.[3] The development of a robust asymmetric version is still an avidly sought goal. The MBH reaction, involving the attack of the intermediate enolate on aldehydes, has been widely studied both experimentally and computationally.[4-7] By contrast, the RC reaction, where the enolate undergoes a Michael addition, has remained underdeveloped for many years due to the low selectivity and enantioselectivity of the process. In 2007, one of our groups reported an enantioselective cysteine-catalyzed RC reaction that afforded the intermolecular RC reactions of bis-enones (see Scheme 1).[8,9]

We have undertaken a study of this peptide-catalyzed reaction, with a long-range goal of designing an enzyme for this reaction. Previous computational designs of enzymes have led to Kemp eliminases,[10] retro-aldolases[11] and Diels-Alderases.[12]

The RC reaction catalyzed by the cysteine derivative, **2**, was found to be extremely sensitive to the reaction conditions, although the experimental yields and enantioselectivities achieved

Correspondence to: Sílvia Osuna; K. N. Houk.

Supporting Information. Figure S1 and S2 with the details of the conformational analysis, Figure S3 with Michael addition, protonation of the enolate and the E1cB process for the lowest energy enantiomer pair, and M06-2X/6-31G(d) optimized Cartesian xyz coordinates (in Å) of all analyzed species.

were synthetically useful. The number of water equivalents as well as the nature of the counterion employed influence the enantioselectivity of the process. Several studies have been published where the role of water in the catalysis of several processes was investigated.[1,4,13-17] It is well known that significant acceleration of the parent MBH reaction is produced in the presence of protic species.[1,4] Therefore, it was hypothesized that the acceleration is produced due to the stabilization of the zwitterionic intermediates formed during the course of the reaction through hydrogen bonding. Subsequent computational studies indicated that these proton donors act as shuttles for proton transfers.[13,18] Similarly, the activation barriers for other 1,2 and 1,3-proton shifts in several processes are decreased by explicit water molecules.[14-17]

The enantioselective cysteine-catalyzed RC reaction is unique in the sense that selectivity is sensitive to the number of water equivalents (20 equivalents of H_2O were found to yield an enantiomeric ratio (er) of 90.5:9.5).[8,9] The er was changed from 71.0:29.0 to 55.0:45.0 by changing the number of water equivalents from 1 to 275, respectively. Potassium and sodium counterions gave different reaction yields and ers. These observations combined with the conformational flexibility of the compounds under study makes the computational exploration of the reaction mechanism a major challenge for theory. We have carried out a detailed investigation of the reaction mechanism of thiolate-catalyzed intramolecular RC reactions and the stereoselectivities of reactions catalyzed by cysteine derivative, **2**. The studies employed conformational analysis programs developed in our group,[19] and along with density functional theory.

Background

The Rauhut-Currier (RC) and the Morita-Baylis-Hillman (MBH) reactions involve an initial nucleophilic conjugate addition and enolate generation. MBH involves the attack of the enolate on an aldehyde, whereas the RC (also known as the vinylogous MBH reaction) involves attack on a second Michael acceptor (see Scheme 2). Although the MBH has been widely studied,[4-6] the RC has received much less attention due to the low reactivity of substrates and the low selectivity of the process.

Since the initial phosphine-catalyzed dimerization of electron-deficient alkenes discovered by Rauhut and Currier[20] in 1963, other nucleophilic catalyts have been discovered. Some recent intramolecular RC reactions are described here. For a complete review of both intra and intermolecular RC, see reference 2. In 1999, Moore and Erguden reported an intramolecular transannular RC reaction catalyzed by thiophenol and sodium thiophenolate for the synthesis of the natural product waihoensene.[21] In 2002, Krische[22-24] and Roush[25] reported the intramolecular RC reaction of symmetrical and unsymmetrical bis-enone substrates using trialkylphosphines. Gladysz and co-workers reported the RC reaction involving bis(thioesters) using a fluorinated phosphine catalyst.[26]

In 2007, thiol/thiolate catalysis of this reaction was disclosed.[8,9,27] Among these disclosures, enantioselective RC reactions using a simple cysteine derivative as an asymmetric catalyst were discovered.[8,9] The cysteine-based catalyst (see Scheme 1) was able to cycloisomerize symmetrical and unsymmetrical bis(enones) in the presence of potassium *tert*-butoxide using acetonitrile as solvent. The reaction was found to be extremely sensitive to reaction conditions, and 20 equivalents of water were found to give the best enantioselectivities. Some experimental assays were performed in order to better understand the mechanism of the reaction. For instance, the cycloisomerization of the aryl bis(enone) **1** under the optimized conditions with 18-crown-6 added gave none of the desired product, **3**. Instead a non-conjugated by-product, **4**, was isolated (26% yield, 92.0:8.0 er, see Scheme 3). In a parallel experiment, the reaction was prematurely quenched after 2h of reaction. Although

the desired product **3** was obtained in 29% yield and 97.5:2.5 er, a mixture of five diastereomeric substrate-catalyst adducts was detected, which after oxidation and elimination led to the desired product with reduced enantioselectivity (70.0:30.0 er). It was suggested that these results are consistent with reversible carbon-carbon bond formation, with deprotonation of the α-proton of the Michael addition product as the irreversible and stereochemistry-determining step. These observations are in agreement with some mechanistic studies of MBH type processes by the Aggarwal and McQuade groups.[28-30] Moreover, the integration of the observations, including the well-established preference for axial disposition of the thiolate leaving group, contributed to initial speculation that the differential energies of transition states could correlate with alternate structures related to the formation of, or reaction of potassium enolates, such as those shown in Scheme 4.

Later, the total synthesis of the natural product Sch-642305 was accomplished with a key RC reaction by cysteine, **2**, via an intramolecular variant of reaction.[31] In a separate study, *ortho*-mercaptobenzoic acid and *ortho*-mercaptophenols were found to efficiently catalyze both the intramolecular RC and MBH processes.[32] Additionally, a combined experimental-theoretical study on the enantioselective intramolecular RC of nitro-olefins with tethered enoates using hydrogen-bonding catalysts has been recently published (see Scheme 5).[33]

The MBH reaction has also been catalyzed by proteins; Reetz reported that the MBH reaction of cyclohexenone and *p*-nitrobenzaldehyde is catalyzed by a common promiscuous enzyme, bovine serum albumin (BSA) as well as certain lipases with up to 35% conversion and 19% enantioselectivity.[34] Liu and coworkers found that a purified enzyme, that they called SpnL, was responsible for the final cross-bridging RC step that completes the tetracyclic core of Spinosyn A, a natural product used as an insecticide. The mechanism of action for this enzyme is not known experimentally. [35] Roush and coworkers also accomplished the non-enzymatic synthesis of Spinosyn A through transannular Diels-Alder and RC reactions.[36]

Computational Methodology

Full geometry optimizations were performed with the hybrid meta exchange-correlation DFT functional M06-2X[37,38] with the 6-31G(d) basis set[39,40] using the Gaussian 09 suite of programs.[41] It has been found that M06-2X provides reasonable energetics of π–π stacking interactions and non-bonded interactions,[37,38] and that M06-2X gives results within 1 kcal/mol of the CBS-QB3 benchmark values for studying the conjugate addition of MeSH to α,β-unsaturated ketones.[42] The M06-2X calculations gave reaction enthalpies and entropies in good agreement with experiment ($\Delta H^{M06\text{-}2X}$= –12.7 kcal/mol and $\Delta S^{M06\text{-}2X}$= –43.5 cal/molK, compared to the experimental values of ΔH^{exp}= –13.9 kcal/mol and ΔS^{exp}= –41.3 cal/molK) for the analogous MBH reaction.[43,44] In contrast, the popular B3LYP provided poor thermodynamic properties in the MBH reaction.

Solvent effects were included in geometry optimizations using the Conductor-like Polarizable Continuum Model (CPCM) with acetonitrile as the solvent.[45,46] For the study of the RC reaction on both models and the complete system, single point calculations using M06-2X/6-311+G(d,p) on the M06-2X geometries (i.e. M06-2X/6-311+G(d,p)//M06-2X/6-31G(d)) were performed. All systems were treated with the spin-restricted formalism. An UltraFine integration grid was used in all cases as it was found to significantly influence energetics.[47] Frequency calculations were used to characterize stationary points by the number of negative eigenvalues of their analytic Hessian matrix (this number is zero for minima and one for transition states). We have also checked that imaginary frequencies exhibit the expected motion, while transition states have also been verified by IRC

calculations.[48,49] All reported reaction and activation energies include zero point energies (ZPEs), Gibbs and thermal corrections ($C_v\Delta T - R\Delta T$) at 298 K to the electronic energies.

Results

1. RC reaction using methanethiolate as nucleophile

The RC reaction mechanism was first studied using methanethiol as the nucleophile. The RC process using this model nucleophile has been studied for the lowest energy conformer leading to the (1S, 2R, 3S) stereoisomer, although the enantiomer would of course be formed at the same rate. Due to the high number of possible conformers and stereosiomers to take into account, we have restricted our study on the model system to the lowest energy conformation. The conformational analysis on the model was performed using the program AMIGO (Automatic Madern's Isomer Generator and Operator)[19] written in our lab. This analysis showed that more than 15 conformers have relative energies within 4 kcal/mol of the lowest energy stereoisomer (see SI for more details). A potassium cation and an explicit water molecule have been included to better reproduce the experimental conditions. The effect of water and coordination by the potassium cation were found in screening experiments to be crucial to achieve high ers.[2,8,9]

In Figure 1, the free reaction profile for the complete process is represented. In Figure 2, the lowest energy transition states for each step are shown. The first step of the reaction, i.e. the conjugate addition of the thiolate is endoergonic by 1.8 kcal/mol. The MeS^- ion can add to the C=C bond in either a *syn* or an *anti* conformation. The *syn* arrangement, **TS1**, reduces the sulfur lone-pair and alkene π orbital repulsion, and also enables an attractive electrostatic interaction between the MeS^- protons and the carbonyl oxygen. The activation barrier of the *syn* addition is 9.7 kcal/mol. Different coordination modes of the K^+ have been studied. The lowest activation barrier is obtained when the potassium cation is coordinated to the carbonyl oxygen of the enone (**TS1**, see Figure 2a). The potassium counterion also interacts with the sulphur atom of the methanethiolate. The conjugate addition is reversible, as is well known in the literature.[42] The K^+ ion does favor the addition process, relative to additions of thiolate to α,β-unsaturated carbonyl compounds.[42]

The second step of the RC reaction is the intramolecular Michael addition, where a cyclohexane and the remaining asymmetric centers are formed. This step determines the stereochemistry of the reaction. Michael additions are usually reversible processes, and indeed many Michael acceptors are key pharmacophores in the design of irreversible inhibitors of clinically relevant proteins.[50,51] In this intramolecular RC reaction, cyclohexane formation (**int3**) is favorable by ca. 18 kcal/mol (compared to **int1**), and the Gibbs free energy activation barrier is only 5.3 kcal/mol. At the transition state, **TS2** has a forming C–C bond distance of 2.488 Å.

The enolate anion, **int3**, can react at either the α-carbon or the carbonyl oxygen to give the ketone or enol. As expected, the formation of the carbonyl compound is 14 kcal/mol more favorable than the enol, although the enol is usually formed kinetically. A water molecule was included in all calculations, and here the water protonates the generated enolate. The protonation of the α-carbon of the enolate by water is endothermic by 16.3 kcal/mol. The activation barrier for the process is 20.4 kcal/mol compared to the previous **int3** intermediate. The K^+ cation is both stabilizing the generated hydroxide anion and the enolate (the distances are 2.591 and 2.869 Å, respectively).

The hydroxide anion then deprotonates the α-position of the other carbonyl group to eliminate the thiolate and form the product, **PROD**. Our calculations indicate that this process follows an E1cB mechanism.[52,53] The carbanion intermediate formed is stabilized,

and the rate-determining step of the reaction corresponds to the formation of this carbanion/enolate. The activation barrier for this step is 11.8 kcal/mol compared to **int1** and 13.5 kcal/mol compared to **int4**. Figure 2d shows the optimized transition state corresponding to the deprotonation step. The potassium counterion is only interacting with the hydroxide anion with a distance of 2.549 Å.

The elimination of the thiolate has a low activation barrier of 8.6 kcal/mol. These results suggest that in the case of (1S, 2R, 3S) the formation of the carbanion/enolate is slow and the subsequent thiol elimination is fast.[52] The breaking C—S bond distance at the transition state is 2.431 Å, which is substantially longer than the forming C—S bond distance of 2.409 Å found for the first conjugate addition of the process (see Figure 2e and 2a, respectively). The potassium ion is interacting with both the methanethiolate and the oxygen atom of the carbonyl group. The water molecule is forming a hydrogen bond with the sulphur atom of the methanethiolate (the S...H distance is 2.326 Å). The final product is 13.8 kcal/mol more stable than the initial intermediate **int1**.

2. RC reaction with a chiral cysteine derivative, 2, as nucleophile

The study of the model system using methanethiol as the nucleophile has shown that the first step of the E1cB elimination of thiol catalyst is rate-determining. The RC study for the cysteine **2**-catalyzed has been restricted to the lowest energy conformation for each possible stereoisomer (8 in total). These lowest energy conformers were found by extensive conformational searches. This restriction of the number of conformers studied is mainly due to the very high number of conformers close in energy, which makes the computational study of the reaction extremely time-consuming. To make the next step feasible, the most stable conformer for each stereoisomer found for the model system was modified to include the complete cysteine substituent. Using our program AMIGO,[19] the conformers involving all the rotatable bonds of the cysteine substituent were investigated. The best 120 conformers according to geometrical criteria were optimized at the PM6 level. Finally, the 30 lowest energy conformers according to PM6 energies were re-optimized at B3LYP/6-31G(d) level (see SI for more information). The complete reaction path for the RC process was then studied on the lowest energy conformer for each of the 8 possible stereoisomers.

In light of the results obtained for the model system, we studied the Michael addition, protonation of the enolate and the E1cB process for all possible stereoisomers using the actual cysteine catalyst (see Figure S3 for the Gibbs-free energy profile for the lowest energy enantiomer pair). Here, we focus on the E1cB process, which is the rate-determining step of the reaction. Figure 3 shows the free energy profile for all possible stereoisomers for the E1cB mechanism. Among all possible 8 stereoisomers, the elimination of the cysteine nucleophile can only occur in the case of the enantiomer pairs (1S, 2R, 3S)/(1R, 2S, 3R) and (1R, 2R, 3S)/(1S, 2S, 3R), where it is axial. Axial departure of the cysteine leads to the formation of the final cyclohexene ring. In Figure 4, the optimized structures for **int5** leading to the (S)-enantiomer are represented. The cysteine elimination does not occur in (1S, 2R, 3R)/(1R, 2S, 3S) (**int5b**) and (1S, 2S, 3S)/(1R, 2R, 3R) (**int5a**), because the cyclohexane ring is unable to undergo the required conformational changes to adopt the half-chair cyclohexene; instead, the equatorial thiolate conformation with chair cyclohexene is preferred but unsuitable for elimination. In all cases, the deprotonation step presents a higher activation barrier compared to the cysteine elimination step. This slow carbanion/enolate formation and subsequent fast cysteine elimination is consistent with an $(E1cB)_i$ mechanism.[52]

As noted in the introduction, it is known in the literature that a great acceleration of the parent MBH reaction is achieved in the presence of protic species.[1,4] For the section studied here, the enantiomeric ratio observed was highly dependent on the number of water

equivalents (i.e., 20 equivalents of H_2O yield an er of 90.5:9.5), as well as on the nature of the counterion used.[8] Computational studies indicated that protic species like water act as shuttles for proton transfer.[13,18] We studied the E1cB process for the lowest energy enantiomeric pair in the absence of counterion, with either K^+ or Na^+ and including either 0 (see Figure 5) or two water molecules (see Figure 6), i.e one water molecule for stabilizing the hydroxide anion and another one for stabilizing the enolate. This strategy of including two water molecules was also used for studying water-catalysis in the MBH reaction.[17] *Ab-initio* MD simulations performed on MBH indicated that only two water molecules are intimately associated with the transition state.[17]

When the E1cB process is studied without explicitly accounting for water molecules and in the absence of counterion, the preferred transition state corresponds to the (1R, 2S, 3R) case. The activation barriers with respect to the previous intermediate **int4** are 9.4 and 8.2 kcal/mol for (1S, 2R, 3S) and (1R, 2S, 3R), respectively (Figure 5). The breaking C—H and forming H—C bonds are approximately 1.31 and 1.35 Å in both cases. The partial negative charge formed on the carbonyl oxygen is basically stabilized through an NH hydrogen bond with the amide substituent of the cysteine. The lower activation barrier obtained for the (*R*)-enantiomer is attributed to the stronger stabilization of the oxyanion, as the HB distances are ca. 1.870 and 1.860 Å in (1S, 2R, 3S) and (1R, 2S, 3R), respectively, as shown in the structures on the left side of Figure 5. When potassium or sodium cations are included in the calculations (Figure 5 center and right), the preferred transition state still corresponds to the (*R*)-enantiomer. This is not surprising as the role of K^+ and Na^+ is basically to stabilize and fix the hydroxide anion close to the deprotonation site; the partial negative charge of the oxygen enolate is still only stabilized by the amide substituent of the cysteine. The activation barriers obtained for the E1cB process in the presence of K^+ and Na^+ are ca. 1.7 and 2.5 kcal/mol higher than the activation barrier computed in the absence of counterion. This higher activation barrier obtained for Na^+ is in agreement with the experimental decrease of the overall reaction yield.[8] Of course, the stabilization of the hydroxide anion is stronger for the smaller Na cation than for K (the Na—O and K—O distances are 2.530 and 2.200 Å, respectively).

In Figure 6, the optimized transition state structures corresponding to the first step of the E1cB process explicitly accounting for two water molecules (highlighted in green) are represented. Again, the reaction has been studied without counterion and with the potassium or sodium cations. When two water molecules are included but no counterion is considered, the preferred transition state still corresponds to the (*R*)-enantiomer. The activation barrier is 10.4 and 9.6 kcal/mol for (1S, 2R, 3S) and (1R, 2S, 3R), respectively. The breaking C—H and forming H—C distances are like those on Figure 5. The main difference of 0.7 kcal/mol between the two activation barriers is attributed to the more stable **int4** and **TS5** structures for (1R, 2S, 3R). In the absence of counterion, the hydroxide anion is not fixed and is displaced far from the reactive site. In the case of (1S, 2R, 3S), the hydroxide anion is situated closer to the lone pairs of the sulphur atom of the cysteine substituent, which leads to a less stable **int4** (3.6 kcal/mol less stable than **int4**$^{(1R,\ 2S,\ 3R)}$ and **TS5** (+4.4 kcal/mol). The calculations in the absence of counterion indicate that the potassium cation is crucial for fixing the hydroxide anion close to the deprotonation site.

In Figure 7, the optimized transition states as well as the reactant complexes for the first step of the E1cB mechanism including two water molecules and the potassium counterion are represented. These are the same as the center TSs in Figure 6. Interestingly, when two explicit waters and either potassium or sodium counterion are included in our calculations to stabilize both the hydroxide anion and the partial negative charge on the enolate, the activation barriers for (1S, 2R, 3S) and (1R, 2S, 3R) are 14.3 and 15.1 kcal/mol, respectively. This leads to a preference for the (*S*)-enantiomer of ca. 0.8 kcal/mol, which

corresponds to a computed enantiomeric ratio of 79.5:20.5 (experimentally, it is found that with 1 equivalent of water the *er* is 71.0:29.0).[8]

IRC calculations performed from the computed located TSs indicate that in the case of (1S, 2R, 3S), the water molecule that stabilizes the hydroxide anion is deprotonated and stabilized by the potassium cation (see left column on Figure 7). In contrast, in **int4** for (1R, 2S, 3R) the potassium ion is slightly displaced so that the hydroxide anion can be directly stabilized (see Figure 7). This arrangement leads to a shorter distance between the proton that is removed to form the enolate and the oxygen of the hydroxide anion in the case of the (*S*)-enantiomer. As already observed, the presence of counterion is crucial for fixing the hydroxide anion close to the deprotonation site, which is more effective in the case of the (1S, 2R, 3S) stereoisomer. These results indicate that the origin of preference for (*S*) found experimentally might be in large part due to the influence of K^+ on OH^- pre-organization.

In addition to the hydroxide pre-organization, the cysteine substituent is more planar in the case of (1R, 2S, 3R). The C(=O)-C-N-C(=O) dihedral angle is –65° and –126° for (1S, 2R, 3S) and (1R, 2S, 3R), respectively. In the pro-(*R*) case, the cysteine substituent adopts a more extended conformation usually found in β-sheet regions.

Conclusions

It is clear that the 2-catalyzed RC reaction is a complex process. Nevertheless, a computational study was possible in which assumptions could be made about the involvement of various molar equivalents of water in light of a wealth of experimental observations. The calculations indicate that the higher activation energy found for the formation of the enolate in the pro-(*R*) case might be mainly attributed to the (a) difference in the pre-organization of the potassium cation and the hydroxide anion and (b) higher distortion energy required to adopt the relatively twisted conformation of the cysteine in the transition state geometry. The experimental dependence of the enantiomeric ratio on the number of water equivalents and the potassium counterion is attributed to the role of water for stabilizing the oxyanion, and of preorganization of hydroxide by K^+.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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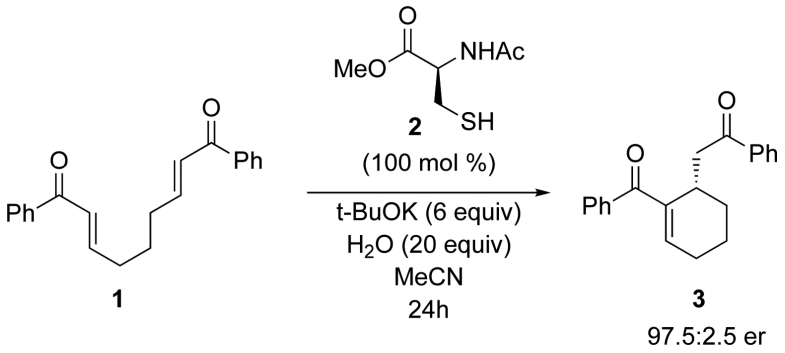
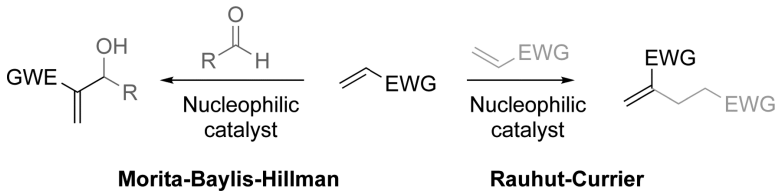
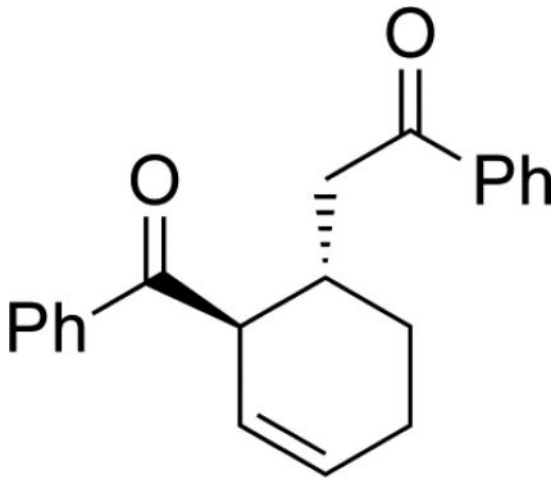


Scheme 1.
Enantioselective cysteine-derivative catalyzed based Rauhut-Currier (RC) reaction.



Scheme 2.
The Morita-Baylis-Hillman (MBH) and Rauhut-Currier (RC) reactions.



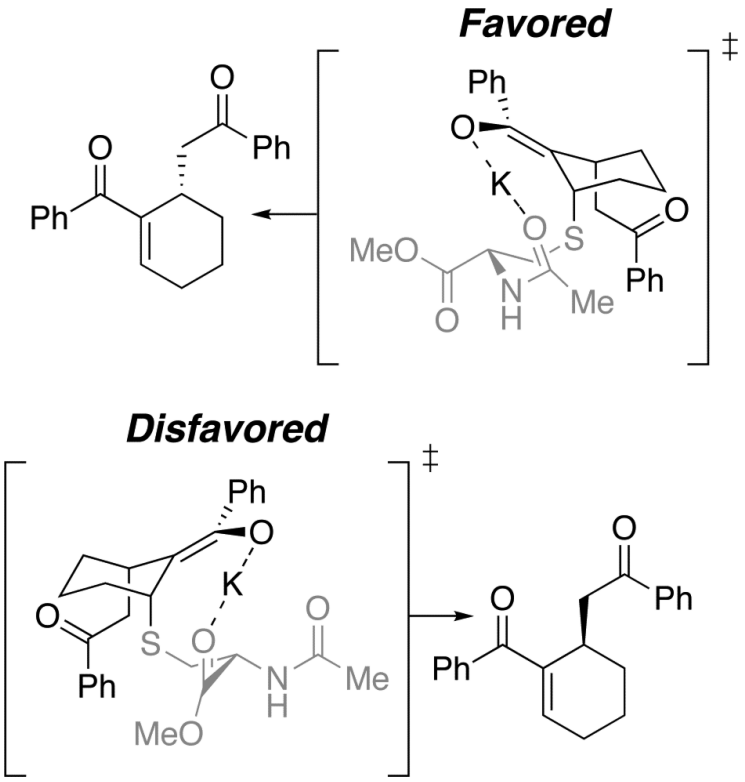
4

26% yield

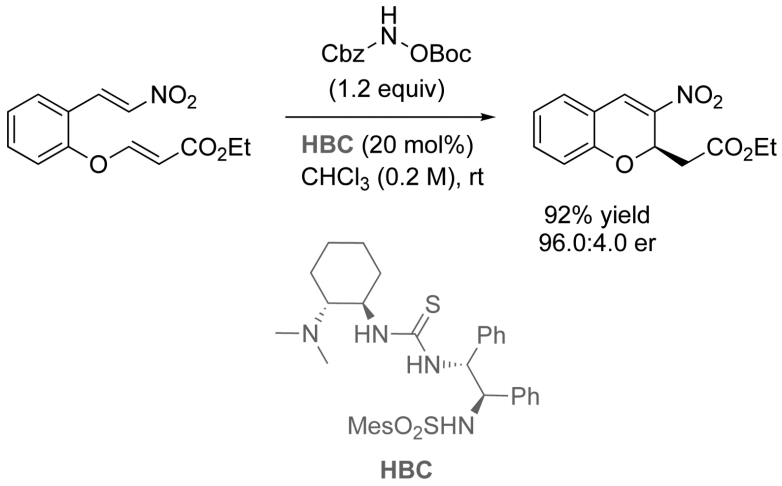
92.0:8.0 er

Scheme 3.

Product of the cycloisomerization of the aryl bis(enone) **1** under the optimized conditions in the presence of 18-crown-6.



Scheme 4.
Initially proposed Transition-state models to explain formation of the observed enantiomer.



Scheme 5.
Enantioselective intramolecular RC of nitro-olefins with tethered enoates using hydrogen-bonding catalysts. [33]

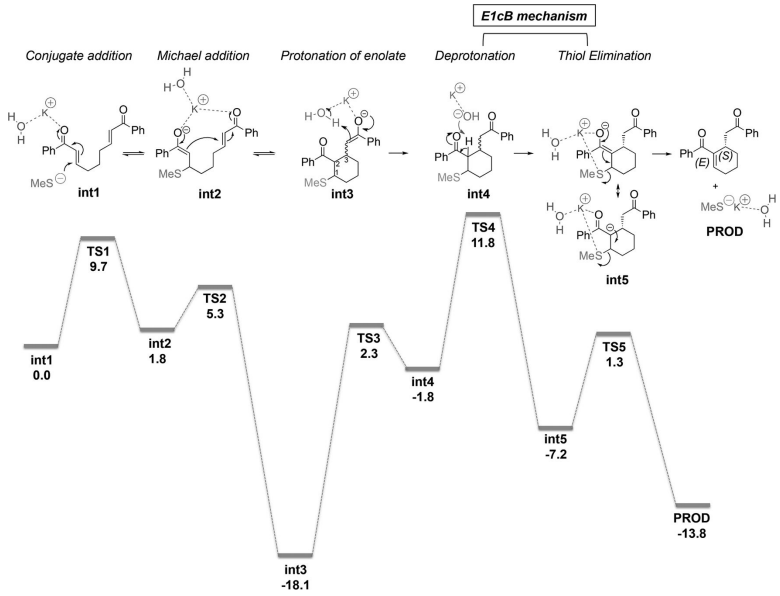


Figure 1.
Gibbs-free energy profile at M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) for the RC reaction with methanethiol as the nucleophile. All energies are in kcal/mol.

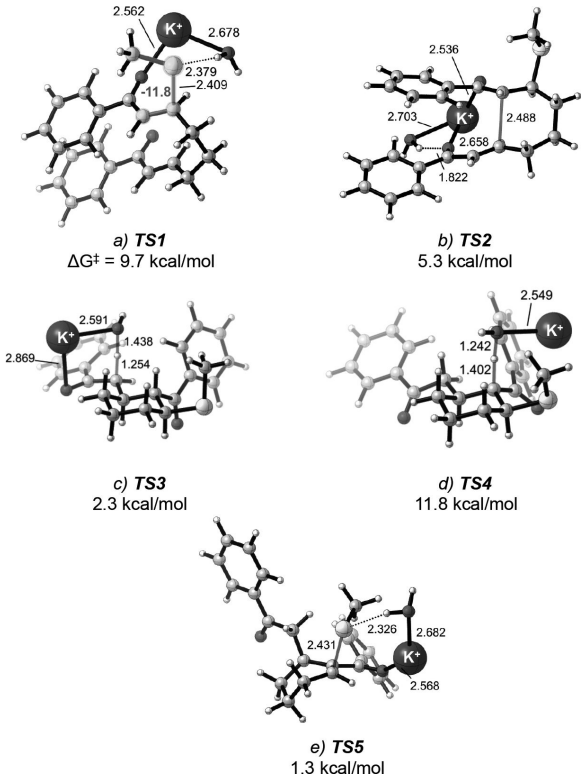


Figure 2.

M06-2X/6-31G(d) optimized transition states corresponding to the different steps of the Rauhut-Currier reaction: a) Conjugate addition (**TS1**), b) Michael addition (**TS2**), c) Protonation of the enolate (**TS3**), d) Deprotonation (**TS4**), and e) Thiol elimination (**TS5**). Gibbs-free activation barriers are by M06-2X/6-311+G(d,p) referred to **int1**. All energies, distances and angles are in kcal/mol, Å, and degrees, respectively.

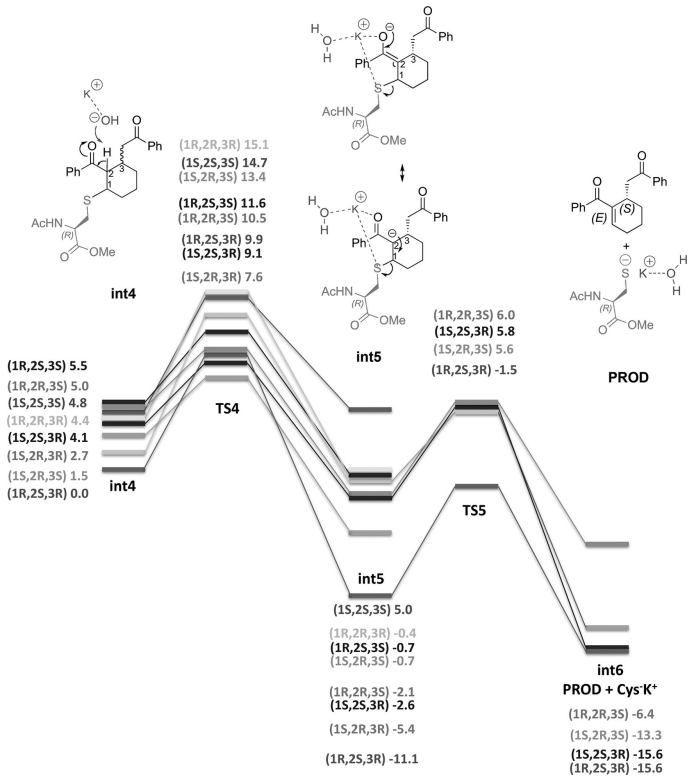


Figure 3.

Gibbs-free energy profile at M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) for the RC reaction for all 8 possible stereoisomers. Those stereoisomers leading to the (*S*)- and (*R*)-enantiomers have been colored using a blue and a red range, respectively. All energies are in kcal/mol and referenced to the lowest energy conformer of **int4**. Experimentally, the (*S*)-enantiomer is obtained.

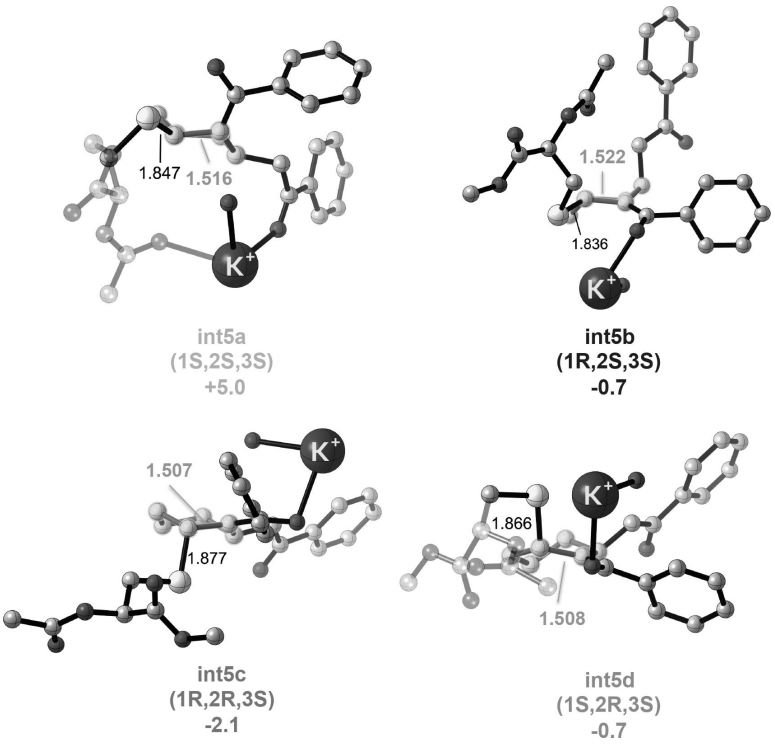


Figure 4.

M06-2X/6-311+G(d,p)//M06-2X/6-31G(d) optimized intermediate structures (**int5**) prior to the thiolate elimination. All hydrogen atoms have been omitted for clarity. All distances are represented in Å. Free relative energies are in kcal/mol and compared to the lowest energy steoreosiomer (1R,2S,3R) of **int4**. Highlighted atoms correspond to the distorted cyclohexane ring.

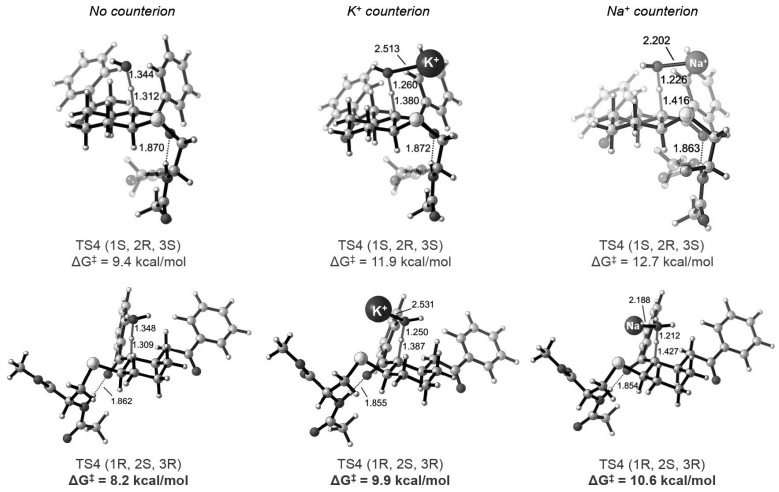


Figure 5.

Optimized transition state structures for the first step of the E1cB process for (1S, 2R, 3S) and (1R, 2S, 3R) enantiomers without counterion (left column), including K^+ (central column) and Na^+ (right column). The activation barriers for the lowest barrier TS are in boldface. All energies and distances and angles are in kcal/mol, and Å, respectively.

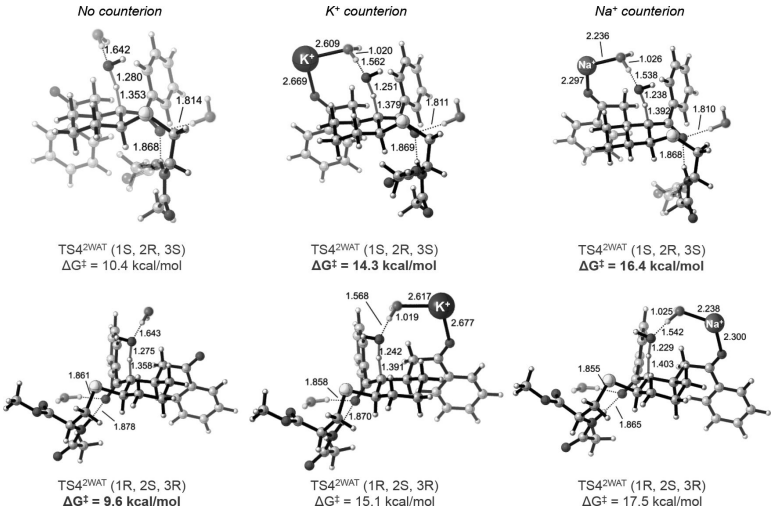


Figure 6.

Optimized transition state structures for the first step of the E1cB process for (1S, 2R, 3S) (first row) and (1R, 2S, 3R) (second row) enantiomers without counterion (left column), including K^+ (central column) and Na^+ (right column) and in the presence of two explicit water molecules. The activation barriers for the lowest barrier TS are in boldface. All energies and distances and angles are in kcal/mol, and Å, respectively.

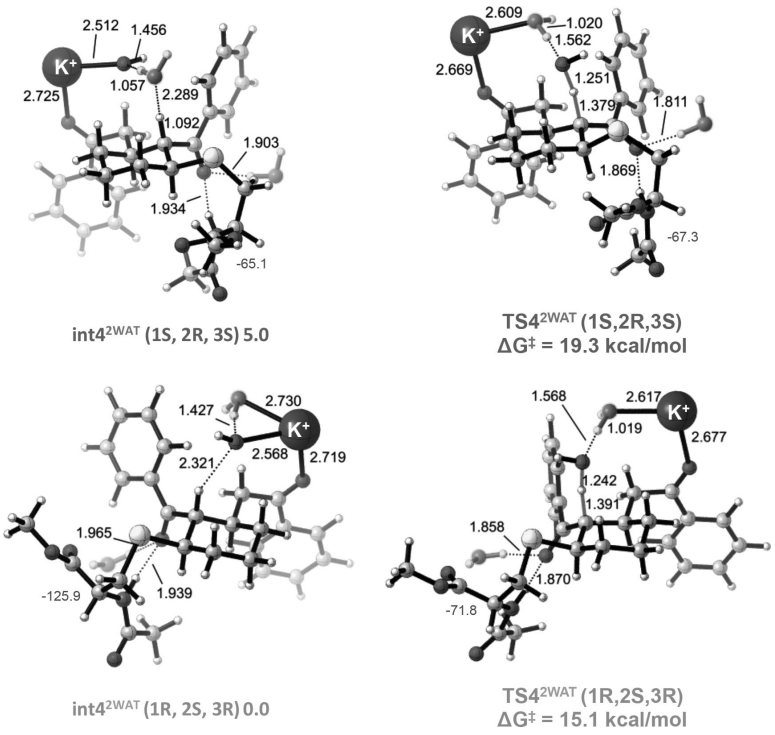


Figure 7.

Optimized transition state and reactant complexes for the first step of the E1cB process for (1S, 2R, 3S) and (1R, 2S, 3R) enantiomers. All energies, distances and angles are expressed in kcal/mol, Å and degrees, respectively.